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Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture

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Genetic association studies have identified 44 common genome-wide significant risk loci for late-onset Alzheimer's disease (LOAD). However, LOAD genetic architecture and prediction are unclear. Here we estimate the optimal P -threshold (P_{optimal}) of a genetic risk score (GRS) for prediction of LOAD in three independent datasets comprising 676 cases and 35,675 family history proxy cases. We show that the discriminative ability of GRS in LOAD prediction is maximised when selecting a small number of SNPs. Both simulation results and direct estimation indicate that the number of causal common SNPs for LOAD may be less than 100, suggesting LOAD is more oligogenic than polygenic. The best GRS explains approximately 75% of SNP-heritability, and individuals in the top decile of GRS have ten-fold increased odds when compared to those in the bottom decile. In addition, 14 variants are identified that contribute to both LOAD risk and age at onset of LOAD.

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Alzheimer's disease (AD) is the most common form of dementia. The majority (~90–95%) of AD cases are sporadic and occur after 65 years of age (late-onset Alzheimer's disease, LOAD)¹. The reported heritability of LOAD liability is 58.0% (95% CI 19.0–87.0%) from twin studies², and its estimated common single nucleotide polymorphism (SNP) based heritability on the liability scale ($h^2_{\text{SNP}(l)}$) ranges from 0.13 to 0.33^{3–5}. *APOE* alleles ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, determined by two coding variants, rs7412 and rs429358 from chromosome 19), especially *APOE* $\epsilon 4$, explain around a quarter of the total heritability^{6,7}, and can be regarded as a proxy monogenic mutation.

In addition to *APOE* alleles, genome-wide association studies (GWASs) have identified over 40 LOAD-associated risk loci^{8–15}. Similar to other brain-related diseases (e.g., schizophrenia^{16,17}, major depression¹⁸ and Parkinson's disease¹⁹), LOAD has been described as polygenic²⁰. A genetic risk score (GRS) derived from 13,959 cases and 35,600 controls based on a large number of SNPs (i.e., SNPs with $P_{\text{GWAS}} \leq 0.5$) was reported to have better prediction accuracy than using SNPs selected with a more stringent P_{GWAS} . However, a recent study¹⁴ with 24,087 AD cases, 47,793 family history proxy cases, 55,058 controls and 328,320 proxy controls showed that the optimal P -threshold (P_{optimal}) for prediction was achieved with a stringent threshold of $\sim 10^{-5}$, which implies that using more SNPs at lower stringency does not improve prediction accuracy. The P_{optimal} of GRS on diseases (e.g., schizophrenia) was previously reported to be related to the discovery sample size²¹. Nevertheless, it was observed that the best fitting P -value for GRS prediction of schizophrenia changed little from 0.2 with 2615 cases and 3338 controls to 0.1 with 32,838 cases and 44,357 controls¹⁶. The reasons for this inconsistency in P_{optimal} for LOAD (from 0.5 to $\sim 10^{-5}$) across studies is unclear, in particular whether it may be solely due to the increase of discovery sample size. These conflicting reports on the number of common risk variants associated with LOAD led us to investigate the genetic architecture of the disease, and to compare the prediction accuracy between a multiple SNP genetic predictor of LOAD (including or excluding *APOE*) versus *APOE* alone.

For LOAD, age at onset (AAO) is also heritable. Its heritability is reported to be 0.42 (s.e. = 0.04)²² and can be predicted genetically using a genetic hazard score (GHS)²³. The effect size of each SNP in GHS is usually estimated based on Cox proportional hazards regression (survival analysis)²⁴. Previous studies have identified four genomic regions (*APOE*, *BIN1*, *MS4A* and *PICALM*) with SNPs genome-wide significantly ($P < 5 \times 10^{-8}$) associated with LOAD AAO, all of these being LOAD risk loci^{13,25–28}. A direct comparison of LOAD risk and AAO on the same data may provide new insight into the genetics of LOAD.

In the present study, we investigate the prediction pattern of GRS to estimate the optimal P -value cut-off, and thereby quantify the genetic architecture of LOAD. To ensure the robustness of our results, we use four sets of (overlapping) GWAS summary statistics to calculate the GRS (with or without SNPs from chromosome 19) and examine their prediction patterns in three independent datasets (out-of-sample prediction). The results suggest that LOAD is oligogenic compared to other disorders of the brain, since only a small number of common SNPs are conditionally associated with LOAD. Furthermore, we compare the prediction performance of GRS against *APOE* and find that individuals in the upper decile of GRS have higher disease risk than those who are *APOE* $\epsilon 4$ heterozygous carriers. Finally, risk of LOAD and AAO of LOAD are found to be genetically similar.

Results

Current GWAS summary statistics on late-onset Alzheimer's disease. To date, eight studies^{8–15} have reported a total of 44

common loci (minor allele frequency > 0.01) that are associated with LOAD at a genome-wide significant level ($P < 5 \times 10^{-8}$) (Supplementary Fig. 1). As expected, the number of reported loci increased with effective sample size (Fig. 1) (Supplementary methods).

We collected four sets of GWAS summary statistics from the public domain to calculate GRS^{12–14}. They are based on samples from stage 1 in Lambert et al.¹², samples from UK Biobank (UKB) parents (a meta-analysis between GWASs on maternal and paternal LOAD), a meta-analysis between summary statistics from Lambert et al.¹² and UKB parents in Marioni et al.¹³, and a recent meta-analysis from Jansen et al.¹⁴. These summary statistics are from samples with partial overlap and some of them are independent (i.e., samples from Lambert et al.¹² and UKB parents). Genetic correlations between these summary statistics estimated by LDscore regression (LDSC)²⁹ were all close to unity (Supplementary Table 1). Among them, two estimates (genetic correlations between Lambert et al. (stage 1)¹²/Marioni et al. (UKB)¹³ and Marioni et al. (meta)¹³) were significantly ($P < 0.05$) different from one (Supplementary Table 1). This discrepancy was not expected since they were all GWAS results on the same trait and had overlapping samples. LDSC assumes that the effect sizes of SNPs follow a normal distribution, we therefore removed all SNPs from chromosome 19 to avoid the potential effect of *APOE* when estimating the genetic correlation. We also re-calculated the sample size for each SNP based on the standard error of its effect size ("Methods"). We used the flag "--intercept-gencov" to constrain the intercept by our calculated value while computing the genetic correlation. We found that the estimated genetic correlation between Marioni et al. (UKB)¹³ and Marioni et al. (meta)¹³ was 1.06 (s.e. = 0.11), and the genetic correlation between Lambert et al. (stage 1)¹² and Marioni et al. (meta)¹³ was 1.14 (s.e. = 0.11), both not significantly ($P > 0.05$) different from unity. We noted that the sample size and therefore the weights used in the meta-analysis of Jansen et al.¹⁴ were not optimal and show that the effective sample size (sample size under balanced design) should be used (Supplementary methods).

Genetic risk score in late-onset Alzheimer's disease. We used 1,056,156 SNPs (1,056,154 HapMap3 SNPs and two *APOE* SNPs: rs429358 and rs7412) shared between all four sets of summary statistics to calculate the GRS (GRS_{full}). We retained HapMap3 SNPs in our study since they are common (minor allele frequency > 0.01), well-imputed and available across all GWASs. For each set of summary statistics, we chose different P -value thresholds (1×10^{-8} , 1×10^{-7} , 1×10^{-6} , 1×10^{-5} , 3×10^{-5} , 1×10^{-4} , 3×10^{-4} , 1×10^{-3} , 3×10^{-3} , 0.01, 0.03, 0.1, 0.3, 1) and performed LD clumping ($R^2 = 0.01$, window size = 1 Mbp) to select near-independent SNPs using PLINK³⁰. Based on the selected SNPs, we calculated the weighted sum of the SNP dosage and used it as the GRS for each individual²¹. We evaluated the performance of GRS_{full} using samples from the Australian Imaging, Biomarker & Lifestyle Study (AIBL, 216 cases and 631 controls), the Sydney Memory and Ageing study (Sydney MAS, 77 cases and 588 controls) and the UKB (383 cases and 1915 controls) (Table 1). We found that the prediction accuracy (R^2) on the liability scale (Fig. 2a) ("Methods") increased when lowering the P -value threshold. Since the prediction pattern could be affected by the SNPs with major effects (e.g., *APOE* $\epsilon 4$ and $\epsilon 2$) (Supplementary Fig. 2) ("Methods"), we removed SNPs from chromosome 19 and re-calculated the GRS based on the remaining 1,037,804 SNPs (termed GRS_{no19}). Although the R^2 reduced compared to that from GRS_{full}, the optimal P -value threshold remained small (Fig. 2b). The P -value thresholds that maximised out-of-sample

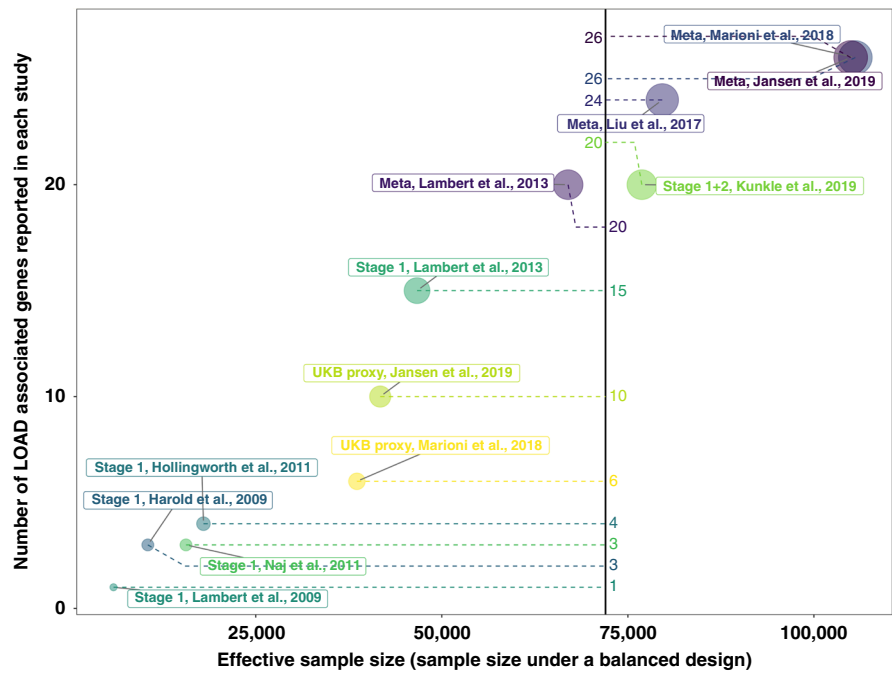


Fig. 1 The relationship between sample size and number of identified genes. Sample size is calculated as the total number of cases and controls under a balanced design (50% cases and 50% controls). Genes associated with LOAD were collected from different studies. They are the closest genes to SNPs (minor allele frequency >0.01) genome-wide significantly ($P < 5 \times 10^{-8}$) associated with LOAD. “Stage 1” means summary statistics based on the samples from stage 1 in that study and “Meta” means summary statistics from the meta-analysis from that study.

Table 1 Description of late-onset Alzheimer's disease cases and controls from different cohorts.					
	$N_{(\text{proxy})}$ case	$N_{(\text{proxy})}$ control	Age ^a (sd) (proxy) case	Age ^a (sd) (proxy) control	Female
AIBL ^b	216	631	77.6 (7.6)	72.2 (6.4)	45.3%
Sydney MAS ^c	77	588	86.8 (4.6)	84.7 (4.5)	55.6%
UKB	383	1915	64.4 (4.5)	64.5 (2.6)	53.0%
UKB mother	22,557	231,767	83.7 (6.8)	78.1 (8.4)	100%
UKB father	13,118	241,206	81.8 (6.9)	76.2 (8.1)	0%

^aFor the UKB mother and father samples, age of parental case was used as a proxy for age at onset.
^bThe Australian Imaging Biomarkers and Lifestyle Study.
^cThe Sydney Memory and Ageing Study.

prediction (R^2) in AIBL were 1×10^{-8} (Lambert et al., stage 1¹²), 1×10^{-7} (Jansen et al., meta¹⁴), 1×10^{-8} (Marioni et al., meta¹³) and 3×10^{-4} (Marioni et al., UKB¹³). Samples from UKB were only evaluated based on summary statistics from Lambert et al. (stage 1)¹² to avoid the sample overlap. Results based on Sydney MAS were highly variable (Fig. 2b) since the number of cases is small, yielding limited power compared to the other two cohorts (Fig. 2b). We found that the odds ratio between individuals in the top 50% of GRS_{no19} and those in the bottom 50% (Supplementary Fig. 3) also increased with a decrease in P -value threshold. We further explored the GRS_{no19} prediction performance of Lambert et al. (stage 1)¹² on the UKB parental LOAD (Table 1). Although the prediction accuracy is small, its pattern is consistent with that from other cohorts (Fig. 2b). Furthermore, we used less stringent R^2 (0.2) to perform LD clumping so that more SNPs could be included in GRS_{no19} . We found no improvement in prediction accuracy or change in the pattern (Supplementary Fig. 4). In addition, we estimated the optimal fraction of causal SNPs for prediction using LDpred³¹ (on SNPs outside of chromosome 19) (“Methods”) (Supplementary Fig. 5), and found the optimal proportion of SNPs was lower than 0.3% in most situations.

Given the LD between SNPs, the number of effective independent markers would be even lower.

The highest prediction accuracy of GRS_{full} (based on 22 SNPs, Supplementary Table 2) was 19.1% (95% bootstrap CI 13.1–26.9%, 1000 replications) of variance explained on the liability scale (“Methods”), with *APOE* (rs429358 and rs7412) contributing the majority (17.4%, 95% bootstrap CI 11.3–25.0%, 1000 replications). We compared this prediction accuracy with the transformed common SNP-based heritability on the liability scale ($h^2_{\text{SNP}(l)}$) reported in previous studies (ranges from 8.9 to 31.2% across studies)^{3–5} (Supplementary Table 3 and Supplementary Fig. 6) (“Methods”). The SNP-heritability was estimated by different methods and our simulations (“Methods”) suggested that when most of the SNP-based heritability was explained by a single variant, the estimated value from LDSC was lower than the simulated heritability, but the result from genome-based restricted maximum likelihood (GREML) was unbiased (Supplementary Fig. 7). Therefore, only $h^2_{\text{SNP}(l)}$ based on GREML is considered here. We found that the prediction accuracy achieved could account for around three quarters of inverse-variance

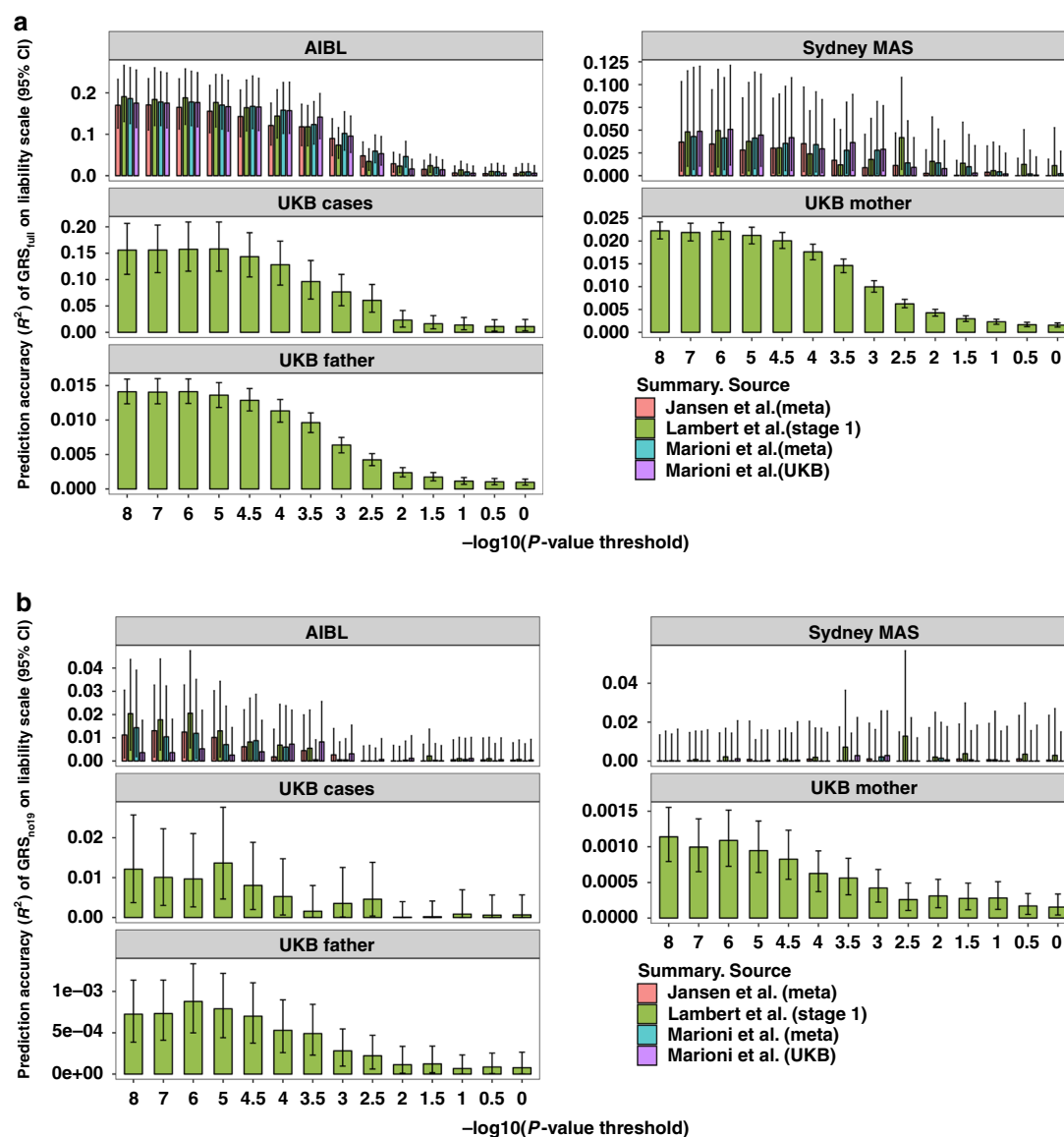


Fig. 2 The prediction performance of genetic risk score (GRS) in different datasets. a The prediction accuracy of GRS_{full} based on SNPs selected using different P -value thresholds. GRS_{full} was calculated based on 1,056,154 HapMap3 SNPs and two *APOE* SNPs. **b** The prediction accuracy of GRS_{no19} based on SNPs selected using different P -value thresholds. GRS_{no19} is calculated based on HapMap3 SNPs excluding SNPs from chromosome 19, to avoid contamination with *APOE*. Prediction results on samples from UKB cases and UKB parents are based on summary statistics from Lambert et al.¹² (stage 1) only. The error bars represent 95% confidence interval, and the confidence interval was calculated based on 1000 bootstrap replications⁵⁹.

weighted average of $h^2_{SNP(l)}$ (26.2%, 95% CI 22.7–29.7%), suggesting that the best GRS_{full} could explain most of the SNP-heritability. Besides, the best GRS_{full} accounts for one-third of the reported total heritability (58.0%, 95% CI 19.0–87.0%) from twin studies² (Supplementary Fig. 8). However, the differences between the prediction accuracy of *APOE*, GRS_{full} , $h^2_{SNP(l)}$, and total heritability are not statistically significant ($P > 0.05$).

Genetic architecture and optimal threshold in GRS. The prediction pattern of GRS on LOAD is different from that of polygenic traits like BMI³², height³², schizophrenia¹⁶ and major depression¹⁸. Our simulation study suggests that this difference is related to their distinct genetic architectures, and that LOAD is much less polygenic compared to these other complex traits. In our simulations, we randomly selected 100,000 unrelated individuals from the UKB and simulated traits with an SNP-heritability of 9% (close to the reported SNP-heritability of LOAD excluding

the effect of *APOE*), varying the number of causal variants (“Methods”)²¹. We selected 10,000 individuals as a (hold-out) test set and chose different number of individuals (from 10,000 to 90,000) as a training set. We ran GWAS on the training set and examined the prediction pattern of the GRS on the test set. We observed an increase in the optimal P -value threshold of GRS as the number of causal SNPs increases (from 16 to 131,072) (Fig. 3 and Supplementary Fig. 9). The pattern of GRS on LOAD was consistent with simulations on fewer than 256 causal SNPs ($P_{optimal} < 1 \times 10^{-5}$). In addition, we used a recently developed Bayesian regression method (SBayesR³³) that estimates the number of SNPs with non-zero effect size from GWAS summary statistics. We only used the Marioni et al. (meta)¹³ summary statistics, since these are based on the largest effective sample size (“Methods”). We estimated the number of SNPs with non-zero effects on LOAD to be 99 (s.e. = 6), which represents only ~0.01% of HapMap3 SNPs. This number decreased to 56 (s.e. = 6), if SNPs from chromosome 19 are removed before the

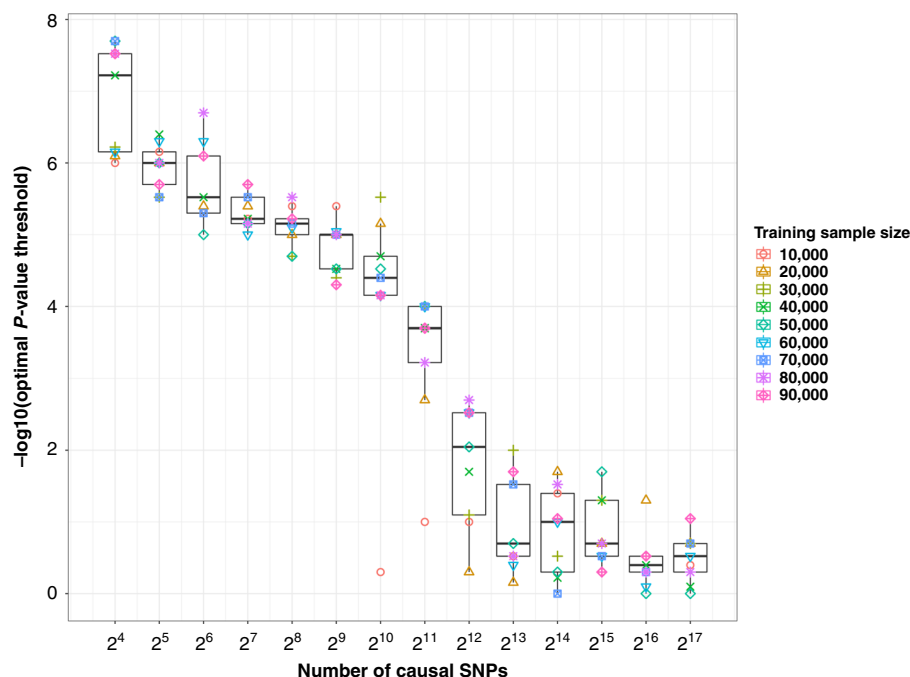


Fig. 3 The relationship between optimal GRS P -value threshold and number of causal SNPs. Causal SNPs were selected from 1,037,804 HapMap3 SNPs. For each scenario, we generated a phenotype of 100,000 individuals based on a specified number of causal SNPs (e.g., 128) with heritability 0.09. We randomly selected 10,000 individuals as the test set. Based on the unselected individuals, we randomly chose 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 70,000, 80,000 and 90,000 individuals separately as training sets and used them to perform GWAS. We examined the performance of genetic risk score (based on LD clumping with 80 separate P -value thresholds) on the test set ($N_{\text{test}} = 10,000$) and selected the optimal P -value threshold. Box plot shows the median (centre line), the interquartile range (box) and whiskers (± 1.5 times interquartile range).

analysis. For context, these estimates are much lower than those of other common diseases such as Parkinson's disease (33,728, s.e. = 11,968), schizophrenia (184,879, s.e. = 25,250) and major depression (172,735, s.e. = 43,219) ("Methods").

Comparison of prediction performance between GRS and *APOE*. For coronary artery disease, GRS could identify individuals with risk equivalent to monogenic mutations³⁴. Here, we compared the prediction performance of *APOE* with GRS (based on the most stringent P -value threshold: 1×10^{-8}). In AIBL, individuals who are *APOE* $\epsilon 4$ heterozygous carriers were found to have a higher disease risk (43.6%) than those in the highest decile of a GRS_{no19} (35.7%). Using both *APOE* SNPs and variants on other chromosomes, the disease risk of individuals in the top decile of the GRS_{full} was 57.1% (Fig. 4a). The odds ratio was 10.0 (95% CI 4.5–22.0) compared to individuals in the bottom decile (Fig. 4b). This disease risk is larger than the individuals who are *APOE* $\epsilon 4$ heterozygous carriers (43.6%), but smaller than individuals who are homozygous for *APOE* $\epsilon 4$ (59.6%). Nevertheless, individuals in the last percentile of GRS_{full} have larger disease risk (75.0%) than individuals who are homozygous for *APOE* $\epsilon 4$. We observed the same pattern in the Sydney MAS and UKB samples (Fig. 4a). Across the different target datasets, around 1% improvement of the area under the ROC curve (AUC) could be achieved by a GRS_{full} (ranges from 57.1 to 73.2%) compared to *APOE*. Ignoring SNPs from chromosome 19, the AUC based on GRS_{no19} ranges from 51.8% (95% CI 51.4–52.3%) to 59.0% (95% CI 54.2–63.1%), all of them are significantly different (P -value < 0.05) from 50% (Supplementary Fig. 10).

Genetic similarity between LOAD risk and AAO. To explore whether there are more genomic loci associated with both LOAD risk and AAO, we tried to detect new AAO loci and investigate

whether they have been identified to be associated with LOAD risk. We used the parental AAO of LOAD as reported in UKB as a proxy of AAO and performed genome-wide survival analysis (GWSA) on maternal and paternal AAO of LOAD separately ("Methods"). Six independent (pairwise $R^2 < 0.01$) genome-wide significant ($P < 5 \times 10^{-8}$) SNPs were identified after meta-analysing the parental AAO results (Supplementary Fig. 11a). Furthermore, we meta-analysed the UKB results with previously reported AAO GWSA summary statistics²⁸, and identified 16 genomic loci with SNPs showing genome-wide significant ($P < 5 \times 10^{-8}$) association with LOAD AAO (Table 2) (Supplementary Fig. 11b). Among these, 14 loci were genome-wide significantly associated ($P < 5 \times 10^{-8}$) with LOAD risk, the remaining two SNPs also have P -values $< 5 \times 10^{-5}$. The correlation between the effect sizes of the 16 SNPs on disease risk and AAO was 1.00 (s.e. = 0.02), suggesting the risk alleles of LOAD also decrease the AAO of LOAD.

Discussion

In this study, we investigated the predictive performance of GRS on LOAD using four sets of summary statistics and applied them to three independent datasets. We found a clear pattern in that prediction performance of GRS increases with the use of a more stringent P -value threshold for SNP selection and therefore with fewer SNPs in the model. Consistent with simulations and direct estimation (SBayesR), we conclude that a relatively small number (in the hundreds) of common variants contribute to LOAD risk. *APOE* was responsible for most of the prediction accuracy of LOAD, but other variants also show significant prediction accuracy (maximum R^2 on liability scale = 2.0%, 95% bootstrap CI 0.5–4.5%, 1000 replications). Genetic variants that contribute to the risk of disease are also associated with an earlier AAO.

Taking all of our results together, we conclude that the empirical data are consistent with an oligogenic common variant

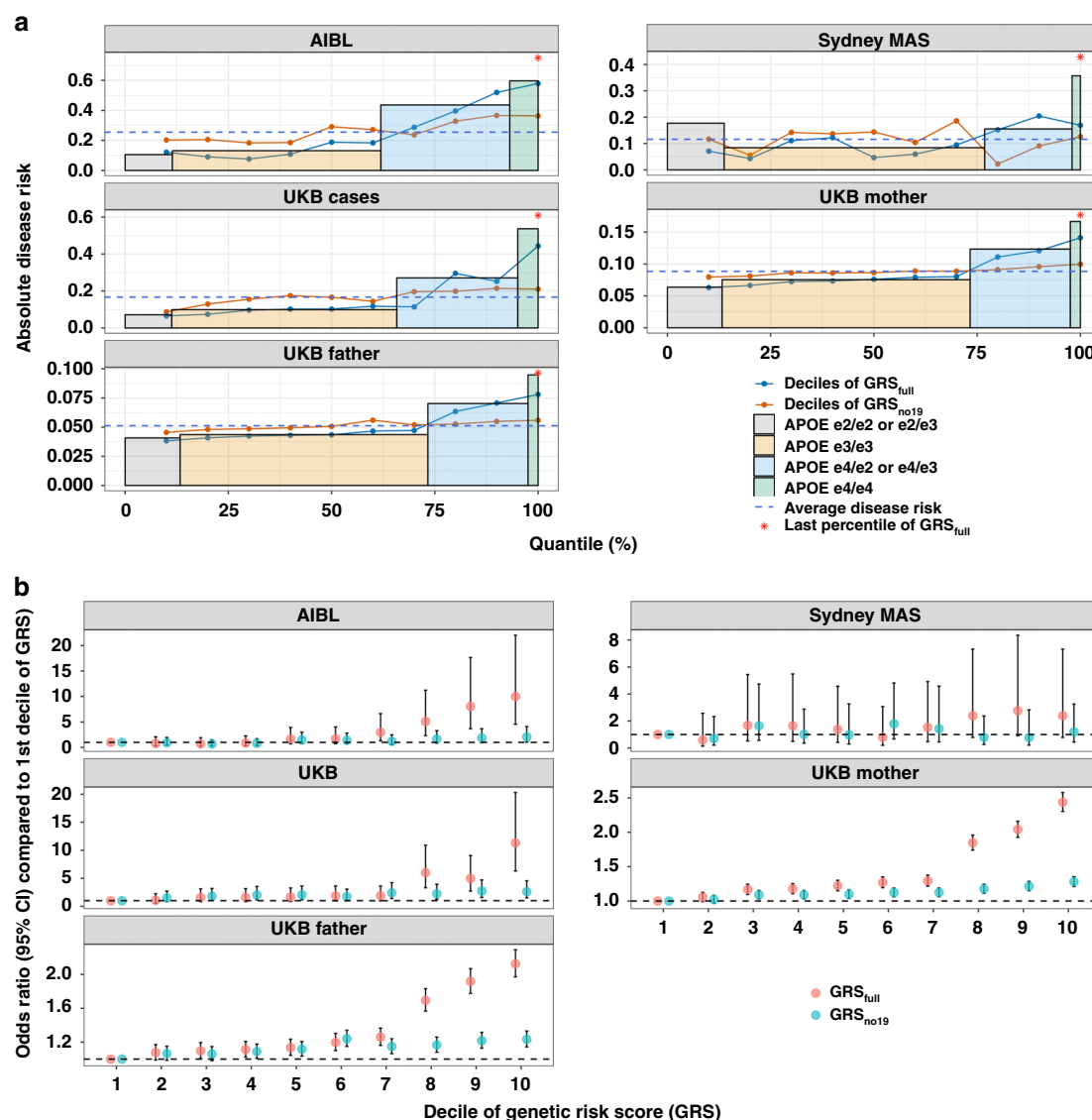


Fig. 4 The comparison of LOAD prediction performance between GRS and APOE. **a** The disease risk of late-onset Alzheimer's disease of individuals in different deciles of GRS (both GRS_{full} and GRS_{no19}), last percentile of GRS_{full} and in individuals with APOE $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$, APOE $\epsilon 3$ homozygotes ($\epsilon 3/\epsilon 3$), APOE $\epsilon 4$ heterozygotes ($\epsilon 4/\epsilon 3$ or $\epsilon 4/\epsilon 2$) and APOE $\epsilon 4$ homozygotes ($\epsilon 4/\epsilon 4$). Samples from AIBL, Sydney MAS, UKB cases, UKB mother and UKB father were examined. **b** Odds ratio between individuals in the other deciles and first decile of GRS. GRS_{full} was calculated based on 1,056,154 HapMap3 SNPs and two APOE SNPs. GRS_{no19} was calculated based on HapMap3 SNPs but excluding SNPs from chromosome 19. Only independent ($R^2 < 0.01$) SNPs with $P < 1 \times 10^{-8}$ were used to calculate the GRS. The error bars in **b** represent 95% confidence interval.

architecture of LOAD (~0.01% of SNPs with MAF > 1% have non-zero effects on LOAD). This is smaller than the polygenicity estimate of 0.26% (s.e. = 0.19%) reported in a previous study³⁵. However, considering the standard error of that estimate, it is not significantly ($P > 0.05$) different from our estimate of 0.01% (s.e. = 0.0006%). Besides, this architecture contrasts with many other common diseases and disorders which are highly polygenic. For comparison, we applied the SBayesR method³³ to GWAS summary statistics for schizophrenia^{16,17}, major depression¹⁸ and Parkinson's disease¹⁹, and estimated the proportion of HapMap3 SNPs with non-zero effects size as 17.5% (s.e. = 2.4%), 3.2% (s.e. = 0.8%) and 16.4% (s.e. = 5.8%), respectively. In addition, their optimal P -value thresholds of GRS for these diseases were all ≥ 0.05 ^{16,18,19}. LOAD was previously labelled as polygenic by Escott-Price et al.²⁰, who reported a best fitting P -value threshold of 0.5. However, most of the control samples (~6000 out of 7277) in their test dataset (Genetic and Environmental Risk in

Alzheimer's Disease consortium) were younger than 60 years old when their disease status was reported, and the ages of most cases were over 75 years¹². Treating these samples as controls might bias prediction results, since the typical AAO of LOAD is above 65 years. In addition, sample overlap between training and test sets would also lead to a large optimal P -value threshold. In Jansen et al.¹⁴, the best fitting P -value threshold was 1.69×10^{-5} when the test set was independent of the training set. For a test set that overlaps with the training set (accounting ~3% of training set³⁶), the optimal P -value threshold was 0.5. Our simulations show that when the test set is part of a training set, the best P -value threshold is close to 1 (Supplementary Fig. 12) ("Methods"), even if the proportion is small (e.g., only 1%), consistent with theory³⁷. Therefore, taken together, we conclude that the previous report of LOAD being polygenic is likely biased by sample overlap and/or the ascertainment of controls that may go on to develop LOAD at a later stage.

Table 2 Genome-wide significant SNPs associated with age at onset (AAO) of late-onset Alzheimer's disease.

CHR	BP	SNP	A1	Closest Gene ^a	BETA_AAO	P_AAO	BETA_RISK ^b	P_RISK ^b
1	207786289	rs6701713 ^c	A	<i>CR1</i>	0.079	3.5E – 12	0.132	1.6E – 28
2	127891427	rs4663105 ^c	A	<i>LOC105373605</i>	–0.139	1.8E – 28	–0.162	7.3E – 49
6	32573415	rs601945 ^c	A	<i>HLA-DRB1</i>	0.070	4.2E – 08	0.106	1.2E – 14
6	47432637	rs9381563 ^c	T	.	–0.066	1.2E – 08	–0.075	5.8E – 14
7	99990364	rs34995835 ^c	T	<i>PILRA</i>	–0.066	1.3E – 10	–0.094	1.1E – 18
8	27464929	rs4236673 ^c	A	<i>CLU</i>	–0.074	1.9E – 10	–0.110	1.1E – 28
11	85867875	rs10792832 ^c	A	<i>PICALM</i>	–0.088	2.9E – 20	–0.124	5.1E – 36
11	121435587	rs11218343 ^c	T	<i>SORL1</i>	0.171	6.1E – 12	0.213	4.8E – 17
11	60021948	rs1582763 ^c	A	<i>MS4A</i>	–0.084	2.5E – 18	–0.088	1.0E – 18
14	92937293	rs4904929 ^c	T	<i>SLC24A4</i>	–0.068	6.0E – 09	–0.075	1.1E – 10
15	59022615	rs442495 ^c	T	<i>ADAM10</i>	0.058	5.3E – 09	0.067	5.5E – 11
17	5139808	rs58124010 ^c	T	<i>SCIMP</i>	0.078	2.6E – 08	0.108	2.0E – 10
19	45412955	rs1081105 ^c	A	<i>APOE</i>	–0.783	5.1E – 216	–0.941	6.5E – 199
19	1039444	rs3795065 ^c	T	<i>ABCA7, CNN2</i>	–0.076	1.2E – 08	–0.077	3.7E – 10
1	161151844	rs11265563 ^d	A	<i>B4GALT3</i>	0.078	8.9E – 09	0.049	4.4E – 05
4	11027619	rs4351014 ^d	T	.	0.057	2.3E – 08	0.060	3.4E – 07

^aClosest gene from variant effect predictor (VEP v98)⁶⁰.^bBETA and P-value from GWAS on LOAD from Marioni et al.¹³. A1 is the effect allele.^cSNPs genome-wide significantly associated with both LOAD AAO and LOAD risk.^dSNPs genome-wide significantly associated with LOAD AAO only.

There is a wide range of LOAD SNP-heritability reported across studies, ranging from 8.9 to 31.2% (Supplementary Table 3). Except for the difference due to the estimation methods, such differences could also be caused by differences in age distributions between datasets (Supplementary Fig. 8), since the genetic effect on LOAD was reported to be age-dependent³⁸. Based on the same method, the estimated heritability in datasets with younger individuals was found to be larger than that using older individuals (Supplementary Table 3). Another potential reason could be heterogeneity between datasets, for example with respect to diagnostic criteria. For the summary statistics based on meta-analysis in particular, this heterogeneity would attenuate heritability estimates⁵.

There are a number of limitations in this study: (1) We focused on the additive effect of common variants, and did not explore non-additive genetic or gene by environment effects; (2) our analysis was based on summary statistics from a meta-analysis of a number of datasets. Heterogeneity (e.g., based on different diagnostic criteria) and measurement error (e.g., proxy cases from UKB are self-reported) in these datasets (and those used in this study) might have affected our result. The estimated number of conditionally associated SNPs could be smaller than reported if there is heterogeneity and/or measurement error; (3) the sample sizes of the datasets with real cases and controls used in this study are small, a larger dataset would be required to test the significance of the difference in prediction accuracy (R^2) between GRSs based on optimal P -value and other P -value thresholds; (4) rare variants were not considered. There are several genes with rare mutations with large effects on LOAD^{39–41}. Those mutations contribute little to heritability and to prediction accuracy in population samples because of their low frequency. Larger GWAS samples should allow identification of the remaining undiscovered common SNPs associated with LOAD but also offer the opportunity to identify rarer SNPs (e.g., MAF in 0.001–0.1) in order to refine and improve the GRS.

Methods

Study populations. *AIBL*: we selected 216 cases and 631 controls (participants with mild cognitive impairment were regarded as controls) with genotype information from the Australian Imaging, Biomarker & Lifestyle Flagship Study (Table 1). We removed SNPs with minor allele frequency smaller than 0.01, SNP

missingness rate larger than 0.05, and not passing Hardy–Weinberg equilibrium test ($P < 5 \times 10^{-6}$). Genotypes were imputed to the sequencing data from the Haplotype Reference Consortium (r1.1) using the Sanger Imputation Service (<https://imputation.sanger.ac.uk>). A total of 6,972,431 SNPs with info score larger than 0.8 were selected after imputation. Data were collected by the AIBL study group. AIBL study methodology and acquisition of genetic data have been reported previously^{42,43}. Ethics approval for the AIBL study and all experimental protocols were provided by the ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital and Edith Cowan University. Informed consent was obtained from all participants.

Sydney MAS: we selected 77 cases and 588 controls (including participants with mild cognitive impairment) with genotype information from the Sydney Memory and Ageing Study⁴⁴ (Table 1). We applied the same quality control steps and imputation as in that in AIBL. In total, 4,303,719 SNPs with info score larger than 0.8 were selected after imputation. Acquisition of genetic data has been described previously⁴⁵. Informed consent was obtained from all participants, and Sydney MAS was approved by the Human Research Ethics Committee of the University of New South Wales (# HC14327).

UKB family history. UKB data (<http://www.ukbiobank.ac.uk>) were collected on over 500,000 individuals aged between 37 and 73 years from across Great Britain (England, Wales and Scotland) at the study baseline (2006–2010), including health, cognitive and genetic data. Family history of AD was ascertained via self-report. Participants were asked “Has/did your father ever suffer from Alzheimer's disease/dementia?” (Data-Field: 20107) and “Has/did your mother ever suffer from Alzheimer's disease/dementia?” (Data-Field: 20110). Self-report data from the initial assessment visit (2006–2010), the first repeat assessment visit (2012–2013) and the imaging visit (2014+) were aggregated. We only included participants with parents older than 60 years or whose parents died after 60 years of age. Only genetically unrelated individuals (genetic relationship correlation < 0.05) with European ancestry were selected. In total, 22,557/13,118 individuals with maternal/paternal LOAD were selected as proxy case samples, 231,767/241,206 individuals without maternal/paternal LOAD were selected as proxy control samples. Imputation and QC steps on SNPs have been detailed elsewhere⁴⁶, 8,545,378 SNPs left after QC.

UKB: additional information on LOAD was obtained for participants themselves from UKB. Briefly, 383 participants with a diagnosis of “Alzheimer's disease” (ICD10 code: G30.1 and G30.9) or “Dementia in Alzheimer's disease” (ICD10 code: F00.1 and F00.9) or “dementia/Alzheimer's/cognitive impairment” (UKB Data-Coding 6: 1263) were selected. We randomly selected 1915 participants (with age at baseline greater than 60) from the remaining samples as controls. These samples were used as a test set. Informed consent was obtained by UKB from all participants, and the ethics approval for the UKB study was obtained from the North West Centre for Research Ethics Committee (11/NW/0382).

The estimation of intercept for LDSC. An inaccurately estimated intercept in LDSC could affect the precision of the estimate of the genetic correlation²⁹. We therefore calculated the intercept directly other than estimating it in LDSC. The intercept was calculated as $\frac{N_1}{\sqrt{N_1 N_2}}$, N_1 and N_2 are the average per SNP sample size in each study, N_3 is the number of overlapping samples between studies. The intercept

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Author contributions

P.M.V., A.F.M. and Q.Z. conceived and designed the study. Q.Z. performed simulations and statistical analyses under the assistance and guidance from J.S., R.E.M., L.Y., J.Y., N.R.W., A.F.M. and P.M.V. Q.Z., A.F.M. and P.M.V. wrote the manuscript with the participation of all authors. B.C.-D., M.J.W., A.M.G., E.M., K.-L.H., T.P., S.M.L., P.S.S., K.A.M., N.J.A., A.T. and H.B. contributed the data. Unless otherwise stated, AIBL consortium authors contributed but did not participate in analysis or writing of this report. All other authors reviewed and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Australian Imaging Biomarkers and Lifestyle (AIBL) Study

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