

ARTICLE



Novel disease associations with schizophrenia genetic risk revealed in ~400,000 UK Biobank participants

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Schizophrenia is a serious mental disorder with considerable somatic and psychiatric morbidity. It is unclear whether comorbid health conditions predominantly arise due to shared genetic risk or consequent to having schizophrenia. To explore the contribution of genetic risk for schizophrenia, we analysed the effect of schizophrenia polygenic risk scores (PRS) on a broad range of health problems in 406 929 individuals with no schizophrenia diagnosis from the UK Biobank. Diagnoses were derived from linked health data including primary care, hospital inpatient records, and registers with information on cancer and deaths. Schizophrenia PRS were generated and tested for associations with general health conditions, 16 ICD10 main chapters, and 603 diseases using linear and logistic regressions. Higher schizophrenia PRS was significantly associated with poorer overall health ratings, more hospital inpatient diagnoses, and more unique illnesses. It was also significantly positively associated with 4 ICD10 chapters: mental disorders; respiratory diseases; digestive diseases; and pregnancy, childbirth and the puerperium, but negatively associated with musculoskeletal disorders. Thirty-one specific phenotypes were significantly associated with schizophrenia PRS, and the 19 novel findings include several musculoskeletal diseases, respiratory diseases, digestive diseases, varicose veins, pituitary hyperfunction, and other peripheral nerve disorders. These findings extend knowledge of the pleiotropic effect of genetic risk for schizophrenia and offer insight into how some conditions often comorbid with schizophrenia arise. Additional studies incorporating the genetic basis of hormone regulation and involvement of immune mechanisms in the pathophysiology of schizophrenia may further elucidate the biological mechanisms underlying schizophrenia and its comorbid conditions.

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INTRODUCTION

Individuals with schizophrenia are at increased risk for numerous additional health problems, including both psychiatric disorders and somatic diseases. Anxiety, depression, obsessive-compulsive disorder, post-traumatic stress disorder, eating disorders, and substance abuse disorders are all observed more often in individuals with schizophrenia compared with the general population [1–3]. Moreover, numerous non-psychiatric disorders are also elevated in individuals with schizophrenia including: stroke, diabetes mellitus, influenza or pneumonia, chronic obstructive pulmonary disease (COPD), autoimmune disorders, metabolic disturbances, and dementia [4–7]. However, the etiology of most of these comorbidities remains elusive. Although there has been growing evidence recently suggesting SNP-based genetic correlations between schizophrenia and multiple traits using linkage disequilibrium score regression (LDSC) [8, 9], questions remain regarding the cause of commonly comorbid conditions due to the difficulties in quantifying a dose-response relationship from LDSC. Furthermore, it remains unclear to what extent the comorbidities stem from underlying shared genetic risk or arise consequent to having schizophrenia (e.g., from poor dietary habits or antipsychotic medication effects).

Strong evidence supports an important role of genetics in the etiology of schizophrenia with heritability estimated at 64–81% [10, 11]. Numerous common genetic variants, copy number variants (CNVs), rare genetic variants, and their interactions are all found to contribute to the risk for schizophrenia [12–16]. Although the contribution of single genetic variants or CNVs to schizophrenia liability is small (e.g., CNVs explain 0.85% of the variance) [13], the accumulation of common variants i.e., polygenic risk scores (PRS) are robustly associated with schizophrenia and explains a significant portion of variance (increased from 3.2% to 22.1%) [12, 17–19]. Thus, PRS provide a tool to quantify and index the genetic risk of schizophrenia in investigations of comorbidity.

The pleiotropic effect of schizophrenia PRS on psychiatric disorders and other medical syndromes was observed in a patient population from the US electronic health system [20]. Even with limited follow-up time and a selected patient sample which included schizophrenia patients, schizophrenia PRS was found to be positively associated with several psychiatric phenotypes including anxiety, mood, and substance use disorders, which previously demonstrated significant positive genetic correlation with schizophrenia [21–24]. Obesity was found to be inversely related to schizophrenia PRS, also supporting a prior negative

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genetic effect [20]. Moreover, most of the phenotypes remained significant after adjusting for schizophrenia status.

Restricting analyses to individuals without schizophrenia may provide insight into whether the relationships between genetic risk for schizophrenia and other health outcomes are due to the direct effect of shared genetic risk or indirect effects from medications and lifestyle differences that follow from having schizophrenia. This approach is central to providing a better understanding of the biological mechanisms giving rise to comorbid conditions.

The present study uses large datasets for both a wide range of phenotypes and the schizophrenia PRS generation to investigate the influence of schizophrenia PRS (as an index of genetic risk for schizophrenia) on various health outcomes in individuals without a schizophrenia diagnosis. Specifically, we investigated the associations between schizophrenia PRS and general health, broad domains of medical conditions indexed by ICD10 main chapters, and a wide range of psychiatric and somatic illnesses in over 400,000 individuals with no schizophrenia diagnosis in UK Biobank.

MATERIALS AND METHODS

Data source and study population

The UK Biobank is a large-scale biomedical research resource consisting of over 500,000 participants aged 39–73 years recruited from England, Wales, and Scotland between 2006 and 2010 [25]. The linkage to the health-related records including primary care, hospital in-patient records, cancer register data, and death records makes it possible to investigate a broad range of health outcomes.

Of 488,264 individuals with available genotype data and linked health data, we restricted analyses to individuals with consistent sex information and White-British ancestry determined on the basis of self-report and genetic data [25]. Individuals ($N = 2087$) with any record of a schizophrenia diagnosis or other type of psychosis or psychotic illness from primary care records, hospital in-patient records, and/or death records demonstrated a 0.53 (95% CI: 0.48–0.58, p value: 2.65×10^{-93}) significantly higher schizophrenia PRS than those without these conditions. They were excluded from further analyses, yielding a final sample of 406,929 individuals.

The use of these data has been approved by the research ethics committee of UK Biobank. All participants included in this study have provided informed consent when enrolled in UK Biobank. This research was conducted under application number 54928.

Schizophrenia-PRS

The PRS were computed using summary statistics from the PGC schizophrenia GWAS as the discovery dataset [12] using PLINK1.9. Detailed information for genotyping and quality control of UK Biobank data was described previously [26]. SNP quality control, including filtering for minor allele frequency (MAF > 0.10) and imputation quality (INFO > 0.9), resulted in a subset of 5,471,645 SNPs. These were clumped into clusters of approximate linkage disequilibrium ($R^2 < 0.1$, within 1000 kb distance). The classic thresholding + clumping approach was used to generate PRS with ten different p value thresholds to select genetic variants, $p < 5e-08$, $p < 1e-06$, $p < 1e-04$, $p < 0.001$, $p < 0.01$, $p < 0.05$, $p < 0.1$, $p < 0.2$, $p < 0.5$, and $p < 1$ [27].

To consolidate predictive power across PRS thresholds and minimize the multiple testing burden, we performed principal component analysis on the set of ten PRS [28] in R, version 4.0.3. The first principal component, PRS-PC1, was then standardized and used for further association testing.

Assessment of outcomes

The linked health data cover primary care data (Read code), hospital inpatient data (ICD-9 and ICD-10 codes), cancer register records (ICD-9 and ICD-10 codes), death register records (ICD-10 codes), and self-reported medical condition codes disclosed at baseline or follow-up [29–31]. A wide range of health outcomes across the linked health data included self-reported phenotypes have been mapped into a 3-digit code of ICD-10 as described in the UK Biobank document [31]. Together with the records from the cancer register, around 1200 unique 3-character ICD10 codes covering ICD10

chapters I–XVII were identified to indicate the first occurrence of health outcomes for each individual. The mapped ICD10 codes were then converted into phenotype codes (phecodes), which were considered to be better aligned with the terminology used in clinical practice [32, 33]. A total of 768 phecodes were matched in the current study.

Outcomes of interest for this study from broad to narrow definitions were obtained from the linked health data including general health, ICD10 main chapters corresponding to phenotypic groupings, and specific somatic and psychiatric illnesses (phecodes). General health measures included self-report overall health rating at baseline (scored 1–4, where a higher number indicates poorer self-rated overall health), total number of all hospital inpatient diagnoses received, total number of all primary care diagnoses received, and total number of all unique phecodes identified throughout the coverage period of UK Biobank registers [29, 30]. In order to enhance the generalizability of the results, we removed a small number of people with extremely high numbers of diagnoses. The upper limit of total number of all hospital in-patient diagnoses received was therefore set to 100. The upper limit for primary care diagnoses was set to 1500, and the upper limit for unique phecodes was set to 60 (Fig. S1). In the next stage of health outcomes, participants who ever received at least one relevant diagnosis in a certain ICD-10 main chapter were defined as cases for that chapter. Thus, 17 binary variables for each of the ICD-10 main chapters were created following the same procedures. When narrowing down to the specific somatic and psychiatric illnesses, participants with at least one relevant ICD-10 code mapped to a phecode were defined as cases, whereas individuals without the phecode of interest were defined as controls. After excluding phecodes with fewer than 200 cases [34], a total of 603 phecodes were retained for further analyses (Supplementary Results Sheet 1).

Statistical analyses

Data management and analyses were performed using R, version 4.0.3, and PRS were computed using PLINK1.9. In the first stage of the analysis, linear regressions (the ‘drgee’ package in R) were used for overall health rating at baseline, total number of all hospital inpatient diagnoses received, total number of all primary care diagnoses received, and total number of all unique illnesses identified from the linked health data adjusting for birth year, sex, attained age, region of the UK (England, Scotland, or Wales), and the first ten genetic principal components. Regression coefficients with 95% confidence intervals (CIs) and corresponding p values were reported. In these linear regressions we used robust (“sandwich”) standard errors, which avoid assuming normality and homoscedasticity of the outcomes [35].

In the second stage of the analysis, logistic regressions (the ‘drgee’ package in R) were used for 17 ICD10 main chapters (except for chapter XVI, due to low prevalence of cases) while adjusting for birth year, sex, attained age, region, and the first ten genetic principal components. Odds ratios (ORs) with 95% CIs were reported as risk estimates for ICD10 main chapters per unit increase of PRS-PC1.

In the third stage of the analysis, we conducted a PheWAS for PRS-PC1, using all phecodes with at least 200 cases. Logistic regressions were carried out through the ‘PheWAS’ package in R of each phecode against the PRS-PC1 adjusting for sex, birth year, attained age, region, and 10 genetic principal components provided by UK Biobank.

For all models, the regression analyses were restricted to participants with complete information on all variables in the model, resulting in slight differences in the sample size of each analysis (Table S1). Correction for multiple tests was implemented using Bonferroni corrections ($p < 0.003$ for ICD main chapters, $p < 8.29 \times 10^{-5}$ for phecodes).

Despite removing individuals with schizophrenia or other psychotic illnesses from analyses, a number of people remained who had been prescribed antipsychotic medications ($N = 9,687$). In order to investigate the extent to which individuals using antipsychotic medications impact the results, we performed further sensitivity analyses in a sub-population with General Practitioner (GP) registration records ($N = 157,018$), and with available GP prescription information ($N = 69,294$) using the same regression models as above and additionally adjusting for antipsychotic use in the models. Since 17.9% of the three-character codes were not able to be matched to phecodes, we also performed a sensitivity analysis using original ICD-9 and ICD-10 codes from hospital inpatient records as an internal validation.

Furthermore, due to the genetic correlation between psychiatric disorders [36, 37], we performed a sensitivity analysis additionally adjusting for mental and behavioral disorder (chapter V) status for all the other ICD10 main chapters to check whether the associations between schizophrenia PRS and those chapters are mediated by mental disorders.

Table 1. Descriptive characteristics of the study population.

	N = 406,929
Sex	
Female (%)	220,153 (54.1)
Male (%)	186,776 (45.9)
Birth year (mean ± SD)	1951 ± 8.0
Attained age ^a (mean ± SD)	56.9 ± 8.0
Region of the UK	
England (%)	296,248 (72.8)
Scotland (%)	25,768 (6.3)
Wales (%)	13,868 (3.4)
Missing (%)	71,045 (17.5)
Self-report overall health rating	
1 = Excellent (%)	67,672 (16.6)
2 = Good (%)	238,009 (58.5)
3 = Fair (%)	82,998 (20.4)
4 = Poor (%)	16,826 (4.1)
Missing (%)	1424 (0.4)
Total inpatient diagnoses	6,881,462
Total primary care diagnoses	101,441,015

^aAttained age is defined as the participants' age at their enrollment in the UK Biobank.

To examine the degree of correlation between the effect estimates from the previous study [20] and ours, we ran a Pearson's correlation test of ORs between our main PheWAS results and the sensitivity analysis (Phecode 295 cases excluded) results from the previous paper matched by phecodes. Pearson's correlation coefficient with 95% CI and *p* value were reported.

RESULTS

The demographic and clinical characteristics of the study population are presented in Table 1. Of the 406,929 UKB individuals, 54.1% were females. The average attained age was 56.9 years. All individuals with available primary care records and hospital inpatient information had collectively received over 101.4 million primary care diagnoses and 6.8 million hospital inpatient diagnoses. The prevalence of cases for each of the ICD10 main chapters is presented in Fig. S2.

Associations of SCZ PRS-PC1 with general health conditions

The estimated differences with 95% CIs and corresponding *p* values for overall health rating, cumulative measurements including total inpatient diagnoses, total primary care diagnoses, and total unique phecodes per standard deviation increase of schizophrenia PRS-PC1 are presented in Table 2.

Higher schizophrenia PRS-PC1 was associated with poorer self-reported overall health rating ($\text{coef} = 0.02, P = 2.02 \times 10^{-32}$). One standard deviation of schizophrenia PRS-PC1 was significantly associated with receiving 0.12 more inpatient diagnoses ($P = 5.24 \times 10^{-5}$) and 0.09 more unique diagnoses ($P = 3.03 \times 10^{-5}$) on average. A similar association was also detected for higher schizophrenia PRS-PC1 and receiving more total primary care diagnoses ($\text{coef} = 0.80, P = 0.35$), albeit not statistically significant, which might be due to the smaller sample size (Table S1).

Primary associations of SCZ PRS-PC1 with ICD10 main chapters

We tested the associations between schizophrenia PRS-PC1 and 16 ICD10 main chapters for 335,874 individuals with complete information on mapped ICD10 codes from primary care data, hospital inpatient data, cancer register records, and death register

Table 2. Linear regression of general health conditions and schizophrenia PRS-PC1.

	Regression coefficient ⁵ (95% CI)	<i>p</i> value
Overall health rating ¹	0.02 (0.013, 0.018)	2.02×10^{-32}
Total diagnoses		
Hospital inpatient ²	0.12 (0.06, 0.19)	5.24×10^{-5}
Primary care ³	0.80 (-0.89, 2.49)	0.35
Unique phecodes ⁴	0.09 (0.05, 0.13)	3.03×10^{-5}

Number of individuals with complete information for each analysis: $N_1 = 334,586$; $N_2 = 324,511$; $N_3 = 151,643$; $N_4 = 324,493$; ⁵Effect sizes are in standard deviations (SDs) of PRS-PC1.

Bold values denote statistical significance at a *p* < 0.05 level.

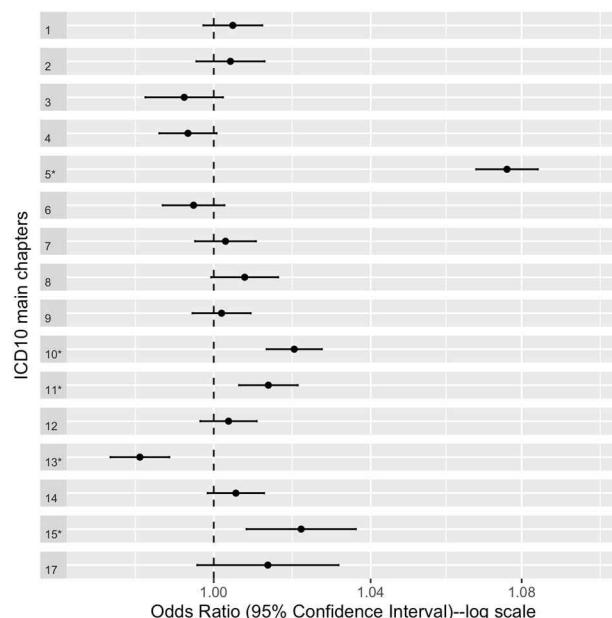


Fig. 1 Odds ratios for ICD10 main chapters corresponding to 1 standard deviation increase in schizophrenia PRS-PC1. The vertical line (odds ratio = 1) reflects no change in risk. Error bars indicate 95% confidence intervals. *Indicates significant associations after Bonferroni correction (*p* value < 0.003). Chapter names corresponding to chapter numbers: 1 = Certain infectious and parasitic diseases; 2 = Neoplasms; 3 = Blood and blood-forming organs and certain disorders involving the immune mechanism; 4 = Endocrine, nutritional and metabolic diseases; 5 = Mental and behavioral disorders; 6 = Nervous system disorders; 7 = Eye and adnexa disorders; 8 = Ear and mastoid process disorders; 9 = Circulatory system disorders; 10 = Respiratory system disorders; 11 = Digestive system disorders; 12 = Skin and subcutaneous tissue disorders; 13 = The musculoskeletal system and connective tissue disorders; 14 = The genitourinary system disorders; 15 = Pregnancy, childbirth and the puerperium; 17 = Congenital malformations, deformations and chromosomal abnormalities.

records, and all covariates. Chapter XVI was not tested for association due to the extremely low prevalence of diagnoses in the study population (Fig. S2). Figure 1 presents the ORs with 95% CIs for ICD10 main chapters corresponding to 1 standard deviation increase in schizophrenia PRS-PC1.

Five ICD10 main chapters remained statistically significant after Bonferroni correction (*P* < 0.003) (Table S2). The strongest and most significant association with schizophrenia PRS-PC1 was Chapter V, mental and behavioral disorders ($\text{OR} = 1.08, \text{SE} = 0.004, P < 2 \times 10^{-16}$), followed by Chapter X, diseases of the respiratory system ($\text{OR} = 1.02, \text{SE} = 0.004, P = 1.24 \times 10^{-8}$), Chapter XV,

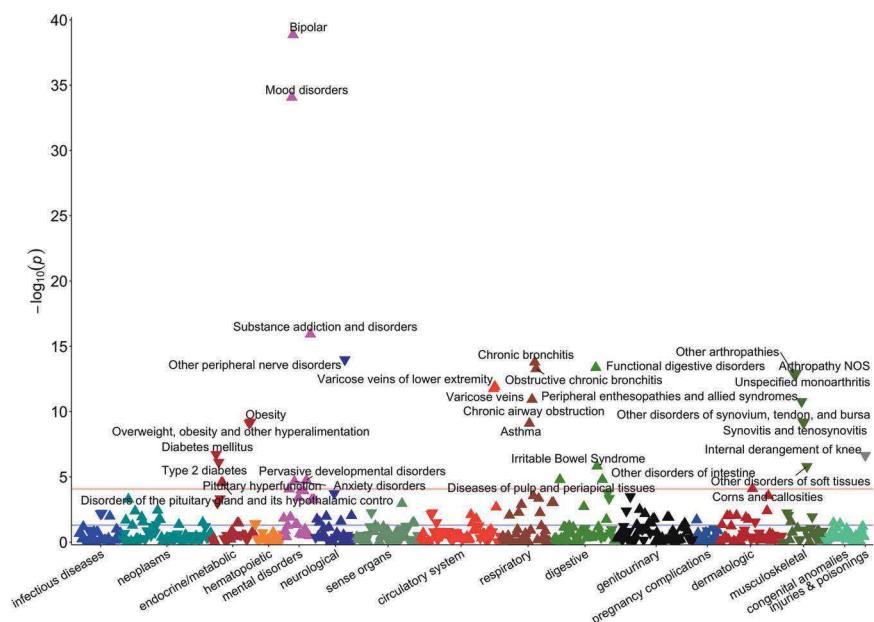


Fig. 2 Schizophrenia PRS-PC1 genome-wide association study Manhattan plot. This depicts association results for schizophrenia PRS-PC1 in UK Biobank (603 phenotypes, 325,992 individuals). The horizontal axis indicates broad disease category and the vertical axis indicates the significance ($-\log_{10} p$) of the association derived by logistic regression. The horizontal red line within the graph indicates genome-wide significance ($p = 8.29 \times 10^{-5}$) using Bonferroni correction, and all phenotypes that pass this threshold are labeled. The vertex of each triangle represents the direction of the association.

pregnancy, childbirth and the puerperium ($OR = 1.02, SE = 0.007, P = 1.76 \times 10^{-3}$), and Chapter XI, diseases of the digestive system ($OR = 1.01, SE = 0.004, P = 2.68 \times 10^{-4}$). We observed a significant negative association between schizophrenia PRS-PC1 and Chapter XIII, diseases of the musculoskeletal system and connective tissue ($OR = 0.98, SE = 0.004, P < 9.08 \times 10^{-7}$).

PheWAS of SCZ PRS-PC1

Figure 2 shows the association between 603 phenotypes and schizophrenia PRS-PC1.

Thirty-one phenotypes including seven musculoskeletal, six endocrine/metabolic, five mental disorders, four respiratory, four digestive, two circulatory system, one neurological, one dermatologic, and one injuries & poisonings phenotypes were significantly associated with schizophrenia PRS-PC1 after Bonferroni correction for the 603 phenotypes tested ($P < 8.29 \times 10^{-5}$). Bipolar disorders yielded the most significant association with the schizophrenia PRS-PC1 (Ncases = 1323, OR = 1.45, SE = 0.03, $P = 1.39 \times 10^{-39}$), followed by mood disorders (Ncases = 2623, OR = 1.28, SE = 0.02, $P = 8.56 \times 10^{-35}$), substance addiction and disorders (Ncases = 8851, OR = 1.10, SE = 0.01, $P = 1.17 \times 10^{-16}$), other peripheral nerve disorders (Ncases = 22 987, OR = 0.95, SE = 0.01, $P = 1.05 \times 10^{-14}$), and chronic bronchitis (Ncases = 17,046, OR = 1.06, SE = 0.01, $P = 1.64 \times 10^{-14}$). Corresponding to the primary associations with ICD10 main chapters, all four phenotypes within the functional digestive disorders group (Ncases = 46 351, OR = 1.04, SE = 0.006, $P = 1.16 \times 10^{-13}$) were significantly positively associated with schizophrenia PRS-PC1. Negative associations were observed for all seven significant phenotypes from the musculoskeletal group under the other arthropathies heading (Ncases = 34 687, OR = 0.96, SE = 0.006, $P = 1.16 \times 10^{-13}$). Five additional phenotypes including obesity, overweight, diabetes mellitus, internal derangement of knee, and type 2 diabetes were significantly inversely associated with schizophrenia PRS-PC1. Although no statistically significant evidence was found in the primary association with the circulatory system chapter, varicose veins (Ncases = 20111, OR = 1.05, SE = 0.007, $P = 1.74 \times 10^{-12}$) were found to be significantly positively associated with

schizophrenia PRS-PC1 after Bonferroni correction. The complete results table with effect sizes for all significant phenotypes can be found in the Supplementary Results Sheet 1.

Sensitivity analysis

As an internal validation, we performed a sensitivity analysis using original ICD-9 and ICD-10 codes from hospital inpatient records to assist mapping the 17.9% previously unmatched 3-character codes. In 332,855 individuals with available information, 43 phenotypes remained significant after Bonferroni correction for 1214 phenotypes tested ($P < 4.12 \times 10^{-5}$) (Supplementary Results Sheet 2). Nearly all associations remained significant with minor variability for most phenotypes. Nonetheless, mental disorders, respiratory, musculoskeletal, and digestive were still the groups with the most significant associated phenotypes (Fig. S3A).

We also explored whether some of the observed associations might be mediated through antipsychotic use via sensitivity analyses additionally adjusting for antipsychotic use in the models. In the sensitivity analysis of a sub-population of 157,018 individuals with GP registration records, 22 phenotypes remained significant after Bonferroni correction for 532 phenotypes tested ($P < 9.40 \times 10^{-5}$) additionally adjusting for antipsychotic use (Supplementary Results Sheet 3). And in a smaller sub-population of 69,294 individuals with GP prescription records, 4 phenotypes remained significant after Bonferroni correction for 427 phenotypes tested ($P < 1.17 \times 10^{-4}$) (Supplementary Results Sheet 4). Bipolar, mood disorders, other disorders of synovium, tendon, and bursa, and synovitis and tenosynovitis remained significant in every sensitivity analysis (Fig. S3B & C). Associations with diabetes, anxiety, irritable bowel syndrome, and other phenotypes which were statistically significant in the main analysis were less robust and significant after adjusting for antipsychotic medication use. However, they consistently remained highly ranked within the results (Supplementary Results Sheet 3 & 4).

After adjusting for mental disorder status, four ICD10 main chapters remained statistically significant after Bonferroni correction ($P < 0.003$) (Fig. S4). Chapter XIII, diseases of the musculoskeletal system and connective tissue, was still strongly negatively associated

with schizophrenia PRS, while chapter III (Blood and blood-forming organs and certain disorders involving the immune mechanism, IV (Endocrine, nutritional and metabolic diseases), VI (Nervous system disorders) were also found to be significantly negatively associated with schizophrenia PRS independent of mental disorder status. Other chapters which were associated with schizophrenia PRS in the main analyses including chapter X (Respiratory system disorders), XI (Digestive system disorders), and XV (Pregnancy, childbirth and the puerperium diseases) were no longer significant after adjusting for mental disorder status after Bonferroni correction, even though the effect sizes were only slightly diminished.

Compared with the previous study [20], there was a significant positive correlation between the effect estimates ($r = 0.25$). On average, the effect estimates from our main analysis were stronger than previous findings (Fig. S5).

DISCUSSION

We investigated associations between schizophrenia PRS and medical conditions from broad to narrow definitions in over 400,000 individuals with no schizophrenia diagnosis in UK Biobank. Our results demonstrate that individuals with higher schizophrenia PRS were more likely to have poorer self-reported overall health ratings, receive more hospital inpatient diagnoses, and suffer from more diseases. In addition to mental and behavioral disorders, schizophrenia PRS was also found to be significantly associated with four other ICD10 chapters: respiratory system disorders; digestive system disorders; musculoskeletal system and connective tissue disorders; and pregnancy, childbirth and the puerperium. Moreover, we identified 31 diseases and disorders (out of 603) significantly associated with schizophrenia PRS from the PheWAS analysis with ORs ranging from 1.02 to 1.41 for positive associations and 0.94–0.97 for negative associations, revealing greater pleiotropic effects of schizophrenia PRS than previously known.

The strongest associations we found were within the mental and behavioral disorder chapter including bipolar disorder, mood disorder, substance addiction and disorders, and anxiety disorders, which is in line with the previous reports of positive genetic correlations and shared genetic risk loci with schizophrenia [21–23]. These findings indicate that genetic factors that are not specific to schizophrenia contribute to the occurrence of the other disorders, supporting the concept of a general psychopathology factor [38]. Prior work attributed associations with several other phenotypes within this chapter, including neurological disorders, personality disorders, suicidal behavior, and memory loss, to being consequences of a schizophrenia diagnosis rather than to shared risk [20]. However, in our analysis, restricting to hospital inpatient diagnoses (which incorporates additional phenotypes and probably more severe cases), all significant associations except for memory loss were replicated in individuals with no schizophrenia diagnosis (Supplementary Results Sheet 2, Fig. S3A), implying that shared genetics may play a role in the development of neurological disorders, personality disorders, and suicidal behavior, but not memory loss.

Novel associations were detected between schizophrenia PRS and respiratory diseases including chronic bronchitis, chronic airway obstruction, and asthma. Prior studies had reported elevated risk of chronic bronchitis and COPD in individuals with schizophrenia [39, 40]. Moreover, asthma was previously found to be associated with later risk of developing schizophrenia [41]. It is known that the rate of smoking is markedly higher in individuals with schizophrenia, which might mediate some associations between schizophrenia and respiratory diseases [39, 42]. Notably, the previously reported genetic correlation between smoking behaviors [9] and our observed positive association between tobacco use and schizophrenia PRS in individuals with no schizophrenia diagnosis (Fig. S3A) indicates that the association between schizophrenia PRS and respiratory diseases might be mediated by smoking. However, the analyses in the subpopulation

with available tobacco smoking information from our study population (24%) suggested that the direct effect of schizophrenia PRS on respiratory diseases exists independent of tobacco smoking (Table S3). Furthermore, asthma and other respiratory diseases are linked to the immune system and inflammation [43]. The earliest and strongest GWAS associations for schizophrenia have been in genomic loci with important immune functions [12, 17]. Shared immune mechanisms might partly explain the association between schizophrenia PRS and asthma.

The associations between schizophrenia PRS and digestive disorders found in our study are also novel. Specifically, functional digestive disorder, irritable bowel syndrome (IBS), disease of pulp and periapical tissues, and other disorders of the intestine were significantly positively associated with schizophrenia PRS. Substantial gastrointestinal comorbidities in schizophrenia and increased psychiatric comorbidities in individuals with gastrointestinal disorders, including IBS, have been reported previously [44–47]. Consistent with previous findings, our results provide evidence for shared genetic factors between schizophrenia and digestive disorders.

Endocrine and metabolic diseases were not found to be significantly associated with schizophrenia PRS at the chapter level. However, significant associations with opposite directions were detected for specific diseases. The positive phenotypic association despite the intriguing negative genetic correlation between schizophrenia and obesity/diabetes has been described in several studies previously [20, 48–51]. Our results corroborate the negative genetic associations between schizophrenia PRS and obesity, overweight, and diabetes with individual-level phenotypic data, suggesting the increased rates of obesity and diabetes among individuals with schizophrenia arise consequent to having this disorder (e.g., medication effects). Further exploration of this paradoxical relationship may assist case definition and treatment improvement for both traits.

In addition, novel positive associations were observed for pituitary hyperfunction and disorders of the pituitary gland and its hypothalamic control with schizophrenia PRS. Larger pituitary volume, which is thought to reflect a greater activation of the hypothalamic–pituitary–adrenal (HPA) axis [52, 53], has been previously reported in individuals with psychosis [54]. Our findings provide evidence for a genetic link between schizophrenia and HPA axis activation. Future studies focusing on the genetic basis of hormone regulation in the pathophysiology of schizophrenia may provide new insights into mechanisms which could be leveraged for treatment development for schizophrenia.

Remarkable negative associations between schizophrenia PRS and musculoskeletal disease were observed in our study. The inverse association between rheumatoid arthritis (RA) and noninflammatory disease of the joints (e.g., osteoarthritis) and schizophrenia has been described in several epidemiological studies [55–57]. One potential explanation for the negative phenotypic association is that individuals with schizophrenia may expose their joints to less damage and subsequent osteoarthritis since they are more likely to be sedentary [58]. However, our results favor an etiological link between schizophrenia and musculoskeletal diseases on a genetic level. RA is an immune-mediated inflammatory joint disease for which the MHC region is the most important genetic locus [59]. As mentioned, previous schizophrenia GWAS also observed MHC associations enriched in tissue with important immune functions [12]. Our results expand the previous findings indicating a possible involvement of immune mechanisms in the pathophysiology of schizophrenia.

The main strengths of this study are the large sample size with long medical follow-up and high-quality phenotype definitions, which enabled screening of a large number of medical conditions and greater reliability for the results. Our design of testing medical conditions from a broad to narrow definitions makes it less constrained by phenotype selection, yielding greater opportunities to identify disease associations despite an incomplete

understanding of mechanistic relationships. Moreover, associations based on genotypes fixed from birth renders reverse causality virtually impossible. Furthermore, restricting analyses to individuals with no schizophrenia diagnosis allows us to investigate the direct effect of schizophrenia PRS independent of the disorder, which provides new insights into the etiology of comorbid conditions as well as previously undocumented associations. In addition, compared to the methods using summary statistics from GWAS (e.g., LDSC) to assess genetic correlation, associations based on schizophrenia PRS enable measurement of dose-response relationships with the possibility of adjusting for environmental confounders. This approach offers individual indices relevant to the etiology which might assist future application of PRS testing in clinical practice.

There are several limitations to consider. First, the coverage period of diagnosis records varied from 20 to 38 years across different registers. However, the coverage period highly correlated with the region of UK, which was adjusted for in all analysis. We also used all possible diagnoses from different sources including primary and secondary care, cancer, and death registers to define phenotypes, which makes under-detection less likely for most of the diseases. Second, around 18% of the 3-character harmonized codes from multiple registers were not able to be matched to phecodes, but the results using original ICD-9 and ICD-10 codes from hospital inpatient records only (which results in more severe cases) were still robust (Fig. S3A). Third, <50% of the individuals had available GP information and only 20% had recorded prescriptions. Nevertheless, the results adjusting for antipsychotic use were still largely consistent despite diminished power and concomitant changes in significance (Fig. S3B & C, Supplementary Results Sheet 3 & 4). Fourth, collider bias could be a potential concern due to restricting the analyses to individuals with no schizophrenia diagnosis or adjusting for mental disorder status in the sensitivity analysis [60]. This could happen if a common cause (other than shared genetics) of both schizophrenia/mental disorders and the tested outcome phenotype/chapter exists. Fifth, since all UK Biobank participants were middle-aged at enrollment, we were not able to capture diseases that commonly occur in early life. Moreover, since our analyses were restricted to individuals with White-British ancestry, the generalizability to individuals of other ancestries merits further exploration. Furthermore, although most of the individuals in the study cohort have passed the risk period of schizophrenia, there is still a small possibility that some people with schizophrenia or related disorders remain undetected. However, given that participants in UK Biobank were found to be healthier and wealthier than the general UK population [61], the number of individuals with undetected schizophrenia or other types of psychotic illness is probably extremely low and unlikely to impact the results. On the other hand, individuals with severe diseases or who died soon after diagnosis were likely not captured by the UK Biobank. The interaction between schizophrenia PRS and education level or socioeconomic status on medical conditions may deserve further investigation.

By studying associations between schizophrenia PRS and multiple medical conditions in ~400,000 individuals with no schizophrenia diagnosis in the UK Biobank, we found that higher genetic loading for schizophrenia was associated with poorer overall health and higher cumulative somatic and psychiatric disease burden. In addition to the replication of associations with mental illness, obesity, diabetes, and synovitis, we also observed novel associations between schizophrenia PRS and respiratory diseases, musculoskeletal diseases, digestive diseases, pituitary hyperfunction, and varicose veins. Additional studies incorporating the genetic basis of hormone regulation and involvement of immune mechanisms in the pathophysiology of schizophrenia are needed to better understand the underlying etiology of schizophrenia, which might provide new insights facilitating treatment development. Further investigations examining the effect of potential mediating factors including

smoking, alcohol consumption, and/or socioeconomic status may assist future application of schizophrenia PRS in disease prediction or clinical practice.

CODE AVAILABILITY

All code used for data preparation and analysis are available upon request.

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AUTHOR CONTRIBUTIONS

SEB conceived of the study idea and supervised its implementation. RZ, AS, CMB, and SEB designed the study. AS extensively contributed to the discussions on methods. AP contributed to the creation of the PRS-PC method for the present work. DL provided the protocol and scripts for PRS computation. RZ implemented and ran all analyses. RZ, AS, CMB, and SEB interpreted the results. RZ drafted the paper. All authors discussed and commented on the paper.

COMPETING INTERESTS

CMB reports: Shire (grant recipient, Scientific Advisory Board member); Idorsia (consultant); Lundbeckfonden (grant recipient); Pearson (author, royalty recipient).

ADDITIONAL INFORMATION

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