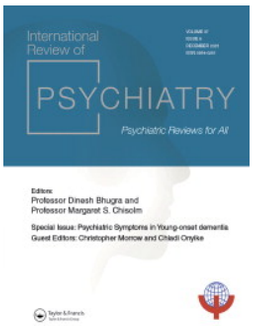

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RESEARCH ARTICLE

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Polygenic risk for psychiatric disorders and its association with neuropsychiatric symptoms in dementia

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ABSTRACT

Neuropsychiatric symptoms are common in Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD), yet their genetic underpinnings remain unclear. To gain insight into biological processes related to neuropsychiatric symptoms in dementia, we investigated whether polygenic risk scores (PRS) for psychiatric disorders – major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BD), and autism spectrum disorder (ASD) – are associated with neuropsychiatric symptoms in dementia. Data included genetic and neuropsychiatric data of 6240 AD patients, 428 FTD patients and 390 DLB patients from five European cohorts (ADC, GR@ACE, DELCODE, AgeCoDe, and DCN). PRS for MDD, BD, SCZ, and ASD were calculated using LDpred2. Neuropsychiatric symptoms were assessed using total scores from the Neuropsychiatric Inventory (NPI) (NPI-12 and NPI-Q) and Geriatric Depression scale (GDS).

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Associations between PRS and symptoms were examined using linear regression models, followed by meta-analyses. In FTD, higher SCZ-PRS associated with lower NPI scores in the meta-analysis (β = −0.12, $p = .001$). No associations were found in AD and DLB. This is the first study to show that genetic liability for SCZ associates with lower NPI in FTD, warranting further investigation.

Introduction

Psychiatric and neurodegenerative disorders are traditionally regarded as distinct, yet they often present with overlapping clinical features. Phenotypically, psychiatric disorders may mimic neurodegeneration through cognitive decline or behavioural disturbance. Conversely, in dementia syndromes such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD), symptoms like depression, psychosis, and agitation can closely resemble those seen in major depressive disorder (MDD), schizophrenia (SCZ), or bipolar disorder (BD) (Taylor et al., 2020; Woolley et al., 2011). Additionally, emerging evidence also suggests that autism-like traits, including impaired social cognition and rigidity, may be present in some dementia syndromes, further blurring diagnostic boundaries (Rhodus et al., 2020, 2022).

The clinical overlap between psychiatric and neurodegenerative disorders contributes to frequent diagnostic delays and misclassifications; up to one-third of individuals with neurodegenerative disease initially receive a psychiatric diagnosis, rising above 50% in FTD (de Boer et al., 2023; Tsoukra et al., 2022; Woolley et al., 2011; Zapata-Restrepo et al., 2021). This clinical ambiguity raises the questions of shared biological mechanisms.

Previous studies have revealed genetic correlations between AD and major psychiatric disorders including MDD, SCZ, and BD, as well as between DLB and SCZ (genetic correlation coefficient, approximately 0.10–0.26) (Reynolds et al., 2023; Wingo et al., 2022). Moreover, psychiatric symptoms within AD appear partially heritable, suggesting that behavioural and psychological symptoms of dementia (BPSD) may reflect underlying genetic liability (Antonsdottir et al., 2024; DeMichele-Sweet et al., 2018, 2021).

Polygenic risk scores (PRS), which aggregate common genetic variants associated with a given trait, provide a means of quantify inherited liability. Previous studies link PRS for schizophrenia to higher negative/disorganized symptoms in individuals with a history of psychotic episodes (Ahangari et al., 2023) and more psychotic episodes, suicide attempts and anhedonia in patients with BD (Coombes et al., 2020). However, the extent to which genetic liability for psychiatric disorders influence neuropsychiatric symptom profiles in dementia remains largely unexplored, particularly across dementia subtypes.

Given that psychiatric and dementia disorders show genetic overlap, we hypothesize that higher PRS for MDD, BD, SCZ, and autism spectrum disorder (ASD) are associated with greater neuropsychiatric burden in dementia. To test this, we assessed associations between psychiatric PRS and symptom severity measured by the Neuropsychiatric Inventory (NPI) and the Geriatric Depression Scale (GDS) in five European cohorts followed by meta-analyses. Elucidating the contribution of psychiatric genetic liability to neuropsychiatric symptom profiles in dementia could enhance clinical diagnostic precision, aid in prognostic stratification, and support the development of individualized management strategies to reduce symptom burden.

Material and methods

Study population

We analysed data from five European cohorts (Figure 1): (1) Amsterdam dementia cohort (ADC), conducted in Amsterdam, the Netherlands (van der Flier et al., 2014; van der Flier & Scheltens, 2018; (2) the GR@ACE cohort (Genome Research at Ace Alzheimer Center Barcelona), which comprises patients across the dementia continuum as well as cognitively healthy controls evaluated at the Ace Alzheimer Center memory clinic in Barcelona (de Rojas et al., 2021; Moreno-Grau et al., 2019; Ruiz et al., 2014); (3), the DZNE-Longitudinal Cognitive Impairment and Dementia (DELCODE) study, conducted across sites in Germany (Jessen et al., 2018); (4) the Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe), based in Germany (Jessen et al., 2011); and (5) Dementia Competence Network (DCN), also based in Germany (Kornhuber et al., 2009).

The ADC and GR@ACE cohorts included individuals diagnosed with AD, DLB or FTD, while DELCODE, AgeCoDe, and DCN focused on individuals with AD. All diagnoses were made using standard clinical criteria (see Supplementary Table 1).

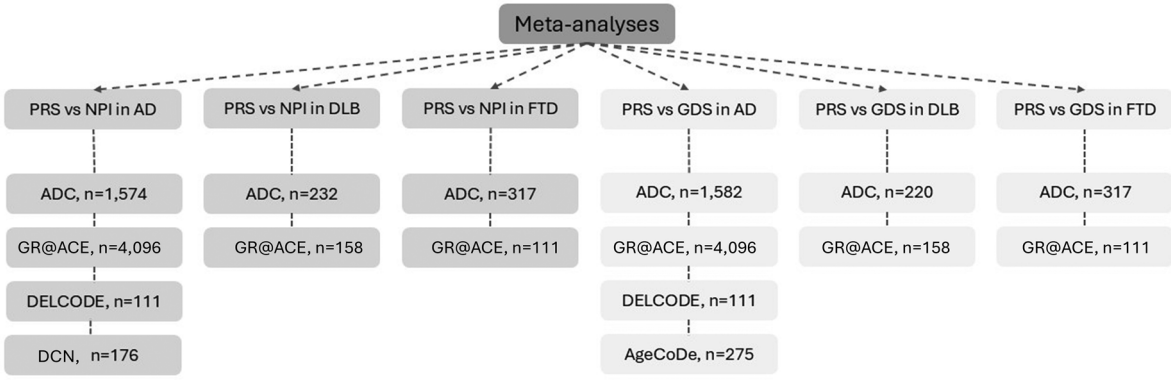

Figure 1. Structure of meta-analyses examining association between polygenic risk scores (PRS) for psychiatric disorders and symptom severity in dementia. The figure illustrates the organization of meta-analyses conducted across five European cohorts (Amsterdam Dementia Cohort [ADC], Genome Research at Ace Alzheimer Center Barcelona [GR@ACE], the DZNE-Longitudinal Cognitie Impairment and Dementia [DELCODE], the Ageing, Cognition and Dementia in Primary Care Patients [AgeCoDe]), and Dementia Competence Network (DCN) stratified by outcome (Neuropsychiatric Inventory [NPI] and Geriatric Depression Scale [GDS]) and dementia subtype (Alzheimer's disease [AD], dementia with Lewy bodies [DLB], and frontotemporal dementia [FTD]). Each cohort contributed data where phenotype availability allowed. All analyses were performed separately within cohorts and subsequently meta-analysed using random-effects models.

For all participating cohorts, the study was approved by the local medical ethics committee and all subjects (or their legal representatives) provided written informed consent for participation in clinical and genetic studies.

Neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed as part of clinical workup, using the Neuropsychiatric Inventory 12-items (NPI-12) (Cummings et al., 1994; Kaufer et al., 2000) (for ADC, DELCODE and DCN), the brief version NPI-Q (Boada et al., 2002; Kaufer et al., 2000) (for GR@ACE) and the Geriatric Depression scale 15-item version (GDS-15) (Sheikh & Yesavage, 1986; Yesavage et al., 1982). In our study, we used the Dutch (for the Netherlands), Spanish (for Spain), and German (for Germany) language versions of the NPI, provided by the Mapi Research Trust (Neuropsychiatric Inventory Questionnaire, 2025), as well as language validated versions of the GDS for all three countries (Bleeker et al., 1985; Fernández-San Martín et al., 2002; Gauggel & Birkner, 1999).

The NPI-12 and NPI-Q include 12 symptom domains: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, nighttime disturbances, and appetite/eating disturbances. Frequency (0–4 points, only for NPI-12) and severity (0–3 points, for both NPI-12 and NPI-Q) of the domains were scored by a close informant. For the NPI-12, the composite NPI score (C-NPI-12) was calculated by summing the product of frequency and severity for each domain (ie sum of frequency x severity for all domains, resulting in scores 0,1,2,3,4,6,8,9, or 12) (Cummings et al., 1994; Wright et al., 2023). For the NPI-Q, the composite NPI-score (C-NPI-Q) was calculated by summing the severity scores (Boada et al., 2002). Given the skewed distribution of the residuals in the linear regressions of PRS and C-NPI, a final logarithm-transformed variable was created. To ensure compatibility across results on C-NPI-12 and C-NPI-Q scales, C-NPI scores were standardized (mean = 0, $SD = 1$).

The GDS-15 is a self-report scale that includes 15 yes/no questions to assess depressive symptoms among older individuals (Wright et al., 2023; Yesavage et al., 1982). GDS-15 was used as a continuous variable. However, as the distribution of the residuals in the linear regression of PRS and GDS-15 was skewed, the variable was logarithm-transformed.

Genetic analyses and polygenic risk scores (PRS)

Genetic variants were determined by standard genotyping and imputation methods, using TOPMED as reference panel, as described previously (Bellenguez et al., 2022; de Rojas et al., 2021; Moreno-Grau et al., 2019; Tesi et al., 2024).

PRS for MDD, BD, SCZ, and ASD were created using the most recent or largest GWAS, including Wray et al. (2018) for MDD-PRS (n cases = 135,458, n controls = 344,901) (Wray et al., 2018), Mullins

et al. (2021) for BD-PRS (*n* cases = 25,060, *n* controls = 449,978) (Mullins et al., 2021), Trubetskoy et al. (2022) for SCZ-PRS (*n* cases = 74,776, *n* controls = 101,023) (Trubetskoy et al., 2022), and Grove et al. (2019) for ASD-PRS (*n* cases = 13,076, *n* controls = 22,664) (Grove et al., 2019). As all GWASs were in build GRCh37 (hg19), we used R package liftOver and University of California (UCSC) chain file to transform coordinates of the summary statistics from hg19 to genotyped coordinates of hg38 (Murphy et al., 2025).

We created PRS using LDpred2 to capture the polygenic nature of the trait (Ni et al., 2021; Privé et al., 2021). LDpred2 PRS were computed using the R package bigsnpr (version 1.4.7), with the approach of a Genome Wide bed file and the infinitesimal model. In short, LDpred2 uses a Bayesian approach to calculate a posterior mean effect size for each SNP based on prior GWAS effect sizes followed by shrinkage using Linkage Disequilibrium (LD) information (Privé et al., 2021). Also, we used a set of HapMap3 SNPs (including 1,054,330 variants) in order to get adequate coverage of the genome, as recommended by the LDpred2 authors (Privé et al., 2021). All PRS were standardized (mean = 0, $SD = 1$).

Statistical analysis

Each cohort conducted independent statistical analyses examining the association between PRS for psychiatric disorders and neuropsychiatric symptom severity. Analyses were stratified by dementia subtype (AD, DLB, FTD). Linear regressions were used to assess the relationship between each PRS (MDD-PRS, BD-PRS, SCZ-PRS, and ASD-PRS) and symptom scores (NPI or GDS), adjusting for age, sex, and population stratification (PC1–PC3). Results are reported as beta coefficient (β), standard errors (SE), and *p* values.

To synthesize findings across cohorts, we conducted random-effects meta-analyses using the metafor package in R. The effect size (β) and SE from each cohort were meta-analysed separately for each PRS-outcome combination and dementia subtype (Supplementary Figure 1). Between-study heterogeneity was assessed using Cochran's Q statistics and the I^2 index, which quantifies the proportion of total variability due to heterogeneity rather than chance, as well as the τ^2, which represents the estimated variance of true effect sizes across studies. A random-effect model was chosen to account for potential heterogeneity in cohort design, recruitment, and assessment procedures. While prior studies have demonstrated a strong correlation between C-NPI-12 and C-NPI-Q scores (interscale correlation = 0.91) (Kaufer et al., 2000), meta-analyses were performed including and excluding the GR@ACE cohort to assess the influence of C-NPI-Q on the results.

Multiple testing correction was addressed using false discovery rate (FDR). A fdr < 0.05 was considered significant.

Results

Demographics and severity of neuropsychiatric symptoms

Demographic characteristics and severity of neuropsychiatric symptoms for each dementia subtype across five European cohorts are presented in Table 1. For the NPI analyses, 5957 AD cases, 390 DLB cases, and 428 FTD cases were included (Figure 1). For the GDS analyses, the corresponding numbers were 6064 AD cases, 378 DLB cases, and 428 FTD cases.

PRS and NPI

In FTD, higher SCZ-PRS was associated with lower NPI total scores in meta-analyses (β = −0.12, $p = .001$, pfdr = 0.02, Figure 2).

No other psychiatric PRS showed association with NPI in AD, FTD, or DLB in either cohort-specific or in meta-analytic models (Supplementary Table 2, Figure 2). Findings from meta-analyses including both C-NPI-12 and C-NPI-Q scores were similar to those based on C-NPI-12 scores alone (Supplementary Figure 1).

PRS and GDS

No association was observed between PRS for psychiatric disorders and GDS scores in either cohort-specific or in meta-analytic models (Figure 3, Supplementary Table 3).

Discussion

In this multi-cohort study, we investigated whether PRS for psychiatric disorders are associated with neuropsychiatric symptom burden across AD, DLB, and FTD. In meta-analyses of FTD cases from the ADC and GR@ACE cohorts, higher genetic liability for SCZ was associated with fewer neuropsychiatric symptoms. No significant associations were observed between psychiatric PRS and neuropsychiatric symptoms in AD and DLB.

Table 1. Sample characteristics by dementia subtype in five European cohorts.

	Alzheimer's disease, *N* = 6064	Dementia with Lewy bodies, *N* = 390	Frontotemporal dementia, *N* = 428
Amsterdam dementia cohort (ADC)			
N = 2131	*n* = 1582	*n* = 232	*n* = 317
Age (mean, *SD*)	65.84 (7.95)	68.83 (6.74)	63.38 (8.06)
Sex (% female, *n*)	52.38% (981)	17.83% (46)	39.74% (155)
APOE ϵ4 (% homozygote, *n*)	21.21% (397)	12.45% (32)	3.35% (13)
NPI-12, median (min, max)	8 (0, 76)	12 (0, 91)	15 (0, 85)
GDS-15, median (min, max)	3 (0, 15)	3 (0, 15)	3 (0, 14)
GR@ACE (Genome Research at Ace Alzheimer Center Barcelona)			
N = 8169	*n* = 4096	*n* = 158	*n* = 111
Age (mean, *SD*)	82.35 (7.61)	81.94 (7.12)	75.81 (9.52)
Sex (% female, *n*)	71.98% (2946)	62.66% (99)	54.95% (61)
APOE ϵ4 (% homozygote, *n*)	5.20% (213)	1.27% (2)	1.80% (2)
NPI-Q, median (min, max)	4 (0, 18)	5 (0, 17)	5 (0, 19)
GDS-15, median (min, max)	5 (1, 7)	5 (4, 7)	5 (1, 7)
The DZNE-Longitudinal Cognitive Impairment and Dementia (DELCODE)			
N = 323	*n* = 111	–	–
Age (mean, *SD*)	75.02 (6.19)	–	–
Sex (% female, *n*)	56.76% (63)	–	–
APOE ϵ4 (% homozygote, *n*)	18.92% (21)	–	–
NPI-12, median (min, max)	3 (0, 18)	–	–
GDS-15, median (min, max)	2 (0, 10)	–	–
The Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe)			
N = 2517	*n* = 275	–	–
Age, mean (*SD*)	86.73 (4.51)	–	–
Sex, % female (*n*)	75.27% (207)	–	–
APOE ϵ4, % homozygote (*n*)	1.48% (4)	–	–
NPI-12, median (min, max)	–	–	–
GDS-15, median (min, max)	3 (0, 14)	–	–
German Research Network on Dementia (DCN)			
N = 176	*n* = 176	–	–
Age, mean (*SD*)	72.12 (8.03)	–	—
Sex, % female (*n*)	61.4 (108)	–	–
APOE ϵ4, % homozygote (*n*)	16.79 (22)	–	—
NPI-12, median (min, max)	4 (0, 42)	–	–
GDS-15, median (min, max)	–	–	–

Note: SD: standard deviation; *APOE ϵ4*:*Apolipoprotein E epsilon 4*; NPI-12: total 12-item Neuropsychiatric Inventory score (sum of frequency*severity across 12 domains); NPI-Q: total Neuropsychiatric Inventory score, brief version (sum of severity across 12 domains); GDS-15: Geriatric Depression Scale total score (15-item version).

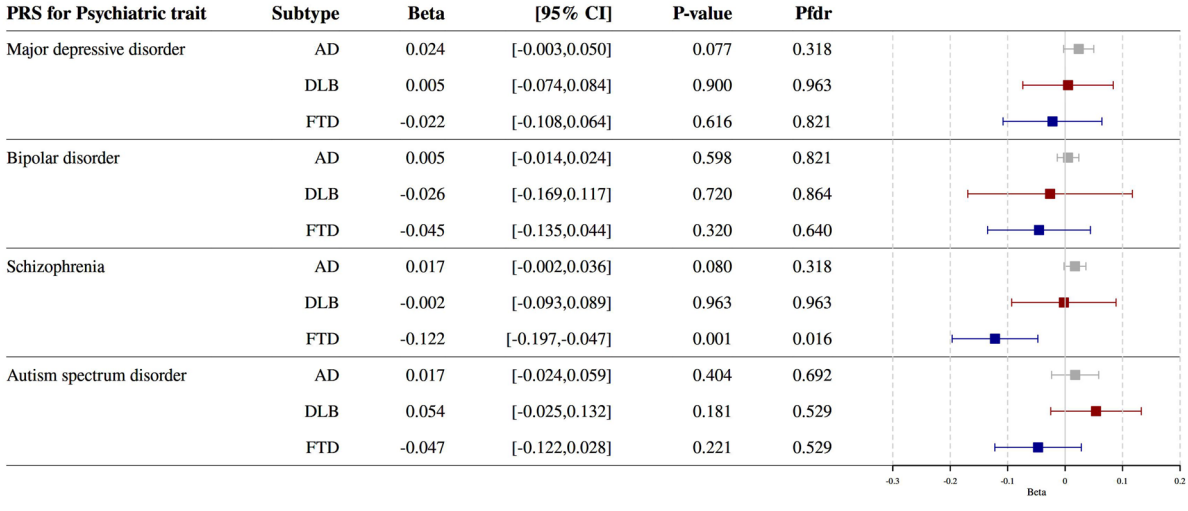

Figure 2. Meta-analyses of psychiatric polygenic risk scores (PRS) in relation to total Neuropsychiatric Inventory (NPI) scores across dementia subtypes (Alzheimer's disease [AD], dementia with Lewy bodies [DLB], and frontotemporal dementia [FTD]). The C-NPI-12 score was log-transformed and calculated as sum of frequency*severity across 12 domains, and the C-NPI-Q was log-transformed and calculated as the sum of severity across 12 domains. To ensure compatibility across C-NPI-12 and C-NPI-Q scores, C-NPI scores were standardized. Forest plot showing the meta-analytic estimates (beta coefficient and 95% confidence intervals [CI]) across for the association between PRS and NPI. Multiple testing correction was addressed using false discovery rate (FDR). A pfdr < 0.05 was considered significant.

PRS for Psychiatric trait	Subtype	Beta	[95% CI]	P-value	Pfdr
Major depressive disorder	AD	0.006	[-0.032,0.043]	0.766	0.919
	DLB	-0.031	[-0.106,0.045]	0.421	0.866
	FTD	0.008	[-0.022,0.038]	0.615	0.866
Bipolar disorder	AD	-0.000	[-0.005,0.005]	0.986	0.986
	DLB	-0.012	[-0.034,0.010]	0.271	0.866
	FTD	0.015	[-0.020,0.051]	0.389	0.866
Schizophrenia	AD	0.002	[-0.005,0.009]	0.649	0.866
	DLB	-0.008	[-0.029,0.014]	0.485	0.866
	FTD	-0.024	[-0.121,0.072]	0.619	0.866
Autism spectrum disorder	AD	0.010	[-0.015,0.034]	0.440	0.866
	DLB	-0.001	[-0.022,0.021]	0.961	0.986
	FTD	-0.010	[-0.040,0.020]	0.509	0.866

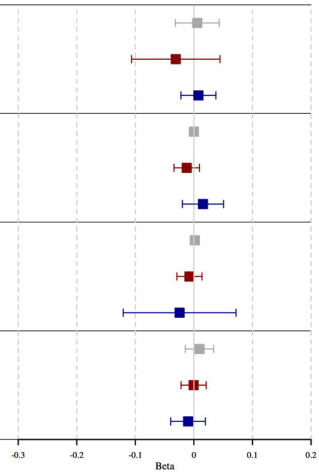

Figure 3. Meta-analyses of psychiatric polygenic risk scores (PRS) in relation to Geriatric Depression Scale (GDS) scores across dementia subtypes (Alzheimer's disease [AD], dementia with Lewy bodies [DLB], and frontotemporal dementia [FTD]). The GDS was based on the total score of the 15-item version and log-transformed. Forest plot showing the meta-analytic estimates (beta coefficient and 95% confidence intervals [CI]) across for the association between PRS and GDS. Multiple testing correction was addressed using false discovery rate (FDR). A pfdr < 0.05 was considered significant.

Studies on the genetic overlap between neurodegenerative and neuropsychiatric disorders have been inconsistent, with some studies reporting genetic overlap between the traits (Drange et al., 2019; Monereo-Sánchez et al., 2021; Reynolds et al., 2023), and others finding little to no overlap (Brainstorm Consortium et al., 2018; Gibson et al., 2017). Explanations for this may be assigned to the power of the used (discovery) summary statistics and (target) cohort, but also to the approach used to assess genetic overlap. For instance, methods incorporating the global (poly)genetic architecture of traits, such as PRS (Gibson et al., 2017) (and global genetic correlation methods; Brainstorm Consortium et al., 2018), may be less likely to detect genetic overlap between traits, possibly due to insufficient power to detect localized genetic effects when averaged across the entire genome. In contrast, methods that focus on overlap with specific local genetic regions may be more sensitive to the detection of shared genetic architecture (Monereo-Sánchez et al., 2021; Reynolds et al., 2023), especially for highly polygenic traits such as neuropsychiatric disorders and traits, but also for bidirectional local genetic effects where one region increases risk for one trait and decreases risk for the other trait (Zhang et al., 2021).

Another explanation is the phenotypic outcome. Previous studies have reported that higher MDD-PRS associate with increased risk for a depression diagnosis in AD (Upadhya et al., 2022), and that higher SCZ-PRS/BP-PRS associate with psychosis in AD (Ahangari et al., 2023). In our study this association in AD was nominally significant in the previously reported direction, with a higher MDD-PRS associating with higher NPI scores. Notably, we did not find any association between psychiatric PRS and GDS scores in dementia, possibly reflecting measurement limitations of GDS-15 in individuals with dementia. For instance, the GDS relies on self-report, and its validity may therefore be reduced in patients with cognitive impairment and anosognosia, which are common in dementia, potentially obscuring true associations (Gilley & Wilson, 1997). Another possibility is that the genetic liability for MDD reflects a broader vulnerability to affective and behavioural dysregulation, which in context of dementia may manifest more clearly through caregiver-observed NPI symptoms such as anxiety, irritability, or agitation, rather than self-reported depressive mood.

Our finding that higher SCZ-PRS was associated with fewer neuropsychiatric symptoms in FTD is contrary to our original hypothesis. We anticipated that higher genetic liability for psychiatric disorders would be associated with more neuropsychiatric symptoms. Instead, this inverse association suggests a more complex relation between genetic risk and symptom expression. One possibility is that schizophrenia-related polygenic architecture influences neural development in ways that, in later life, it may buffer against neuropsychiatric symptom expression in the context of neurodegeneration. Another possibility is that individuals with higher genetic risk for SCZ may exhibit longstanding, premorbid, negative traits– such as social withdrawal or emotional blunting – that could result

in fewer observable behavioural changes and therefore lower NPI scores. In support of this, one previous UK Biobank study showed that higher SCZ-PRS was associated with negative behavioural traits in the general population without history of SCZ or related disorders (Socrates et al., 2021).

To our knowledge, no previous study has demonstrated an association between SCZ-PRS and total neuropsychiatric symptom burden in FTD. A related but distinct finding has been reported in a large study of psychosis in AD: higher SCZ-PRS was associated with reduced risk of psychosis, an effect replicated in an independent sample (DeMichele-Sweet et al., 2018). Unlike our study, the previous report focused specifically on psychotic symptoms rather than the broader range neuropsychiatric features. Nonetheless, the authors proposed that schizophrenia risk variants may exert different effects depending on neurodevelopmental timing, disease context, and brain health – potentially acting as protective factors in the setting of an active neurodegenerative process (DeMichele-Sweet et al., 2018). Moreover, such variants may serve as expression quantitative trait loci (eQTLs) for multiple genes, influencing complex molecular cascades that differ between psychiatric and neurodegenerative disorders (DeMichele-Sweet et al., 2018). Our findings extend this framework, suggesting that polygenic risk for psychiatric disorders may influence dementia phenotypes in domain- and subtype-specific manners.

This study has several limitations. First, psychiatric symptom burden in dementia likely reflects a complex interplay of genetic, neurobiological, and environmental factors, of which PRS capture only a small fraction. Second, differences in recruitment setting, clinical characteristics, and demographics across cohorts may have introduced heterogeneity. Third, symptom burden was assessed using composite scores (eg total NPI-12, NPI-Q and GDS), which may obscure symptom-specific associations. In addition, while the NPI is more suitable for dementia populations compared to the GDS, its scoring irregularities and skewed distributions can complicate statistical modelling (Cummings et al., 1994; Lai, 2014), even when addressed though log transformation. Moreover, cohorts differed in the NPI instrument used (ie C-NPI-12 for ADC, DELCODE and DCN and C-NPI-Q for GR@ACE). Although meta-analysis results including and excluding the NPI-Q results were consistent, the use of different NPI instruments could have introduced measurement bias. Fourth, symptom assessment was cross-sectional, limiting our ability to capture fluctuation in neuropsychiatric symptoms over time. This may have reduced the sensitivity to detect associations with stable genetic risk. Future studies should include large, deeply phenotyped cohorts with longitudinal symptom assessments to replicate and extend these findings.

In conclusion, this is the first study to demonstrate that higher genetic liability for schizophrenia was associated with lower burden in frontotemporal dementia. This finding highlights the need for further research into the role of psychiatric polygenic risk in shaping dementia phenotypes, potentially informing future strategies for symptom prediction and personalized care.

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Data availability statement

The individual-level data used in this study are subject to ethical and legal restrictions but may be shared upon request and in line with GDPR and institutional policies.

Declaration of AI use

The authors used ChatGPT (OpenAI, San Francisco, USA) to assist primarily with coding and analysis support, and in some instances to improve the clarity of the language. All content was checked and verified by the authors.

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