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Special Issue "Neurodevelopmental Neurodiversity": Research Report

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

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ARTICLE INFO

Article history:
Received 28 April 2023
Reviewed 18 July 2023
Revised 22 September 2023
Accepted 23 November 2023
Action editor chris Jarrold
Published online 8 December 2023

Keywords:
Ageing
Brain age
Schizophrenia
Genetic risk
ALSPAC

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 = −.21; 95% CI −2.00, 1.58; p = .82; Cohen's d = −.034; partial R^2 = .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

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https://doi.org/10.1016/j.cortex.2023.11.015

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 et al., 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 et al., 2016; Kirkpatrick et al., 2008; Kirkpatrick & 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., 2017). 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 (Murray et al., 2017; Owen & O'Donovan, 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 & 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 body mass index), diabetes, dementia, major depression, and mortality (Ning et al., 2020; 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 of +3.55 years after adjusting for age, sex, and scanning site; Cohen's $d = 0.48$) (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^2_{SNP}) 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 et al., 2020). Variation in SCZ-PRS in the general population has been associated with phenotypes of brain morphometry previously implicated in schizophrenia, including global or regional reductions in cortical thickness and subcortical structures, possibly reflecting vulnerability to the disorder (Jameei et al., 2023; Neilson et al., 2019; Stauffer et al., 2021).

Studies of the genetic architecture of brain age suggest that brain-PAD is moderately heritable ($h^2 \geq .5$; $h^2_{SNP} = .24$) (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

We report how we determined our sample size (Section 2.1), all data exclusions, all inclusion/exclusion criteria (Sections 2.1, 2.2 and 2.5), whether inclusion/exclusion criteria were established prior to data analysis (Section 2.6), all manipulations, and all measures in the study (Sections 2.1–2.6).

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., 2007). 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 $p \leq .05$ 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: −.51 to (−3.27)] for low SCZ-PRS; mean Z-score = +1.42 [range: .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 (Dimitriadis 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 and 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 1 mm thickness (TR = 7.9 sec, TE = 3.0 msec, TI = 450 msec, flip angle 20°, FOV = 256 mm × 256 mm × 176 mm to yield 1 mm 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 × 34) and cortical surface area (2 × 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).

2.3. 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 (Abram et al., 2023; Clausen et al., 2022; Constantinides et al., 2022; Han et al., 2022). 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 (Yu et al., 2023; https://centilebrain.org), 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 in 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 et al., 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 & 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 substudy (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 et al., 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; Saunders 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 al, 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 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., 2013). 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 > .015 at alpha = .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 et al., 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 (v. 4.3.0) 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 = .82] *vs* 22.53 [SD = .71] years at time of scanning; $p = .001$), 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).

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 $r = .12$ and $r = .06$ 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 Fig. 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 = .02; 95% CI -.18, .22; $p = .854$; Cohen's $d = .029$; partial $R^2 = .00021$; see Supplementary material A2 for more details).

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 ± .71 (21.25–24.25)	22.88 ± .82 (21.08–24.50)	**.001**
Sex: female	189 (93/96)	50 (53.76%)	51 (53.13%)	.93
Handedness: right-handed	185 (93/92)	81 (87.10)	80 (86.96)	.98
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%)	.24
Birth weight (grams)	180 (88/92)	3411 ± 509 (1407–4710)	3409 ± 518 (1960–4820)	.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)	.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)	.45
SDQ-emotional symptoms score at age ~ 17y	158 (82/76)	.00 [.00–2.00; .00–10.00]	1.00 [.00–2.25; .00–6.00]	.10
Depressive symptoms (sMFQ) score at age ~ 22y	146 (72/74)	5.00 [2.00–9.00; .00–21:00]	4.00 [2.00–7.00; .00–22:00]	.79
Generalised anxiety disorder at age ~ 24y: yes	158 (78/80)	7 (8.97)	<5	.54
Psychotic experiences by age ~ 24y: yes	160 (79/81)	–	–	–
Suspected/definite (ever)	–	11 (13.92)	15 (18.52)	–
Disorder (ever)	–	<5	<5	.64
AUDIT total score at age ~ 18y	146 (72/74)	7.11 ± 5.12 (.00–21.00)	6.55 ± 4.14 (.00–18.00)	.70
CAST score ≥ 1 at age ~ 20y: yes	148 (75/73)	<5	<5	.44

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.

[a] N indicates non-missing observations in the total sample (and in low/high SCZ-PRS group).

[b] Statistics 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 $\alpha = .05$.

[d] Past or current university attendance for degree or other higher education qualification was assessed at age 26 years.

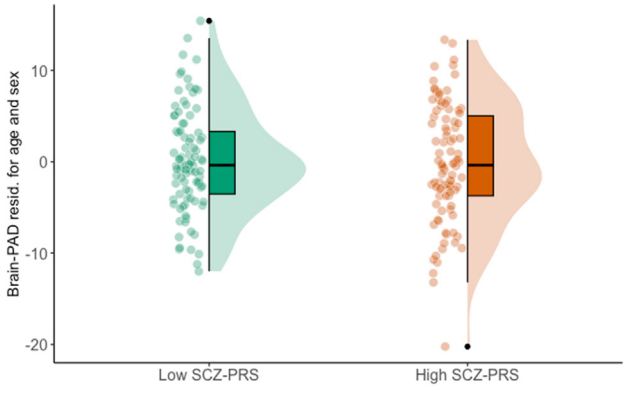

Fig. 1 – Difference in brain-PAD between low- and high-SCZ-PRS. ENIGMA-derived brain-PAD among participants with low SCZ-PRS (left) and high SCZ-PRS (right). Brain-PAD estimates are residualized for age and sex. Group-level analyses did not show a difference in mean brain-PAD between high- and low-SCZ-PRS (b = −.21; 95% CI −2.00, 1.58; p = .82; Cohen's d = −.034; partial R^2 = .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 = .80; 95% CI .14, 1.47; p = .018), however no evidence for moderation by SCZ-PRS was found (b = .25; 95% CI -.80, 1.31; p = .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 = .10; p = .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 (Marconi et al., 2016; Myles et al., 2012; Vancampfort et al., 2015) and brain age (Kolbeinsson et al., 2020; Meier et al., 2022; Ning et al., 2020). Alternatively, previously observed case-control differences in brain-PAD may partly reflect downstream illness effects such as cognitive deficits (Haas et al., 2022) or somatic comorbidities (Ryan et al., 2022), 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 $R^2 > .015$ (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: .001–.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 et al., 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 and 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 samples, 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., 2023; 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 (Cole et al., 2019; de Lange et al., 2022), 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: .70–2 years) (Drobinin et al., 2022; Modabbernia et al., 2022; Holm et al., 2023; 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 ~ .80 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; Jirsaraie 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.

Funding

The UK Medical Research Council (MRC) and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and CC and EW will serve as guarantors for the contents of this paper. A comprehensive list of grant funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf). The recall-by genotype imaging sub-study was supported by grant MR/K004360/1 from the MRC titled: "Behavioural and neurophysiological effects of schizophrenia risk genes: a multilocus, pathway based approach" and by the MRC Centre for Neuropsychiatric Genetics and Genomics (G0800509). GWAS data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. The work reported in this publication was funded from the European Union's Horizon Europe/2020 research and innovation programme under the European Research Council grant agreement No 848158 (EarlyCause) and P/Y015037/1 (BrainHealth, fulfilled by UKRI) to EW. EW also received funding from the National Institute of Mental Health of the National Institutes of Health (award number R01MH113930). CC was supported by grant MR/N0137941/1 for the GW4 BIOMED Doctoral Training Partnership awarded to the Universities of Bath, Bristol, Cardiff and Exeter from the Medical Research Council (MRC)/UK Research & Innovation (UKRI). LH was funded by the Rubicon award (grant number 452020227) from the Dutch Research Council (NWO). SZ is supported by the NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol.

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/).

Open practices

The study in this article earned Preregistered badge for transparent practices. The preregistered studies are available for access at: https://osf.io/hrka4.

Declaration of competing 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.

Acknowledgements

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. We also thank Dr. Sophia Frangou for providing useful background information on the training and validation of the CentileBrain model.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2023.11.015.

REFERENCES

Abel, K. M., Wicks, S., Susser, E. S., Dalman, C., Pedersen, M. G., Mortensen, P. B., & Webb, R. T. (2010). Birth weight, schizophrenia, and adult mental disorder: Is risk confined to the smallest babies? *Archives of General Psychiatry, 67*(9), 923–930. https://doi.org/10.1001/ARCHGENPSYCHIATRY.2010.100

Abram, S. V., Roach, B. J., Hua, J. P. Y., Han, L. K. M., Mathalon, D. H., Ford, J. M., & Fryer, S. L. (2023). Advanced brain age correlates with greater rumination and less mindfulness in schizophrenia. *NeuroImage: Clinical, 37*, Article 103301. https://doi.org/10.1016/J.NICL.2022.103301

Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., & Silver, D. (1995). Development of a short questionnaire for use

in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research, 5*(4), 237–324.

Annamalai, A., Kosir, U., & Tek, C. (2017). Prevalence of obesity and diabetes in patients with schizophrenia. *World Journal of Diabetes, 8*(8), 390. https://doi.org/10.4239/WJD.V8.I8.390

Archibald, L., Brunette, M. F., Wallin, D. J., & Green, A. I. (2019). Alcohol use disorder and schizophrenia or schizoaffective disorder. *Alcohol Research: Current Reviews, 40*(1), e1–e9. https://doi.org/10.35946/ARCR.V40.1.06

Baecker, L., Garcia-Dias, R., Vieira, S., Scarpazza, C., & Mechelli, A. (2021). Machine learning for brain age prediction: Introduction to methods and clinical applications. *EBioMedicine, 72*. https://doi.org/10.1016/J.EBIOM.2021.103600

Bashyam, V. M., Erus, G., Doshi, J., Habes, M., Nasralah, I., Truelove-Hill, M., Srinivasan, D., Mamourian, L., Pomponio, R., Fan, Y., Launer, L. J., Masters, C. L., Maruff, P., Zhuo, C., Völzke, H., Johnson, S. C., Fripp, J., Koutsouleris, N., Satterthwaite, T. D., … Davatzikos, C. (2020). MRI signatures of brain age and disease over the lifespan based on a deep brain network and 14 468 individuals worldwide. *Brain: A Journal of Neurology, 143*(7), 2312–2324. https://doi.org/10.1093/BRAIN/AWAA160

Bashyam, V., Shou, H., & Davatzikos, C. (2021). Reply: From 'loose fitting' to high-performance, uncertainty-aware brain-age modelling. *Brain, 144*(3). https://doi.org/10.1093/BRAIN/AWAA455. e32–e32.

Blake, K. V., Ntwatwa, Z., Kaufmann, T., Stein, D. J., Ipser, J. C., & Groenewold, N. A. (2023). Advanced brain ageing in adult psychopathology: A systematic review and meta-analysis of structural MRI studies. *Journal of Psychiatric Research, 157*, 180–191. https://doi.org/10.1016/J.JPSYCHIRES.2022.11.011

Bøstrand, S. M. K., Vaher, K., de Nooij, L., Harris, M. A., Cole, J. H., Cox, S. R., Marioni, R. E., McCartney, D. L., Walker, R. M., McIntosh, A. M., Evans, K. L., Whalley, H. C., Wootton, R. E., & Clarke, T. K. (2022 Jan). Associations between alcohol use and accelerated biological ageing. *Addiction Biology, 27*(1), Article e13100. https://doi.org/10.1111/adb.13100. Epub 2021 Oct 12. PMID: 34636470; PMCID: PMC7614236.

Boyd, A., Golding, J., Macleod, Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2013). Cohort profile: The 'children of the 90s' – The index offspring of the Avon longitudinal study of parents and children. *International Journal of Epidemiology, 42*(1), 111–127. https://doi.org/10.1093/IJE/DYS064

Braga, R. J., Reynolds, G. P., & Siris, S. G. (2013). Anxiety comorbidity in schizophrenia. *Psychiatry Research, 210*(1), 1–7. https://doi.org/10.1016/J.PSYCHRES.2013.07.030

Brouwer, R. M., Schutte, J., Janssen, R., Boomsma, D. I., Hulshoff Pol, H. E., & Schnack, H. G. (2021). The speed of development of adolescent brain age depends on sex and is genetically determined. *Cerebral Cortex, 31*(2), 1296–1306. https://doi.org/10.1093/CERCOR/BHAA296

Choi, S. W., Mak, T. S. H., & O'Reilly, P. F. (2020). Tutorial: A guide to performing polygenic risk score analyses. *Nature Protocols, 15*(9), 2759–2772. https://doi.org/10.1038/s41596-020-0353-1

Chung, Y., Addington, J., Bearden, C. E., Cadenhead, K., Cornblatt, B., Mathalon, D. H., McGlashan, T., Perkins, D., Seidman, L. J., Tsuang, M., Walker, E., Woods, S. W., McEwen, S., van Erp, T. G. M., & Cannon, T. D. (2018). Use of machine learning to determine deviance in neuroanatomical maturity associated with future psychosis in youths at clinically high risk. *JAMA Psychiatry, 75*(9), 960–968. https://doi.org/10.1001/JAMAPSYCHIATRY.2018.1543

Clausen, A. N., Fercho, K. A., Monsour, M., Disner, S., Salminen, L., Haswell, C. C., Rubright, E. C., Watts, A. A., Nicole Buckley, M., Maron-Katz, A., Sierk, A., Manthey, A., Suarez-Jimenez, B., Olatunji, B. O., Averill, C. L., Hofmann, D., Veltman, D. J., Olson, E. A., Li, G., … Morey, R. A. (2022). Assessment of brain age in posttraumatic stress disorder: Findings from the ENIGMA PTSD and brain age working groups. *Brain and Behavior, 12*(1). https://doi.org/10.1002/BRB3.2413

Cohen, A. A., Kennedy, B. K., Anglas, U., Bronikowski, A. M., Deelen, J., Dufour, F., Ferbeyre, G., Ferrucci, L., Franceschi, C., Frasca, D., Friguet, B., Gaudreau, P., Gladyshev, V. N., Gonos, E. S., Gorbunova, V., Gut, P., Ivanchenko, M., Legault, V., Lemaître, J. F., … Fülöp, T. (2020). Lack of consensus on an aging biology paradigm? A global survey reveals an agreement to disagree, and the need for an interdisciplinary framework. *Mechanisms of Ageing and Development, 191*, Article 111316. https://doi.org/10.1016/J.MAD.2020.111316

Cohen, J. W., Ramphal, B., DeSerisy, M., Zhao, Y., Pagliaccio, D., Colcombe, S., Milham, M. P., & Margolis, A. E. (2022). Relative brain age is associated with socioeconomic status and anxiety/depression problems in youth. *BioRxiv*. https://doi.org/10.1101/2022.09.15.505331, 2022.09.15.505331.

Cole, J. H. (2020). Multimodality neuroimaging brain-age in UK Biobank: Relationship to biomedical, lifestyle, and cognitive factors. *Neurobiology of Aging, 92*, 34–42. https://doi.org/10.1016/j.neurobiolaging.2020.03.014

Cole, J. H., & Franke, K. (2017). Predicting age using neuroimaging: Innovative brain ageing biomarkers. *Trends in Neurosciences, 40*(12), 681–690.

Cole, J. H., Franke, K., & Cherbuin, N. (2019). *Quantification of the biological age of the brain using neuroimaging*. Cham: Springer. https://doi.org/10.1007/978-3-030-24970-0_19

Cole, J. H., Poudel, R. P. K., Tsagkrasoulis, D., Caan, M. W. A., Steves, C., Spector, T. D., & Montana, G. (2017). Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *NeuroImage, 163*, 115–124. https://doi.org/10.1016/J.NEUROIMAGE.2017.07.059

Cole, J. H., Ritchie, S. J., Bastin, M. E., Valdés Hernández, M. C., Muñoz Maniega, S., Royle, N., Corley, N., Pattie, A., Harris, S. E., Zhang, Q., Wray, N. R., Redmond, P., Marioni, R. E., Starr, J. M., Cox, S. R., Wardlaw, J. M., Sharp, D. J., & Deary, I. J. (2018). Brain age predicts mortality. *Molecular Psychiatry, 23*, 1385–1392.

Constantinides, C., Han, L. K. M., Alloza, C., Antonucci, L. A., Arango, C., Ayesa-Arriola, R., Banaj, N., Bertolino, A., Borgwardt, S., Bruggemann, J., Bustillo, J., Bykhovski, O., Calhoun, V., Carr, V., Catts, S., Chung, Y.-C., Crespo-Facorro, B., Díaz-Caneja, C. M., Donohoe, G., … Walton, E. (2022). Brain ageing in schizophrenia: Evidence from 26 international cohorts via the ENIGMA schizophrenia consortium. *Molecular Psychiatry, 14*, 1–9. https://doi.org/10.1038/s41380-022-01897-w

Corbin, L. J., Tan, V. Y., Hughes, D. A., Wade, K. H., Paul, D. S., Tansey, K. E., Butcher, F., Dudbridge, F., Howson, J. M., Jallow, M. W., John, C., Kingston, N., Lindgren, C. M., O'Donavan, M., O'Rahilly, S., Owen, M. J., Palmer, C. N. A., Pearson, E. R., Scott, R. A., … Timpson, N. J. (2018). Formalising recall by genotype as an efficient approach to detailed phenotyping and causal inference. *Nature Communications, 9*(1), 1–11. https://doi.org/10.1038/s41467-018-03109-y

Correll, C. U., Solmi, M., Nicola Veronese, Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P. B., Gaughran, F., Carvalho, A. F., & Stubbs, B. (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: A large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry, 16*(2), 163–180. https://doi.org/10.1002/wps.20420

Cropley, V. L., Klauser, P., Lenroot, R. K., Bruggemann, J., Sundram, S., Bousman, C., Pereira, A., Di Biase, M. A.,

Weickert, T. W., Weickert, C. S., Pantelis, C., & Zalesky, A. (2017). Accelerated gray and white matter deterioration with age in schizophrenia. *American Journal of Psychiatry, 174*(3), 286–295. https://doi.org/10.1176/APPI.AJP.2016.16050610/ASSET/IMAGES/LARGE/APPI.AJP.2016.16050610F4.JPEG

de Lange, A.-M. G., Anatürk, M., Rokicki, J., Han, L. K. M., Franke, K., Alnaes, D., Ebmeier, K. P., Draganski, B., Kaufmann, T., Westlye, L. T., Hahn, T., James, & Cole, H. (2022). Mind the gap: Performance metric evaluation in brain-age prediction. *Human Brain Mapping*. https://doi.org/10.1002/HBM.25837

de Lange, A. M. G., & Cole, J. H. (2020). Commentary: Correction procedures in brain-age prediction. *NeuroImage: Clinical, 26*, Article 102229. https://doi.org/10.1016/J.NICL.2020.102229

Demro, C., Shen, C., Hendrickson, T. J., Arend, J. L., Disner, S. G., & Sponheim, S. R. (2022). Advanced brain-age in psychotic psychopathology: Evidence for transdiagnostic neurodevelopmental origins. *Frontiers in Aging Neuroscience,* 14. https://doi.org/10.3389/FNAGI.2022.872867

Dieset, I., Andreassen, O. A., & Haukvik, U. K. (2016). Somatic comorbidity in schizophrenia: Some possible biological mechanisms across the life span. *Schizophrenia Bulletin, 42*(6), 1316–1319. https://doi.org/10.1093/schbul/sbw028

Dimitriadis, S. I., Lancaster, T. M., Perry, G., Tansey, K. E., Jones, D. K., Singh, K. D., Zammit, S., Smith, G. D., Hall, J., O'Donovan, M. C., Owen, M. J., & Linden, D. E. (2021). Global brain flexibility during working memory is reduced in a high-genetic-risk group for schizophrenia. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 6*(12), 1176–1184. https://doi.org/10.1016/J.BPSC.2021.01.007

Dimitriadis, S. I., Perry, G., Lancaster, T. M., Tansey, K. E., Singh, K. D., Holmans, P., Pocklington, A., Davey Smith, G., Zammit, S., Hall, J., O'Donovan, M. C., Owen, M. J., Jones, D. K., & Linden, D. E. (2023). Genetic risk for schizophrenia is associated with increased proportion of indirect connections in brain networks revealed by a semi-metric analysis: Evidence from population sample stratified for polygenic risk. *Cerebral Cortex, 33*(6), 2997–3011. https://doi.org/10.1093/CERCOR/BHAC256

Drobinin, V., Van Gestel, H., Helmick, C. A., Schmidt, M. H., Chris, V. B., & Uher, R. (2022). The developmental brain age is associated with adversity, depression, and functional outcomes among adolescents. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 7*(4), 406–414. https://doi.org/10.1016/j.bpsc.2021.09.004

Fischl, B. (2012). FreeSurfer. *NeuroImage, 62*(2), 774–781. https://doi.org/10.1016/J.NEUROIMAGE.2012.01.021

Franke, K., & Gaser, C. (2019). Ten years of brainage as a neuroimaging biomarker of brain aging: What insights have we gained? *Frontiers in Neurology, 10*(JUL), 789.

Franke, K., Ziegler, G., Klöppel, S., & Gaser, C. (2010). Estimating the age of healthy subjects from T1-weighted MRI scans using Kernel methods: Exploring the influence of various parameters. *NeuroImage, 50*(3), 883–892. https://doi.org/10.1016/J.NEUROIMAGE.2010.01.005

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., Henderson, J., Macleod, J., Molloy, L., Ness, A., Ring, S., Nelson, S. M., & Lawlor, D. A. (2013). Cohort profile: The Avon longitudinal study of parents and children: ALSPAC mothers cohort. *International Journal of Epidemiology, 42*, 97–110.

Gage, S. H., Hickman, M., & Zammit, S. (2016). Association between cannabis and psychosis: Epidemiologic evidence. *Biological Psychiatry, 79*(7), 549–556. https://doi.org/10.1016/j.biopsych.2015.08.001

Goodman, R. (1997). The strengths and difficulties questionnaire: A research note. *Journal of Child Psychology and Psychiatry, 38*, 581–586. pmid:925570.

Haas, S. S., Ge, R., Sanford, N., Modabbernia, A., Reichenberg, A., Whalley, H. C., Kahn, R. S., & Frangou, S. (2022). Accelerated global and local brain aging differentiate cognitively impaired from cognitively spared patients with schizophrenia. *Frontiers in Psychiatry, 13*. https://doi.org/10.3389/FPSYT.2022.913470

Hahn, T., Fisch, L., Ernsting, J., Winter, N. R., Leenings, R., Sarink, K., Emden, D., Kircher, T., Berger, K., & Dannlowski, U. (2021). From 'loose fitting' to high-performance, uncertainty-aware brain-age modelling. *Brain, 144*(3). https://doi.org/10.1093/BRAIN/AWAA454. e31–e31.

Hajek, T., Franke, K., Kolenic, M., Capkova, J., Matejka, M., Propper, L., Uher, R., Stopkova, P., Novak, T., Paus, T., Kopecek, M., Spaniel, F., & Alda, M. (2019). Brain age in early stages of bipolar disorders or schizophrenia. *Schizophrenia Bulletin, 45*(1), 191–198. https://doi.org/10.1093/schbul/sbx172

Han, L. K. M., Dinga, R., Hahn, T., Ching, C. R. K., Eyler, L. T., Aftanas, L., Aghajani, M., Aleman, A., Baune, B. T., Berger, K., Brak, I., Busatto Filho, G., Carballedo, A., Connolly, C. G., Couvy-Duchesne, B., Cullen, K. R., Dannlowski, U., Davey, C. G., Dima, D., … Schmaal, L. (2020). Brain aging in major depressive disorder: Results from the ENIGMA major depressive disorder working group. *Molecular Psychiatry*, 1–16. https://doi.org/10.1038/s41380-020-0754-0

Han, L. K. M., Dinga, R., Leenings, R., Hahn, T., Cole, J. H., Aftanas, L. I., Amod, A. R., Besteher, B., Colle, R., Corruble, E., Couvy-Duchesne, B., Danilenko, K. V., Fuentes-Claramonte, P., Gonul, A. S., Gotlib, I. H., Goya-Maldonado, R., Groenewold, N. A., Hamilton, P., Ichikawa, N., … Schmaal, L. (2022). A large-scale ENIGMA multisite replication study of brain age in depression. *NeuroImage: Reports, 2*(4), Article 100149. https://doi.org/10.1016/J.YNIRP.2022.100149

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009 Apr). Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42*(2), 377–381.

Healy, C., Brannigan, R., Dooley, N., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). Childhood and adolescent psychotic experiences and risk of mental disorder: A systematic review and meta-analysis. *Psychological Medicine, 49*(10), 1589–1599. https://doi.org/10.1017/S0033291719000485

Hjorthøj, C., Stürup, A. E., McGrath, J. J., & Nordentoft, M. (2017). Years of potential life lost and life expectancy in schizophrenia: A systematic review and meta-analysis. *The Lancet Psychiatry, 4*(4), 295–301. https://doi.org/10.1016/S2215-0366(17)30078-0

Holm, M. C., Leonardsen, E. H., Beck, D., Dahl, A., Kjelkenes, R., de Lange, A. G., & Westlye, L. T. (2023 Feb 22). Linking brain maturation and puberty during early adolescence using longitudinal brain age prediction in the ABCD cohort. *Developmental Cognitive Neuroscience, 60*, Article 101220. https://doi.org/10.1016/j.dcn.2023.101220. Epub ahead of print. PMID: 36841180; PMCID: PMC9972398.

International Schizophrenia Consortium, Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., & Sklar, P. (2009 Aug 6). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature, 460*(7256), 748–752. https://doi.org/10.1038/nature08185. Epub 2009 Jul 1. PMID: 19571811; PMCID: PMC3912837.

Jameei, H., Rakesh, D., Zalesky, A., Cairns, M. J., Reay, W. R., Wray, N. R., & Di Biase, M. A. (2023). Linking polygenic risk of schizophrenia to variation in magnetic resonance imaging brain measures: A comprehensive systematic review. *Schizophrenia Bulletin*. https://doi.org/10.1093/SCHBUL/SBAD087, 24 June 2023.

Jirsaraie, R. J., Gorelik, A. J., Gatavins, M. M., Engemann, D. A., Bogdan, R., Barch, D. M., & Sotiras, A. (2023). A systematic

review of multimodal brain age studies: Uncovering a divergence between model accuracy and utility. *Patterns, 4*(4). https://doi.org/10.1016/J.PATTER.2023.100712

Kaufmann, T., van der Meer, D., Trung Doan, N., Schwarz, E., Lund, M. J., Agartz, I., Alnæs, D., Barch, D. M., Baur-Streubel, R., Bertolino, A., Bettella, F., Beyer, M. K., Bøen, E., Borgwardt, S., Brandt, C. L., Buitelaar, J., Celius, E. G., Cervenka, S., Conzelmann, A., … Westlye, L. T. (2019). Common brain disorders are associated with heritable patterns of apparent aging of the brain. *Nature Neuroscience, 22*(10), 1617–1623. https://doi.org/10.1038/s41593-019-0471-7

Kinzina, E. D., Podolskiy, D. I., Dmitriev, S. E., & Gladyshev, V. N. (2019). Patterns of aging biomarkers, mortality, and damaging mutations illuminate the beginning of aging and causes of early-life mortality. *Cell Reports, 29*(13), 4276–4284.e3. https://doi.org/10.1016/j.celrep.2019.11.091

Kirkpatrick, B., & Kennedy, B. K. (2018). Accelerated aging in schizophrenia and related disorders: Future research. *Schizophrenia Research, 196*, 4–8. https://doi.org/10.1016/j.schres.2017.06.034

Kirkpatrick, B., Messias, E., Harvey, P. D., Fernandez-Egea, E., & Bowie, C. R. (2008). Is schizophrenia a syndrome of accelerated aging? *Schizophrenia Bulletin, 34*(6), 1024–1032.

Kolbeinsson, A., Filippi, S., Panagakis, Y., Matthews, P. M., Elliott, P., Dehghan, A., & Tzoulaki, I. (2020). Accelerated MRI-predicted brain ageing and its associations with cardiometabolic and brain disorders. *Scientific Reports, 10*, 19940. https://doi.org/10.1038/s41598-020-76518-z

Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., Falkai, P., Riecher-Rossler, A., Moller, H. J., Reiser, M., Pantelis, C., & Meisenzahl, E. (2014). Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. *Schizophrenia Bulletin, 40*(5), 1140–1153. https://doi.org/10.1093/schbul/sbt142

Lancaster, T. M., Dimitriadis, S. I., Perry, G., Zammit, S., O'Donovan, M. C., & Linden, D. E. (2021). Morphometric analysis of structural MRI using schizophrenia meta-analytic priors distinguish patients from controls in two independent samples and in a sample of individuals with high polygenic risk. *Schizophrenia Bulletin*. https://doi.org/10.1093/SCHBUL/SBAB125

Lancaster, T. M., Dimitriadis, S. L., Tansey, K. L., Perry, G., Ihssen, N., Jones, D. K., Singh, K. D., Holmans, P., Pocklington, D., Davey Smith, D., Zammit, D., Hall, J., O'Donovan, M. C., Owen, M. J., & Linden, D. E. (2019). Structural and functional neuroimaging of polygenic risk for schizophrenia: A recall-by-genotype-based approach. *Schizophrenia Bulletin, 45*(2), 405–414. https://doi.org/10.1093/SCHBUL/SBY037

Legleye, S., Karila, L., Beck, F., & Reynaud, M. (2009). Validation of the CAST, a general population cannabis abuse Screening test. *Journal of Substance Use, 12*(4), 233–242. https://doi.org/10.1080/14659890701476532

Le, T. T., Kuplicki, R. T., McKinney, B. A., Yeh, H.-W., Thompson, W. K., & Paulus, M. P. (2018). A nonlinear simulation framework supports adjusting for age when analyzing BrainAGE. *Frontiers in Aging Neuroscience, 10*, 317. https://doi.org/10.3389/fnagi.2018.00317

Leonardsen, E. H., Vidal-Piñeiro, D., Roe, J. M., Frei, O., Shadrin, A. A., Iakunchykova, O., Lange, A.-M. G. de, Kaufmann, T., Taschler, B., Smith, S. M., Andreassen, O. A., Wolfers, T., Westlye, L. T., & Wang, Y. (2023). Genetic architecture of brain age and its casual relations with brain and mental disorders. *MedRxiv*. https://doi.org/10.1101/2023.01.09.23284310

Lewis, G., Pelosi, A. J., Araya, R., & Dunn, G. (1992). Measuring psychiatric disorder in the community: A standardized assessment for use by lay interviewers. *Psychological Medicine, 22*(2), 465–486. https://doi.org/10.1017/S0033291700030415

Liang, H., Zhang, F., & Niu, X. (2019). Investigating systematic bias in brain age estimation with application to post-traumatic stress disorders. *Human Brain Mapping, 40*(11), 3143–3152. https://doi.org/10.1002/HBM.24588

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016 Sep). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin, 42*(5), 1262–1269. https://doi.org/10.1093/schbul/sbw003. Epub 2016 Feb 15. PMID: 26884547; PMCID: PMC4988731.

Martin, J., Tilling, K., Hubbard, L., Stergiakouli, E., Thapar, A., Davey Smith, G., O'Donovan, M. C., & Zammit, S. (2016). Association of genetic risk for schizophrenia with nonparticipation over time in a population-based cohort study. *American Journal of Epidemiology, 183*(12), 1149–1158. https://doi.org/10.1093/AJE/KWW009

Meier, M. H., Caspi, A., Ambler, A., Hariri, A. R., Harrington, H., Hogan, S., Houts, R., Knodt, A. R., Ramrakha, S., Richmond-Rakerd, L. S., Poulton, R., & Moffitt, T. E. (2022 Oct). Preparedness for healthy ageing and polysubstance use in long-term cannabis users: A population-representative longitudinal study. *The Lancet Healthy Longevity, 3*(10), e703–e714. https://doi.org/10.1016/S2666-7568(22)00201-X. PMID: 36202130; PMCID: PMC9552770.

Mitchell, A. J., Vancampfort, D., Kim, S., van Winkel, R., Yu, W., & De Hert, M. (2013). Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—A systematic review and meta-analysis. *Schizophrenia Bulletin, 39*(2), 306–318. https://doi.org/10.1093/schbul/sbr148

Modabbernia, A., Whalley, H. C., Glahn, D. C., Thompson, P. M., Kahn, R. S., & Frangou, S. (2022). Systematic evaluation of machine learning algorithms for neuroanatomically-based age prediction in youth. *Human Brain Mapping, 43*(17), 5126–5140. https://doi.org/10.1002/HBM.26010

Murray, R. M., Bhavsar, V., Tripoli, G., & Howes, O. (2017). 30 Years on: How the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. *Schizophrenia Bulletin, 43*(6), 1190–1196. https://doi.org/10.1093/SCHBUL/SBX121

Myles, N., Newall, H. D., Curtis, J., Nielssen, O., Shiers, D., & Large, M. (2012 Apr). Tobacco use before, at, and after first-episode psychosis: A systematic meta-analysis. *Journal of Clinical Psychiatry, 73*(4), 468–475. https://doi.org/10.4088/JCP.11r07222. PMID: 22579146.

Neilson, E., Shen, X., Cox, S. R., Clarke, T. K., Wigmore, E. M., Gibson, J., Howard, D. M., Adams, M. J., Harris, M. A., Davies, G., Deary, I. J., Whalley, H. C., McIntosh, A. M., & Lawrie, S. M. (2019). Impact of polygenic risk for schizophrenia on cortical structure in UK Biobank. *Biological Psychiatry, 86*(7), 536–544. https://doi.org/10.1016/J.BIOPSYCH.2019.04.013

Nenadić, I., Dietzek, M., Langbein, K., Sauer, H., & Gaser, C. (2017). BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder. *Psychiatry Research – Neuroimaging, 266*, 86–89. https://doi.org/10.1016/j.pscychresns.2017.05.006

Ning, K., Zhao, L., Matloff, W., Sun, F., & Toga, A. W. (2020). Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. *Scientific Reports, 10*, 10. https://doi.org/10.1038/s41598-019-56089-4

Northstone, K., Lewcock, M., Groom, A., Boyd, A., Macleod, J., Timpson, N. J., & Wells, N. (2019). The Avon longitudinal study of parents and children (ALSPAC): An updated on the enrolled sample of index children in 2019. *Wellcome Open Research, 4*, 51. https://doi.org/10.12688/wellcomeopenres.15132.1

Owen, M. J., & O'Donovan, M. C. (2017). Schizophrenia and the neurodevelopmental continuum: Evidence from genomics.

World Psychiatry, 16(3), 227–235. https://doi.org/10.1002/WPS.20440

Popescu, S. G., Glocker, B., Sharp, D. J., & Cole, J. H. (2021). Local brain-age: A U-net model. *Frontiers in Aging Neuroscience, 13*. https://doi.org/10.3389/FNAGI.2021.761954

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., Maller, J., Sklar, P., De Bakker, P. I. W., Daly, M. J., & Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics, 81*(3), 559–575. https://doi.org/10.1086/519795

Rokicki, J., Wolfers, T., Nordhøy, W., Tesli, N., Quintana, D. S., Alnæs, D., Richard, G., de Lange, A. M. G., Lund, M. J., Norbom, L., Agartz, I., Melle, I., Nærland, T., Selbæk, G., Persson, K., Nordvik, J. E., Schwarz, E., Andreassen, O. A., Kaufmann, T., & Westlye, L. T. (2021). Multimodal imaging improves brain age prediction and reveals distinct abnormalities in patients with psychiatric and neurological disorders. *Human Brain Mapping, 42*(6), 1714–1726. https://doi.org/10.1002/HBM.25323

Ryan, M. C., Hong, L. E., Hatch, K. S., Gao, S., Chen, S., Haerian, K., Wang, G., Goldwaser, E. L., Du, X., Adhikari, B. M., & Kochunov, P. (2022). The additive impact of cardio-metabolic disorders and psychiatric illnesses on accelerated brain aging. *Human Brain Mapping, 43*(6), 1997–2010. https://doi.org/10.1002/HBM.25769

Sanford, N., Ge, R., Antoniades, M., Modabbernia, A., Haas, S. S., Whalley, H. C., Galea, L., Popescu, S. G., Cole, J. H., & Frangou, S. (2022). Sex differences in predictors and regional patterns of brain age gap estimates. *Human Brain Mapping, 43*(15), 4689–4698. https://doi.org/10.1002/HBM.25983

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R., & Grant, M. (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction, 88*(6), 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421–427. https://doi.org/10.1038/NATURE13595

Schnack, H. G., Van Haren, N. E. M., Nieuwenhuis, M., Pol, H. E. H., Cahn, W., & Kahn, R. S. (2016). Accelerated brain aging in schizophrenia: A longitudinal pattern recognition study. *American Journal of Psychiatry, 173*(6), 607–616. https://doi.org/10.1176/appi.ajp.2015.15070922

Schulz, J., Sundin, J., Leask, S., & Done, D. J. (2014). Risk of adult schizophrenia and its relationship to childhood IQ in the 1958 British birth cohort. *Schizophrenia Bulletin, 40*(1), 143. https://doi.org/10.1093/SCHBUL/SBS157

Sharp, T. H., McBride, N. S., Howell, A. E., Evans, C. J., Jones, D. K., Perry, G., Dimitriadis, S. I., Lancaster, T. M., Zuccolo, L., Relton, C., Matthews, S. M., Breeze, T., David, A. S., Drakesmith, M., Linden, D. E. J., Paus, T., & Walton, E. (2020). Population neuroimaging: Generation of a comprehensive data resource within the ALSPAC pregnancy and birth cohort, 2020 *Wellcome Open Research, 5*, 203. https://doi.org/10.12688/wellcomeopenres.16060.1.

Smith, S. M., Elliott, L. T., Alfaro-Almagro, F., McCarthy, P., Nichols, T. E., Douaud, G., & Miller, K. L. (2020 Mar 5). Brain aging comprises many modes of structural and functional change with distinct genetic and biophysical associations. *eLife, 9*, Article e52677. https://doi.org/10.7554/eLife.52677. PMID: 32134384; PMCID: PMC7162660.

Smith, S. M., Vidaurre, D., Alfaro-Almagro, F., Nichols, T. E., & Miller, K. L. (2019). Estimation of brain age delta from brain imaging. *NeuroImage, 200*, 528–539. https://doi.org/10.1016/j.neuroimage.2019.06.017

Stauffer, E. M., Bethlehem, R. A. I., Warrier, V., Murray, G. K., Romero-Garcia, R., Seidlitz, J., & Bullmore, E. T. (2021). Grey and white matter microstructure is associated with polygenic risk for schizophrenia. *Molecular Psychiatry, 26*, 7709–7718. https://doi.org/10.1038/s41380-021-01260-5

Stroup, T. S., Olfson, M., Huang, C., Wall, M. M., Goldberg, T., Devanand, D. P., & Gerhard, T. (2021). Age-specific prevalence and incidence of dementia diagnoses among older US adults with schizophrenia. *JAMA Psychiatry, 78*(6), 632–641. https://doi.org/10.1001/JAMAPSYCHIATRY.2021.0042

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry, 60*(12), 1187–1192. https://doi.org/10.1001/ARCHPSYC.60.12.1187

Sullivan, S. A., Kounali, D., Cannon, M., David, A. S., Fletcher, P. C., Holmans, P., Jones, H., Jones, P. B., Linden, D. E. J., Lewis, G., Owen, M. J., O'Donovan, M., Rammos, A., Thompson, A., Wolke, D., Heron, J., & Zammit, S. (2020 Apr 1). A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. *The American Journal of Psychiatry, 177*(4), 308–317. https://doi.org/10.1176/appi.ajp.2019.19060654. Epub 2020 Jan 7. PMID: 31906710.

Teeuw, J., Ori, A. P. S., Brouwer, R. M., de Zwarte, S. M. C., Schnack, H. G., Hulshoff Pol, H. E., & Ophoff, R. A. (2021). Accelerated aging in the brain, epigenetic aging in blood, and polygenic risk for schizophrenia. *Schizophrenia Research, 231*, 189–197. https://doi.org/10.1016/j.schres.2021.04.005

Trubetskoy, V., Pardiñas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., Bryois, J., Chen, C. Y., Dennison, C. A., Hall, L. S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J. C., Koopmans, F., Magnusson, S., Richards, A. L., Sidorenko, J., … van Os, J. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature, 604*(7906), 502–508. https://doi.org/10.1038/s41586-022-04434-5

Truelove-Hill, M., Erus, G., Bashyam, V., Varol, E., Sako, C., Gur, R. C., Gur, R. E., Koutsouleris, N., Zhuo, C., Fan, Y., Wolf, D. H., Satterthwaite, T. D., & Davatzikos, C. (2020 Feb 5). A multidimensional neural maturation index reveals reproducible developmental patterns in children and adolescents. *The Journal of Neuroscience, 40*(6), 1265–1275. https://doi.org/10.1523/JNEUROSCI.2092-19.2019. Epub 2020 Jan 2. PMID: 31896669; PMCID: PMC7002145.

Upthegrove, R., Marwaha, S., & Birchwood, M. (2017). Depression and schizophrenia: Cause, consequence, or trans-diagnostic issue? *Schizophrenia Bulletin, 43*(2), 240–244. https://doi.org/10.1093/SCHBUL/SBW097

Vancampfort, D., Stubbs, B., Mitchell, A. J., De Hert, M., Wampers, M., Ward, P. B., Rosenbaum, S., & Correll, C. U. (2015 Oct). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. *World Psychiatry, 14*(3), 339–347. https://doi.org/10.1002/wps.20252. PMID: 26407790; PMCID: PMC4592657.

van Erp, T. G. M., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., Agartz, I., Westlye, L. T., Haukvik, U. K., Dale, A. M., Melle, I., Hartberg, C. B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D. W., … Turner, J. A. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry, 21*(4), 547–553. https://doi.org/10.1038/mp.2015.63

van Erp, Theo, G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., Pearlson, G. D., Yao, N., Fukunaga, M., Hashimoto, R., Okada, N., Yamamori, H., Bustillo, J. R., Clark, V. P., Agartz, I., Mueller, B. A., Cahn, W., de Zwarte, S. M. C., Hulshoff Pol, H. E., … Turner, J. A. (2018). Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium. *Biological Psychiatry, 84*(9), 644–654. https://doi.org/10.1016/j.biopsych.2018.04.023

Vidal-Pineiro, D., Wang, Y., Krogsrud, S. K., Amlien, I. K., Baaré, W. F. C., Bartres-Faz, D., Bertram, L., Brandmaier, A. M., Drevon, C. A., Düzel, S., Ebmeier, K., Henson, R. N., Junqué, C., Kievit, R. A., Kühn, S., Leonardsen, E., Lindenberger, U., Madsen, K. S., Magnussen, F., … Fjell, A. (2021). Individual variations in 'brain age' relate to early-life factors more than to longitudinal brain change. *eLife, 10*.

Wagen, A. Z., Coath, W., Keshavan, A., James, S. N., Parker, T. D., Lane, C. A., Buchanan, S. M., Keuss, S. E., Storey, M., Lu, K., Macdougall, A., Murray-Smith, H., Freiberger, T., Cash, D. M., Malone, I. B., Barnes, J., Sudre, C. H., Wong, A., Pavisic, I. M., … Schott, J. M. (2022). Life course, genetic, and neuropathological associations with brain age in the 1946 British birth cohort: A population-based study. *The Lancet Healthy Longevity, 3*(9), e607–e616. https://doi.org/10.1016/S2666-7568(22)00167-2

Wechsler, D., Golombok, S., & Rust, J. (1992). *Intelligence scale for children*. UK Manual (3rd ed.). Sidcup, UK: The Psychological Corporation.

Weye, N., Momen, N. C., Christensen, M. K., Iburg, K. M., Dalsgaard, S., Laursen, T. M., Mortensen, P. B., Santomauro, D. F., Scott, J. G., Whiteford, H. A., McGrath, J. J., & Plana-Ripoll, O. (2020). Association of specific mental disorders with premature mortality in the Danish population using alternative measurement methods. *JAMA Network Open, 3*(6), Article e206646. https://doi.org/10.1001/jamanetworkopen.2020.6646

Yu, Y., Cui, H.-Q., Haas, S. S., New, F., Sanford, N., Yu, K., Zhan, D., Yang, G., Gao, J.-H., Wei, D., Qiu, J., Bernhardt, B., Thompson, P., Frangou, S., Ge, R., & Center, E. W. A. (2023). Brain-Age Prediction: Systematic Evaluation of Site Effects, and Sample Age Range and Size. *BioRxiv*, 2023.11.06.565917. https://doi.org/10.1101/2023.11.06.565917

Zammit, S., Kounali, D., Cannon, M., David, A. S., Gunnell, D., Heron, J., Jones, P. B., Lewis, S., Sullivan, S., Wolke, D., & Lewis, G. (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry, 170*, 742–750. https://doi.org/10.1176/Appi.Ajp.2013.12060768