Assessing the association between global structural brain age and polygenic risk for schizophrenia in early adulthood: a recall-by-genotype study

Constantinos Constantinides [1], Vilte Baltramonaityte [1], Doretta Caramaschi [2], Laura K.M. Han [3,4], Thomas M Lancaster [1], Stanley Zammit [5,6], Tom P Freeman [7], Esther Walton [1 *]

[1] Department of Psychology, University of Bath, UK
[2] Department of Psychology, Faculty of Health and Life Sciences, University of Exeter, UK
[3] Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia
[4] Orygen, Parkville, Australia
[5] MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, UK
[6] Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[7] Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath, UK

* Correspondence to:

Esther Walton, PhD
Department of Psychology, University of Bath, UK
Email address: E.Walton@bath.ac.uk
Telephone/fax: +44 (0) 1225 386563
Postal address: Claverton Down Campus, BA2 7AY, Bath, United Kingdom

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Abstract

Neuroimaging studies consistently show advanced brain age in schizophrenia, suggesting that brain structure is often 'older' than expected at a given chronological age. Whether advanced brain age is linked to genetic liability for schizophrenia remains unclear. In this pre-registered secondary data analysis, we utilised a recall-by-genotype approach applied to a population-based subsample from the Avon Longitudinal Study of Parents and Children to assess brain age differences between young adults aged 21-24 years with relatively high (n=96) and low (n=93) polygenic risk for schizophrenia (SCZ-PRS). A global index of brain age (or brain-predicted age) was estimated using a publicly available machine learning model previously trained on a combination of region-wise gray-matter measures, including cortical thickness, surface area and subcortical volumes derived from T1-weighted magnetic resonance imaging (MRI) scans. We found no difference in mean brain-PAD (the difference between brain-predicted age and chronological age) between the high- and low- SCZ-PRS groups, controlling for the effects of sex and age at time of scanning (b = - 0.21; 95% CI -2.00, 1.58; p = 0.82; Cohen's *d* = - 0.03; partial R^2 = 0.00029). These findings do not support an association between SCZ-PRS and brain-PAD based on global age-related structural brain patterns, suggesting that brain age may not be a vulnerability marker of common genetic risk for SCZ. Future studies with larger samples and multimodal brain age measures could further investigate global or localised effects of SCZ-PRS.

1. Introduction

Schizophrenia (SCZ) is a highly heritable (h^2 ~ 80%) psychiatric disorder associated with substantial functional impairment, high prevalence of age-related diseases (including cardiometabolic disease and dementia), and an average decrease in life expectancy of approximately 15 years (Correll et al. 2017; Hjorthøj et al. 2017; Mitchell et al. 2013; Stroup et al. 2021; Sullivan, Kendler, and Neale 2003; Weye et al. 2020). The increased risk of age-related comorbidities and shortened lifespan in SCZ may partly be explained by "accelerated" ageing of the body and brain (Dieset, Andreassen, and Haukvik 2016; Kirkpatrick et al. 2008; Kirkpatrick and Kennedy 2018). In keeping with this hypothesis, neuroimaging studies provide robust evidence for advanced biological age of the brain in people with SCZ (Blake et al. 2023; Constantinides et al. 2022; Kaufmann et al. 2019). However, whether apparent advanced brain ageing is linked to genetic liability for schizophrenia in young people remains unclear. Symptoms of SCZ typically start in late adolescence or early adulthood and structural brain alterations in patients persist - or even increase - with age (van Erp et al., 2016; 2018; Cropley et al., 2019). Despite this apparent neurodegenerative profile, several studies have instead suggested a neurodevelopmental origin of SCZ and a role of early-life risk factors for disease aetiology (Owen and O' Donovan, 2017; Murray et al, 2017). Similarly, ageing is often considered in the context of old age and degeneration, when it is equally possible that ageing lies on a continuum with developmental processes that start at birth (Cohen et al., 2020; Kinzina et al., 2019). In this case, and considering the large genetic component of SCZ, it is plausible that a link between genetic liability for schizophrenia and advanced brain ageing could emerge earlier in development in at-risk populations and before disease onset."

Using structural magnetic resonance imaging (sMRI), it is possible to estimate the underlying biological age of the brain via supervised machine learning (Cole and Franke 2017; Franke et al., 2010). Brain age (or brain-predicted age) can differ from actual chronological age, and the discrepancy between the two is captured by the brain-predicted age difference (brain-PAD; also known as brain age gap). While the interpretation of brain-PAD is complex (Vidal-Pineiro et al., 2021), a brain-PAD greater than zero indicates a brain that appears 'older' than the person's chronological age, and thus may be interpreted as 'advanced' brain ageing, whereas a brain-PAD lower than zero reflects a brain 'younger' than expected at a given chronological age (i.e., "delayed" brain ageing) (Franke and Gaser 2019). Higher brain-PAD scores have been associated with a range of health-related factors and outcomes, including smoking, higher alcohol intake, blood pressure, obesity (or higher BMI), diabetes, dementia, major depression, and mortality (Ning et al., 2021; Bøstrand et al., 2022; Kolbeinsson et al., 2020; Kaufmann et al., 2019; Han et al., 2022; Cole et al., 2018). Hence, brain-PAD may be a marker of overall brain health (Baecker et al., 2021).

We recently showed a greater brain-PAD in SCZ relative to controls in a multi-cohort study (mean difference in brain-PAD of 3.55 years after adjusting for age, sex, and scanning site) (Constantinides et al., 2022), in line with previous work (Demro et al., 2022; Kaufmann et al.,2019; Koutsouleris et al, 2014; Nenadić et al., 2017). A greater brain-PAD was also observed in adolescents and young adults with SCZ (Truelove-Hill et al., 2020) or at high risk for psychosis (Chung et al., 2018; Koutsouleris et al., 2014), and in first-episode patients (Hajek et al., 2019). Importantly, cross-sectional studies did not find evidence for an association between illness duration and brain-PAD among people with SCZ or closely related disorders (Constantinides et al., 2022, Demro et al., 2022; Koutsouleris et al., 2014), and longitudinal data indicate that this gap widens predominantly during the first few years after illness onset before stabilising (Demro et al.,

2022; Schnack et al., 2016). Taken together, research to date suggests that advanced brain age in schizophrenia may partly reflect deviations from typical neuromaturation trajectories.

Single nucleotide polymorphism-based heritability (h_{SNP}^2) estimates for schizophrenia indicate that approximately a quarter of the liability to the disorder is explained by common variants, each conferring a small increase in risk. Genome-wide association studies (GWAS) have identified hundreds of such variants to date, with the latest study implicating 287 genetic loci in SCZ (PGC wave 3; Trubetskoy et al., 2022). The cumulative effect of these variants can be summarised into a polygenic risk score that estimates an individual's genetic liability to schizophrenia (SCZ-PRS) as conferred by common frequency alleles (Choi, Mak, and O'Reilly, 2020). Variation in SCZ-PRS in the general population has been associated with phenotypes of brain morphometry previously implicated in schizophrenia, including global and regional reductions in cortical thickness and subcortical structures, possibly reflecting vulnerability to the disorder (Neilson et al., 2019; Stauffer et al., 2021; Jammei et al., 2023)

Studies of the genetic architecture of brain age suggest that brain-PAD is moderately heritable ($h^2 \geq 0.5$; $h_{SNP}^2 = 0.24$) (Cole et al., 2017; Kaufmann et al., 2019), with implicated genes overlapping with those previously linked to SCZ (Kaufmann et al., 2019). Moreover, a recent study found an association between SCZ-PRS and brain-PAD in a clinical sample of individuals with SCZ and controls aged 16-67 years (Teeuw et al., 2021). However, this association was no longer significant after adjusting for disease status, possibly reflecting downstream effects of the disorder or confounding factors. In the current study, we aimed to examine whether brain-PAD is associated with polygenic liability for SCZ, as assessed in a population-based sample of young adults aged 21-24 years. The study utilised a recall-by-genotype (RbG) design, which increases variance in SCZ-PRS by sampling participants from the tails of the genotypic distribution (i.e., with either

extremely high- or low- SCZ-PRS), while minimising problems with reverse causation that often exist in clinical samples (Corbin et al., 2018; Lancaster et al., 2019). In our prospectively registered Open Science Framework secondary data analysis (https://osf.io/hrka4), we hypothesised a greater brain-PAD score in the high SCZ-PRS group relative to the low SCZ-PRS group. Evidence for an association between SCZ-PRS and brain-PAD in young individuals recruited from the general (largely unaffected) population could reflect a contribution of common genetic risk for SCZ to brain-PAD, rather than brain-PAD being shaped by the potential effects of disorder pathophysiology or medication. In addition, we conducted exploratory analyses of associations between brain-PAD and other risk factors or co-occurring phenotypes relevant to schizophrenia (e.g., birth weight, BMI, depressive/emotional symptoms) and whether SCZ-PRS might moderate those associations.

2. Methods

2.1 Study population and SCZ-PRS stratification

We used data from the Avon longitudinal Study of Parents and Children (ALSPAC) SCZ-RbG sub-study (high SCZ-PRS vs. low SCZ-PRS), which was previously established to investigate the effects of genetic variants contributing to SCZ on brain developmental and behavioural outcomes (Lancaster et al, 2019; Sharp et al, 2020). This recall-by-genotype (RbG) neuroimaging study is nested within ALSPAC, a population-based cohort established to identify factors influencing child health and developmental outcomes. Briefly, the broader ALSPAC study originally invited pregnant women residing in Avon (South-West England) with expected delivery dates between 1st April 1991 and 31st December 1992. The initial number of pregnancies enrolled was 14,541, resulting in 13,988 children who were alive at 1 year of age. The phases of enrolment and study representativeness are described in more detail in the cohort profile paper and its updates (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019).

Following genotyping of most participants within ALSPAC and subsequent quality control of raw genome-wide data, a sub-sample of 8,365 children underwent SCZ-PRS estimation following a normal distribution (Lancaster et al., 2019). Construction of the SCZ-PRS followed the methods described by the International Schizophrenia Consortium (2009), using summary data from the largest discovery SCZ-GWAS of the Psychiatric Genomics Consortium (PGC-SCZ wave-2; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) available at the time of participant recruitment. A polygenic score was individually calculated using the "score" command in PLINK (version 1.07; Purcell et al., 2017). SCZ-PRS was created by summing the number of risk alleles present for each single nucleotide polymorphism (SNP; i.e., 0, 1, or 2) weighted by the logarithm of each SNP's odds ratio for SCZ from the PGC GWAS summary statistics. This was based upon a PRS generated from SNPs with a GWAS training set $P \leq 0.05$ threshold, as it captured the maximum SCZ liability in the primary PRS analysis of the PGC-SCZ GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). To recruit a target of 100 sex-matched participants from each tail of the SCZ-PRS distribution of the genotyped population (N=8365) for a multi-modal imaging sub-study, the ALSPAC team sent out 1,241 invitations in total (470 to the 'low' and 771 to the 'high' SCZ-PRS group). Individuals were excluded if they were receiving any psychotropic medication. A total of 197 individuals from either tail of the SCZ-PRS distribution (99 with low SCZ-PRS and 98 with high SCZ-PRS) were originally enrolled in the imaging sub-study (see Fig. 1 in Lancaster et al., 2019). Due to a lower response rate among high SCZ-PRS individuals, the recruited low- and high- SCZ-PRS groups were mostly within the lowest 5th and highest 10th percentiles of the genotyped ALSPAC sample, respectively. On average, there was approximately a 3 standard deviations difference in SCZ-PRS between the two groups (mean Z-score = -1.71 [range: -0.51 - (-3.27)] for low SCZ-PRS; mean Z-score = + 1.42 [range: 0.52 - 3.40] for high SCZ-PRS), making them highly distinct from each other. Further details about the SCZ-RbG sample (including genotyping and quality control) can be found in the sample description (Lancaster et al., 2019; Sharp et al., 2020) and in subsequent publications (Dimitriades

et al., 2021; 2023; Lancaster et al., 2021). For the current analysis we excluded a small number of participants from the original RbG sample, mostly due to failed quality control of image processing (see next subsection for details), leaving a total of 93 participants with low SCZ-PRS and 96 with high-SCZ-PRS (N=189). All participants were aged between 21-24 years at the time of scanning.

The ALSPAC website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (https://www.bristol.ac.uk/alspac/researchers/our-data/). Study data gathered from participants at age 22 and onwards was collected and managed using REDCap electronic data capture tools hosted at the University of Bristol (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees (listed at http://www.bristol.ac.uk/alspac/researchers/research-ethics/). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendation of the ALSPAC Ethics and Law Committee at the time. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

2.2. Structural image acquisition and processing

Structural MRI scans were acquired for each participant using a 3T GT HDx system at Cardiff University Brain Research Imaging Centre (CUBRIC), Cardiff, UK. High-resolution 3-dimensional T1-weighted images were acquired using a 3-dimensional fast spoiled gradient echo sequence (FSPGR) with contiguous sagittal slices of 1mm thickness (TR=7.9s, TE=3.0 ms, TI= 450ms, flip angle 20º, FOV = 256mm X 256mm X 176mm to yield 1mm isotropic voxel resolution images) (Lancaster et al., 2019). In the current study, we relied on the image-derived phenotypes extracted centrally by the researchers involved in the ALSPAC neuroimaging resource initiative, which are

available via the variable search tool (http://variables.alspac.bris.ac.uk/; Sharp et al., 2020). Briefly, T1-weighted images were processed using FreeSurfer (version 6.0.0) to extract cortical and subcortical measures from multiple regions of interest (ROIs) based on the Desikan-Killiany atlas and Aseg atlas (Fischl 2012). Reconstructed images and their cortical and subcortical parcellations/segmentations underwent quality control following standardised protocols developed by the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Each T1-weighted MRI scan was segmented and parcellated bilaterally into volumes for 7 subcortical gray-matter regions (left and right nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus) and 2 lateral ventricles, 34 regional cortical thickness (2 x 34) and cortical surface area (2 x 34) measures, and total intracranial volume (ICV; $N_{measures}$ = 153). Out of 197 RbG participants, two had missing values in SCZ-PRS status (n=1) or all Freesurfer measures (n=1; possibly due to failed image reconstruction) and thus were excluded from the current analyses. Six participants were further excluded due to failed quality control for cortical parcellation and/or subcortical segmentation. Further details on image processing and quality control can be found in the relevant data note by Sharp et al., 2020.

2.4. Brain age prediction

To predict brain age in the current sample we primarily used the publicly available ENIGMA brain age model (Han et al. 2020; https://www.photon-ai.com/enigma_brainage), which has been independently validated in previous brain age studies covering almost the entire adult lifespan (Clausen et al., 2022; Constantinides et al., 2022; Han et al., 2022, Abram et al., 2023). The model was trained separately in 952 male and 1,236 female healthy controls aged 18–75 years from the ENIGMA-MDD consortium, using ridge regression. FreeSurfer measures from the left and right hemispheres were combined by calculating the mean ((left + right)/2)) of volumes for subcortical regions (n=7), lateral ventricles (n=1), and thickness (n=34) and surface area (n=34) for cortical regions, and ICV, resulting in a total of 77 input features for brain age prediction (Han et al., 2020).

In addition to our pre-registered plan to use the ENIGMA model, and to assess the robustness of our primary results, we also applied an age group-specific brain age model developed by the CentileBrain team (https://centilebrain.org; manuscript in preparation), which was trained for the age range 20 to 30 years (see supplementary material A2 for more details). The parameters of the pre-trained sex-specific brain age model(s) were applied individually to each participant within the current sample. Importantly, the current sample was not included in the training sets for any of the two models. To assess model generalisation performance in the current sample, we calculated the (1) mean absolute error (MAE) between predicted brain age and chronological age, the (2) Pearson correlation coefficients between predicted brain age and chronological age (r), and (3) the proportion of chronological age variance explained by the model predictions (R^2). These metrics were calculated and reported with respect to sex and SCZ-PRS group. Global (i.e., whole-brain) brain-PAD was then calculated for each participant by subtracting chronological age from brain age (i.e., brain-based predicted age minus chronological age).

2.4. Brain age bias adjustment

There is a well-described age-related bias inherent to the 'brain age' prediction framework, where brain age is overestimated in younger individuals and underestimated in older individuals, relative to the age distribution of the training data, and most accurately estimated for individuals with an age closer to the average age of the training data (de Lange et al., 2022; Le et al., 2018; Liang, Zhang, and Niu 2019; Smith et al., 2019). Several bias-adjustment procedures have been developed to account for this chronological age dependency (for an overview, see de Lange and Cole 2020). Unless otherwise specified, here we added chronological age as a covariate in subsequent statistical analyses to account for linear relationships between brain-PAD and chronological age (Le et al., 2018). In addition, individual brain-PAD estimates were residualised for age, where appropriate, for data visualisation only.

2.5. Non-imaging variables

As part of the ALSPAC study, a wide range of questionnaire and clinical assessment data have been collected periodically from parents and their offspring since September 1990. Phenotypes of interest were selected for descriptive purposes and/or exploratory analyses based on relevance to SCZ or psychotic disorders more broadly, including birth weight (Abel et al., 2010), childhood IQ (Schulz et al., 2014), body mass index (Annamalai et al., 2017), alcohol or cannabis abuse (Archibald et al., 2019; Gage et al., 2016), depressive or anxiety/emotional symptoms (Braga et al., 2013; Upthegrove et al., 2017), and psychotic-like experiences (Healy et al., 2019). Selection of these risk-factors or co-occurring phenotypes was also based on data availability with respect to the majority of the SCZ-RbG sample and proximity to the time of the imaging sub-study (where applicable). Birth weight was identified through a variety of sources including obstetric data and birth notifications. Childhood IQ was assessed at ~8 years of age using a short form of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, Golombok, and Rust, 1992). Emotional problems were assessed at age ~17 using the emotional symptoms scale of the child-reported Strength and Difficulties Questionnaire (SDQ; Goodman, 1997). Risk for problematic alcohol use was assessed at age ~18 using the Alcohol Use Disorder Identification Test (AUDIT total score; Saunder et al, 1993). Problematic cannabis use was assessed at age ~ 20 was assessed using the Cannabis Abuse Screening Test (CAST; Legleye et al., 2009). A CAST score of 1 or more was used as a measure of some level of risk for problematic or abusive use. Depressive symptoms were assessed at age ~22 using the short Mood and Feeling Questionnaire (sMFQ; Angold et al., 1995). Ascertainment of generalised anxiety disorder at age ~24 was based on the Clinical Interview Schedule-Revised (CIS-R) (Lewis et a.l, 1992). The semi-structured Psychosis-Like Symptoms Interview (PLIKS) was used to assess psychotic experiences (hallucinations, delusions, or experiences of thought interference) at age ~24 (Sullivan et al., 2020). Individuals were deemed to

have had a psychotic experience if rated as having ever had one or more suspected or definite psychotic experiences between the ages of 12 and 24 years. Individuals were further classified as ever having had a psychotic disorder if they met the following criteria: (1) definite psychotic experiences not attributable to sleep or fever; (2) they had recurred regularly (at least once per month) over a 6-month period and 3) were either very distressing or having a very negative impact on their social/occupational life or led them to seek help from a professional source. Given the possibility of measurement error or attrition bias (Sullivan et al., 2020), data from assessment at age ~ 24 was supplemented with available information from a previous PLIKS assessment at age ~18 (Zammit et al, 2018). Body mass index (BMI) was assessed during a clinic visit at the age of ~24 years by dividing a person's weight in kilograms (kg) by height in metres squared(m^2). Of note, no part of the above-described ALSPAC/RbG study design, data collection, or imaging processing procedures was pre-registered prior to the current analyses being conducted.

2.6. Statistical analyses

As described in our pre-registered analysis plan (https://osf.io/hrka4), we used multivariable linear regression with brain-PAD as the continuous outcome variable and SCZ-PRS (i.e., high vs. low) as the binary predictor of interest (reference group: low SCZ-PRS). In addition to chronological age, sex was added as a covariate in the model to account for independent effects of sex on brain-PAD (Brouwer et al., 2021; Sanford et al., 2022; Wagen et al., 2022). We used a two-tailed null hypothesis test to evaluate the association between SCZ-PRS and brain-PAD. A prior simulation-based power analysis accounting for the enriched variance in SCZ-PRS within the original RbG sample indicates that the current analysis has approximately 80% power to detect a relatively small effect size of SCZ-PRS ($R^2 > 0.015$ at alpha=0.05; see supplementary material in Lancaster et al., 2019 for more details). Of note, age and sex were not included in this priori power analysis as the two SCZ-PRS groups were matched sex and had a similar mean age in the original RbG sample.

As polygenic risk score analyses are generally susceptible to confounding by population genetic structure (Choi, Mak, and O'Reilly, 2020), a model additionally adjusting for genetic principal components (PCs) in a subset of the sample was run as a sensitivity analysis (see supplementary material A1 for details). In addition, we inspected the data for the presence of any brain-PAD outliers (here defined as +/- 3SD away from the mean of each SCZ-PRS group), and subsequently excluded one identified outlier in a sensitivity analysis. Exploratory analyses were performed using multivariable linear regressions with brain-PAD as the outcome variable and each non-imaging phenotype (e.g., depressive symptoms) and its interaction with SCZ-PRS as the main predictors of interest, adjusting for the main effects of SCZ-PRS, age and sex. All analyses were performed in R and the code used can be accessed on OSF (https://osf.io/hrka4).

3. Results

3.1. Sample characteristics

The current sample consisted of 93 individuals with low SCZ-PRS and 96 individuals with high SCZ PRS (N=189). Table 1 provides a summary of demographic and other characteristics for each SCZ-PRS group. While the high-SCZ PRS group was slightly older than the low-SCZ PRS group (22.88 [SD=0.82] versus 22.53 [SD=0.71] years at time of scanning; p=0.001), levels (or frequency) of depressive symptom severity, generalised anxiety disorder, and psychotic experiences around the age of 22-24 years were similar across groups (see Table 1).

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Table 1. Sample characteristics

Characteristic	N [a]	Low SCZ-PRS, N=93[b]	High SCZ-PRS, N=96[b]	p-value [c]
Age at time of scanning (years)	189 (93/96)	22.53 ± 0.71 (21.25-24.25)	22.88 ± 0.82 (21.08-24.50)	**0.001**
Sex: female	189 (93/96)	50 (53.76%)	51 (53.13%)	0.93
Handness: right-handed	185 (93/92)	81 (87.10)	81 (86.96)	0.47
Ethnicity: white	189 (93/96)	93 (100.00)	96 (100.00)	-
Education: studied at university level [d]	145 (73/72)	55 (75.34%)	60 (83.33%)	0.24
Birth weight (grams)	180 (88/92)	3411 ± 508.91 (1407-4710)	3403 ± 518.48 (1960-4820)	0.72
BMI (kg/m^2) at age ~ 24y	161 (80/81)	24.21 ± 4.34 (18.66-43.87)	24.35 ± 4.14 (15.69-38.01)	0.56
Childhood IQ at age ~ 8y	175 (91/84)	111.2 ± 14.78 (77.00-140.00)	112.2 ± 14.87 (70.0-138.00)	0.45
SDQ-Emotional symptoms score at age ~ 17y	158 (82/76)	0.00 [0.00-2.00; 0.00-10.00]	1.00 [0.00-2.25; 0.00-6.00]	0.10
Depressive symptoms (sMFQ) score at age ~ 22y	146 (72/74)	5.00 [2.00-9.00; 0.00-21:00]	4.00 [2.00-7.00; 0.00-22:00]	0.79
Generalised anxiety disorder at age ~ 24y: yes	158 (78/80)	7 (8.97)	< 5	0.54
Psychotic experiences by age ~ 24y: yes	159 (78/81)	-	-	-
Suspected/definite (ever)	-	11 (14.10)	15 (18.52)	-
Disorder (ever)	-	< 5	< 5	0.87
AUDIT total score at age ~ 18y	147 (72/75)	7.11 ± 5.11 (0.00-21.00)	6.55 ± 4.14 (0.00-18.00)	0.70
CAST score ≥ 1 at age ~ 20y: yes	148 (75/73)	< 5	< 5	0.44

[a] N indicates non-missing observations in the total sample (and in low / high SCZ-PRS group).
[b] Satistics presented: mean ± standard deviation (minimum-maximum); n (%). Median [interquartile range; minimum-maximum] is provided if the distribution of a continuous variable was highly skewed.
[c] Statistical tests performed: wilcoxon rank-sum test; chi-square test/Fisher's exact test. Bold p-values indicate significance at α=0.05.
[d] Past or current university attendance for degree or other higher education qualification was assessed at age 26 years.
BMI: Body Mass Index: SDQ: Strength and Difficulties Questionnaire; sMFQ: short Mood and Feeling Questionnaire; AUDIT: Alcohol Use Disorder Identification Test; CAST: Cannabis Abuse Screening Test.

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3.2. Brain age prediction performance

Regardless of SCZ-PRS status, the ENIGMA model moderately predicted chronological age with MAE of 5.25 (SD = 4.05) in males and 6.33 (SD = 4.62) in females in the current sample. Correlation between chronological age and brain-predicted age was r = 0.12 and r=0.06 in males and females, respectively (see Supplementary Table B1 for more details on model performance). Of note, the age range of the current sample was very restricted (21.08-24.50 years), which generally leads to less covariance between predicted age and true age regardless of prediction accuracy (de Lange et al., 2022). Despite the narrow range of chronological age in the current sample, there was substantial variation in brain-predicted age (mean = 26.76, SD = 6.09, range = 7.46-43.00 years; see Supplementary Figure B1). Brain-predicted age was systematically overestimated by the ENIGMA model across the current sample, with no observed linear dependence of brain-PAD on age (SFig. B2). Nonetheless, age was added as a covariate in subsequent statistical analyses to account for shared variance between predictors. The generalisation performance of the CentileBrain model in the current sample is summarised in supplementary material A2, and we return to the issue of moderate performance of the ENIGMA model in the discussion section of this article.

3.3. Brain age in high- versus low- SCZ-PRS

The mean ENIGMA-derived brain-PAD was +4.21 (SD = 5.68) years in the low SCZ-PRS group and +3.90 (SD = 6.46) years in the high SCZ-PRS group. There was no difference in mean brain-PAD between the two SCZ-PRS groups after adjusting for age and sex (see Fig. 1, and STable B2 for full model parameters). Further adjustment for genetic PCs and/or exclusion of outliers did not meaningfully alter this result (see supplementary material A1 and A3). Repeating these analyses with brain-PAD estimates derived from the CentileBrain brain-age model led to highly comparable

results (b = 0.02; 95% CI -0.18, 0.22; p = 0.854; Cohen's *d* = 0.03; partial R^2 = 0.00021; see supplementary material A2 for more details).

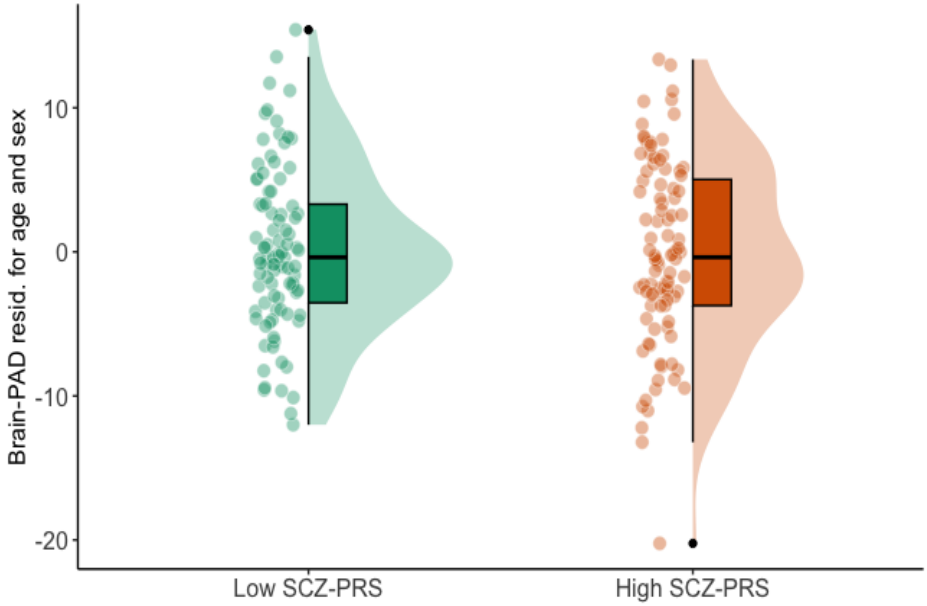

Figure 1. Difference in brain-PAD between low- and high- SCZ-PRS. ENIGMA-derived brain-PAD among participants with low SCZ-PRS (left) and high SCZ-PRS (right). Brain-PAD estimates are residualized for age and sex. Group-level analyses did not show a difference in mean brain-PAD between high- and low- SCZ-PRS (b = - 0.21; 95% CI -2.00, 1.58; p = 0.82; Cohen's *d* = - 0.03; partial R^2 = 0.00029).

3.4. Brain age and phenotypes of interest with respect to SCZ-PRS

We explored associations between different phenotypes of interest and brain-PAD, and particularly whether those associations were moderated by SCZ-PRS status. Emotional symptoms at age ~17 was associated with ENIGMA-derived brain-PAD (b = 0.80; 95% CI 0.14, 1.47; p = 0.018), however no evidence for moderation by SCZ-PRS was found (b = 0.25; 95% CI -0.80,1.31; p = 0.64). No significant associations were found between brain-PAD and depressive symptoms, psychotic-like experiences, childhood IQ, birth weight, BMI, or level of risk for problematic alcohol use, and/or any interactions thereof with SCZ-PRS (STable B3). Results were largely consistent when analyses were repeated with CentileBrain-derived brain-PAD (supplementary material A2).

4. Discussion

We investigated the association between a putative biomarker of brain ageing and polygenic liability for schizophrenia using an RbG approach, comparing individuals at the tails of the SCZ-PRS distribution within a population-based cohort. Contrary to our hypothesis, we did not find evidence for a difference in structural MRI-based brain-PAD between the low- and high- SCZ-PRS groups. To our knowledge, this is the first study to investigate the relationship between SCZ-PRS and brain age in a young population-based sample.

The null results of the current study are congruent with previous studies using a range of techniques. Teeuw et al. (2021) found a weak nominal correlation (r = 0.10; p = 0.048) between SCZ-PRS and brain-PAD in a clinical sample of people with SCZ and controls (age range: 17-67 years; N=394). However, the observed association was no longer significant after accounting for diagnostic status, possibly reflecting downstream illness effects of SCZ on brain age. Demro et al. (2022) performed an analysis of brain age and genetic liability for psychosis as proxied by first-degree biological relatives of individuals with SCZ and associated psychotic disorders (aged 18-69; N=103 relatives). The authors did not find a greater brain-PAD in relatives (affected or unaffected) compared to unrelated controls, suggesting that brain age may not be an index of familial risk for psychotic psychopathology. Similarly, we found no evidence for a link between SCZ-PRS and brain age in a young population-based sample, suggesting that this link - if present - might develop later in life after disease onset. While our findings could cast doubt on the neurodevelopmental origins of SCZ, it is equally possible that the brain-PAD paradigm and this current sample (given the narrow age range) are less well suited to address this question.

Our results also converge with the lack of genetic correlations between brain-PAD and SCZ that has been reported as part of the largest genome-wide association study of brain age to date

(N>28,000) (Leonardsen et al., 2023). Moreover, follow-up Mendelian randomization analyses did not find evidence for a causal relationship between brain-PAD and SCZ, in either direction (Leonardsen et al., 2023). Taken together, while our results and those of previous studies do not rule out a causal relationship between brain-PAD and SCZ, they may suggest that previously reported case-control differences in brain age are more likely to partly reflect the effect of environmental risk or confounding factors. For example, smoking, obesity and cannabis use have previously been associated with both SCZ (Myles et al., 2012; Vancampfort et al., 2015; Marconi et al, 2016) and brain age (Ning et al., 2020; Kolbeinsson et al., 2020; Meier et al., 2022). Alternatively, previously observed case-control differences in brain-PAD may partly reflect downstream illness effects (e.g., cognitive deficits or somatic comorbidities) and future studies utilising clinically-ascertained samples could also examine whether such effects might be moderated by SCZ-PRS.

A key strength of the current study is the use of an RbG approach. SCZ-PRS typically accounts for only up to ~7% of the variance in SCZ liability (Trubetskoy et al., 2022), but because there is considerably increased SCZ risk between the high- and low- SCZ-PRS groups, the current study offered considerably more power than a randomly sampled population-based study of similar size (Lancaster et al., 2019). However, while our null finding may rule out a shared variance between SCZ-PRS and brain-PAD at the level $R^2 > 0.015$ (i.e., our estimated minimum detectable effect size), the current study was not powered to detect smaller effect sizes, such as those previously detected in a large-scale studies of SCZ-PRS and other MRI-derived cortical phenotypes (R^2: 0.001 – 0.008) (Neilson et al. 2019; Stauffer et al, 2021). Further work in larger samples utilising summary data from the most powerful SCZ-GWAS available is therefore warranted (Choi, Mak, and O'Reilly, 2020). In addition, it is possible that the relatively lower response rate among high SCZ-PRS individuals at participant recruitment might have influenced our results through participation bias (Martin et al., 2016).

The current study utilised a subsample of young adults from longitudinal birth cohort, and thus all participants were aged between 21-24 years. This narrow age range might have helped eliminate the effects of potential confounders that could have been present in a younger or older sample, such as puberty during childhood/adolescence or chronic age-related diseases (or associated risk factors) that arise around middle adulthood or later (Holm et al., 2022; Kolbeinsson et al, 2020). Nonetheless, an effect of SCZ-PRS on brain age could vary across the life course and thus the generalizability of our null results may be limited to early adulthood. Future studies may either use a wider age range or focus on different stages of the life course.

The observed positive association between emotional symptoms (SDQ) at age ~17 years and brain-PAD (at age ~22) is intriguing but preliminary at this stage, as it comes from an exploratory analysis. Given that adolescence represents a sensitive and dynamic period of development, a preliminary interpretation is that emotional difficulties during this period may be linked to advanced brain maturation in early adulthood (and regardless of SCZ-PRS). This is in contrast with a recent study in youth (age range: 5-17 years) reporting an association between worsening anxiety/depression symptoms (as measured by CBCL) and lower brain-PAD (i.e., delayed brain maturation) (Cohen et al., 2022). In addition, we found no association between depressive symptoms (sMFQ) and brain-PAD. While this discrepancy in findings might be explained by differences in sample or methodological characteristics (e.g., lack of, or partial equivalence between depression/anxiety measures), it highlights the need for further work in larger and carefully selected longitudinal samples. Another limitation of our exploratory analyses is the discrepancy in timing of brain scanning and that of ascertaining modifiable variables (e.g., BMI, alcohol use), that might have precluded detecting associations with brain-PAD.

Further limitations of the current study relate to the estimation of brain age. First, although model performance is not directly comparable between different studies (de Lange et al., 2022; Cole et al., 2019), the mean absolute error achieved by the ENIGMA model in the current study (MAE > 5 years) is considerably higher than that reported by previous studies in youth using other brain age models (overall age range: 5-22 years; MAE range from testing samples: 0.7-2 years) (Drobinin et al., 2022; Modabbernia et al., 2022; Holm et al., 2022; Truelove-Hill et al., 2020). While this discrepancy can partly be attributed to the relatively wider age range of its training set (18-75 years), the moderate fit of the ENIGMA model could reflect more noise and may be less sensitive to subtle individual brain age differences expected within the narrow age range of the current population-based sample of emerging adults (21-24 years). To address this, we have performed a sensitivity analysis using a second model (i.e., CentileBrain) trained with a restricted age range of 20-30 years that more closely resembles that of the current sample (whilst preserving a similar set of features and use of sex-specific model variants). Although the mean absolute error of the CentileBrain model in the current sample was considerably lower (MAE ~ 0.8 years; see supplementary material A2 for a more detailed discussion on this) and more consistent to that of previous studies in youth, results of subsequent analyses aligned closely across the two brain age models. Nonetheless, while a lower mean absolute error is intuitively appealing in the context of predictive modelling, it remains unclear whether higher age-prediction accuracy translates to improved capacity for detecting individual differences in downstream analyses of brain age (Bashyam et al., 2020; 2021; Hahn et al., 2021; Jirsaraire et al., 2023). This is a topic of ongoing discussion in the field and warrants further systematic examination**.** Second, while T1-weighted MRI data is considered highly reliable for brain age estimation and allows us to place our results in context with previous work, brain ageing (or maturation) is a heterogeneous process and different factors would likely affect different aspects of brain structure and function (Smith et al., 2020). Future studies could employ brain age measures based on other or multiple MRI modalities that may capture different aspects of naturally occurring variation and may be more sensitive to factors impacting brain health (Cole 2020; Rokicki

et al., 2021). Lastly, as most brain age studies to date, the current study was focused on a single "global" measure of brain age, which could overlook any localised (or region-specific) effects on brain age (Popescu et al. 2021; Sanford et al. 2022).

In summary, the current study did not find evidence for an association between SCZ-PRS and advanced global structural brain age in young adults, suggesting that greater brain-PAD is not a vulnerability marker of common genetic risk for schizophrenia. Future studies with larger samples and/or more comprehensive brain age measures could help identify any global or localised effects of polygenic risk for SCZ on brain age.

5. Author Contributions

Conceptualization: CC, EW, TF. *Methodology*: CC, EW, TF, LH, TL, VB. *Software*: LH, CC, VB. *Formal analysis*: CC, VB. *Visualisation*: CC. *Resources*: EW, LH, TL. *Writing - Original Draft*: CC. *Writing - Review & Editing*: CC, EW, TF, LH, TL, DC, VB, SZ. *Supervision*: EW, TF, TL, DC, SZ. *Project administration*: CC, EW, TF.

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8. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

9. Data availability

The authors do not have permission to share data. Researchers can request the original dataset used directly from ALSPAC (https://www.bristol.ac.uk/alspac/researchers/).

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