A comprehensive analysis of methods for assessing polygenic burden on Alzheimer’s disease pathology and risk beyond APOE

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*Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. The members of Alzheimer’s Disease Neuroimaging Initiative are listed in the Appendix.

Genome-wide association studies have identified dozens of loci that alter the risk to develop Alzheimer’s disease. However, with the exception of the APOE-e4 allele, most variants bear only little individual effect and have, therefore, limited diagnostic and prognostic value. Polygenic risk scores aim to collate the disease risk distributed across the genome in a single score. Recent works have demonstrated that polygenic risk scores designed for Alzheimer’s disease are predictive of clinical diagnosis, pathology confirmed diagnosis and changes in imaging biomarkers. Methodological innovations in polygenic risk modelling include the polygenic hazard score, which derives effect estimates for individual single nucleotide polymorphisms from survival analysis, and methods that account for linkage disequilibrium between genomic loci. In this work, using data from the Alzheimer’s disease neuroimaging initiative, we compared different approaches to quantify polygenic disease burden for Alzheimer’s disease and their association (beyond the APOE locus) with a broad range of Alzheimer’s disease-related traits: cross-sectional CSF biomarker levels, cross-sectional cortical amyloid burden, clinical diagnosis, clinical progression, longitudinal loss of grey matter and longitudinal decline in cognitive function. We found that polygenic scores were associated beyond APOE with clinical diagnosis, CSF-tau levels and, to a minor degree, with progressive atrophy. However, for many other tested traits such as clinical disease progression, CSF amyloid, cognitive decline and cortical amyloid load, the additional effects of polygenic burden beyond APOE were of minor nature. Overall, polygenic risk scores and the polygenic hazard score performed equally and given the ease with which polygenic risk scores can be derived; they constitute the more practical choice in comparison with polygenic hazard scores. Furthermore, our results demonstrate that incomplete adjustment for the APOE locus, i.e. only adjusting for APOE-e4 carrier status, can lead to overestimated effects of polygenic scores due to APOE-e4 homozygous participants. Lastly, on many of the tested traits, the major driving factor remained the APOE locus, with the exception of quantitative CSF-tau and p-tau measures.

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Introduction

The capability to predict disease risk from a person’s genome has invaluable applications, ranging from stratifying people for interventions, enrolling them in screening programmes to capture the first signs of disease onset and enriching clinical trials. Accurate prediction of both developing disease and approximate timing can be made in familial diseases where a single genetic variant is causative of the disorder, e.g. APP, PSEN1 and PSEN2 mutations in familial Alzheimer’s disease (Bateman et al., 2012) and the HTT trinuclear repeat in Huntington’s disease (MacDonald et al., 1993). The ability to predict disease risk or the age of symptom onset from genetic information is more complex in the sporadic manifestations of various neurodegenerative disorders, despite, in the case of Alzheimer’s disease, it being highly heritable ($h^2$ range 0.58–0.79; Gatz et al., 2006) and highly polygenic (Kunkle et al., 2019). In the context of late-onset Alzheimer’s disease, with a minor allele frequency of 0.14, the ε4 allele of the APOE gene is the strongest common genetic risk factor in people with central European ancestry (odds ratio about 3.5). Consequently, the effect of APOE-ε4 on various Alzheimer’s disease biomarkers has been studied extensively over the last decades [reviewed by Belloy et al. (2019)] and modifying demographic factors such as ethnicity and sex have been identified (Farrer et al., 1997; Ungar et al., 2013; Altmann et al., 2014).

Despite genetic studies with ever-increasing size (Lambert et al., 2013; Jansen et al., 2019; Kunkle et al., 2019) other variants with equivalent risk to APOE-ε4 have failed to materialize. Most variants discovered through genome-wide association studies (GWAS) exhibit only minor effects on Alzheimer’s disease risk (odds ratios between 0.8 and 1.2; Kunkle et al., 2019). One notable exception is the R47H substitution in the TREM2 gene which confers a similar level of risk to develop Alzheimer’s disease as APOE-ε4 (odds ratio about 2.0) but occurs very rarely in the population (global minor allele frequency of 0.0025; Guerreiro et al., 2013). However, if a single variant cannot deliver predictive accuracy equivalent to APOE-ε4, then a combination of known risk variants could be of use. This is the rationale behind genome-wide polygenic risk scores (PRRs), which combine the effects of multiple independent risk variants in a person’s genome into a single score capturing an individual’s overall genetic disease risk (International
Schizophrenia Consortium et al., 2009). Owing to the ease of access to results from GWAS and the availability of dedicated software (Euesden et al., 2015; Vilhjálmsson et al., 2015), such scores can be built easily and have been adopted rapidly in the genetics field. In recent reports, their capacity to predict disease in common disorders was found to be equivalent to that of (rare) monogenic mutations (Khera et al., 2018). In the context of Alzheimer’s disease PRS have been shown to be associated with clinical diagnosis (Escott-Price et al., 2015), cortical thickness (Sabuncu et al., 2012), memory, hippocampal volume and cognitive decline (Mormino et al., 2016), disease progression (Scelsi et al., 2018) and lastly pathological confirmed cases of Alzheimer’s disease (Escott-Price et al., 2017). Furthermore, Alzheimer’s disease PRS, which are conceptually based on GWAS of late-onset Alzheimer’s disease, modulate disease risk and age of disease onset in familial late-onset Alzheimer’s disease as well as sporadic early-onset Alzheimer’s disease (Tosto et al., 2017; Cruchaga et al., 2018).

Methods for developing and refining PRS have gained increased attention over the recent years and ever-increasing sample sizes in GWAS result in better-calibrated risk scores for out of sample predictions (Dudbridge, 2013). Beyond these improved effect estimates for single variants, methodological improvements have included the explicit modelling of linkage disequilibrium dependencies between variants (Vilhjálmsson et al., 2015; Ge et al., 2019). A recent conceptual novelty in this domain is the polygenic hazard score (PHS), which seeks to gain predictive power by deriving effect sizes for genetic variants from the time to disease onset in a survival analysis, rather than from wide-spread case-control analyses that are traditionally used (Desikan et al., 2017). A series of recent studies have demonstrated very strong associations between a PHS for Alzheimer’s disease and a range of quantitative measurements related to Alzheimer’s disease pathology including clinical dementia rating (CDR), clinical conversion rates, cognitive tests, cortical in vivo amyloid uptake, change in cortical volumes and post-mortem neuropathology (Tan et al., 2017, 2018, 2019). The PHS introduced by Desikan et al. (2017) comprises 33 genetic markers (two of which are APOE-ε4 and APOE-ε2) and is highly correlated with APOE-ε4 burden [Supplementary Fig. 1 in Desikan et al. (2017)]. Previous works claimed that the PHS is superior to PRS (Tan and Desikan, 2018) and exhibits predictive power beyond APOE; however, the published analyses controlled only for APOE-ε4 status rather than APOE-ε4 allele burden (Desikan et al., 2017; Tan et al., 2017, 2018, 2019).

We hypothesized that by failing to adjust for APOE genotype—i.e. adjusting for ε2 and ε4 allele count rather than only for ε4 carrier status—previous reports on the predictive power of PHS over APOE were overestimating the impact of PHS. In this work, we investigated whether PRS or PHS are associated with Alzheimer’s disease-related biomarkers and clinical outcomes beyond the APOE locus.

### Methods

#### Data

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of the ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer’s disease. For up-to-date information, see www.adni-info.org. ADNI study data were accessed through the R-package ADNIMERGE (accessed: 7 March 2019).

#### Preparation of genetic data

At the time of this study, single nucleotide polymorphism (SNP) genotyping data were available for n = 1674 subjects across all ADNI phases. Genotyping was conducted using three different platforms: Human610-Quad, HumanOmniExpress and Omni 2.5 M (Illumina; Saykin et al., 2010). Prior to imputation subject-level quality control (QC) steps based on call rate (10% cutoff) and concordance between chip-inferred sex and self-reported sex were performed separately for each genotyping chip. On SNP-level standard QC steps ensuring compatibility with the reference panel used for imputation (strand consistency, allele names, position, Ref/Alt assignments and minor allele frequency discrepancy (MAF; 0.2 cutoff) were conducted. Imputation was carried out using the Sanger Imputation Server (https://imputation.sanger.ac.uk/) with SHAPEIT for phasing (Delaneau et al., 2012), Positional Burrows-Wheeler Transform (Durbin, 2014) for imputation and the entire Haploype Reference Consortium (release 1.1) reference panel (McCarthy et al., 2016). Data from the three different genotyping platforms were imputed separately. As part of post-imputation QC, multi-allelic variants and SNPs with imputation INFO score <0.3 were removed and genotype calls with posterior probability <0.9 were set to missing (i.e. hard called). Following the initial QC, genotypes from the three platforms were merged. Further information on the imputation and QC process is detailed in Scelsi et al. (2018) and https://rpubs.com/maffleur/432627. Using the merged data, we retained SNPs with MAF ≥1% and genotyping rate >0.9.

SNPweights (Chen et al., 2013) was used to infer genetic ancestry from genotyped SNPs using the reference panel comprising Central European, Yoruba Africans and East Asian samples from HapMap 3 (The International HapMap 3 Consortium et al., 2010) and native Americans from Reich et al. (2012). Subjects with predicted central European ancestry of 80% or more were retained. Next, using the imputed and merged data
genetic relatedness between central European subjects was computed. First, the SNP content was restricted to SNPs with MAF ≥5% and LD-pruning was carried out in PLINK v1.9 (–indep-pairwise 1000 50 0.1). The genetic relatedness matrix was computed using the remaining autosomal SNPs and the dataset was trimmed to remove subjects with relatedness >0.1 (–rel-cutoff 0.1). For the remaining subjects, the first five PCA components were computed in PLINK v1.9 and were used to account for population structure in the data.

**Polygenic risk scores**

PRSs were computed using the software PRSice v2.1.9 (Euesden et al., 2015). As base GWAS the stage 1 results of the most recent Alzheimer’s disease GWAS featuring a pure Alzheimer’s disease phenotype was used (Kunkle et al., 2019; this is opposed to a larger GWAS including subjects with parental Alzheimer’s disease diagnosis resulting in diagnosis-by-proxy (Jansen et al., 2019)). For PRS computation, SNPs with MAF ≥5% were considered and SNPs were selected using LD-clumping (1000 KB, $R^2$ of 0.1 and $P$-value threshold of 1.0), missing SNPs were simply ignored on subject level (using the setting–missing SET_ZERO) and the APOE region was excluded (hg19 coordinates chr19 from 44 400 000 to 46 500 000). Effects for APOE-$\epsilon$2 and APOE-$\epsilon$4 were manually added using effect sizes from (Kunkle et al., 2019): 1.2017 ($\epsilon$4) and -0.4673 ($\epsilon$2). For this study, two $P$-value inclusion cut-offs were used: SNPs passing genome-wide suggestive ($P = 1.0 \times 10^{-05}$) and $P = 0.5$, which was found to be an optimal choice in an earlier study (Escott-Price et al., 2015). The resulting scores are referred to as PRS1 and PRS2, respectively. In addition to this conventional approach, PRS were generated using posterior effect size estimates generated with PRS-CS (Ge et al., 2019). The effect estimates were generated using the auto setting and the PRS are referred to as PRS-cs. PRSs were computed for all ADNI participants with genome-wide genotyping data.

**Polygenic hazard score**

The derivation of the PHS was described in detail in Desikan et al. (2017). The conceptual difference between PRS and PHS is that PHS uses SNP-level effect size estimates from survival analysis (Cox proportional hazards model) as opposed to odds ratios from case–control analyses. The second difference is that effect sizes in PRS were derived univariately while the hazard ratios used for PHS were derived using a multivariate approach, i.e. effects for each SNP are estimated in the presence of the remaining ones. For this work, we extracted the PHS values provided by the ADNI database (desikanlab table).

**Statistical analyses**

A series of association analyses were conducted to measure the effect of PHS on imaging, CSF and cognitive biomarkers in Alzheimer’s disease. First, we aimed to replicate the results on ADNI data presented in Tan et al. (2019) by only correcting for APOE-$\epsilon$4 carrier status (i.e. including a variable that takes the values 0 or 1), referred to as ‘PHS (status)’. Next, the association strength of PHS beyond the APOE locus was tested by accounting for APOE-$\epsilon$4 and APOE-$\epsilon$2 dosage (i.e. including two variables that take values 0, 1 or 2), referred to as ‘PHS (burden)’. In addition, in absence of a real polygenic score, the effect of APOE-$\epsilon$4 dosage beyond the effect of APOE-$\epsilon$4 carrier status was quantified, referred to as ‘APOE-$\epsilon$44’. That is, in this setting APOE-$\epsilon$4 acts as a ‘polygenic’ score that only counts the number of APOE-$\epsilon$4 alleles. Lastly, PHS was compared with standard PRS at two $P$-value cut-offs (1e-05 and 0.5), referred to as ‘PRS1’ and ‘PRS2’, respectively, and PRS-cs. All these methods were adjusted for APOE locus. However, previously ADNI contributed 441 samples to the Alzheimer’s Disease Genetics Consortium (ADGC), which in turn contributed to the IGAP study. Base GWAS and target data must be independent from each other to avoid overly optimistic results due to overfitting (Dudbridge, 2013). Thus, $n = 441$ subjects that contributed to the ADGC GWAS were removed for the comparison between PHS and PRS. Furthermore, analyses were restricted to subjects with predicted central European ancestry and self-reported white non-Hispanic ethnicity. Using large $P$-value thresholds (e.g. $P < 0.05$) results in the PRS comprising many SNPs and potentially makes the score more susceptible to geographical differences in genetic structure (Kerminen et al., 2019). To account for this bias in PRS2 and PRS-cs, we additionally tested associations while also adjusting for population structure by including the first five principal components of the genetic relatedness matrix in the corresponding models.

**Disease status**

Association between polygenic scores and latest recorded clinical diagnosis were conducted using logistic regression. In particular, four contrasts were explored: CN versus Alzheimer’s disease, CN versus MCI, MCI versus Alzheimer’s disease and CN versus MCI or Alzheimer’s disease. The model was adjusted for sex, years of education and age in addition to APOE (either for ‘status’ or for ‘burden’). For subjects with the CN diagnosis the latest recorded age was used; for Alzheimer’s disease subjects the earliest age with recorded Alzheimer’s disease diagnosis was used; for MCI subjects the earliest date of MCI diagnosis was used in the comparison to CN subjects (CN versus MCI and CN versus MCI or Alzheimer’s disease contrasts) and the latest age was used in the comparison with Alzheimer’s disease. In addition
to these statistical association tests, we estimated the predictive performance of the logistic regression using 10-fold cross-validation. We used receiver operating characteristics (ROC) curves as well as the area under the ROC curve (AUC) as means to quantify and compare the model performance. Improvement by including polygenic scores over the ‘status’ or the ‘burden’ model was tested using a signed paired Wilcoxon rank-sum test on the 10 AUC estimates obtained from the cross-validation.

**Baseline CSF biomarkers**

The ADNI database provides data on Alzheimer’s disease-related CSF biomarkers amyloid β protein fragment 1–42 (Aβ), total tau (tau) and tau phosphorylated at threonine 181 (p-tau). The association between polygenic scores and baseline CSF biomarkers was tested using linear regression models. Prior to the analysis, the biomarker values were log-transformed to render their distribution more normal. Analyses were adjusted for age at baseline visit, sex, years of education and APOE (either for ‘status’ or for ‘burden’). Moreover, genetic influence may vary by disease stage, thus linear regression models were estimated for each clinical disease group (CN, MCI and Alzheimer’s disease); effect sizes were combined using the inverse variance method for meta-analyses to obtain an overall effect size and P-value. In addition to these statistical association tests, we estimated the predictive performance of the linear regression using 10-fold cross-validation. We used Pearson’s correlation coefficient as means to quantify the model performance. Improvement by including polygenic scores over the ‘status’ or the ‘burden’ model was tested using a signed paired Wilcoxon rank-sum test on the 10 correlation coefficient estimates obtained from the cross-validation.

**Cross-sectional amyloid PET**

We followed the analytical setup by Tan et al. (2019): associations of the polygenic scores with regional load of amyloid were computed. Amyloid load was derived from PET using the florbetapir tracer (AV45). Florbetapir synthesis and image acquisition details are described in detail elsewhere (http://adni-info.org, Landau et al., 2013). Processed regional AV45 levels were obtained from ‘ucberkeleyav45’ table providing values for cortical regions of the Desikan-Killiany Atlas (Desikan et al., 2006). Regional AV45 levels were divided by AV45 level in the cerebellum region to obtain regional SUVRs. Values for the right and left hemisphere were averaged. For each of the 34 cortical regions, a linear regression was estimated to quantify the effect of polygenic score on regional amyloid load. The models were adjusted for age at imaging, sex, years of education as well as APOE (either for ‘status’ or for ‘burden’). In addition to the setup by Tan et al. (2019) and as in the case for the CSF biomarkers, an analysis stratified by disease status was carried out. Multiple-testing correction for the tests across the 34 regions was conducted using false discovery rate (FDR).

**Disease progression**

Longitudinal data from ADNI were used to quantify the association of polygenic scores with clinical disease progression, i.e. clinical conversion. The effect of polygenic scores on clinical conversion was tested in a Cox proportional hazards model using subjects without a dementia diagnosis at the baseline visit. We defined clinical conversion as a dementia diagnosis in previously not demented participants. A left-truncated (age at entry) right-censored (age at event or last visit) design was chosen (Altmann et al., 2014). The model was adjusted for age at baseline, sex and years of education, APOE (either for ‘status’ or for ‘burden’) and stratified for baseline diagnosis (CN or MCI). In addition to these statistical association tests, we estimated the predictive performance of the Cox regression using 10-fold cross-validation. We used the concordance index, which is conceptually related to AUC, as means to quantify the model performance. Improvement by including polygenic scores over the ‘status’ or the ‘burden’ model was tested using a signed paired Wilcoxon rank-sum test on the 10 concordance indices obtained from the cross-validation.

**Cognitive decline**

We followed the analytical setup by Tan et al. (2019): The effect of polygenic scores on longitudinal measures of cognitive performance was assessed using linear mixed-effects models in non-demented people. In particular, the longitudinal development of clinical dementia rating sum of boxes (CDR-SB) obtained from ADNIMERGE and composite scores for memory (MEM) and executive function (EF) derived using item response theory methods (Crane et al., 2012) and obtained through ADNIMERGE (table uwpsychsum). The first model was exactly specified as in Tan et al. (2019), where the target variable was the change from the baseline cognitive measurement (ΔC) and the fixed effects were interactions between time since baseline (t) and sex, years of education, age, volume of the entorhinal cortex, amyloid burden in the frontal lobe, APOE (either for ‘status’ or for ‘burden’) and PHS and a random intercept for each subject. The variable of interest was the interaction of time and PHS. This model is referred to as ‘intercept only’. In addition, a linear mixed-effects model that included random effects for subject-level decline (random slopes) was used. Model likelihoods were compared with determine which model provides the better fit for the data. Random slope models have been previously used to explore longitudinal changes in ADNI (Holland et al., 2013). Moreover, we added fixed effects that did not interact with time as well as time itself as a fixed
longitudinal change in grey matter mass was quantified using the boundary shift integral (BSI; Leung et al., 2010). We accessed precomputed BSI values through ADNIMERGE (foxlabbsi table). BSI measures from volumetric T1-weighted MRIs were used that did not use the accelerated acquisition. Moreover, if for the same baseline/repeat pair a set of 1.5T as well as a set of 3.0T scans were available, the 3.0T scan was used. The association between BSI and polygenic scores was tested using a linear mixed-effects model as described above (with random intercepts and slopes). In particular, the BSI rep-
Adding PHS to the model that uses APOE burden led only to statistically significant improvement for the CN versus Alzheimer’s disease classification (AUC increased from 0.765 to 0.777; P < 0.006; Supplementary Table 2 and Fig. 2).

After removal of ADGC participants, PHS (burden) was compared with PRS1, PRS2 and PRS-cs on the same dataset including comprehensive modelling of the APOE locus for all scores. PHS on the reduced dataset showed comparable results to the full dataset, i.e. significant P ≤ 1.28e-03 effects for contrasts involving CN subjects. PRS1 and PRS2 both replicated the pattern of associations seen with PHS: associations on contrasts including CN (P ≤ 0.031) but not detectable between MCI and Alzheimer’s disease (P ≥ 0.14). PRS-cs showed P-values of the same magnitude as PHS (burden). After adjusting the model for PRS2 in addition for population structure the association with diagnosis was more pronounced (P = 4.12e-07 with population structure compared with P = 0.031 without) for the other contrasts no such pronounced effect was observed. The PRS-cs model with additional adjustment for population structure showed slightly improved P-values over the model without adjustment. However, owing due to only a marginal change in results, the adjustment for population structure in the PRS-cs model was not investigated further.

Predictive performance over the model using APOE burden was improved by adding PHS when classifying CN versus MCI (AUC increase of 0.018) or by including PHS or PRS-cs when classifying CN versus MCI or Alzheimer’s disease (AUC increase of 0.011 or 0.02; Supplementary Table 2 and Fig. 2).

### Polygenic scores are associated with CSF tau but not CSF Aβ beyond APOE

The association of polygenic scores with log-transformed baseline CSF biomarkers (Aβ, tau and p-tau) was tested using linear models stratified by disease group. When adjusting only for APOE ε4 status (i.e. ε4+/−) PHS (status) showed a strong association with baseline CSF Aβ levels (Table 3; P = 9.99e-07). However, the effect was driven by homozygous APOE-ε4 carriers (APOE-ε44, P = 2.54e-10). After comprehensive adjustment for the APOE locus, the association between PHS (burden) and Aβ disappeared (P = 0.87). This held true also on the reduced dataset for PHS (burden) as well as PRS1, PRS2 and PRS-cs (Table 3; P > 0.31). In contrast, the effect of polygenic scores (PHS and PRS) on either tau and p-tau was not driven by APOE-ε4 homozygotes (P ≥ 0.067). PHS (status) showed significant associations with both CSF tau (P = 1.06e-03) and p-tau levels (P = 9.25e-04), which remained significant after comprehensive adjustment for the APOE locus in PHS (burden) (P < 3.15e-

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### Table 1 Baseline demographics of the full cohort

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>MCI</th>
<th>Alzheimer’s disease</th>
<th>Total</th>
<th>P-value (F-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>417</td>
<td>712</td>
<td>275</td>
<td>1404</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>205</td>
<td>39</td>
<td>118</td>
<td>603</td>
<td>0.004 (5.37)</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>74.5 (5.6)</td>
<td>73.1 (7.5)</td>
<td>75.1 (7.7)</td>
<td>73.9 (7.1)</td>
<td>4.28e-05 (10.13)</td>
</tr>
<tr>
<td>APOE-ε4 (0/1/2)</td>
<td>297/110/10</td>
<td>347/286/79</td>
<td>90/134/51</td>
<td>735/530/140</td>
<td>&lt;2e-16 (64.67)</td>
</tr>
<tr>
<td>MMSE (IQR)</td>
<td>29 (29–30)</td>
<td>28 (26–29)</td>
<td>23 (22–25)</td>
<td>28 (26–29)</td>
<td>&lt;2e-16 (1061)</td>
</tr>
<tr>
<td>Education</td>
<td>16.48 (2.64)</td>
<td>16.02 (2.84)</td>
<td>15.27 (2.92)</td>
<td>16.01 (2.83)</td>
<td>2.37e-07 (15.42)</td>
</tr>
<tr>
<td>Amyloid PET (−/+/NA)</td>
<td>146/76/195</td>
<td>171/216/325</td>
<td>14/107/154</td>
<td>331/399/674</td>
<td>&lt;2e-16 (53.24)</td>
</tr>
</tbody>
</table>

Comprising n = 1404 individuals after QC of the genetic data. Age given as mean, MMSE given as median, years of education as mean, amyloid PET as negative (−) or positive (+) and unavailable (NA). CN = cognitively normal; MCI = mild cognitive impairment.

### Table 2 Association of polygenic scores with most recent diagnosis

<table>
<thead>
<tr>
<th>Score</th>
<th>CN/AD</th>
<th>CN/MCI</th>
<th>MCI/AD</th>
<th>CN/MCI+AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort (n = 1404)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHS (status)</td>
<td>9.46E-10</td>
<td>4.32E-06</td>
<td>0.044</td>
<td>1.48E-09</td>
</tr>
<tr>
<td>PHS (burden)</td>
<td>8.45E-09</td>
<td>1.54E-03</td>
<td>0.092</td>
<td>2.21E-05</td>
</tr>
<tr>
<td>APOE-ε44</td>
<td>6.50E-04</td>
<td>7.74E-03</td>
<td>0.30</td>
<td>5.99E-04</td>
</tr>
<tr>
<td>PHS (burden)</td>
<td>1.28E-03</td>
<td>6.75E-05</td>
<td>0.32</td>
<td>8.49E-05</td>
</tr>
<tr>
<td>PRS1</td>
<td>0.028</td>
<td>7.78E-03</td>
<td>0.68</td>
<td>5.99E-03</td>
</tr>
<tr>
<td>PRS2</td>
<td>0.031</td>
<td>2.91E-04</td>
<td>0.14</td>
<td>4.98E-04</td>
</tr>
<tr>
<td>PRS2⁺</td>
<td>4.12E-07</td>
<td>8.26E-03</td>
<td>0.010</td>
<td>3.44E-05</td>
</tr>
<tr>
<td>PRS-cs</td>
<td>7.02E-03</td>
<td>2.80E-05</td>
<td>0.30</td>
<td>3.06E-05</td>
</tr>
<tr>
<td>PRS-cs⁺</td>
<td>2.69E-04</td>
<td>7.37E-04</td>
<td>0.43</td>
<td>2.80E-05</td>
</tr>
</tbody>
</table>

Reduced cohort (n = 994) |           |           |            |           |
| Score               | CN/AD     | CN/MCI    | MCI/AD     | CN/MCI+AD |
| Entire cohort (n = 1404) |           |           |            |           |
| PHS (status)        | 9.46E-10  | 4.32E-06  | 0.044      | 1.48E-09  |
| PHS (burden)        | 8.45E-09  | 1.54E-03  | 0.092      | 2.21E-05  |
| APOE-ε44            | 6.50E-04  | 7.74E-03  | 0.30       | 5.99E-04  |
| PHS (burden)        | 1.28E-03  | 6.75E-05  | 0.32       | 8.49E-05  |
| PRS1                | 0.028     | 7.78E-03  | 0.68       | 5.99E-03  |
| PRS2                | 0.031     | 2.91E-04  | 0.14       | 4.98E-04  |
| PRS2⁺               | 4.12E-07  | 8.26E-03  | 0.010      | 3.44E-05  |
| PRS-cs              | 7.02E-03  | 2.80E-05  | 0.30       | 3.06E-05  |
| PRS-cs⁺             | 2.69E-04  | 7.37E-04  | 0.43       | 2.80E-05  |

Results show the uncorrected P-values obtained from logistic regression while adjusting for age, sex, education and APOE (either for ‘status’ or for ‘burden’). Scores with * are additionally adjusted for five principal components reflecting population structure. Reduced cohort does not include subjects who contributed to ADGC. CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer’s disease.
0.03). This held true also for the PHS (burden) and PRS1 on the reduced dataset (Table 3). These associations were corroborated by the performance of the predictive models where adding PHS and PRS1 to the APOE burden baseline model improved the model for tau and p-tau but not Aβ (Supplementary Table 3).

**Polygenic scores show only moderate association with cortical amyloid beyond APOE**

In addition to CSF Aβ1-42, cortical amyloid load was quantified using Florbetapir (18F) PET (AV45) and tested for association with polygenic scores for Alzheimer’s disease. There were \( n = 917 \) subjects with AV45 scans (730 obtained at baseline visit). When adjusting for APOE-e4 status there were significant associations between PHS (status) and regional amyloid in all 34 cortical ROIs (\( P_{FDR} \) range from 1.41e-03 to 6.22e-07; Supplementary Fig. 3 and Table 4) confirming earlier results by Tan et al. (2019). Similar to CSF amyloid, cortical amyloid was significantly associated with APOE-e4 burden over APOE-e4 status (28 of 34 regions with \( P_{FDR} \) from 0.035 to 6.65e-04; Supplementary Fig. 3 and Table 4). Consequently, comprehensive adjustment for the APOE locus reduced the association strength of PHS (burden) with regional amyloid, but all of the 34 ROIs remained significantly associated (\( P_{FDR} < 0.0478 \); Supplementary Fig. 3 and Table 4). Additional stratification by disease status at amyloid imaging, left only one significant ROI with an \( P_{FDR} = 0.0444 \): transverse temporal gyrus; another 26 ROIs were associated at trend level (\( P_{FDR} < 0.1 \); Supplementary Fig. 3 and Table 4). This pattern remained unchanged on the reduced dataset without the ADGC participants (Fig. 1; Supplementary Table 5) comprising \( n = 822 \) participants with AV45 scans (730 obtained at baseline visit). On the same dataset, PRS1 showed consistent association with regional amyloid despite comprehensive adjustment for APOE burden and stratification by disease group (26 of 34 ROIs; \( P_{FDR} \) from 0.0446 to 4.00e-04; Fig. 1; Supplementary Table 5). Neither, PRS-cs nor PRS2 (with or without correction for population structure) showed any association with regional amyloid load (Supplementary Table 5).

**Clinical conversion**

The longitudinal design of the ADNI study was leveraged to test the association of polygenic scores with clinical progression to Alzheimer’s disease in non-demented participants. Results in the top part are for the entire cohort (\( n = 1008 \)) and in the bottom part after excluding ADGC subjects (\( n = 807 \)). The model indicated with * was additionally adjusted for genetic population structure.

---

**Table 3** Associations between polygenic scores and CSF biomarkers Aβ, total tau and phosphorylated tau

<table>
<thead>
<tr>
<th>Sample size (N)</th>
<th>Score</th>
<th>Aβ</th>
<th>Tau</th>
<th>p-tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>1008</td>
<td>PHS (status)</td>
<td>9.99E-07</td>
<td>1.06E-03</td>
<td>9.25E-04</td>
</tr>
<tr>
<td>807</td>
<td>PHS (burden)</td>
<td>0.87</td>
<td>2.33E-03</td>
<td>3.15E-03</td>
</tr>
<tr>
<td></td>
<td>APOE-e4</td>
<td>2.54E-10</td>
<td>0.067</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>PHS (burden)</td>
<td>0.37</td>
<td>1.04E-03</td>
<td>6.85E-04</td>
</tr>
<tr>
<td></td>
<td>PRS1</td>
<td>0.31</td>
<td>1.33E-04</td>
<td>5.96E-05</td>
</tr>
<tr>
<td></td>
<td>PRS2</td>
<td>0.49</td>
<td>0.053</td>
<td>0.087</td>
</tr>
<tr>
<td></td>
<td>PRS2*</td>
<td>0.42</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>PRS-cs</td>
<td>0.82</td>
<td>0.15</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Biomarker values were log-transformed. The table depicts uncorrected \( P \)-values from linear models adjusted for age, sex, education and APOE (either for ‘status’ or for ‘burden’). Results in the top part are for the entire cohort (\( n = 1008 \)) and in the bottom part after excluding ADGC subjects (\( n = 807 \)). The model indicated with * was additionally adjusted for genetic population structure.

---

**Table 4** Effect of polygenic scores on clinical conversion obtained from Cox proportional hazards models

<table>
<thead>
<tr>
<th>Sample size (N)</th>
<th>Score</th>
<th>Beta</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1092</td>
<td>PHS (status)</td>
<td>0.290</td>
<td>0.09</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>PHS (burden)</td>
<td>0.372</td>
<td>0.15</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>APOE-e4</td>
<td>0.295</td>
<td>0.17</td>
<td>0.088</td>
</tr>
<tr>
<td>813</td>
<td>PHS (burden)</td>
<td>-0.005</td>
<td>0.20</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>PRS1</td>
<td>-0.029</td>
<td>0.15</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>PRS2</td>
<td>-0.016</td>
<td>0.08</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>PRS2*</td>
<td>0.290</td>
<td>0.11</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>PRS-cs</td>
<td>-0.181</td>
<td>0.12</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Clinical conversion was defined as a dementia diagnosis in previously not demented participants. Rows correspond to different polygenic scores and estimates for the full dataset (top) and after removal of ADGC subjects (bottom). Beta = log hazards ratio; SE = standard error.* was additionally adjusted for genetic population structure.

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**Figure 1** Regional associations between polygenic risk scores and regional uptake of amyloid. The colour code represents the -log10 FDR-corrected \( P \)-values obtained from linear models adjusted for age, sex, education, APOE-e4 count, APOE-e2 count and stratified by disease group at the time of imaging. There were no associations with \( P_{FDR} < 0.05 \) for PRS2 and PRS-cs.
participants using Cox proportional hazards models. There were 1092 non-demented subjects (406 CN, 686 MCI) of whom 318 converted to Alzheimer’s disease (29 CN, 289 MCI). When adjusting for APOE-e4 status in the Cox regression, PHS (status) showed a significant effect on clinical progression (P = 0.002), with higher polygenic hazard increasing the risk of conversion, while APOE-e4 burden showed a trend over APOE-e4 status (P = 0.09). Comprehensive adjustment for the APOE locus led to a decline in association of PHS (burden) with clinical conversion but remained significant (P = 0.013). On the reduced dataset, there were 813 subjects (258 CN, 555 MCI) of whom 179 converted to Alzheimer’s disease (11 CN, 168 MCI). None of the scores showed a significant association with clinical conversion (P ≥ 0.11, Table 4). However, PRS2 adjusted for population structure showed an association with clinical conversion (P = 0.012; Table 4). None of the polygenic scores improved the predictive performance of the baseline models in the Cox regression (Supplementary Table 6).

**Cognitive decline**

The effect of polygenic burden on cognitive decline was assessed on 4465 observations obtained from 601 non-demented subjects (220 CN, 381 MCI) using linear mixed effect models with an initial setup as described in Tan et al. (2019) followed by a more refined model (see Methods section). Initially, in a model adjusted for APOE-e4 status and using only random intercepts PHS (status) showed a very strong association with decline in CDR-SB (P = 7.8e-09), memory (P = 8.15e-03) and EF (P = 1.32e-03) replicating earlier results (Tan et al., 2019). Using the same model with only random intercepts, APOE-e4 burden exhibited effects of similar strength (Table 5). Consequently, after comprehensive adjustment for APOE, PHS (burden) only showed moderate association with CDR-SB (P = 3.95e-03) and none for memory or EF (P > 0.10). Using a linear mixed-effects model with random slopes and random intercepts (while adjusting only for APOE-e4 status), substantially reduced the association between PHS (status) and CDR-SB (P = 5.92e-03), memory (P = 0.012) and marginally for EF (P = 3.7e-03) compared with random intercepts model (Table 5). Models using random slopes and random intercepts showed significantly higher likelihood (P < 2.2e-16) than models using only random intercepts (Supplementary Table 7). Combining comprehensive adjustment for the APOE locus and the linear mixed effects model with random slopes and random intercept left no significant association (P ≥ 0.08) between the PHS (burden) and decline in cognitive scores. On the same dataset (i.e. there were no ADGC participants), PRS1 showed a moderate significant association with decline in CDR-SB (P = 3.57e-03) but not with decline in memory or EF (P ≥ 0.42). There was neither a significant association for PRS2 (P ≥ 0.21) nor for PRS-cs (P ≥ 0.34). After additional adjustment for population structure, PRS2 showed a trending association with decline in CDR-SB (P = 0.059) but neither with memory nor with EF decline (P ≥ 0.40).

**Grey matter decline**

The BSI (Leung et al., 2010) was used to quantify longitudinal decline in grey matter for the whole brain, the ventricles as well as left and right hippocampus. On the entire dataset, there were n = 1250 subjects with 3909 scans for whole brain and ventricular BSI. A reduced number of subjects (n = 618) and scans (n = 1714) was available for hippocampal BSI. Using a linear mixed-effects model with random intercepts and random slopes, there was a strong association between PHS (status) and whole brain and ventricular BSI (P ≤ 2.38e-05) and trend for hippocampal BSI (P ≤ 0.091). Some of these effects were driven by APOE-e4 homozygotes (Table 6) and consequently, the association between PHS (burden) and BSI measures was reduced (P ≤ 4.12e-03 for whole brain and ventricular; P ≥ 0.3 for hippocampi). On the dataset lacking the ADGC participants, there was no significant association between PHS (burden) or PRS2 and any BSI measures (P ≥ 0.19). PRS1 was associated with whole brain and ventricular BSI (P ≤ 1.7e-03) and marginally for right hippocampus and trending for left hippocampus (Table 6). Similarly, PRS-cs showed at least trend-level association (P ≤ 0.061) for any BSI.

**Discussion**

In a series of statistical tests, we investigated whether polygenic scores are associated with a range of Alzheimer’s disease-related traits beyond the APOE locus. We found that polygenic scores were associated beyond APOE with clinical diagnosis, CSF-tau levels and, to a minor degree, with progressive atrophy. However, for
many other tested traits such as clinical disease progression, CSF amyloid, cognitive decline and cortical amyloid load, the additional effects of polygenic scores beyond APOE were of minor nature. Our results demonstrate that incomplete adjustment for the APOE locus can lead to severely overestimated effects of polygenic scores due to APOE-e4 homozygous participants. For instance, while our analysis confirmed the PHS’s association with a range of Alzheimer’s disease-related measures beyond APOE-e4 carrier status first reported by Tan et al. (2019), these effects mostly disappeared when using a comprehensive correction for the APOE locus comprising the number of APOE-e2 and APOE-e4 alleles, mainly owing to the high correlation between PHS and APOE-e4 burden. Conversely, on the same cohort of subjects, we tested a simple ‘polygenic’ score comprising only the APOE-e4 allele count and could demonstrate its statistical effects beyond APOE-e4 carrier status. Thus, taken together these results suggest that the previously observed associations of PHS with Alzheimer’s disease-related measures (Tan et al., 2017, 2018, 2019) were partially driven by APOE-e4 homozygous participants. Our analysis also uncovered a second source of statistical modeling that led to overestimated effects of PHS on longitudinal changes in cognition and atrophy. The linear mixed-effects models used in PHS analyses (Desikan et al., 2017; Tan et al., 2017, 2018, 2019) only allowed for subject-specific intercepts, i.e. requiring that the rate of decline is shared between all subjects regardless of disease group, baseline characteristics and genetics, and only modulated by the few variables included as fixed effects. More flexibility is provided by allowing individual rates of decline that are subject-specific (random slopes) in addition to random intercepts. Such random slope linear mixed-effects models have been used recently to analyze longitudinal changes in ADNI data (Holland et al., 2013; Mormino et al., 2016) and are likely to more accurately model ‘real-life’ scenarios where individuals decline at very heterogenous rates. Indeed, the addition of random slopes resulted in a significantly better model fit \((P < 2.2e-16)\) on our data than models using only random intercepts (Supplementary Table 7). Here, using random slopes in addition to random intercepts led to dramatically reduced associations between PHS and longitudinal changes in cognitive decline. In combination with a corrected adjustment for APOE-e4 burden, this led to a complete lack of association between the PHS-by-time interaction and CDR-SB \((P = 0.08)\), which showed initially a very strong association \((P = 7.80E-09)\) with the same setup as in Tan et al. (2019) (who reported \(P = 2.44e-10\)).

Overall, we found that PHS and PRS1, which was based on SNPs exceeding the genome-wide suggestive threshold \((P = 1e-05)\), were highly correlated \((r^2 = 0.75; Supplementary Fig. 1)\). This confirms earlier results comparing PHS and PRS, which reported that despite the different nature of the statistical analysis, the estimated effects per SNP were very similar (Leonenko et al., 2019b). Consequently, the association profile of the two scores was quite similar across the tested Alzheimer’s disease-related measures. In addition to PRS1, we tested two other PRS scores: PRS2, which was based on SNPs exceeding the \(P = 0.5\) threshold, and PRS-cs using a novel method that adjust GWAS-derived effect size estimates for local LD structure. PRS-cs was based on all available SNP data, making it in theory more similar to PRS2, but the correction effect, which emphasized variants with strong effects, rendered the final score to be more correlated to PRS1 rather than to PRS2.

PRS2 showed poorer association with traits compared with PRS1. However, PRS2 was quite sensitive to the correction of population structure (as reflected by substantial correlations between PRS2 and principal components reflecting population structure). The effect was most pronounced when testing for an association with clinical diagnosis where the \(P\)-value improved from \(P = 0.031\) (without correction) to \(P = 4.12e-07\) (with correction) in the CN versus Alzheimer’s disease contrast (Table 2). A recent study in the Finnish population demonstrated that polygenic scores are sensitive to geographic patterns even in relatively homogenous populations (Kerminen et al., 2019). Furthermore, the observed bias increased with the inclusion of more variants in the polygenic scores. Thus, while PRS1 (and PHS) may be relatively robust to population bias, PRS2 is more sensitive but requires additional correction for population structure. Overall PRS-cs was less biased by this effect, probably owing to the emphasis on high effect size variants, which is expressed by the high correlation with PHS and PRS1.

After comprehensive adjustment for the APOE locus and stratification for disease group, there was no association between polygenic scores and amyloid (measured in CSF or through amyloid PET). In initial reports, PHS showed a strong association with cortical amyloid (Tan et al., 2019, with strongest association seen in Rostral

### Table 6: Associations between polygenic scores and atrophy

<table>
<thead>
<tr>
<th>Subjects (scans)</th>
<th>Score</th>
<th>BBSI</th>
<th>VBSI</th>
<th>HRBSI**</th>
<th>HLBSI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 1250</td>
<td>PHS (status)</td>
<td>1.54e-5</td>
<td>2.38e-5</td>
<td>9.14e-2</td>
<td>5.45e-2</td>
</tr>
<tr>
<td>(n = 3909)</td>
<td>PHS (burden)</td>
<td>2.56e-3</td>
<td>4.12e-3</td>
<td>0.82</td>
<td>0.30</td>
</tr>
<tr>
<td>n = 878</td>
<td>APOE-e4</td>
<td>4.93e-3</td>
<td>1.50e-2</td>
<td>1.25e-2</td>
<td>2.96e-2</td>
</tr>
<tr>
<td>(n = 2754)</td>
<td>PHS (burden)</td>
<td>0.19</td>
<td>0.42</td>
<td>0.82</td>
<td>0.30</td>
</tr>
<tr>
<td>n = 1250</td>
<td>PRS1</td>
<td>6.7e-4</td>
<td>1.7e-3</td>
<td>0.02</td>
<td>0.065</td>
</tr>
<tr>
<td>n = 878</td>
<td>PRS2</td>
<td>0.65</td>
<td>0.91</td>
<td>0.88</td>
<td>0.29</td>
</tr>
<tr>
<td>n = 1250</td>
<td>PRS2**</td>
<td>0.02</td>
<td>7.7e-3</td>
<td>0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>n = 878</td>
<td>PRS-cs</td>
<td>0.0041</td>
<td>0.031</td>
<td>0.061</td>
<td>0.004</td>
</tr>
</tbody>
</table>

P-values for a time-by-polygenic score interaction effect on longitudinal changes in grey matter quantified by the BSI. Columns correspond to different target regions and/or measures of BSI. BBSI = whole brain BSI; VBSI = Ventricular BSI; HRBSI = Right side hippocampal BSI; HLBSI = Left side hippocampal BSI. * indicates a reduced threshold \((P < 1e-05)\), were highly correlated \((r^2 = 0.75; Supplementary Table 7)\). This confirms earlier results comparing PHS and PRS, which reported that despite the different nature of the statistical analysis, the estimated effects per SNP were very similar (Leonenko et al., 2019b). Consequently, the association profile of the two scores was quite similar across the tested Alzheimer’s disease-related measures. In addition to PRS1, we tested two other PRS scores: PRS2, which was based on SNPs exceeding the \(P = 0.5\) threshold, and PRS-cs using a novel method that adjust GWAS-derived effect size estimates for local LD structure. PRS-cs was based on all available SNP data, making it in theory more similar to PRS2, but the correction effect, which emphasized variants with strong effects, rendered the final score to be more correlated to PRS1 rather than to PRS2.

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After comprehensive adjustment for the APOE locus and stratification for disease group, there was no association between polygenic scores and amyloid (measured in CSF or through amyloid PET). In initial reports, PHS showed a strong association with cortical amyloid (Tan et al., 2019, with strongest association seen in Rostral...
Middle Frontal gyrus; \( P_{\text{FDR}} = 5.82 \times 10^{-8} \); replicated in this study with \( P_{\text{FDR}} = 6.21 \times 10^{-7} \). Implementing adjustments for \( \text{APOE} \) locus and disease status, only one ROI remained significant (Transverse Temporal gyrus, \( P_{\text{FDR}} = 0.038 \)). Likewise, CSF Aβ did not show any association with polygenic scores beyond \( \text{APOE} \) (\( P > 0.34 \)). Only CSF tau and p-tau were consistently associated with polygenic risk beyond \( \text{APOE} \) and clinical diagnosis, with the strongest effects for PHS and PRS1. We found that the genes contributing to PRS1 were significantly enriched (\( P = 4.1 \times 10^{-04} \)) among the protein-interaction partners of tau (Supplementary results). The association with tau rather than amyloid pathology confirms recently published results by Leonenko et al. (2019a) showing that amyloid pathology is mainly driven by \( \text{APOE} \) genotype and that polygenic risk contributes to risk further conversion to Alzheimer’s disease. Moreover, recent works suggest that brain amyloid deposition is driven by the \( \text{APOE} \) locus (Yan et al., 2018) and that a genome-wide significant variant in the Alzheimer’s disease risk gene \( \text{BIN1} \) (rs744373) is associated with tau pathology instead of amyloid pathology (Franzmeier et al., 2019).

For some analyses, we conducted predictive modelling to assess the effect of polygenic scores in addition to the statistical association tests. The results supported our findings: using \( \text{APOE} \) burden as opposed to \( \text{APOE}\)-e4 status provided better diagnostic prediction, however, adding PRSs to models already using \( \text{APOE} \) burden yielded only marginal gains (Supplementary Table 2). CSF tau and p-tau were better predicted by adding PHS or PRS1 to the models, but it was not the case for CSF Aβ (Supplementary Table 3). Lastly, there was no predictive gain by using polygenic scores on clinical progression in the survival analysis (Supplementary Table 6).

One limitation of this study was that, owing to sample overlap, the entire ADNI cohort could not be used for the PHS and PRS comparison. However, in order to demonstrate the effect of being \( \text{APOE}\)-e4 homozygous, we tested \( \text{APOE}\)-e4 burden in addition to \( \text{APOE}\)-e4 status and compared the results to PHS on the entire cohort, finding broadly consistent results.

In summary, this work presents a comprehensive comparison of PHS, PRS and PRS-cs and their relation to a range of Alzheimer’s disease-related traits within the ADNI cohort. The results showed that there are not many effective differences between PHS and PRS1 in terms of associations with disease stage or biomarkers. In fact, many associations of PHS reported in earlier works were inflated due to lack of adjustment for the \( \text{APOE} \) locus, clinical diagnosis or underspecified statistical models. Given the ease with which PRS can be derived (i.e. from publicly available summary statistics) compared with PHS (i.e. requires reanalysis of the GWAS data), we believe the PRS constitutes the more practical choice. Moreover, on many of the tested traits, the major driving factor remained the \( \text{APOE} \) locus, with the sole exception of quantitative CSF-tau and p-tau measures.

## Supplementary material

Supplementary material is available at Brain Communications online.

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Competing interests

J.M.S. has received research funding and PET tracer from AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly); has consulted for Roche, Eli Lilly, Biogen and Merck, GE; received royalties from Oxford University Press and Henry Stewart Talks; given education lectures sponsored by Eli Lilly, Biogen and GE; and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE.

References


Effects of polygenic risk beyond APOE


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