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The differential influence of immune, endocytotic and lipid metabolism genes on amyloid deposition and neurodegeneration in subjects at risk of Alzheimer's disease

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Abstract

BACKGROUND: Over 20 single-nucleotide polymorphisms (SNPs) are associated with increased risk of Alzheimer's disease (AD). We categorised these loci into immunity, lipid metabolism and endocytosis pathways, and associated the polygenic risk scores (PRS) calculated, with AD biomarkers in mild cognitive impairment (MCI) subjects. **OBJECTIVE:** The aim of this study was to identify associations between pathway-specific PRS and AD biomarkers in patients with MCI and healthy controls. **METHODS:** AD biomarkers ([18F]Florbetapir-PET SUVR, FDG-PET SUVR, hippocampal volume, CSF tau and amyloid beta levels) and neurocognitive tests scores were obtained in 258 healthy controls and 451 MCI subjects from the ADNI dataset at baseline and at 24-month follow up. Pathway-related (immunity, lipid metabolism and endocytosis) and total polygenic risk scores were calculated from 20 SNPs. Multiple linear regression analysis was used to test predictive value of the polygenic risk scores over longitudinal biomarker and cognitive changes.

RESULTS: Higher immune risk score was associated with worse cognitive measures and reduced glucose metabolism. Higher lipid risk score was associated with increased amyloid deposition and cortical hypometabolism. Total, immune and lipid scores were associated with significant changes in cognitive measures, amyloid deposition and brain metabolism. **CONCLUSION:** Polygenic risk scores highlights the influence of specific genes on amyloid-dependent and independent pathways; and these pathways could be differentially influenced by lipid and immune scores respectively.

Key words: genetic risk; polygenic score; Alzheimer's disease; biomarkers; SNPs;

Short title: Polygenic risk in Alzheimer's disease

Word count: 3385

Introduction

Alzheimer's Disease (AD) is the most common cause of dementia affecting individuals over 65 years of age [1]; 50 million people have dementia worldwide, and there are nearly 10 million new cases every year [2]. With the ageing population, the burden of AD on healthcare systems and society is set to rise [3, 4]. The failure of clinical trials to improve cognitive function and halt disease progression in AD, together with the demonstration of a long preclinical phase of the disease, highlights the need for early intervention, and indeed challenges our understanding of the disease.

Subjects with mild cognitive impairment (MCI) are at increased risk of developing AD dementia with 50% of amyloid positive MCI subjects converting to AD within 2 years [5, 6]. Thus, predicting which MCI patients will actually progress is of utmost importance, which is now helped by biomarkers including cerebrospinal fluid (CSF) levels of amyloid beta (Aβ) and tau, and neuroimaging modalities [7, 8].

Individual risk for AD is determined by genetic, environmental and demographic factors, as well as interactions among them [9]. Unlike familial AD, where genetic mutations in APP, PSEN1 and PSEN2 are mostly fully penetrant and of autosomal dominant inheritance, sporadic AD (sAD) also has significant heritability [10]. Inheritance of the ε4 allele of the apolipoprotein E (APOE) is the most important genetic risk factor for sAD, increasing risk 3-fold in heterozygotes and 15-fold in homozygotes [11].

Recently, genome wide association studies (GWAS) have been able to identify over 30 risk loci associated with the development of sAD [12-18]. Although the effect of the single locus might be small, a polygenic risk score (PRS) allows us to evaluate the combined effects of gene variants. To date, several studies have used this polygenic approach to estimate the risk of AD progression and to evaluate the association of AD genetic risk with endophenotypes of the disease. Harrison et al have demonstrated the association between a total PRS and hippocampal

thinning in healthy individuals [19]. Other studies have shown that an association exists between PRS and CSF biomarkers and disease progression [20], as well as between PRS and plasma inflammatory biomarkers [21]. A PRS can improve the diagnostic accuracy of APOE alone at identifying AD cases [22], predict the age of AD onset [23] and it can generally improve risk prediction in healthy older adults [24, 25]. Moreover, a PRS has been demonstrated to predict cognitive decline and neurodegeneration in subjects at risk of AD [26]. Recently, pathway-specific PRS have been associated with AD biomarkers, grouping risk loci together according to their biological functions [27] and, in some cases, finding that pathway-specific PRS might hold higher predictive value over total PRS [28].

In this study we categorised 20 of the single nucleotide polymorphisms (SNPs) susceptibility loci into the three pathways of endocytosis, immunity and lipid metabolism to create a PRS for each of them, and also a total PRS. We selected SNPs identified by the International Genomics of Alzheimer's Project (IGAP) [12, 14]. The immune pathway contained nine loci (*CR1, INPP5D, MEF2C, HLA-DRB5/HLA-DRB1, EPHA1, CLU, MS4A6A, ABCA7, CD33*), the endocytosis pathway contained six loci (*BIN1, CD2AP, EPHA1, PICALM, SORL1, CD33*), the lipid pathway contained three (*CLU, SORL1, ABCA7*), with five loci overall contributing to more than one pathway. The total PRS comprised all the above plus seven variants that, due to lack of strong biological evidence, were not attributed to any of the specific pathways (*NME8, ZCWPW1, PTK2B, CELF1, FERMT2, SLC24A4/RIN3, CASS4*). These were compared against the main pathological substrates of AD: amyloid deposition (CSF Aβ and amyloid PET), tau aggregation (CSF phosphorylated tau) and neurodegeneration (CSF total tau, fludeoxyglucose (FDG) PET and MRI volumes). The aim was to identify possible associations between pathway-specific PRS and AD biomarkers in patients with MCI and healthy controls. To date, no previous study has compared PRS to such an extensive range of biomarkers [20, 24, 29].

Methods

Data collection was downloaded from the Alzheimer's disease Neuroimaging initiative from October 2017 to December 2017 (ADNI). ADNI is an on-going international longitudinal study aimed at the identification of markers for the early detection and monitoring of Alzheimer's disease such as proteomics, CSF tau and amyloid, MRI, FDG and tau PET scans, including baseline demographics of healthy controls, MCI and AD subjects. According to the ADNI guidelines, MCI is defined by a mini mental state examination (MMSE) score of 24-30, an education adjusted cut-off on the Logical Memory II subscale from the Wechsler Memory Scale clinical dementia rating scale (CDR) of 0.5, and preserved daily functioning at home confirmed by a study partner. For this study, we included FDG-PET and amyloid ([18F]Florbetapir) PET standard uptake value ratio (SUVR), hippocampal volumes, CSF total and phosphorylated tau, CSF Aβ, neurocognitive tests (ADAS COG-11 and 13, CDR-SB, MMSE), APOE4 status, and level of education, which were obtained from the ADNI dataset. We retrieved baseline and 24-months follow up data for 258 healthy controls (HC) and 451 MCI subjects.

For Florbetapir scans, 370 MBq (10.0 mCi) ± 10% of tracer was injected, and scans were acquired in 4 X 5minute frames with acquisition time of 50-70 min post-injection. For, FDG PET, 185 MBq (5.0 mCi) ± 10% of tracer was injected and scans were acquired for 30 min (6X5min frames) with an acquisition time of 30-60 min post-injection. For image processing, either six five-minute frames (ADNI1) or four five-minute frames (ADNI GO/2) are acquired 30 to 60 minutes post-injection. Each extracted frame is co-registered to the first extracted frame of the raw image file (frame acquired at 30-35 min post-injection). Coregistered image is generated simply by averaging different time frames.

FDG-PET scans were analysed using target to pons ratio as detailed in the ADNI proocol which provided SUVR for a set of pre-defined regions of interest (MetaROIs) based on coordinates

cited frequently in other FDG studies comparing AD, MCI, and normal subjects and including left and right temporal lobe, left and right angular gyrus and the posterior cingulate. SUVR for FDG uptake were calculated using a pons/vermis reference region [30]. [18F]Florbetapir-PET scans provided SUVR values for the frontal, parietal and temporal lobe, cingulate gyrus, the medial temporal lobe (MTL), for both the left and right side and the total cortical amyloid load, using the cerebellum as a reference region [31]. All regional values were derived from ADNI dataset. Data for hippocampal volume were derived from 3D-MPRAGE MRI scans using a semi-automated hippocampal volumetry tool.

Available genotype data for the ADNI cohort (818 individuals genotyped on the Illumina Omni2.5 array) was downloaded from the ADNI website and subjected to quality control. Individuals were excluded if they had a call rate <98%, were outliers on principal components analysis based on a pairwise identity by descent matrix, or were related to another genotyped ADNI participant at the level of first cousin or closer. Variants were excluded if they departed from Hardy-Weinberg equilibrium ($P<10^{-4}$). As not all susceptibility SNPs identified through GWAS had been genotyped on the Illumina Omni2.5 array, IMPUTE2 was used to impute genotypes for these variants, using 1,000 Genomes haplotypes as a reference panel (Phase I integrated variant set release (produced using SHAPEIT2) in NCBI build 37 coordinates). All missing variants were successfully imputed with info scores > 0.95. Imputed dosage data was converted to hard-called genotypes using GTOOL.

Immune, endocytotic and lipid risk scores were calculated in PLINK, based on 20 of the SNPs common variants identified by the meta-analysis conducted by the IGAP [12, 14] (see Supplemental Table 1 for the SNPs assigned to each pathway-specific score). Moreover, a total PRS was calculated. Weighted risk scores were calculated per person as the sum of the product of the number of risk alleles of the selected SNPs and the natural log of the corresponding odds ratio reported in the IGAP meta-analysis [12, 14]. To compare subjects with high or low PRS,

the 10th and 90th percentile of each of the scores were calculated, with an approach also used by others [26].

Statistical analysis was performed using SPSS 25. Normality was evaluated with Kolmogorov-Smirnov test on the whole population. The total, immune and endocytotic PRS were normally distributed, while the lipid PRS did not follow a normal distribution. Independent sample t test was used to compare normally distributed variables at baseline and paired sample t tests to determine significant difference at follow up. When the sample variable was non-linear, non-parametric Mann-Whitney U test was used. Simple linear regression was performed for normally distributed variables and Spearman's rank test was used to test correlation between the lipid PRS and biomarkers. Multiple linear regression analysis was conducted on the delta variables of biomarkers and cognitive measures testing the different PRS as predictors, with or without APOE4 status, and adjusting for age and gender.

Results

The baseline characteristics of the HC and MCI groups are shown in Table 1. As expected, the MCI group was significantly impaired in the neuropsychometric tests evaluated, compared to the HC. The number of APOE4 carriers was similar between HC and MCI. Interestingly, the mean total and immune PRS were higher in MCI compared to HC, while the endocytotic and lipid metabolism PRS were similar between the two groups. There was no difference between males and females in terms of any of the PRSs scores, both in the group as a whole and in HC and MCI separately.

When looking at the baseline biomarkers (Table 2), the MCI showed significantly higher brain Aβ deposition compared to HC, as detected by [18F]Florbetapir-PET in all the predefined regions. Based on the cut-off of 1.1 for [18F]Florbetapir in composite cortical region [31], 48/139 HC and 159/297 MCI were Aβ positive. The CSF levels of Aβ, tau and p-tau were not significantly different between the two groups, although the CSF data were only available for a small subgroup of subjects (16 HC and 27 MCI). The biomarkers of neurodegeneration (hippocampal volume and FDG uptake in all the predefined regions) were significantly lower in MCI subjects compared to HC, as expected. When stratifying the population according to APOE4 and Aβ status, we found that APOE4+/Aβ+ subjects (n=121) had significantly higher PRSs compared to APOE4-/Aβ- (n=181) subjects.

To evaluate the relationship between the PRSs and biomarkers at baseline, we run linear regression between the immnune, endocytotic, lipid and total PRS and both CSF and imaging biomarkers. As shown in Figure 1, significant inverse association was shown between the immune PRS and FDG uptake in the left angular gyrus (r^2=.01, p=.019), while direct association were shown between the immune PRS and [18F]Florbetapir uptake in frontal, temporal, parietal, mid-temporal lobes and cingulate gyrus (correlation with frontal

[18F]Florbetapir uptake is shown in Figure 1, r^2=.02, p=.00). The total PRS showed significant inverse association with FDG uptake in the left angular gyrus (r^2=.007, p=.049). The endocytotic PRS showed a significant direct association with CSF tau levels (r^2=.13, p=.01), while the lipid PRS did not show any significant correlations with any of the biomarkers.

To better clarify which biomarkers can be associated with the pathway-specific PRS, we compared the 10th and 90th percentile of each of the four PRS (total, immune, endocytotic and lipid) to see how the low and high PRS groups differ in terms of biomarkers. The mean PRS values for 10th and 90th percentile and the number of subjects included in the percentile groups of each PRS are shown in Supplemental Table 2.

The 10th and 90th percentile groups of the total PRS differed significantly in terms of cognitive measures (CDRSB, ADAS13, MMSE), [18F]Florbetapir uptake and CSF tau levels (Supplemental Table 3). The comparison between 10th and 90th percentile of the immune PRS indicated that the two groups differed in terms of cognitive measures (CDRSB, ADAS11, ADAS13) and FDG uptake in the left angular gyrus (Supplemental Table 4). There were no significant differences in any of the biomarkers when comparing the 10th and 90th percentiles of the endocytotic PRS. The 10th and 90th percentile groups of the lipid PRS differed significantly in terms of [18F]Florbetapir uptake in all the predefined regions and FDG uptake in the left temporal lobe (Supplemental Table 5).

The 10th and 90th percentile groups of total, immune and endocytotic PRS did not differ in terms of prevalence of APOE4 carriers, while there were significantly more APOE4 carriers in the 90th percentile of lipid PRS compared to the 10th percentile group (56.4% vs 43.6%, p=0.044). Moreover, the 10th and 90th percentile groups of total, lipid and endocytotic PRS did not differ in terms of prevalence of MCI subjects compared to control subjects. However, there

were significantly more MCI subjects in the 90th percentile immune PRS group compared to the 10th percentile group (60.4% vs 39.6%, p=0.001).

In the whole population, the parameters that significantly changed from baseline to follow up were: CDRSB, ADAS11, ADAS13, MMSE, CSF Aβ, CSF total Tau, FDG uptake in all the predefined regions, [18F]Florbetapir uptake in all the predefined regions, left and right hippocampal volume (Supplemental Table 6).

We calculated delta variables for each of the above using the following formula: ((xf – xi)/xi)*100, where xf is the follow up value and xi is the baseline value.

Then we compared the delta variables between 10th and 90th percentile for each of the polygenic scores. The parameters showing significant differences are reported in Figure 2.

Significant variations from baseline to follow up were observed in ADAS11 and ADAS13 scores, as well as in temporal FDG between 10th and 90th percentiles of total PRS.

A significant variation in MMSE scores and in frontal [18F]Florbetapir uptake was observed between 10th and 90th percentiles of immune PRS, while 10th and 90th percentiles of lipid PRS showed significant longitudinal changes in MMSE scores and FDG uptake in the left angular gyrus.

Moreover, on a subset of 367 subjects, we retrieved information on stability or clinical progression at 24 months. Overall, 33 subjects progressed (from HC to MCI or from MCI to AD) and 334 remained stable. When looking at baseline PRSs scores in stable subjects versus progressing subjects, we did not find significant differences in the scores.

Finally, we performed multiple regression analysis for each of the delta variables, building two models including each of the PRSs as a predictor, with or without APOE4 carrier status. Significant associations were observed only for changes in CDRSB and FDG uptake in

posterior cingulate and left temporal lobe, as shown in Table 3. Interestingly, the immune PRS was an independent predictor of FDG longitudinal change in posterior cingulate and left temporal lobe, even when APOE was not included in the model. The immune PRS was not significantly associated with changes in amyloid deposition, CSF biomarkers or cognitive measures. The total PRS was a significant predictor of CDRSB changes, while the lipid score was not independently associated with any changes in the biomarkers. Overall, the variance explained by the models, with or without APOE status, was between 1.9% and 3.3%.

Discussion

In this study we have demonstrated the association between PRS for critical molecular pathways involved in AD pathogenesis (immunity, endocytosis and lipid metabolism) and biomarkers in a cohort of subjects at risk of AD. The calculation of the PRS has been performed based on the individual genetic risk from the 20 loci identified by IGAP. Our data indicate that higher immune PRS was associated with hypometabolism of the angular gyrus and worse cognitive performance at baseline and with increased longitudinal amyloid deposition. Moreover, immune PRS was an independent predictor of hypometabolism in the posterior cingulate and left temporal lobe. A higher lipid PRS was associated with increased cortical amyloid uptake and left temporal hypometabolism at baseline and with longitudinal reduction in FDG uptake. The endocytotic PRS correlated with baseline total CSF tau levels but not with longitudinal changes in any of the biomarkers, neither with baseline differences between high and low PRS. The total PRS, which includes all the 20 SNP scores, was associated with worse cognitive performance and higher total CSF tau levels at baseline, and with longitudinal changes in cognitive measures and temporal hypometabolism. Moreover, the total PRS was an independent predictor of CDRSB longitudinal changes. To our knowledge, this is the first study aiming at evaluating all these biomarkers profiles changes in the AD risk trajectory and their association with gene variations grouped according to their function. The results of this study indicate which AD endophenotypes are more likely to be affected by genes involved in immunity, endocytosis and lipid metabolism, shedding further light on the possible mechanisms underlying the 20 genes function. Indeed, as an endophenotype is influenced by fewer genetic risk factors than the disease as a whole, it can provide important information about the biological pathway through which a gene might act [32].

Other studies have evaluated PRS in AD progression, based on the hypothesis that an aggregated genetic risk score could perform better than any individual variant. Escott-Price et

al have recently demonstrated that PRS analysis has a good predictive value for AD in pathologically confirmed case-control series [33] and PRS have been validated in both Black and White populations [34]. PRS analysis has also suggested that sporadic late onset AD and familial and early onset forms might share a common genetic architecture and that in early onset cohorts the PRS is associated with CSF ptau/Aβ ratio [35]. A PRS has been associated with longitudinal hippocampal thinning in older adults [19], with CSF Aβ42 levels [20] and with plasma inflammatory biomarkers [21]. It has been demonstrated that PRS is associated with younger age of AD onset, worse cognitive performance over time and worse biomarker profile [23] and, recently, with longitudinal cognitive decline in preclinical AD and MCI [26]. However, some authors, when considering a PRS based on nine AD-related risk loci, were not able to show a predictive role in progression from MCI to AD in four independent large cohorts [9]. Our study does not only explore the relationship between PRS and AD biomarkers but, by grouping the 20 risk loci according to their biological role, provides further evidence on the pathways underlying biomarkers changes in the AD continuum (Figure 3).

Our immune PRS takes into account the cumulative genetic risk given by the known SNP in the following genes implicated in immune function: *CR1, INPP5D, MEF2C, HLA-DRB5/HLA-DRB1, EPHA1, CLU, MS4A6A, ABCA7, CD33* [36-41]. In our dataset, higher immune PRS was associated with worse cognitive profile and brain hypometabolism in the angular gyrus, as well as with longitudinal cortical amyloid accumulation. Moreover, it was a significant predictor of brain hypometabolism. Overall, while our data confirm the literature evidence of a strong relationship between brain immune function and Aβ accumulation, they also indicate an association with biomarkers of neurodegeneration and with cognitive status. In particular, while the association between mediators of neuroinflammation and Aβ accumulation and aggregation in early AD stages is well established [42], recent preclinical evidence suggest that

the same mediators are also associated with markers of neurodegeneration and with cognitive decline [43-45].

The lipid PRS score in our study considers the risk alleles of the following genes: *CLU, SORL1 and ABCA7* [46]. Our subjects with high lipid PRS showed increased cortical Aβ levels at baseline and longitudinal brain hypometabolism, indicating that the influence of the three genetic risk variants included in our score is mainly exerted onto Aβ accumulation and brain metabolism. However, we would also have to consider the higher prevalence of APOE4 carriers in the 90th percentile group of the lipid score. Moreover, probably because only three variants were included in the lipid PRS, its predictive value over longitudinal biomarker changes was not significant.

The endocytotic PRS is made of cumulative risk from gene variants in: *BIN1, CD2AP, EPHA1, PICALM, SORL1 and CD33* [32, 47, 48]. Probably due to the cumulative effect of the different genes on tau pathology, our endocytotic PRS showed a significant direct correlation with baseline CSF tau levels in this cohort, despite the small number of subjects for whom CSF data was available.

Some of the known risk variants have not been included in the pathway-specific PRS but are part of the total PRS we used in our study. These include: *NME8, ZCWPW1, PTK2B, CELF1, FERMT2, SLC24A4, CASS4* [36, 38, 49-52]. The total PRS, considering all the genes variants, provides with information related to the cumulative effects of the 20 genes. In our cohort, higher total PRS was associated with worse cognitive measures, increased [18F]Florbetapir uptake and higher CSF tau levels, as well as with longitudinal cognitive decline and brain hypometabolism. All the aspects of AD pathology are associated with total PRS, as expected, as this score carries risk from all genes, involved in multiple pathways and overlapping functions.

Although a total PRS can help stratifying patients according to their cumulative genetic risk, our data suggest that for enrichment strategies in clinical trials the use of specific PRS looking at the different pathways (immunity, lipid metabolism, endocytosis) might be more effective in selecting the appropriate populations for specific treatment and thus reducing the number of subjects needed to test a specific outcome. Although the associations identified between our PRS and biomarkers were small, accounting for 1.9%–3.3% of the variance within the population, these effect sizes are consistent with other biomarker studies assessing polygenic scores [53]. With an approach widely used by other researchers in different fields [54, 55], we stratified our cohort in percentiles of PRS and compared the bottom (10th percentile) and top (90th percentile) ends of the distribution of PRS in order to evaluate the differences between subjects in low or high risk categories. Because PRS provide a measure of relative risk for a condition, the percentile value for the individual subject might be more meaningful [56]. Indeed, studies utilizing PRS for targeting specific treatments have shown that for highly prevalent conditions, precision can be better than one in two for the top decile, and most patients will benefit from treatment, so that over half of preventable events can be avoided by targeting just the high-risk decile [57].

While some of the strengths of using the ADNI database are the large sample size, the standardised methodology and detailed biomarkers information, one of the limitations of the present study is that not all measures were available for all biomarkers at the time of data access. In particular, while cognitive data were available on the whole cohort, imaging data were available on a varying subset of subjects according to the modality. Moreover, a 2-year follow up might be too short to look at significant changes associated with genetic risk variants. Indeed, based on available data, 9.5% of the subjects progressed at 2 years and there was no difference in baseline PRS between stable and progressing participants. However, a longer follow up, as reported by Mormino et al and others, might have outlined significant longitudinal

associations between PRSs and clinical conversion [26, 53]. In addition to that, some of the 20 genes have overlapping functions, thus the results of one PRS are not independent from another PRS. Moreover, replicating these results in larger longitudinal cohorts and expanding the PRS calculation to include novel SNPs would allow for a better understanding of the endophenotypes associated with early changes in AD biomarkers in presymptomatic subjects.

In conclusion, this study highlights that polygenic risk scores can be a good indicator of AD-related changes in biomarkers and cognitive function in a population of HC and MCI subjects with varying degrees of AD risk. In particular, specific risk scores based on the function of genes are associated with different endophenotypes that characterize the AD continuum. This study highlights the influence of different pathways (inflammation, endocytosis and lipid metabolism) on different pathological process in AD. This is the first study highlighting that immune pathway may influence neurodegeneration affecting amyloid independent pathway, while lipid pathway may be influencing AD through amyloid dependent pathway. These findings underline the importance of enrichment strategies for clinical trials evaluating specific biomarkers for specific treatment. This also highlights the importance of evaluating different pathways further to better understand how different therapeutic strategies could be employed in subsets of AD populations. This also implies that for an effective therapeutic strategy in AD, it may be essential to target immunity, endocytosis and lipid metabolic pathways.

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Table 1. Baseline characteristics of healthy controls and MCI subjects

	HC		MCI	
		N		N
Male n (%)	131 (50.78)	258	271 (60.09)	451
Age mean (SD) (years)	74.71 (5.49)	258	72.52 (7.41)*	451
GWS SNP score mean (SD)	1.23 (0.16)	258	1.25 (0.16)*	451
Immune SNP score mean (SD)	0.42 (0.11)	258	0.44 (0.11)*	451
Endocytotic SNP score mean (SD)	0.55 (0.11)	258	0.56 (0.10)	451
Lipid metabolism SNP score mean (SD)	0.36 (0.07)	258	0.37 (0.08)	451
CDRSB mean (SD)	0.03 (0.14)	258	1.43 (0.86)*	451
ADAS11 mean (SD)	5.85 (2.90)	258	9.57 (4.31)*	450
ADAS13 mean (SD)	9.16 (4.21)	258	15.34 (6.62)*	448
MMSE mean (SD)	29.07 (1.16)	258	27.92 (1.67)*	451
ApoE4 Non carrier n (%)	175 (67.8)	258	259 (57.4)	451
ApoeE4 Heterozygous n (%)	72 (27.9)	258	158 (35.0)	451
ApoeE4 Homozygous n (%)	11 (4.3)	258	34 (7.5)	451
Years of Education mean (SD)	16.43 (2.64)	258	16.01 (2.9)	451
Hx of Smoking n (%)	104 (40.30)	258	182 (40.4)*	451
Right handed n (%)	240 (93.0)	258	408 (90.5)	451

*. Significant difference between HC and MCI at $p<0.05$

Data displayed in the table is represented as mean (standard deviation), or number (percentage). N = number of total available subjects for which data was available, HC = health controls, MCI = mild cognitive impairment;

Table 2. Baseline biomarkers of healthy controls and MCI subjects

	HC		MCI	
		N		N
[18F]Florbetapir Frontal lobe mean (SD)	1.30 (0.28)	141	1.39 (0.30)*	301
[18F]Florbetapir Parietal lobe mean (SD)	1.32 (0.28)	141	1.40 (0.30)*	301
[18F]Florbetapir Temporal lobe mean (SD)	1.23 (0.25)	141	1.30 (0.27)*	301
[18F]Florbetapir Cingulate gyrus mean (SD)	1.42 (0.29)	141	1.50 (0.31)*	301
[18F]Florbetapir Left MTL mean (SD)	1.22 (0.27)	141	1.31 (0.28)*	301
[18F]Florbetapir Right MTL mean (SD)	1.26 (0.25)	141	1.33 (0.29)*	301
CSF ABETA mean (SD)	211.61 (59.68)	16	178.07 (55.80)	27
CSF TAU mean (SD)	78.3 (51.66)	16	93.47 (40.34)	27
CSF PTAU mean (SD)	33.95 (18.85)	16	45.87 (27.68)	27
L Hippocampal volume mean (SD) (mm^3)	2315.20 (291.02)	19	1901.01 (361.07)*	19
R Hippocampal volume mean (SD) (mm^3)	2253.31 (358.51)	19	1909.00 (440.25)*	19

FDG Left angular gyrus mean (SD)	1.32 (0.12)	190	1.26 (0.16)*	373
FDG Right angular gyrus mean (SD)	1.31 (0.13)	190	1.26 (0.15)*	373
FDG Posterior cingulate gyrus mean (SD)	1.39 (0.14)	190	1.36 (0.17)*	373
FDG Left Temporal lobe mean (SD)	1.27 (0.13)	190	1.21 (0.14)*	373
FDG Right Temporal lobe mean (SD)	1.24 (0.12)	190	1.20 (0.12)*	373

*. Significant difference between HC and MCI at $p<0.05$

Data displayed in the table is represented as mean (standard deviation), or number (percentage). N = number of total available subjects for which data was available, HC = health controls, MCI = mild cognitive impairment;

Table 3. Effects of PRSs on longitudinal cognitive and biomarker changes

	Regression coefficients for longitudinal CDRSB variation					
	Model A (without APOE)			Model B (with APOE)		
	β	95% CI	R2	β	95% CI	R2
Immune PRS	112.56	-30.17, 255.29		101.70	-40.90, 244.29	
Endocytotic PRS	78.28	-71.59, 228.15		62.59	-87.50, 212.68	
Lipid PRS	182.96	-18.36, 384.28		167.47*	-33.72, 368.65	0.024
Total PRS	**119.34***	19.48, 219.21	0.020	**106.30***	5.72, 206.89	0.028
	Regression coefficients for longitudinal variation in FDG uptake in posterior cingulate					
	Model A (without APOE)			Model B (with APOE)		
	β	95% CI	R2	β	95% CI	R2
Immune PRS	**-5.26***	-10.31, -0.22	0.020	-4.78†	-9.81, 0.25	0.033
Endocytotic PRS	-1.19	-6.47, 4.09		-0.54	-5.81, 4.74	
Lipid PRS	-0.82	-7.94, 6.29		-0.12*	-7.21, 6.98	0.025
Total PRS	-3.28*	-6.73, 0.18	0.019	-2.76*	-6.23, 0.70	0.022
	Regression coefficients for longitudinal variation in FDG uptake in left temporal lobe					
	Model A (without APOE)			Model B (with APOE)		
	β	95% CI	R2	β	95% CI	R2
Immune PRS	**-7.07***	-12.8, -1.34	0.020	**-6.76***	-12.50, -1.02	0.024
Endocytotic PRS	-2.35	-8.35, 3.66		-1.92	-7.95, 4.11	
Lipid PRS	-4.11	-12.20, 3.99		-3.65	-11.75, 4.46	
Total PRS	-4.06	-7.99, -0.13		-3.74	-7.70, 0.22	

All models are additionally adjusted for age and gender

*p< 0.05 and †p<0.01 for the model

Significant PRS predictors within the model are in bold

Figures legend

Figure 1. Linear regression between PRS and AD biomarkers

Direct association was shown between the immune PRS and [18F]Florbetapir uptake in frontal lobe (panel A) while significant inverse association was shown between the immune PRS and FDG uptake in the left angular gyrus (panel B). The endocytotic PRS showed a significant direct association with CSF tau levels (panel C). The total PRS showed significant inverse association with FDG uptake in the left angular gyrus (panel D).

Figure 2. Significant delta variables between 10th and 90th percentile of total, immune and lipid PRS.

Significant variations from baseline to follow up were observed in ADAS11 (panel A) and ADAS13 scores (panel B), as well as in temporal FDG (panel C) between 10th and 90th percentiles of total PRS. A significant variation in MMSE scores (panel D) and in frontal [18F]Florbetapir uptake (panel E) was observed between 10th and 90th percentiles of immune PRS, while high and low lipid PRS showed significant longitudinal changes in MMSE scores (panel F) and FDG uptake in the left angular gyrus (panel G).

Figure 3. Genes involved in the immune, lipid and endocytotic pathways

Schematic representation of how the 20 genes grouped into the polygenic risk scores of immunity, lipid metabolism and endocytosis might affect the amyloid cascade, neurofibrillary tangles (NFT) formation and neuroinflammation in AD (see text for details on genes function).

Supplemental Table 1. SNP used to calculate the polygenic risk scores and their implicated pathways (data accessed from October 2017 to December 2017)

SNP	Function			Risk Allele	Risk effect beta	Gene
rs6656401	immune			A	0.165514438	CR1
rs6733839		endo		T	0.198850859	BIN1
rs35349669	immune			T	0.076961041	INPP5D
rs190982	immune			A	0.072570693	MEF2C
rs111418223	immune			C	0.104360015	HLA-DRB5/HLA-DRB1
rs10948363		endo		G	0.09531018	CD2AP
rs2718058				A	0.072570693	NME8
rs1476679				T	0.094310679	ZCWPW1
rs11771145	immune	endo		G	0.105360516	EPHA1
rs28834970				C	0.09531018	PTK2B
rs9331896	immune		lipid	T	0.15082289	CLU
rs10838725				C	0.076961041	CELF1
rs983392	immune			A	0.105360516	MS4A6A
rs10792832		endo		G	0.139262067	PICALM
rs11218343		endo	lipid	T	0.261364764	SORL1
rs17125944				C	0.131028262	FERMT2
rs10498633				G	0.094310679	SLC24A4/RIN3
rs4147929	immune		lipid	A	0.139761942	ABCA7

rs3865444	immune	endo		C	0.061875404	CD33
rs7274581				T	0.127833372	CASS4

CR1: Complement Receptor Type 1; BIN1: Bridging Integrator 1; INPP5D: Inositol Polyphosphate-5-Phosphatase D; MEF2C: Myocyte Enhancer Factor 2C; HLA-DRB5/HLA-DRB1: Major Histocompatibility Complex, Class II, DR Beta 5, Beta 1; CD2AP: CD2 Associated Protein; NME8: NME/NM23 Family Member 8; ZCWPW1: Zinc Finger CW-Type And PWWP Domain Containing 1; EPHA1: EPH Receptor A1; PTK2B: Protein Tyrosine Kinase 2 Beta; CLU: Clusterin; CELF1: CUGBP Elav-Like Family Member 1; MS4A6A: Membrane Spanning 4-Domains A6A; PICALM: Phosphatidylinositol Binding Clathrin Assembly Protein; SORL1: Sortilin Related Receptor 1; FERMT2: Fermitin Family Member 2; SLC24A4/RIN3: Solute Carrier Family 24 Member 4/ Ras And Rab Interactor 3; ABCA7: ATP Binding Cassette Subfamily A Member 7; CD33: CD33 Molecule; CASS4: Cas Scaffolding Protein Family Member 4;

Supplemental Table 2. 10th and 90th percentiles values of polygenic scores

	10th percentile	**90th percentile**
GWS SNP score	1.05057000 (n=71)	1.45118000 (n=71)
Immune SNP score	.290574000 (n=71)	.580297000 (n=71)
Endocytotic SNP score	.42860100 (n=79)	.69205700 (n=73)
Lipid SNP score	.26136500 (n=88)	.48199300 (n=71)

Supplemental Table 3. Significantly different baseline characteristics of the population comparing 10th and 90th percentiles values of GWS score

	10th percentile		90th percentile	
		N (HC/MCI)		N (HC/MCI)
CDRSB mean (SD)	0.71 (0.77)	71 (32/39)	1.04 (1.01)	71 (22/49)
ADAS13 mean (SD)	11.55 (5.66)	71 (32/39)	14.10 (6.41)	70 (22/48)
MMSE mean (SD)	28.86 (1.19)	71 (32/39)	28.27 (1.57)	71 (22/49)
[18F]Florbetapir Frontal lobe mean (SD)	1.30 (0.22)	43 (17/26)	1.49 (0.32)	47 (13/34)
[18F]Florbetapir Parietal lobe mean (SD)	1.34 (0.25)	43 (17/26)	1.51 (0.31)	47 (13/34)
[18F]Florbetapir Temporal lobe mean (SD)	1.23 (0.20)	43 (17/26)	1.41 (0.30)	47 (13/34)
[18F]Florbetapir Cingulate gyrus mean (SD)	1.41 (0.23)	43 (17/26)	1.62 (0.33)	47 (13/34)
[18F]Florbetapir Left MTL mean (SD)	1.22 (0.21)	43 (17/26)	1.43 (0.33)	47 (13/34)
[18F]Florbetapir Right MTL mean (SD)	1.26 (0.22)	43 (17/26)	1.46 (0.32)	47 (13/34)
CSF TAU mean (SD)	48.6 (13.90)	5 (3/2)	111.2 (43.23)	5 (1/4)

The data shown represent significant differences between 10th and 90th percentiles at $p<0.05$

Supplemental Table 4. Significantly different baseline characteristics of the population comparing 10th and 90th percentiles values of Immune score

	10th percentile		**90th percentile**	
		N (HC/MCI)		N (HC/MCI)
CDRSB mean (SD)	0.69 (0.81)	71 (33/38)	1.21 (0.96)	71 (13/58)
ADAS11 mean (SD)	8.12 (4.50)	71 (33/38)	9.84 (4.35)	71 (13/58)
ADAS13 mean (SD)	12.74 (6.88)	71 (33/38)	15.30 (6.79)	71 (13/58)
FDG Left angular gyrus mean (SD)	1.31 (0.16)	60 (28/32)	1.25 (0.17)	60 (12/48)

The data shown represent significant differences between 10th and 90th percentiles at $p<0.05$

Supplemental Table 5. Significantly different baseline characteristics of the population comparing 10th and 90th percentiles values of Lipid score

	10th percentile		90th percentile	
		N (HC/MCI)		N (HC/MCI)
[18F]Florbetapir Frontal lobe mean (SD)	1.34 (0.29)	52 (20/32)	1.48 (0.29)	47 (13/34)
[18F]Florbetapir Parietal lobe mean (SD)	1.36 (0.30)	52 (20/32)	1.49 (0.28)	47 (13/34)
[18F]Florbetapir Temporal lobe mean (SD)	1.27 (0.25)	52 (20/32)	1.39 (0.26)	47 (13/34)
[18F]Florbetapir Cingulate gyrus mean (SD)	1.46 (0.30)	52 (20/32)	1.59 (0.30)	47 (13/34)
[18F]Florbetapir Left MTL mean (SD)	1.25 (0.26)	52 (20/32)	1.39 (0.29)	47 (13/34)
[18F]Florbetapir Right MTL mean (SD)	1.30 (0.29)	52 (20/32)	1.42 (0.28)	47 (13/34)
FDG Left Temporal lobe mean (SD)	1.26 (0.12)	68 (27/41)	1.19 (0.14)	56 (17/39)

The data shown represent significant differences between 10th and 90th percentiles at $p<0.05$

Supplemental Table 6. Baseline and 24-month characteristics of healthy controls and MCI subjects

	Baseline	24-month Follow up
CDRSB mean (SD)	0.90 (0.96)	1.40 (1.82) *
ADAS11 mean (SD)	8.05 (4.10)	8.50 (5.92) *
ADAS13 mean (SD)	12.80 (6.36)	13.50 (8.62) *
MMSE mean (SD)	28.39 (1.59)	27.82 (2.71) *
[18F]Florbetapir Frontal lobe mean (SD)	1.34 (0.28)	1.36 (0.33) *
[18F]Florbetapir Parietal lobe mean (SD)	1.35 (0.28)	1.38 (0.33) *
[18F]Florbetapir Temporal lobe mean (SD)	1.26 (0.25)	1.28 (0.29) *
[18F]Florbetapir Cingulate gyrus mean (SD)	1.45 (0.30)	1.48 (0.35) *
[18F]Florbetapir Left MTL mean (SD)	1.25 (0.28)	1.28 (0.32) *
[18F]Florbetapir Right MTL mean (SD)	1.29 (0.27)	1.31 (0.31) *
CSF ABETA mean (SD)	190.55 (58.89)	182.43 (56.67) *
CSF TAU mean (SD)	87.83 (44.89)	99.67 (54.89) *
CSF PTAU mean (SD)	41.44 (25.20)	45.00 (36.57)
L Hippocampal volume mean (SD) (mm^3)	2099. 45 (387.14)	2038.30 (376.52) *
R Hippocampal volume mean (SD) (mm^3)	2076.31 (437.65)	2029.90 (409.70) *

FDG Left angular gyrus mean (SD)	1.29 (0.15)	1.26 (0.16) *
FDG Right angular gyrus mean (SD)	1.29 (0.14)	1.27 (0.15) *
FDG Posterior cingulate gyrus mean (SD)	1.38 (0.16)	1.35 (0.17) *
FDG Left Temporal lobe mean (SD)	1.24 (0.14)	1.21 (0.15) *
FDG Right Temporal lobe mean (SD)	1.22 (0.12)	1.20 (0.13) *

* Significant difference between baseline and 24-month follow up at $p<0.05$

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The Authors have no conflicts of interests to declare related to this work.

The data that support the findings of this study are available from the corresponding author upon reasonable request.