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Title Page

Title: Impact of polygenic risk for Schizophrenia on cortical structure in UK Biobank

Short Title: Polygenic risk for schizophrenia and cortical structure

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Key Words: Cortical thickness, cortical surface area, cortical volume, polygenic risk, schizophrenia, birth weight

Abstract

Background Schizophrenia is a neurodevelopmental disorder with many genetic variants of individually small effect contributing to phenotypic variation. Lower cortical thickness (CT), surface area (SA) and cortical volume (CV) have been demonstrated in schizophrenia. Furthermore, a range of obstetric complications (e.g. lower birth weight) are consistently associated with an increased risk for schizophrenia. We investigated whether a high polygenic risk score for schizophrenia (PGRS-SCZ) is associated with CT, SA and CV in UK Biobank, a population-based sample, and tested for interactions with birth weight.

Methods Data were available for 2,864 participants ($n_{\text{males}}/n_{\text{females}} = 1382/1482$; mean age = 2.35 years, $\pm$ S.D = 7.40). Linear mixed models were used to test for associations between PGRS-SCZ and CV, SA and CT and between PGRS-SCZ and birth weight. Interaction effects of these variables on cortical structure were also tested.

Results We found a significant negative association between PGRS-SCZ and global CT; a higher PGRS-SCZ was associated with lower CT across the whole brain. We also report a significant negative association between PGRS-SCZ and insular lobe CT. PGRS-SCZ was not associated with birth weight and no PGRS-SCZ $\times$ birth weight interactions were found.

Conclusions These results suggest that individual differences in CT are partly influenced by genetic variants and are most likely not due to factors downstream of disease onset. This approach may help to elucidate the genetic pathophysiology of schizophrenia. Further investigation in case-control and high-risk samples could help identify any localised effects of PGRS-SCZ, and other potential schizophrenia risk factors, effects on CT as symptoms develop.

Text

1. Introduction

Schizophrenia is a heterogeneous psychiatric disorder with twin heritability estimates (h^2) of ~80% (1-3). Recent evidence suggests that the disorder is polygenic in nature, (1-4) with genome-wide association studies (GWAS) identifying schizophrenia-infering loci (3, 5, 6). Supporting a neurodevelopmental theory of schizophrenia, cortical decreases have been consistently associated with the disorder, thought to predate disorder onset (7-9) and are caused by a combination of genetic and environmental factors (7, 8). Limited research has explored the links between polygenic risk for schizophrenia (PGRS-SCZ) and cortical structure with consideration of other schizophrenia risk factors.

Differences in some aspects of brain structure have been consistently detected in groups of schizophrenia patients compared to healthy controls (10). Recently, the field has moved towards studying cortical volume (CV), thickness (CT) and surface area (SA) of the brain. These metrics are considered to have distinct developmental trajectories (11) and are heritable; h^2 ranges from 66-97% for CV (12) and averages around 80% for global CV (13, 14), 81% for CT (15), and 89% for SA (15).

CV has been most studied in schizophrenia, reporting lower CV in widespread areas of the brain in patients (10, 16-24) and in the healthy relatives of individuals with schizophrenia as compared to controls (21, 25-27). However, as CV is the product of CT and SA (11, 15, 28), studying volume alone may obscure some schizophrenia and brain structure associations (10, 15). Lower CT has been evidenced in several brain regions (10, 29-35) and widespread areas across the cortex (10, 21, 31, 35-40) in those at greater genetic risk of/with schizophrenia. Furthermore, CT differences have been found in frontal and temporal lobes of individuals at

familial high-risk of schizophrenia when compared to controls (21, 40-44) and thus may be more easily identified in those with a higher genetic risk of the disorder. SA has been less researched, and with more contradictory results (24). Some studies suggest SA is lower in schizophrenia patients compared to controls both globally (45) and in specific regions (18, 24, 30, 35, 45), whereas others have found SA to be higher (34, 46) or no different (36, 47) in these groups.

Recently, large GWAS ($n_{\text{individuals}} = 36,989$ cases, 113,075 controls) have been used to derive PGRS-SCZ (3, 5, 6); higher scores relating to a greater risk of developing schizophrenia. PGRS-SCZ allows for the assessment of genetic liability in the general population – even among people who may never develop schizophrenia - and enables use of large-scale samples such as UK Biobank (UKB; <http://www.ukbiobank.ac.uk/>).

A small number of studies have tested PGRS-SCZ in relation to structural brain imaging phenotypes with inconsistent results. Reus *et al.* (48) found no associations between regional subcortical volume or white matter microstructure and PGRS-SCZ, using a subset of the same sample as the current study ($n = 978$), but did not assess any cortical metrics. Some studies have reported higher PGRS-SCZ to be associated with a decrease in global gray and/or white matter volume (49-51) ($n_{\text{individuals}}$ range = 89-274) with relatively small effect sizes and amount of variance explained ($\beta = -.151$, $\Delta R^2 = .023$ (change in R^2 for regional white matter volume when PGRS-SCZ is added to hierarchical regression analyses), $R^2 = .042$ (total brain volume); whilst others did not find an effect (52, 53) ($n_{\text{individuals}}$ range = 122-763). Higher PGRS-SCZ has also been previously associated with lower global CT in a case-control sample, regardless of group (54) ($\eta^2 = .116$ (left hemisphere); $.121$ (right hemisphere)). Lancaster *et al.* (55) found no such association in a control sample but did report nominal regional CT effects. Due to the

limited sample sizes in these CT investigations ($n_{\text{individuals}}$ range = 75-99), further testing is required.

Another important consideration, as per neurodevelopmental theories of the disorder (7-9), relates to potential effects of other risk factors for schizophrenia and their interactions between schizophrenia liability and cortical structure. Several obstetric complications (OCs), for example, have been consistently identified as risk factors for schizophrenia (56-63) with some, such as birth weight, considered to be influenced by both genetic and environmental components (64). Previous studies have also suggested that OCs are associated with greater cortical structure deficits in schizophrenia patients compared to controls (27, 63). All three of the current cortical metrics are considered to be highly susceptible to both genetic and environmental factors (65) with subtle differences in birth weight, in particular, previously linked to lower CV, SA (66-68) and CT (67) later in life. Moreover, evidence suggests that a genetic liability for schizophrenia can lead to higher susceptibility for experiencing OCs (69, 70) and that these complications could themselves be associated with the schizophrenia-associated genes (56). Given these findings, we also tested whether PGRS-SCZ was associated with birth weight and if any interactions were present between the two in relation to cortical structure.

The current study tests for associations between PGRS-SCZ and cortical structure (CV, SA and CT), in a population-based sample, with the specific hypothesis that a higher PGRS-SCZ would be associated with lower global CT. Lower global, frontal and temporal CT in particular has been found in those at familial high-risk and global CT has been previously associated with a higher PGRS-SCZ (54). Furthermore, we predicted that these effects would interact with birth

weight; individuals with a higher PGRS-SCZ with lower birth weight would have smaller CV, CT and SA.

2. Methods and Materials

2.1 Participants Detailed participant information for UKB has been reported previously (71) (<http://www.ukbiobank.ac.uk/participants/>) and in **Supplementary Material**. The current sample included individuals with complete genetic and cortical data for three parameters (CV, SA and CT). Participants were excluded based upon overlap in Psychiatric Genomics Consortium (PGC) prediction samples and schizophrenia status, see *Derivation of Polygenic Risk Scores* and **Supplementary Material**. Global cortical outliers (± 3 S.Ds), were removed for all three parameters. Thus, the current sample consisted of 2,864 individuals ($n_{\text{males}}/n_{\text{females}} = 1382/1482$; mean age at time of scan = 62.35 years, $\pm$ S.D = 7.40 years, range = 46-78 years). Ethical approval for UKB was received from the research ethics committee (REC reference 11/NW/0382) under application 4844. Informed consent was provided by all participants (<http://biobank.ctsuo.ox.ac.uk/crystal/field.cgi?id=200>).

2.2 Imaging Procedures UKB imaging details are described in full elsewhere (71-73) (https://biobank.ctsuo.ox.ac.uk/crystal/docs/brain_mri.pdf). Briefly, structural images were acquired on a single 3T Siemens Skyra scanner. Structural brain images were acquired in the sagittal plane using a T1-weighted MPRAGE sequence (1×1×1mm resolution). Further information on the imaging protocol (<http://biobank.ctsuo.ox.ac.uk/crystal/refer.cgi?id=2367>) and acquisition parameters (<http://biobank.ctsuo.ox.ac.uk/crystal/refer.cgi?id=1977>) are documented online. Brain scans were processed locally in Edinburgh, using FreeSurfer (v5.3, <http://surfer.nmr.mgh.harvard.edu/>), on a server cluster at Centre for Cognitive Ageing and Cognitive Epidemiology (CCACE, <http://www.ccace.ed.ac.uk/>).

2.3 MRI Analysis T1-weighted volumes from the first UKB imaging release were used to derive cortical measures of CT (mm), SA (mm²) and CV (mm³). Parcellation was conducted using the Desikan-Killiany neuroanatomical atlas (74), generating 34 bilateral cortical parcels, attributed to eight lobar structures, each with CV, SA and mean CT measures (74). Eleven parcels were combined into four larger regions as previous (75, 76); resulting in 27 bilateral regions of interest in total, see **Supplementary Material**. X, Y and Z co-ordinates of the centre of the brain mask within the scanner were fitted as covariates for the current analyses to account for varying head positions in the scanner; see **Supplementary Material**.

2.4 MRI Quality Control Procedures Quality checks of T1-weighted images were initially carried out by UKB (Brain Imaging Documentation V1.1, <http://www.ukbiobank.ac.uk>, (77)) with further local Quality Control (QC) procedures (see (76), <http://enigma.ini.usc.edu/protocols/imaging-protocols/> and **Supplementary Materials**).

2.5 Genotyping and Imputation Processing Procedures for genotyping, imputation and quality control for UKB have been reported previously (79-81). Briefly, 488,377 blood samples were assayed using two different genotyping arrays; Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (79) and Applied Biosystems UKB Axiom Array (<http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary-2014.pdf>), see **Supplementary Material**.

Genetic QC was performed using the approach described by Howard *et al.* (81). Firstly, participants were excluded based on shared genetic relatedness up to the third degree using kinship coefficients (>.044) identified using the KING toolset (82), as previous (81, 83). To maximise the sample, we subsequently added back in one member from each group of related

individuals, using a genomic relationship matrix, and selected only those with a relatedness of less than .025 with any other individual. Individuals were also excluded based upon a combination of both self-reported ethnicity and a principal component (PC) analysis (see **Supplementary Material**) which revealed individuals with similar ancestral backgrounds. Final QC exclusion criteria included variant missing-ness per individual (>2%), gender mismatch, variant call rate (<98%), Hardy-Weinberg equilibrium ($P < 10^{-6}$), minor allele frequency < .01, an imputation quality < .1, resulting in 331,374 individuals and 7,730,951 variants.

2.6 Derivation of Polygenic Risk Score PGRS-SCZ were constructed using PLINK v1.9 (84) to calculate the sum of all alleles that are associated with schizophrenia, across many genetic loci, and weighting these alleles by their effect sizes. These effect sizes have been previously estimated (PGC-SCZ, <https://www.med.unc.edu/pgc/pgc-workgroups>) GWAS (36, 989 cases, 113,075 controls) (5). Individual identifiers were not available for PGC-SCZ within this sample thus, in an attempt to reduce the likelihood of any potential overlap between PGC-SCZ and the current sample, individuals from the PGC Major Depressive Disorder (MDD) working group prediction sample (85) were excluded ($n = 92$). For the same reason, UKB individuals who reported a diagnosis of schizophrenia were also excluded ($n = 812$, see **Supplementary Fig S1**). Schizophrenia status was determined from two separate variables within UKB: International Classification of Diseases (ICD-10) diagnosis (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=41202>; F20-F29 Schizophrenia, schizotypal and delusional disorders) and non-cancer illness (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20002>). The former is a summary of the distinct diagnoses given from episodes in hospital; the latter was coded by a trained nurse based on the description of a non-cancer illness given by the participant.

To create a SNP-set in approximate linkage equilibrium, clump-based linkage disequilibrium pruning was performed with a r^2 of < 0.25 within a 200kb window. For the remaining SNPs, marker weights (logarithm of the Odds Ratio) and p-value association statistics for individual SNPs were derived from the most recent PGC GWAS of schizophrenia (9.8 million autosomal SNPs) (5). Five scores were generated for each individual, using SNPs selected according to the significance of their association with the phenotype in the discovery GWAS at nominal P-value thresholds of $\leq 0.01, 0.05, 0.1, 0.5, 1$, as previously described (3). The SNP inclusion threshold was set at $P \leq 0.1$ for the current paper, as this threshold was shown to explain the most phenotypic variance in the discovery cohort (5). There were 86,124 SNPs, available in the current sample after QC, using the $P \leq 0.1$ threshold (see **Supplementary Material**). For results produced using the remaining SNP inclusion thresholds ($P \leq 0.01, 0.05, 0.5$ and 1), see **Supplementary Materials**. PCs were also calculated to account for population stratification (see **Supplementary Materials**), the first 15 PCs were used in the current analysis.

2.7 Measure of Birth Weight Participants were asked to provide their own BW information (see **Supplementary Materials**). Recalled BW has been shown to have high agreement with recorded BW and considered a valid measure for epidemiological studies (86). BW range = .91-5.78kg (mean = 3.40kg, $\pm$ S.D = .61kg).

2.8 *Covariates* *Socioeconomic* *Deprivation*

(<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=189>) was measured using the Townsend deprivation index (see **Supplementary Materials**) (range = -6.26 – 9.16, mean = -1.98, $\pm$ S.D = 2.68). *Standing height* (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=50>) was measured using a Seca 202 device (range = 143 – 196cm, mean = 169.74cm, $\pm$ S.D = 9.20cm).

2.9 Statistical Analysis

All analyses were conducted in R (v3.2.3).

2.9.1 Associations Between PGRS-SCZ and Cortical Structure Linear mixed effects (LME) models (package “nlme”, v3.1-127) were used to determine whether PGRS-SCZ were associated with cortical structures.

LME models were first conducted in a repeated measures format, with hemisphere fitted as a random factor, as previous (48, 78). PGRS-SCZ*hemisphere interactions were also tested to determine if analysis of left and right homologous structures separately was required.

For the main analyses, an LME model was tested which included age, age², sex, genotype array, 15 PCs and X, Y and Z co-ordinates of the brain mask within the scanner, as fixed effects. Intracranial volume (ICV) was included as a fixed effect for lobar and parcellation analyses. Standardised regression coefficients are reported throughout. Utilising the ‘p.adjust’ function (‘stats’ package v3.2.3), the false discovery rate (FDR) method, with a rate of $P < .05$ (87), was used to correct results for multiple comparisons. Henceforth, FDR-corrected P values will be referred to as p(FDR).

In the first instance and in line with our main hypothesis, we tested for associations between PGRS-SCZ and global cortical structure. These PGRS-SCZ global cortical associations were FDR corrected across CV, CT and SA at each PGRS-SCZ SNP inclusion threshold individually. Associations between PGRS-SCZ and regional cortical structures were tested for if global cortical associations were evident; first at the lobar and then parcellation level. Thus, for post-hoc regional associations, p(FDR) was calculated for each cortical metric individually, by correcting over all 8 possible lobar structures or 27 parcellations for each PGRS-SCZ P -threshold.

In the main text, we only report statistically significant associations ($p(\text{FDR}) < .05$) between PGRS-SCZ and cortical brain structure. Furthermore, the reported results were analysed using the SNP inclusion threshold of $P \leq 0.1$ as this threshold explained the most phenotypic variation in the discovery cohort ($R^2 = \sim 0.18$ (5)). Non-significant associations and results for all other thresholds as can be found in **Supplementary Material**.

2.9.2 Associations Between PGRS-SCZ and Birth Weight Using the full sample of individuals with cortical, genotype and BW information, excluding global cortical outliers ($n = 1,659$, $n_{\text{males}}/n_{\text{females}} = 696/963$; mean age at time of scan = 60.79 years, $\pm$ S.D = 7.41 years, range = 46-78 years), a generalised linear model regression (package “glm2”, v1.1.3) was used, to test for associations between PGRS-SCZ and birth weight. This model included all fixed effects used in the previous model, with the addition of height and socioeconomic deprivation, see (67, 68), as fixed effects. LME models, using these same fixed effects, hemisphere as a random factor and an additional PGRS-SCZ $\times$ BW interaction, along with main effects terms, were also used to test for potential interactional effects on cortical structure.

3. Results

3.1 Demographics

Statistical analyses were conducted to determine if any of the demographic variables were associated with PGRS-SCZ at threshold $P \leq 0.1$ (see **Table 1**). No significant associations were found ($P > 0.05$).

 Insert Table 1 here

3.2 Associations Between PGRS-SCZ and Cortical Structure

Results for PGRS-SCZ $\times$ hemisphere interactions on cortical structure can be found in **Supplementary Material (Table S2-4)**. No significant hemisphere interactions were found in the current study ($P > 0.05$) thus all analyses were conducted utilising the aforementioned repeated measure design.

Significant negative associations between PGRS-SCZ and global CT ($\beta = -.043$, $p = .012$, $R^2 = .002$) and CV ($\beta = -.033$, $p = .039$, $R^2 = .001$) were found, in that a higher PGRS-SCZ was associated with lower CT and CV across the whole brain. However, only the association with CT remained significant after multiple correction across all three metrics (CT $p(\text{FDR}) = .036$, CV $p(\text{FDR}) = .059$). PGRS-SCZ was also negatively associated with insular lobe CT ($\beta = -.050$, $p(\text{FDR}) = .025$, $R^2 = .002$).

No significant associations between PGRS-SCZ and SA were found; this was true for all global, lobar and parcellation measures, see **Supplementary Material**.

3.3 Associations Between PGRS-SCZ and Birth Weight There was no significant association between PGRS-SCZ and birth weight (see **Table 2**).

Insert Table 2 here

3.4 Effects of Interactions Between Birth Weight and PGRS-SCZ on Cortical Structure No significant interactions between birth weight and PGRS-SCZ were found with respect to associations with global CV or CT. See **Table S6-8** in **Supplementary Materials** for full results.

4. Discussion

We report an association between an increased genetic liability for developing schizophrenia and lower global CT and CV, as well as insular lobe CT. In this and previous studies (54, 88) we primarily test and report corrected results using SNPs with $P \leq 0.1$. We also include results corrected over all three cortical metrics to illustrate the effects of more stringent control for multiple comparisons, and note that the association between PGRS-SCZ and global CV was not significant after this correction. This is one of the first studies to analyse associations for CV, CT and SA measures within a single large, population-based sample, and to examine the association between these parameters and PGRS-SCZ. Overall, these results suggest that lower CT, commonly reported in schizophrenia patients, may be driven by a genetic liability for schizophrenia and are most likely not due to factors downstream of disease onset (e.g. medication use (89)). No significant associations were found for SA.

Previous study of associations between PGRS-SCZ and brain volume have been inconsistent. Lee *et al.* (90) found ICV to be significantly linked with enrichment of schizophrenia-associated genetic variants but could not determine the direction of these effects. Another study, utilising a PGRS-SCZ created from the first PGC-SCZ GWAS (91) found an association between decreased total brain volume and higher PGRS-SCZ (49) but attempts to replicate

these results, with the most recent PGC-SCZ GWAS findings (5), have so far been unsuccessful (52, 53). However, the sample sizes used within these studies are relatively small ($n_{\text{individuals}}$ range = 122-763). This is especially pertinent when considering that, despite the current sample being much larger ($n_{\text{individuals}}$ = 2,864) than these previous studies, our CV result did not survive FDR corrections for multiple comparisons over all three cortical metrics. Thus, further testing in an even larger population-based samples is desirable.

The global CT association is consistent with previous familial high-risk studies for schizophrenia, which also found thinning in widespread areas of the cortex both longitudinally (42, 44, 47) and cross-sectionally (21, 40, 41, 43). A genetic enrichment study also found several CT parcels to be associated with schizophrenia risk variants (90). Furthermore, a case-control study found that a higher PGRS-SCZ was associated with lower global CT in both the schizophrenia patient only analysis and in the whole sample (54). Specific links between reduced insular CT and genetic risk for schizophrenia have been less commonly reported, although reductions in this region, among others, have been found in schizophrenia patients compared to controls and individuals at genetic high-risk of the disorder (41). Additionally, the insula is a region commonly reported to be involved in schizophrenia symptomatology (e.g. auditory hallucinations (92)).

That no PGRS-SCZ associations were found for SA is not entirely surprising. Evidence of SA abnormalities associated with schizophrenia has been inconsistent (24) and has been described as a ‘weak intermediate phenotype’ for schizophrenia (20). However, evidence does suggest that this phenotype is highly heritable (15) and is associated with some deficits in the healthy relatives of schizophrenia patients (21). A general limitation of PGRS, at present, is that the amount of phenotypic variation that they explain is far smaller than the heritability of the

phenotype (48, 93); thus, it may be that the predictive power of PGRS-SCZ in combination with the current sample size are not large enough to detect an effect with SA.

No association was found between PGRS-SCZ and birth weight, nor were there interaction effects between these two factors within global CT. As previous studies have found lower birth weight to be associated with lower CV (66-68), thinning and thickening across the cortex (67, 94), an increased risk of schizophrenia (60-62) and several independent SNPs (95, 96); we expected to find a link between these factors. However, the current findings suggest that genetic variants for schizophrenia and birth weight could have independent effects on CT. Further investigation is needed to determine this.

4.1 Strengths and Limitations

The main limitation of the current study and PGRS-SCZ studies in general, is that, at present, the variance of schizophrenia explained by PGRS is relatively small (around 2-3% (3)) and that larger sample sizes could significantly increase the power of this method (97). Despite this study being the largest imaging PGRS study to date, with 2,864 individuals (48, 49, 52, 53), it is still relatively small compared to other PGRS studies (e.g. (98-100)). Furthermore, a post-hoc analysis (see **Supplementary Material**) suggests that the current study was underpowered (5-41%) for some analyses, highlighting the need for even larger imaging samples. Current calculations suggest a sample of at least ~21,500 to reliably detect some effects of current PGRS-SCZ on cortical structure. Given UKB's goal of acquiring 100,000 scans by 2022 (<https://imaging.ukbiobank.ac.uk/>), we should be able to improve our sample size in the near future. This sample size, coupled with larger discovery GWAS, will allow for detection of smaller effects (48, 101, 102) and may eventually allow PGRS to be used in the development of personalised medicine (101) however, further research would be necessary.

A further limitation, related to the derivation of the PGRS-SCZ, is that we were unable to remove any individuals utilised in the discovery dataset for the PGC schizophrenia working group that may also be included in the current UKB sample, as this information is not currently available. However, due to the methodological efforts made to overcome this issue (e.g. exclusion of schizophrenia cases and IDs from the PGC MDD group) we believe this limitation to be relatively minor as effects will be restricted to controls only.

Although multi-centre collaborations have made larger samples more achievable, different acquisition protocols could lead to variability in image contrast and, in turn, discordance over brain segmentation between sites; necessitating the development of reliable acquisition protocols to attempt to reduce such issues (35, 103). A strength of the current study is that all brain images were collected on a single scanner using the same protocol and analysis pipeline thus, by-passing multi-scanner variability problems and the need to assess reliability. Furthermore, as UKB is a population-based sample and all schizophrenia cases were excluded, we are also able to test for associations whilst avoiding confounds such as secondary effects of illness or antipsychotic medication use (89).

Previous studies have reported that individuals at familial high-risk, who developed schizophrenia, have significantly higher PGRS-SCZ than those at high-risk who remained well and that these PGRS are positively associated with gyrification (88). It is possible that there are different genetic associations for different brain measures than derived for in the current study. Given the current sample consisted of older individuals (46-78 years, mean = 62.3), compared to most schizophrenia studies (49, 50, 52, 53, 104), which commonly include age ranges that more closely map to age of disorder onset (18-55 years), we cannot rule out effects

of ageing on the current results. Further investigation in prospective case-control samples is required.

Although the inclusion of birth weight, a proxy for OCs and risk factor for schizophrenia which is influenced by both genetic and environmental factors (60-62, 65), is a strength of the current paper, we cannot rule out environmental effects on our current findings. For example, both cannabis use and developmental trauma have been linked with reductions in CT (105) and an accumulation of environmental risk factors (including migration, cannabis use, urbanicity, OCs and adverse events) has been associated with lower temporal CT (54). Furthermore, cannabis use has been found to moderate the link between PGRS-SCZ and cortical maturation (106). Thus, environmental risk factors should be explored in further studies of potential gene-environment interactions on structural brain measures in schizophrenia.

5. Conclusion

In summary, the current finding that lower global CT, as well as insular lobe CT, is associated with an increased genetic loading for schizophrenia. This provides further evidence that individual differences in CT are, at least partly, influenced by a genetic component. Importantly, these findings also suggest that the schizophrenia and CT associations, reported here and in previous literature, are most likely not confounded by factors downstream of disorder onset (e.g. use of medication). Furthermore, it suggests that using a PGRS approach may help to elucidate the genetic pathophysiology of the disorder, as GWAS and genomic imaging studies get larger they could identify how more specific genetic, expression and pathway effects impact upon global and/or particular brain structures, connections and networks. Further consideration of environmental risk factors for schizophrenia will also be

crucial to understanding the nature of the relationship between schizophrenia and cortical structure.

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Author Contributions Collected data: UKB team. Analysed the data: EN. and XS.; supervision of analysis: SML, AMM. and HCW. Contributed reagents/materials/analysis tools: XS, SRC, TK-C, MJA, DMH, EMW and JG. Aided in quality control of MRI and genetic data: EN, XS, SRC., EMW, JG, DMH, MJA, MAH, SH and GD. Manuscript preparation: E.N.; additional editing: SML, IJD, DMH, TK-C. All authors commented on drafts of the paper.

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Tables

Table 1. Descriptive statistics for demographic variables and their associations with PGRS-SCZ

	Range	Mean	S.D	Test statistic, <i>P</i> -value
Gender (<i>n</i> _{males} / <i>n</i> _{females} =1382/1482)	-	-	-	$X^2 = 2707.8, p = .513$
Age	46 - 78	62.35	7.40	$r = -.003, p = .863$
Birth weight (kg)	.91 – 5.78	3.40	.61	$r = -.044, p = .069$
Height (cm)	143 - 196	169.73	9.12	$r = -.033, p = .077$
Townsend Deprivation Scale	-6.26 – 9.16	-1.98	2.68	$r = .017, p = .363$

. $p \leq .10$, X^2 = chi-squared, r = Pearson's correlation

Mean, standard deviation (S.D) and range of all demographic variables within the current sample as well as test statistics for associations with PGRS-SCZ at the $P \leq 0.1$ threshold ($n = 2,864$)

Table 2. Results for associations between PGRS-SCZ and birth weight at all P thresholds

PGRS Threshold	Effect Size	S.D	P-value	p(FDR)
$P \leq 0.01$	-0.016	0.024	0.513	0.513
$P \leq 0.05$	-0.037	0.024	0.122	0.305
$P \leq 0.1$	-0.041	0.024	0.090	0.305
$P \leq 0.5$	-0.021	0.024	0.380	0.513
$P \leq 1$	-0.019	0.024	0.423	0.513

Standardised Betas (Effect Size), standard deviations (S.D) and P -values for all associations as well as FDR corrected P -values (p(FDR)) over all five PGRS SNP inclusion thresholds ($n = 1,659$)