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Polygenic score analysis identifies distinct genetic risk profiles in Alzheimer's disease comorbidities

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Alzheimer's disease (AD) is usually accompanied by comorbidities such as type 2 diabetes (T2D), epilepsy, major depressive disorder (MDD), and migraine headaches (MH) that can significantly affect patient management and progression. As AD, these comorbidities have their own cumulative common genetic risk component that can be explored in a single individual through polygenic scores. Utilizing data from the UK Biobank, we investigated the correlation between polygenic scores (PGS) for these comorbidities and their actual presentation in AD patients. We show that individuals with higher PGS values showed an elevated risk of developing T2D (OR 2.1, $p = 1.07 \times 10^{-11}$) and epilepsy (OR 1.5, $p = 0.0176$). High T2D-PGS is also associated with an earlier AD onset in individuals at high genetic risk for AD (AD-PGS). In contrast, no significant genetic associations were found for MDD and MH. Our findings show distinct common genetic risk factors for T2D and epilepsy carried by AD patients that are associated with increased prevalence and earlier disease onset. These results highlight the contribution of common genetic variation to the broader clinical landscape of AD and will contribute to future tailored patient management strategies for individuals at high genetic risk.

Keywords PGS, Comorbidities, Common variants, PRS

Comorbidities are common in AD patients and significantly impact their quality of life[1]. Among these, Diabetes, cardiovascular disease, depression, and inflammatory bowel disease[2] are the most common. Additionally, AD has been linked to epilepsy (EPI) and migraine headaches (MH)[3–6]. These comorbidities not only serve as indicators of cognitive impairment and AD progression but may also share overlapping biological mechanisms with AD[7].

There is evidence suggesting that type 2 diabetes (T2D) is associated with an increased risk of developing AD[8]. Obesity and T2D significantly and independently increase the risk of AD, with physiological changes common to these conditions possibly promoting AD[9]. Similarly, EPI has been associated with neuronal hyperexcitability and amyloid-β accumulation, both of which are implicated in AD progression[10,11]. MDD has been suggested as a potential prodromal stage of AD, sharing overlapping biological pathways such as dysregulation of the hypothalamic-pituitary-adrenal axis[7,12]. MH, on the other hand, has been linked to cognitive impairment and shares vascular and inflammatory pathways with AD, highlighting a possible connection through shared physiological mechanisms[6,13,14].

From a genetic perspective, Genome-Wide Association Studies (GWAS) have identified common genetic risk variations associated to AD. The largest GWAS to date identified 75 genetic loci independently associated with AD in European populations[15]. Moreover, recent GWAS identified 82 AD susceptibility loci that achieved genome-wide significance[16].

Polygenic scores (PGS) derived from these large-scale GWAS can be used to identify individuals carrying extreme risk or protection against the disease given by the additive effect of thousands of common variants[17]. These PGS can be as high as to the risks associated with single monogenic variations[18]. PGSs have been investigated in AD[19] as well as in multiple other common diseases that can present themselves as AD comorbidities such as diabetes, depression, and epilepsy, among others[13,14,20–22]. While PGS are widely used to predict disease risk in

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the general population, their effect on AD presentation, particularly through comorbidities, is less understood. Exploring how genetic predispositions to comorbidities influence AD onset and progression is essential for tailoring management strategies and improving prognostic accuracy. By addressing these genetic contributions, we can refine approaches to care that consider the complex interplay of AD and its associated comorbidities.

This study aims to explore the interaction between comorbidity-specific PGSs and AD. Specifically, we sought to determine whether individual PGSs for common AD comorbidities—T2D, EPI, MDD, and MH—are significantly higher in AD patients who develop these comorbidities compared to those who do not. Through this analysis, we aim to provide new insights into the genetic contributions of these conditions within the context of AD.

Results

We examined the relationship between common genetic variants associated with different comorbidities, as assessed by Polygenic Scores (PGS), and their impact on the risk of Alzheimer's disease (AD) patients developing these comorbidities. To achieve this, we used publicly available Genome-Wide Association Studies (GWAS) summary statistics to calculate PGSs for selected comorbidities in AD patients from the UK Biobank. To avoid overfitting, we selected GWAS that were not entirely based on UKB participants, prioritizing large-scale datasets with sufficient statistical power. Our analysis focused on GWAS for Type 2 diabetes (T2D), major depressive disorder (MDD), migraine headaches (MH), and epilepsy (EPI) as detailed in (Supplementary Table 1).

We set an age cutoff to include individuals over 50 years old. Following quality control procedures, the remaining UK Biobank cohort encompassed 301,434 individuals, among whom 2,893 were AD cases and 298,541 were general population controls. The demographic characteristics and prevalence of comorbidities are elaborated in (Table 1).

To account for potential biases related to age distribution across clinical phenotypes, we included the age distribution for each group in (Supplementary Fig. 1). The distribution is relatively homogeneous across groups, reducing the likelihood of age-related biases.

Comorbidity-PGS in AD patients

We observed that AD patients with T2D and Epilepsy showed higher T2D-PGS (p-value = 6.44×10^{-10}) and EPI-PGS (p-value = 0.0052) values, respectively compared to AD patients without the comorbidity. In contrast, no significant differences were found for AD patients with and without MDD or MH (MDD: p-value = 0.673; MH: p-value = 0.453) (Fig. 1).

Next, we analyzed the mean PGS values across three groups: the general population, AD patients without comorbidities, and AD patients with comorbidities. For T2D, we found significant differences between AD patients with and without T2D (p-value = 4.74×10^{-14}) and between the general population and AD patients with T2D (p-value = 3.33×10^{-14}). However, we observed no differences between the general population and AD patients without T2D (p-value = 0.126). A similar pattern was seen for EPI, with significant differences between AD patients with and without EPI (p-value = 0.00138) and between the general population and AD patients with EPI (p-value = 0.00163), but not between the general population and AD patients without EPI (p-value = 0.793).

For MDD and MH, we found no significant differences between AD with and without comorbidities (MDD: p-value = 0.383; MH: p-value = 0.938) (Fig. 2). As negative control, we analyzed height PGS from Yengo et al.[23], and no association with the presence of comorbidities was found (Supplementary Fig. 2).

Elevated genetic risk for T2D and epilepsy in AD

We further compared the tails of the PGS distribution. We calculated the odds ratio (OR) for the top distribution, considering 20, 10, and 5% cutoffs, using logistic regression adjusted by age, sex, PC1-4 and TDI (Townsend deprivation Index), to account for age and sex related association and population stratification (Table 2). Our results indicated an increased risk for T2D and epilepsy in the distributions. For T2D, we observed significant results for the top 20% (OR 2.1, p-value: 1.07×10^{-11}; Table 2), top 10% (OR 2.1, p-value: 6.06×10^{-7}; Table 2), and top 5% (OR 2.1, p-value: 8.64×10^{-5}; Table 2) distributions. Additionally, EPI showed significant results only for the top 20% distribution (OR 1.5, p-value: 0.0176; Table 2).

Diagnosis (ICD10)	Group	*n*	Age	Male (%)	*n*	Age	Males (%)
		General population			Alzheimer disease		
Type 2 diabetes (F32)	Controls	271,291	60.3 ± 5.4	121,204 (44.7)	3,382	63.2 ± 4.5	2,074 (61.3)
	Cases	27,250	62 ± 5.1	16,432 (60.3)	640	63.5 ± 4.4	447 (69.8)
Depression (E11)	Controls	280,417	60.5 ± 5.3	130,953 (46.7)	3,285	63.3 ± 4.5	2,113 (64.3)
	Cases	18,124	60.4 ± 5.5	6,683 (36.9)	737	63.0 ± 4.6	408 (55.4)
Migraine headache (G43)	Controls	294,172	60.5 ± 5.4	136,521 (46.4)	3,942	63.3 ± 4.5	2,492 (63.2)
	Cases	4,369	60.1 ± 5.5	1,115 (25.5)	80	62.1 ± 5.8	29 (36.2)
Epilepsy (G40)	Controls	293,591	60.5 ± 5.4	135,077 (46.0)	3,834	63.3 ± 4.5	2,400 (62.6)
	Cases	4,950	60.8 ± 5.4	2,559 (51.7)	188	63.3 ± 4.8	121 (64.4)
All cohort	All	298,541	60.5 ± 5.4	137,636 (46.1)	2,893	65.0 ± 3.7	1,381 (47.7)

Table 1. Cohort description.

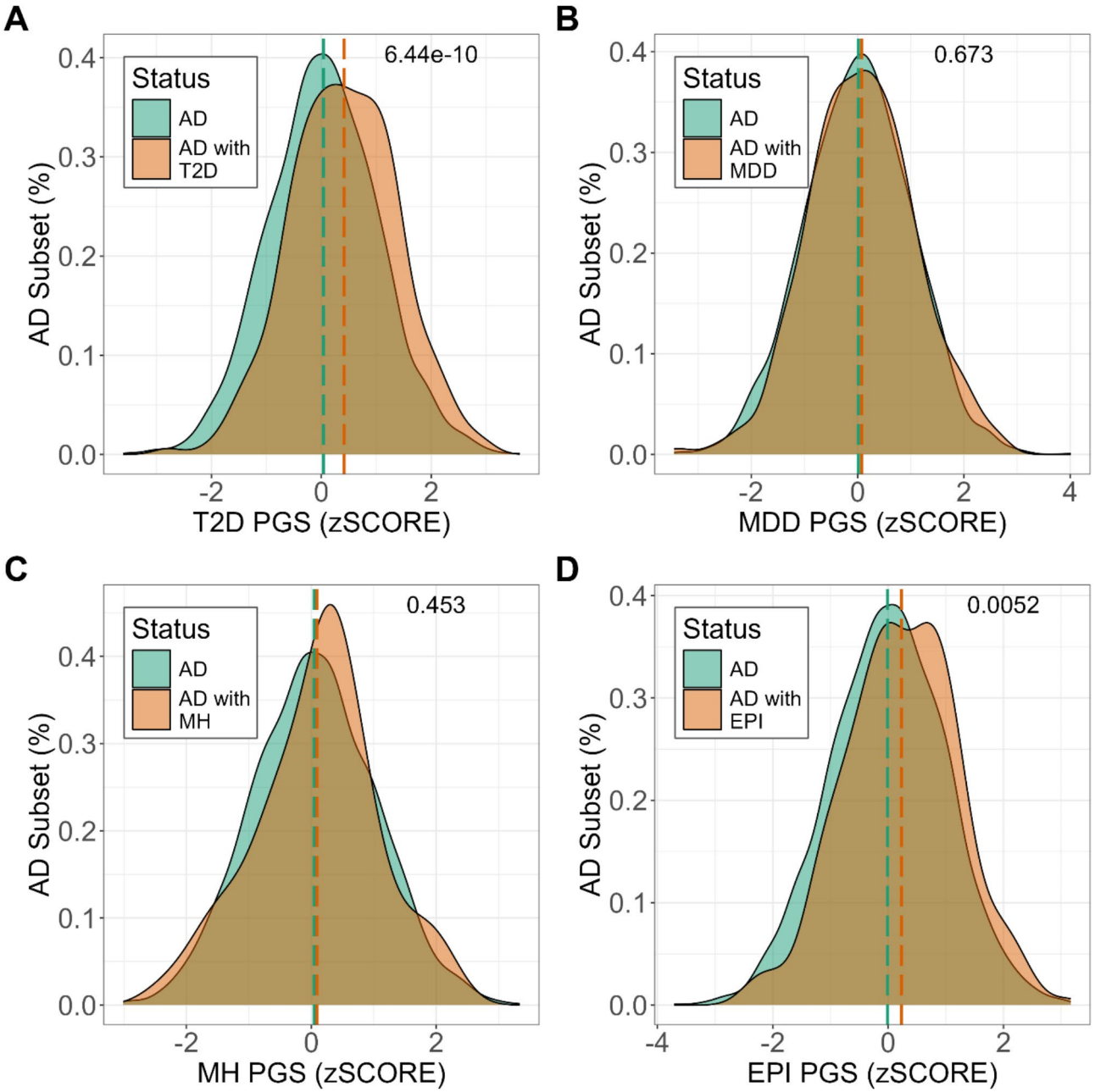

Fig. 1. Distribution comorbidity-PGS in Alzheimer's disease patients of UK biobank. PGS distribution between the AD subset in green and AD with (**A**) type 2 diabetes, (**B**) major depressive disorder, (**C**) migraine headache, (**D**) epilepsy in orange. The colored lines indicate the mean for each group. The P-value was calculated with Kolmogorov-Smirnov to compare the normal distribution between the groups.

There was no correlation between T2D and Epilepsy comorbidity-PGS scores, also these PGS are independent from AD-PGS, suggesting independent genetic contributions to the comorbidity manifestation (Supplementary Fig. 3). We also analyzed individuals carrying the ApoE ε4 risk variant (rs423958) and compared their comorbidity polygenic scores (PGS) with those who do not carry the variant. Our results showed no significant differences in comorbidities between the two groups (Supplementary Fig. 4).

Impact of comorbidity-PGSs on AD onset

To investigate whether there is a relationship between comorbidity-PGSs levels and the age of AD onset, we performed a linear regression analysis of PGSs and age at onset. The results showed no correlation between comorbidity-PGSs and AD onset (Supplementary Fig. 5). Also, we note that most AD cases developed their comorbidities prior to the onset of AD: 77.4% of AD cases developed T2D before AD, and 44.4% developed EPI.

We further analyzed the top 20% of the PGS distribution across different age-at-onset ranges: 50–60 ($n = 26$), 60–70 ($n = 330$), 70–80 ($n = 1{,}927$) and over 80 ($n = 610$). In the group with onset between the 50–60 no significant

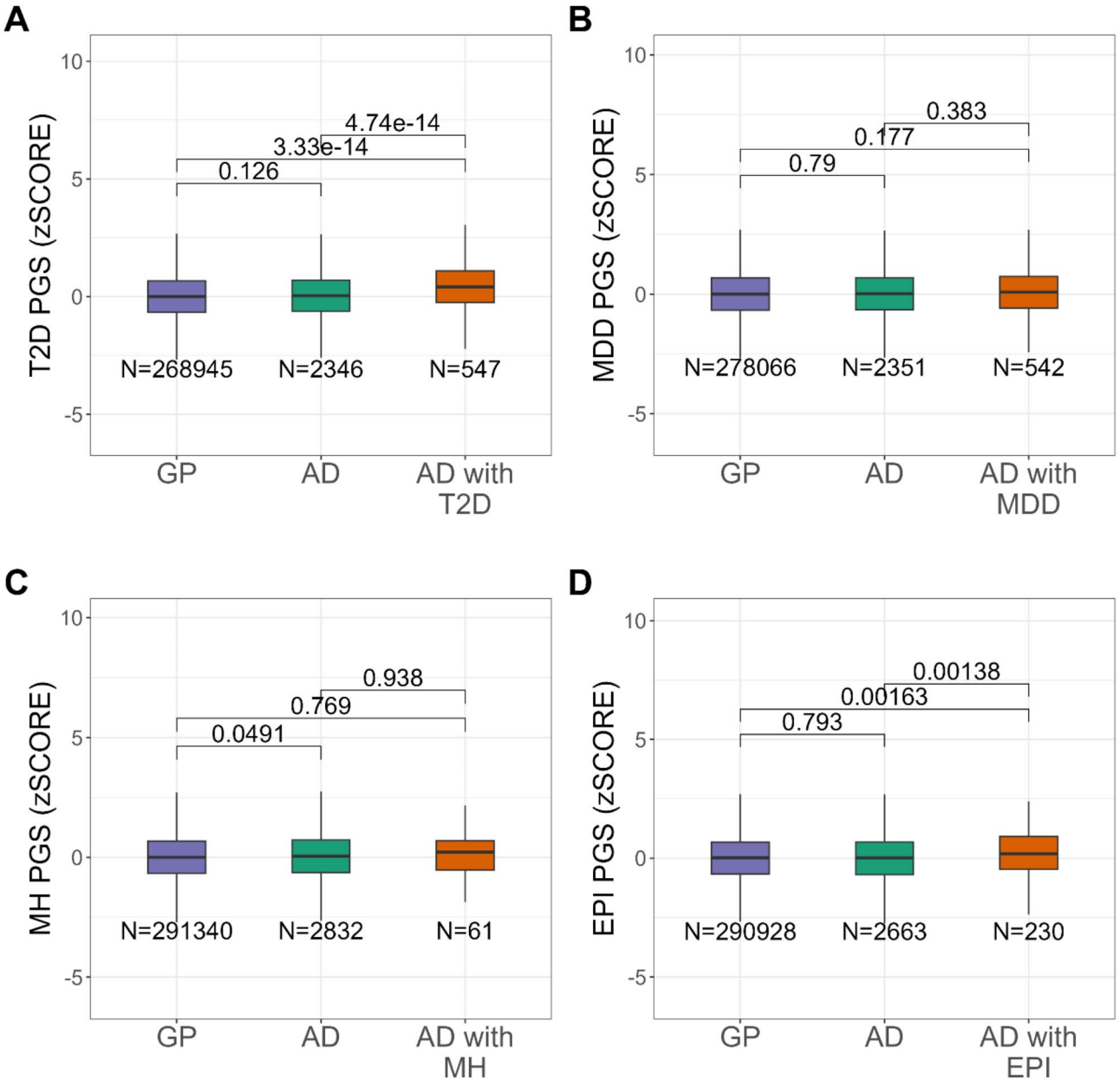

Fig. 2. Comorbidity-PGS in Alzheimer's disease patients and general population of UK biobank. PGS comparison between general population in purple, AD patients in green and AD with (**A**) type 2 diabetes, (**B**) major depressive disorder, (**C**) migraine headache, (**D**) epilepsy in orange. P-values were obtained using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons. Each group shows the number of individuals included in each group.

associations were observed for any comorbidity-PGSs (Supplementary Table 2). We observed consistent risk for T2D in all age of onset groups (60–70: OR 2.19, p-value: 0.0215; 70–80: OR 1.93, p-value: $1{,}15 \times 10^{-06}$; >80: OR 3.19, p-value: 4.03×10^{-07}). For EPI-PGS, the genetic risk is concentrated only in the 70–80 onset group (60–70: OR 1.25, p-value: 0.520; 70–80: OR 1.72, p-value: 7.27×10^{-03}; >80: OR 0.825, p-value: 0.739) (Supplementary Table 2, Fig. 3A).

High AD-PGSs are known to be associated with an earlier AD onset[24]. To assess the interaction between AD-PGS and our comorbidity-PGSs, we first evalueated the linear reltionship between AD-PGS and AD onset (Supplementary Fig. 6). Next, we interrogated a subset of individuals with AD who had a high AD-PGS (top 20%) and compared the age at onset between those with high and low PGS for comorbidities (EPI and T2D). No significant differences were found for EPI-PGS (0.352) (Fig. 3B). For T2D we observed that individuals at high AD-PGS and high T2D-PGS had a significantly earlier AD onset compared to those with only high AD-PGS (p-value: 0.00514) (Fig. 3C).

	OR	95% CI	*p*-value	Case/control high PGS	Case/control low PGS
T2D-PGS					
20% top PGS	2.1	1.69–2.60	1.07×10^{-11}	166/417	385/1947
10% top PGS	2.1	1.60–2.76	1.06×10^{-7}	88/204	463/2160
5% top PGS	2.1	1.45–3.01	8.64×10^{-5}	45/101	506/2263
EPI-PGS					
20% top PGS	1.5	1.07–2.02	0.0176	63/520	170/2162
10% top PGS	1.3	0.839–1.95	0.254	29/263	204/2419
5% top PGS	1.4	0.782–2.41	0.269	15/131	218/2551

Table 2. Comorbidity-PGS for the extreme distribution in individuals with AD from UK biobank.

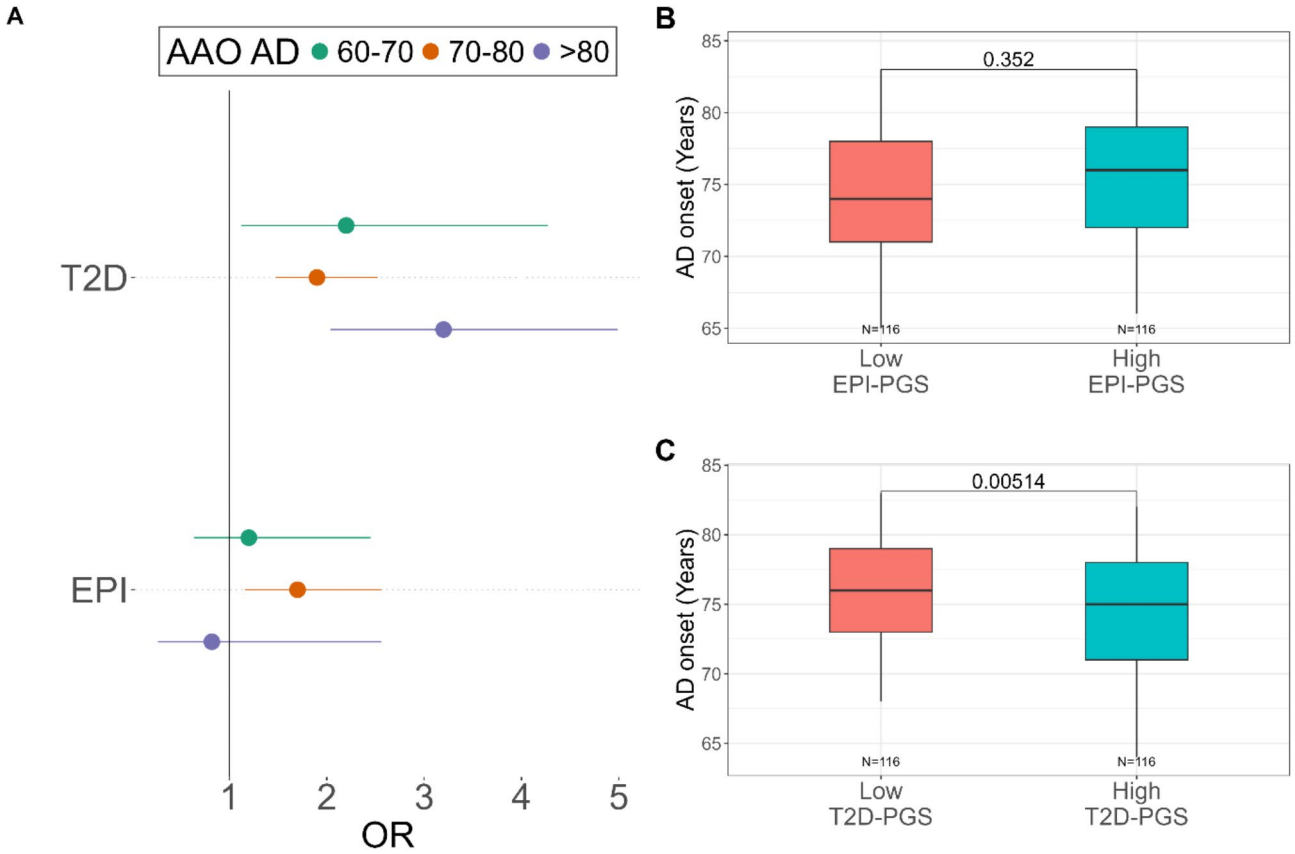

Fig. 3. Association of comorbidity-PGSs with AD onset in individuals from the UK biobank: (**A**) Shows are the OR and the 95% confidence interval for AD comorbidities in the AD subset, 60–70 (Green), 70–80 (Red) and > 80 (Purple) age at onset. OR was obtained with a logistic regression for comorbidity using age, sex and the first four PC as covariates comparing 20% of high PGS with the rest of the group in each age interval. (**B**,**C**) Comparison of AD onset in a subset of AD patients with High AD-PGS in groups with high and low (**B**) EPI-PGS and (T2D-PGS). The mean comparison was assessed with the T student test.

Discussion

We identified distinct genetic risks for type 2 diabetes (T2D) and epilepsy (EPI) in AD patients. In contrast, for major depressive disorder (MDD) and migraine headache (MH), we did not observe any association between comorbidity PGS and AD presentation, suggesting a genetic independence of these comorbidities from common genetic factors. These results highlight the importance of studying PGSs in disease-specific contexts, as some comorbidities may be more strongly influenced by non-genetic factors in neurodegenerative conditions like AD. The observed negative results for MDD and MH highlight the variability in genetic contributions and provide valuable insights into the interplay between AD and its comorbidities.

The main findings suggest that AD patients with higher PGS for T2D and EPI are at increased risk for developing these comorbidities (Figs. 1 and 2). The lack of significant correlation among comorbidity-PGS scores indicates that these genetic risks operate independently (Supplementary Fig. 3). Furthermore, the APOE

ε4 variant, a known risk factor for AD, does not appear to influence the genetic risk for these comorbidities (Supplementary Fig. 4).

Our findings reveal that a substantial portion of AD cases develop comorbidities such as T2D and EPI before the onset of AD, suggesting a potential common genetic contribution to the risk of AD. Highlighting that EPI risk is concentrated in the >70 age group, this finding indicates that the genetic risk for EPI may be more prominent in individuals who develop AD later in life (Fig. 3A). Additionally, we observed that comorbidity-PGS of comorbidities modifies the effect of AD-PGS on the onset of AD. Demonstrating that CMRB-PGS is useful in describing the interaction of the genetic burden of comorbidity with AD.

Epilepsy and Alzheimer's disease

A growing body of evidence has demonstrated a link between AD and epilepsy. Epilepsy can occur at any stage of AD and are six to ten times more likely in patients with AD than in controls[10], leading to functional deterioration and behavioral changes[25]. Seizures in AD lead to the accumulation of amyloid-β and tau, promoting neurodegeneration[11]. This can result in an accelerated cognitive decline and increased mortality, adding to the medical and economic burden[26]. Recognizing and treating seizures early in these patients is critical. However, diagnosing seizures in AD is challenging due to difficulty in identifying non-motor focal seizures, obtaining patient histories, and the low sensitivity of standard scalp electroencephalogram (EEG) methods, as well as nonspecific cerebrospinal fluid (CSF) and radiological findings[27]. This bidirectional relationship suggests that epilepsy is a risk factor for AD, and vice versa in old age[28].

Type 2 diabetes and Alzheimer's disease

Individuals with an increased risk of developing AD[29]. The strong epidemiological connection implies a common pathophysiology, particularly involving insulin resistance and impaired glucose metabolism[30]. Disruptions in brain insulin signaling mechanisms contribute to the molecular, biochemical, and histopathological abnormalities in AD[31,32].

Cognitive impairments in individuals with diabetes primarily impact psychomotor efficiency, attention, learning, memory, mental flexibility, speed, and executive function. Even after controlling for diabetic vascular disease and inadequate cerebral circulation, increased cortical and subcortical atrophy have been observed in T2D patients[33,34]. Hyperglycemia poses a risk for cognitive dysfunction and dementia, while recurrent hypoglycemic episodes can result in sub-clinical brain damage and permanent cognitive impairment[35,36].

Our finding that AD patients with T2D and epilepsy exhibit higher T2D-PGS aligns with emerging evidence suggesting complex interactions between T2D, genetic susceptibility, and neurodegenerative diseases. Studies, such as those by Yang et al. (2022), highlight that T2D-PGS can predict cognitive decline, including the conversion from amnestic mild cognitive impairment to AD, independent of shared genetic loci[37]. This supports the notion that T2D genetic risk contributes not only to metabolic dysregulation but also to neurodegenerative processes.

However, the relationship between T2D and AD remains complex and sometimes contradictory. Hardy et al.[38] found limited evidence of a direct genetic correlation between T2D and AD, suggesting that both conditions may arise independently or share environmental risk factors without a strong genetic overlap[38]. On the other hand, Litkowski et al.[39] reported that diabetes-related genetic variants increase the risk for vascular dementia rather than AD, underscoring the heterogeneity of dementia subtypes and their differential association with metabolic disorders[39].

Given these mixed findings, our observation of elevated T2D-PGS in AD patients with T2D may reflect a unique interaction of multiple genetic and environmental factors. Future research should further explore how T2D-PGS interacts with other comorbidities, such as epilepsy, to influence the progression of neurodegenerative diseases. This integrative approach will be essential to unravel the shared and distinct pathways underlying these interconnected conditions and refine predictive models for personalized interventions.

Limitations and future research

It's important to note that our study has limitations. The small sample size of AD patients with specific comorbidities (Sample size: T2D 371, MDD 312; MH 33; EPI 117) may impact the statistical power of our findings. Additionally, relying on ICD-10 codes for identifying comorbidities could potentially introduce misclassification bias[22].

Moving forward, it would be beneficial for future research to expand genetic analyses to include rare variants and explore the complex interactions among multiple comorbidities. Rare variants, contribute to the missing heritability of complex traits by capturing genetic influences that PGS might overlook[40]. Aggregating the effects of rare variants through burden testing further reveals associations undetectable through common variant analysis alone, providing a deeper understanding of disease[41]. Moreover, rare variant plus PGS enhance predictive models by addressing population-specific variation and mitigating biases from sequencing platforms, refining the assessment of genetic risk for AD and its comorbidities[42]. Finally, examining the potential synergistic effects of epilepsy (EPI) and type 2 diabetes (T2D) on AD development could uncover valuable insights into how these conditions interact at the genetic level. This knowledge would further advance efforts in precision medicine for AD and its related disorders.

Conclusion

Our findings highlight the contribution of additional genetic factors in to the broader clinical landscape of AD and will contribute to the future development of proactive management strategies.

Materials and methods

UK biobank and cohort configuration

Initiated in 2006, the UK Biobank is a comprehensive cohort study from the United Kingdom. As of April 2024, it includes data on 502,187 participants aged 40 to 69, with a follow-up period of up to 15 years[43]. This dataset offers extensive genetic and phenotypic information, including lifestyle, biomarkers, and body and brain imaging. Diseases were identified using ICD-10 Codes (International Classification of Diseases, 10th Revision)[44], specifically using the G30 code to find Alzheimer's disease cases, E11 for Type 2 diabetes, F32 for major depressive disorder, G43 for migraine headaches, and G40 for epilepsy.

Cohort quality control

Imputed genetic data were accessed from UK Biobank data field 21,007. Quality control and imputation of single nucleotide variants (SNVs) were conducted by Bycroft et al.. and the NHLBI trans-omics for precision medicine (TOPMed) Consortium[43,45]. The SNV-QC criteria included a call rate above 95%, a minor allele frequency (MAF) greater than 0.01, and variants deviating from Hardy-Weinberg equilibrium with $p < 0.001$. Imputed SNVs with an R2 > 0.3 were selected. Initially, heterozygosity outliers and samples with discordant sex status were removed. Related individuals were identified using a kinship coefficient (data field 22021) greater than 0.0442, and one from each pair was excluded based on their phenotype. Ancestry outliers were then removed based on Principal Component Analysis (PCA - data field 22009), ensuring the inclusion of only individuals of European ancestry as indicated in Bycroft et al.[43]. For downstream analysis, we identified and mapped the ApoE ε4 genotype on the UK Biobank cohort with Plink using the imputed SNP rs429358a (Lyall et al., 2019).

Genome-wide association studies summary statistics curation

Summary statistics were obtained from the largest available GWAS for T2D, MDD, MH and epilepsy. Specifically, T2D from Mahajan et al.[46], MDD from Howard et al.. (2019)[12], MH from Gormley et al. (2016)[47], and epilepsy from Stevelink et al. (2023)[48]. To address potential biases due to overlapping participants between the UK Biobank and selected GWASs, specific strategies were employed to exclude UK Biobank individuals from each comorbidity's GWAS summary statistics. For MH, 23andMe, Inc. summary statistics were used to exclude UK Biobank participants, minimizing overfitting risks. For MDD, we used meta-analysis results from Howard et al.. excluding the UK Biobank cohort reported in Wray et al.[49]. We conducted the meta-analysis using METAL[50] software, adjusting for the effective sample size with 23andMe data. For T2D, as Mahajan et al.. summary statistics included UK Biobank data, we used the R package Metasubtract[51] to simulate a meta-analysis excluding UK Biobank participants. For correlation and onset analysis, we used AD-PGS extracted from pre-calcualted-PGS from UK Biobank[52]. As negative control, we used height summary statistics obtained from Yengo et al.[23].

PGS calculation

Polygenic scores (PGS) were calculated based on the overlap between UK Biobank QC-SNVs and the reported SNVs in each comorbidity's GWAS summary statistics (T2D, MDD, MH, and epilepsy). Comorbidity-PGSs were calculated as previously described by Leu et al.. with minor modifications[22]. Duplicated and ambiguous SNVs (A/T or C/G) were excluded, and the UK Biobank data were pruned to retain independent SNVs (r2 < 0.1 within 500 kb of the most significant SNVs in GWAS SS). PGSs were calculated for each individual using the allelic score function in Plink 1.9 software, with SNV weights from the specified GWAS summary statistics. PGSs were computed at various p-value thresholds, and thresholds maximizing the explained variance in a validation dataset (80% training, 20% validation) were selected. Comorbidity risks were evaluated by comparing all PGS deciles to the first decile and the top distribution (20, 10, 5%) to the remaining population.

PGS standardization

To determine the empirical PGS p-value threshold that explains the most variability, we performed a logistic regression of comorbidity status against PGS, adjusted for sex, age, first four principal components, and the Townsend deprivation index (TDI). We assessed the explained variance using Nagelkerke's pseudo-R2 by comparing the full model to the null model (excluding PGS). We standardized PGSs calculating the mean and standard deviation (SD) for controls and normalizing the entire cohort data. Assuming a normal distribution, we normalized data subtracting the mean and dividing by the SD. We used PGS to compare the distribution between cases and controls within the AD subset. These comparisons were stratified by age (50–60, 60–70, 70–80, > 80). We assessed the prevalence of comorbidities and AD based on the onset of AD.

Statistical analyses

We generated PGSs to compare different groups. We calculated odds ratios (OR) for the tails of the PGS distribution, using logistic regression adjusted by age, sex, PC1-4 and TDI (Townsend deprivation Index), to account for age and sex related association and population stratification. The Kolmogorov-Smirnov was used to assess differences in distribution between AD cases and controls. For comparisons of mean PGS values across multiple groups, we performed one-way ANOVA with Tukey post hoc correction. Age at onset mean was compared using a t-test. We plotted all graphs using R version 4.2.2[53] and the ggplot2 R library[54].

Data availability

The analysis code and scripts used in this study are openly available in the GitHub repository Laboratorio-de-Neurogenetica-Clinica/PGS-AD-Comorbidities.

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Author contributions

C.H. and E.P.P. conceived of the presented idea. C.H. developed the theory and performed the computations. C.V., C.L. and E.P.P. verified the analytical methods. C.H. and E.P.P wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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