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Association Between Genetic Risk for Psychiatric Disorders and the Probability of Living in Urban Settings

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IMPORTANCE Urban residence has been highlighted as an environmental risk factor for schizophrenia and, to a lesser extent, several other psychiatric disorders. However, few studies have explored genetic effects on the choice of residence.

OBJECTIVE To investigate whether individuals with genetic predisposition to a range of psychiatric disorders have an increased likelihood to live in urban areas.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional retrospective cohort study including genotypes, address history, and geographic distribution of population density in the UK based on census data from 1931-2011 was conducted. Polygenic risk score (PRS) analyses, genome-wide association studies, genetic correlation, and 2-sample mendelian randomization analyses were applied to 385 793 UK Biobank participants with self-reported or general practitioner registration–based address history. The study was conducted from February 2018 to May 2021, and data analysis was performed from April 2018 to May 2021.

MAIN OUTCOMES AND MEASURES Population density of residence at different ages and movement during the life span between urban and rural environments.

RESULTS In this cohort study of 385 793 unrelated UK Biobank participants (207 963 [54%] were women; age, 37-73 years; mean [SD], 56.7 [8] years), PRS analyses showed significant associations with higher population density across adult life (age 25 to >65 years) reaching highest significance at the 45- to 55-year age group for schizophrenia (88 people/km^2; 95% CI, 65-98 people/km^2), bipolar disorder (44 people/km^2; 95% CI, 34-54 people/km^2), anorexia nervosa (36 people/km^2; 95% CI, 22-50 people/km^2), and autism spectrum disorder (35 people/km^2; 95% CI, 25-45 people/km^2). The schizophrenia PRS was also significantly associated with higher birthplace population density (37 people/km^2; 95% CI, 19-55 people/km^2; $P = 8 \times 10^{-5}$). Attention-deficit/hyperactivity disorder PRS was significantly associated with reduced population density in adult life (−31 people/km^2; 95% CI, −42 to −20 people/km^2 at age 35-45 years). Individuals with higher PRS for schizophrenia, bipolar disorder, anorexia nervosa, and autism spectrum disorder and lower PRS for attention-deficit/hyperactivity disorder preferentially moved from rural environments to cities (difference in PRS with Tukey pairwise comparisons for schizophrenia: 0.05; 95% CI, 0.03 to 0.60; bipolar disorder: 0.10; 95% CI, 0.08 to 0.13; anorexia nervosa: 0.05; 95% CI, 0.03 to 0.07; autism spectrum disorder: 0.04; 95% CI 0.03 to 0.06; and attention-deficit/hyperactivity disorder: −0.09, 95% CI, −0.12 to −0.06). Genetic correlation results were largely consistent with PRS analyses, whereas mendelian randomization provided support for associations between schizophrenia and bipolar disorder and living in high population-density areas.

CONCLUSIONS AND RELEVANCE These findings suggest that a high genetic risk for a variety of psychiatric disorders may affect an individual's choice of residence. This result supports the hypothesis of genetic selection of an individual's environment, which intersects the traditional gene-environment dichotomy.

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Supplemental content

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Urbanicity is a well-established risk factor for schizophrenia, with numerous studies reporting an association with urban living and upbringing.[1,2] The evidence comes mainly from northern European countries[3]; studies in low- and middle-income[4] or southern European countries[5] have not supported this association. These findings challenge traditional hypotheses for the increased risk of schizophrenia in urban settings and shift the focus of studies from replication to studies exploring causal links.[6]

The association of urbanicity with schizophrenia risk could reflect a possibly causal environmental effect or, alternatively, reverse causation through selective migration or higher case identification in cities due to better access to mental health facilities. A common explanation for selective migration is the social selection hypothesis,[7] whereby the symptoms of schizophrenia lead to lower socioeconomic status, which influences people to move into more deprived and densely populated areas.[8] However, incidence studies have shown that urbanicity at birth or before illness onset is a risk factor for schizophrenia.[9] Furthermore, this risk remains increased after controlling for family history, indicating that this association is not explained by the movement of families into cities following the onset of the disorder in a family member.[10] Studies adjusting for other risk factors (eg, advanced paternal age, migration rates, or cannabis use) have also supported the association.[11,12]

A less examined possibility is genetic confounding. Family-based studies have suggested that familial effect (combining genetic and shared environmental effects) accounts for a large part of the association of birth in densely populated areas with schizophrenia.[13,14] Under this hypothesis, familial factors may influence intergenerational drift of families into socioeconomically deprived and densely populated areas and increased schizophrenia risk in offspring.

Schizophrenia is a polygenic disorder with a continuum of genetic risk in the population partially underlying the liability to disease.[15,16] Subthreshold symptoms or traits associated with increased genetic risk may affect an individual's behavior; for example, genetic risk for schizophrenia and other mental disorders is associated with psychotic experiences in UK Biobank (UKB) participants.[17] Such subtle symptoms may in turn influence an individual's lifestyle including choice of residence. Under this hypothesis, it is possible that people with increased genetic risk for schizophrenia preferentially move to cities and, in addition to transmitting higher genetic risk, give birth to and raise descendants in more urban environments. One study found that people living in more densely populated areas had higher genetic loading for schizophrenia and reported evidence consistent with an association between the liability to schizophrenia and urban living in adulthood,[18] whereas a study using spatial mapping identified hot spots for schizophrenia, demonstrating the potential of incorporating geolocation into genetic studies.[19]

Beyond schizophrenia, urbanicity is a risk factor for a variety of mental health disorders. A study from Denmark using a large population-based cohort reported an association of birth in urban areas with an increased incidence of most psychiatric disorders, including bipolar disorder, substance use, and autism spectrum disorder.[20] Hence, it is useful to explore broader genetic influences on the place of residence.

Key Points

Question Are individuals genetically predisposed to a range of psychiatric disorders more likely to be born in or to move to urban areas?

Findings In this cross-sectional cohort study of approximately 386 000 adults from the UK Biobank, genetic risk for schizophrenia, bipolar disorder, anorexia nervosa, and autism spectrum disorder was associated with living in and moving to urban areas. Results were largely consistent across polygenic risk score, genetic correlation, and mendelian randomization analyses.

Meaning The results from this study support the hypothesis of genetic selection of an individual's environment, which intersects the traditional gene-environment dichotomy in the pathogenesis of mental disorders.

In the present study, we investigated the association between genetic risk for 8 psychiatric disorders and population density at birth and across lifetime in the UKB and explored the selective migration hypothesis through polygenic risk score (PRS) analysis in a cohort stratified by migration patterns into or out of city centers. Furthermore, we performed genome-wide association studies (GWASs) of birth and current population density and estimated the heritability of these variables. We estimated genetic correlations between population density and psychiatric disorders using the LDSC regression software method[21] and explored possible associations in a proxy gene × environment mendelian randomization (MR) framework.[22]

Methods

Study Population and Genetic Analysis

We analyzed genetic and phenotype data on participants from the UKB (aged 37-73 years).[23] To avoid confounding by ethnic minority status, we restricted our sample to individuals of European ancestry (eMethods 1 in the Supplement). Genotype quality control procedures included removal of single-nucleotide variants (SNVs) with missingness greater than 0.02, minor allele frequency less than 0.01, or deviation from Hardy-Weinberg equilibrium at a threshold of $P < 1 \times 10^{-8}$. Imputed SNVs were selected if they had minor allele frequency greater than 0.01 and an information score greater than 0.6 (eMethods 2 in the Supplement). Individual quality control involved the exclusion of participants with missingness greater than 0.01, sex discordance, and relatedness (Kinship-based Inference for Genome-wide Association Studies, >0.044), resulting in a sample size of 385 793 participants (eMethods 3 in the Supplement). The study was conducted from February 2018 to May 2021, and data analysis was performed from April 2018 to May 2021. All participants provided written informed consent and the study was approved by the UK Biobank Ethics and Governance Council.

Population Density

The primary phenotype analyzed was population density, derived by linking the participants' address history with historical census data from 1931 to 2011 provided by the Vision of Britain.[24] Participants provided birthplace and current address during baseline data collection and were encouraged to update with address changes. Additional address history was collected via registration with each participant's primary care physician. Address history was cross-referenced with population density data from the census year closest to the date the address was provided (eMethods 4 in the Supplement). For the participants' birth and current addresses, we also derived a binary urban vs rural variable using land cover maps from the UK Centre for Ecology & Hydrology.[25] Postcode areas were defined as urban or rural based on whether they reached a threshold percentage coverage of urban land cover type (eMethods 5, eTable 1, and eFigure 1 in the Supplement).

Statistical Analysis

PRS Analyses

Polygenic risk scores were calculated with genotyped SNVs using GWAS summary statistics from the largest published study available for schizophrenia,[26] bipolar disorder,[27] major depressive disorder,[28] autism spectrum disorder,[29] anorexia nervosa,[30] anxiety and stress-related disorders,[31] attention-deficit/hyperactivity disorder (ADHD),[32] and cannabis use disorder[33] (eTable 2 in the Supplement). We computed posterior effect sizes from each of the GWAS summary statistics using SBayesR.[34] Polygenic risk scores were computed using PLINK, version 1.9[35] as the sum of risk alleles weighted by SNV effect sizes (eMethods 6 in the Supplement).

Associations between PRSs and population density were estimated in a linear regression model adjusted for the first 20 principal components, UKB batch, age, and sex (eMethods 7 in the Supplement). A Bonferroni-adjusted *P* value threshold of 3×10^{-4} was applied to control for 144 tests in total. Furthermore, we performed sensitivity analyses by excluding 49 645 participants identified as being diagnosed with psychiatric disorders (eTable 3 in the Supplement).

We also investigated whether there were differences in each PRS between participants who moved into or out of urban environments over their lifetime by using the birth and current (at baseline data collection) residence addresses. The sample was divided into 4 groups who were (1) born and stayed in an urban center (stayed in city), (2) born and stayed in the rural or suburban settings (stayed in rural/suburban), (3) born in the rural or suburban setting and moved to an urban area (rural/suburban to city), and (4) born in the city and moved to a rural or suburban setting (city to rural/suburban). Covariates as in the previous analyses were regressed out of the PRS, and differences between the 4 groups were tested using analysis of variance and Tukey pairwise comparisons with a Bonferroni-adjusted *P* value threshold of .001 for the latter.

GWAS, SNV Heritability, and Post-GWAS Analyses

We used BOLT-REML[36] to estimate heritability (using 560 173 genotyped SNVs) and BOLT-LMM[37] to perform GWASs (using 9 830 370 imputed SNVs) of population density at birth (n = 423 973) and current addresses (n = 453 662) (eMethods 8 in the Supplement).[38] Analyses were adjusted for age, sex, UKB batch, and 20 ancestry-informed principal components (generated on 385 793 unrelated participants using GCTA software, version 1.930beta).[39] For the current population density, we performed 2 additional analyses adjusting for the Townsend Deprivation Index (TDI) provided by the UKB as a proxy measure for socioeconomic status[40] and educational attainment provided as a binary variable on whether participants obtained a college or university degree. These traits show high geographic clustering, not adequately controlled by ancestry components, and strong genetic correlations with a variety of regional characteristics.[41] Genetic correlations between current population density and psychiatric disorders were estimated using linkage disequilibrium score regression.[21,42] A Bonferroni-adjusted *P* value threshold of .002 was applied to control for multiple testing. Mendelian randomization was conducted with the generalized summary data-based mendelian randomization method.[43] We performed bidirectional 2-sample MR using lead SNVs from our GWAS of birth and current population density and GWAS summary statistics for the psychiatric disorders (eMethods 9 in the Supplement).

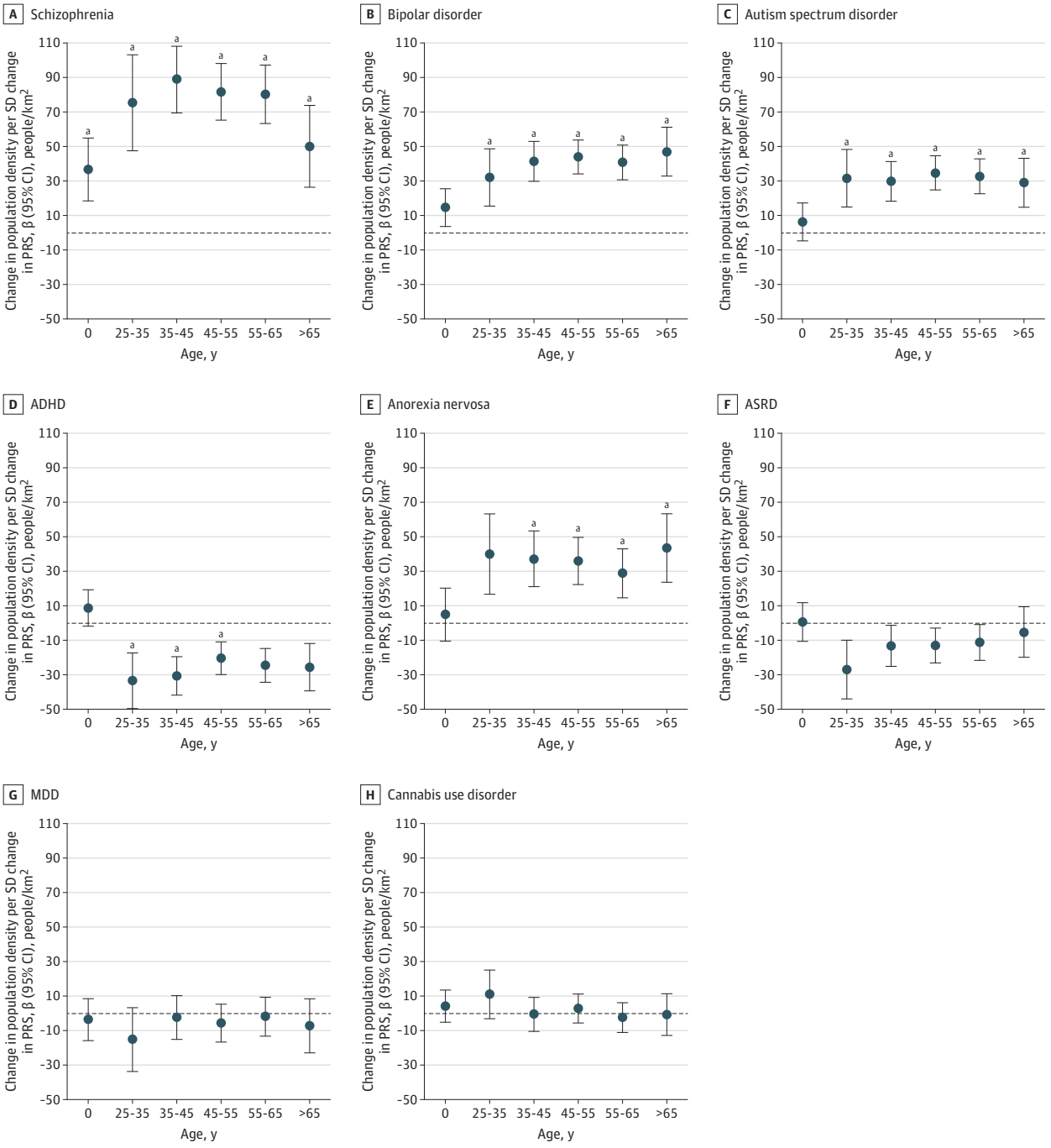
Results

PRS Analyses

Of the 385 793 study participants, 207 963 (54%) were women and 177 663 (46%) were men (data on sex were missing for 167 participants); age range was 37 to 73 years (mean [SD], 56.7 [8] years). Polygenic risk scores showed significant associations with increased population density across adult life (age 25 to >65 years) reaching highest significance at the 45- to 55-year age group for schizophrenia (88 people/km^2; 95% CI, 65-98 people/km^2), bipolar disorder (44 people/km^2; 95% CI, 34-54 people/km^2), anorexia nervosa (36 people/km^2; 95% CI, 22-50 people/km^2), and autism spectrum disorder (35 people/km^2; 95% CI, 25-45 people/km^2). Conversely, the ADHD PRS was significantly associated with reduced population density, for example, at age 35 to 45 years (−31 people/km^2; 95% CI, −42 to −20 people/km^2). The only significant association for birthplace population density was with the schizophrenia PRS (β = 37 people/km^2; 95% CI, 19-55 people/km^2; $P = 8 \times 10^{-5}$). The results are summarized in **Figure 1**. Results were generally consistent for sex-stratified analyses (eTable 4 in the Supplement) and sensitivity analyses excluding individuals diagnosed with psychiatric disorders (eFigure 2, eTable 5 in the Supplement).

We investigated whether there were significant differences in the PRS for psychiatric disorders in people who moved into or out of cities between birth and their enrollment in the UKB. Differences between the 4 groups (stayed in city, stayed in rural/suburban, rural/suburban to city, city to rural/suburban) tested using analysis of variance were significant for schizophrenia ($F = 24$; $P = 4 \times 10^{-20}$), bipolar disorder ($F = 85$; $P = 2 \times 10^{-25}$), anorexia nervosa ($F = 14$; $P = 4 \times 10^{-8}$), ADHD ($F = 54$; $P = 4 \times 10^{-15}$), autism spectrum disorder ($F = 30$;

Figure 1. Polygenic Risk Score (PRS) Association With Population Density Across the Life Span

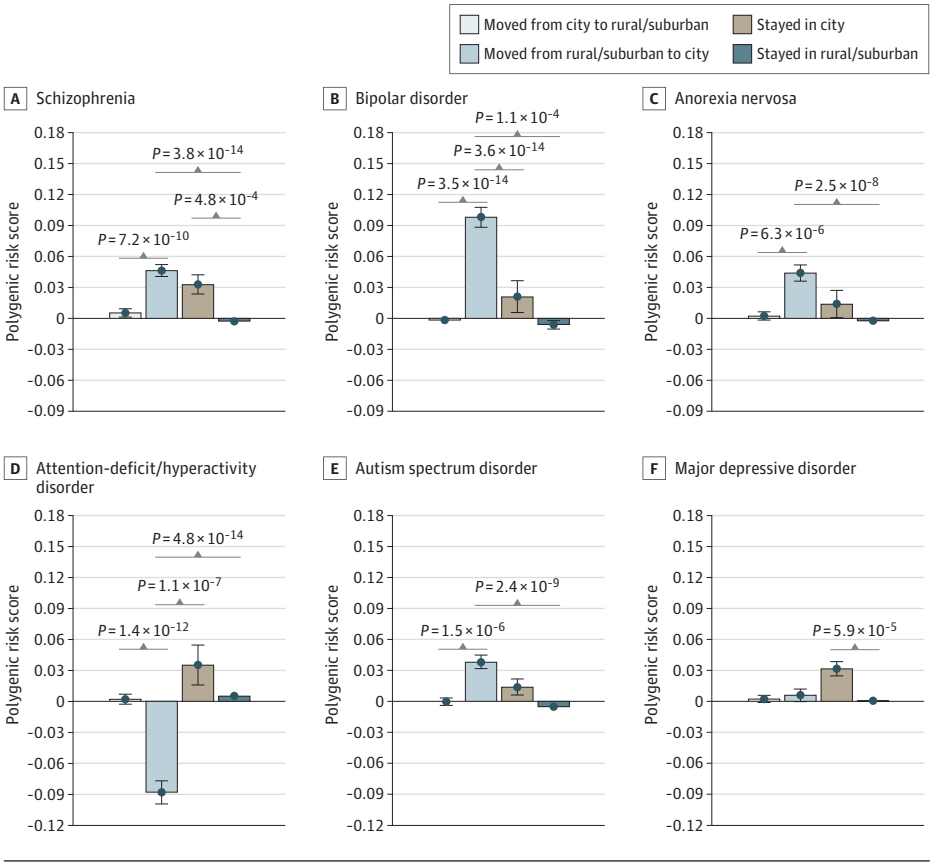


Results from linear regression model between population density at different ages and PRSs for schizophrenia, bipolar disorder, anorexia nervosa, autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), anxiety and stress-related disorder (ASRD), major depressive disorder (MDD), and cannabis use disorder. All analyses were adjusted for the first 20 principal components, UK Biobank batch, and age. Polygenic risk scores were standardized; therefore, the effect size is change in population density per SD change in PRS.

[a] Associations passed the Bonferroni-adjusted *P* value threshold ($P < 3 \times 10^{-4}$).

$P = 1 \times 10^{-9}$), and major depressive disorder ($F = 12$; $P = .00017$) (eResults 1, eTable 6 in the Supplement). The mean PRSs in each of the 4 groups are reported in **Figure 2** along with significant Tukey pairwise comparisons (eTable 7 in the Supplement). When we compared people who were born and stayed in rural/suburban environments with people who moved from rural/suburban to cities, we found the following differences in PRS: for schizophrenia: 0.05; 95% CI, 0.03 to 0.60; bipolar disorder: 0.10; 95% CI, 0.08 to 0.13; anorexia nervosa: 0.05; 95% CI, 0.03 to 0.07; autism spectrum disorder: 0.04; 95% CI 0.03

Figure 2. Polygenic Risk Scores (PRSs) and Migration Patterns In or Out of Cities



Means and SEs of 6 psychiatric disorder PRSs in 4 groups of the UK Biobank participants based on locations at birth and current address. Cities were defined as postal regions surpassing a threshold of percentage urban land cover (details in eMethods 5 and eResults 1 in the Supplement). Polygenic risk scores were adjusted by regressing out the following covariates: the first 20 principal components, UK Biobank batch, and age. *P* values determined from Tukey pairwise comparison between the 4 groups are included on plots if they passed a Bonferroni-corrected threshold of $P < .001$.

to 0.06; and attention-deficit/hyperactivity disorder: −0.09, 95% CI, −0.12 to −0.06. These results suggest that individuals with the higher PRSs for schizophrenia, bipolar disorder, anorexia nervosa, and autism spectrum disorder and the lower PRS for ADHD preferentially moved from the rural environment to cities. Individuals with the higher PRS for major depressive disorder were born and stayed in cities.

GWAS and SNV-Based Heritability

The GWAS identified 3 genome-wide significant SNVs on chromosome 4 associated with birth population density and 9 SNVs associated with current population density in 8 independent genomic loci (eResults 2, eTables 8-11, and eFigures 3-10 in the Supplement). The SNV-based heritability of birth population density was 0.074 (95% CI, 0.069-0.079); of the current population density, 0.066 (95% CI, 0.061-0.071); after adjustment for TDI, 0.080 (95% CI, 0.075-0.085); and after adjustment for educational attainment, 0.055 (95% CI, 0.050-0.060).

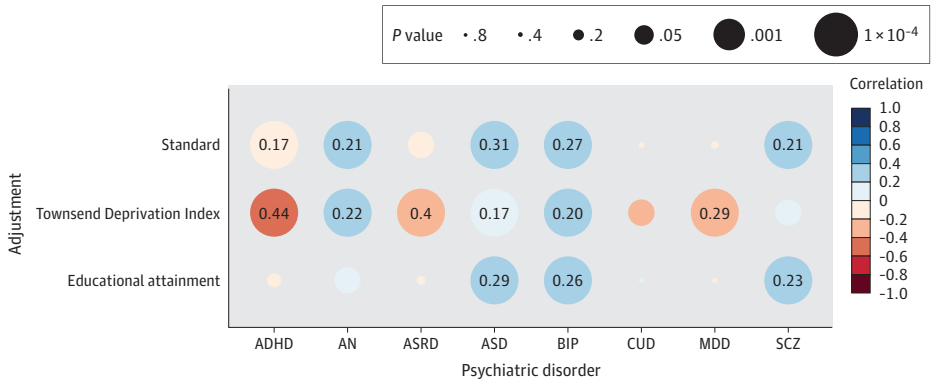
Genetic Correlation Analyses

Under a standard adjustment for the first 20 principal components, UKB batch, age, and sex, population density was positively genetically correlated with schizophrenia (r_g = 0.21; $P = 8 \times 10^{-10}$), bipolar disorder (r_g = 0.27; $P = 6 \times 10^{-11}$), autism spectrum disorder (r_g = 0.31; $P = 3 \times 10^{-10}$), and anorexia nervosa (r_g = 0.21; $P = 4 \times 10^{-5}$). The first 3 correlations remained unchanged when adjusted for educational attainment and were attenuated when adjusted for TDI. The correlation with anorexia nervosa remained unchanged when adjusted for TDI and became nonsignificant when adjusted for educational attainment. Major depressive disorder and anxiety and stress-related disorders were negatively correlated with population density only in the model adjusted for TDI, and cannabis use disorder was not correlated with population density in any of the 3 models. In addition, ADHD was negatively genetically correlated with population density in the standard model (r_g = −0.17; $P = 2.1 \times 10^{-5}$), which was strengthened when adjusted for TDI (r_g = −0.4; $P = 1.2 \times 10^{-35}$) and became nonsignificant when adjusted for educational attainment (**Figure 3**; eTable 12 in the Supplement).

Mendelian Randomization Analyses

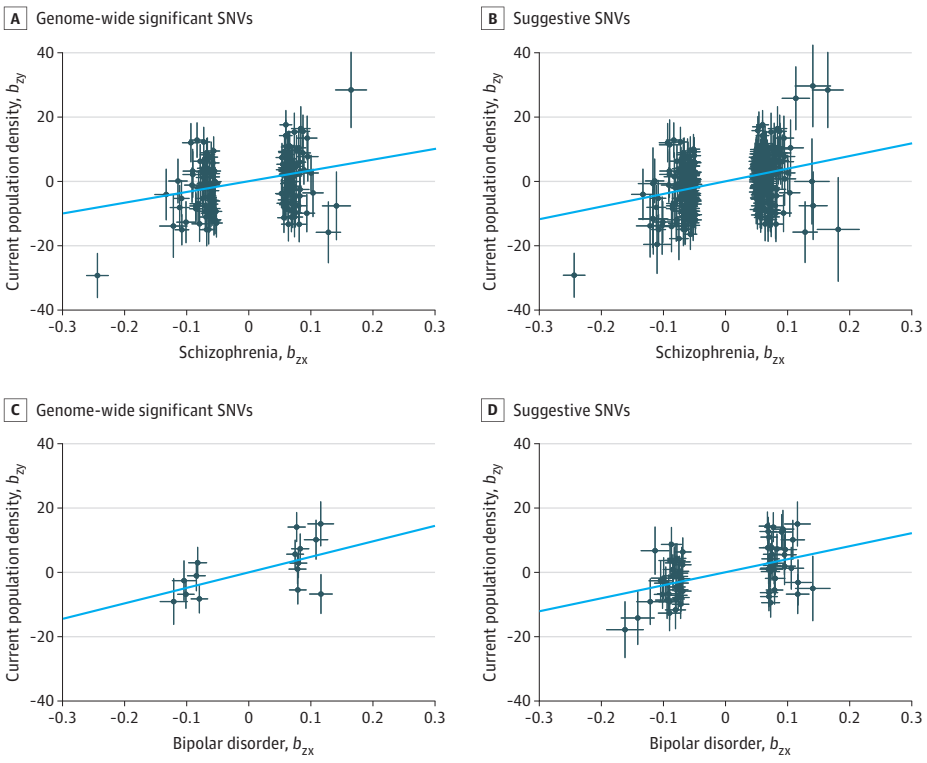
In MR analyses, birthplace and current population density as exposures were not associated with the psychiatric outcomes. Genetic variants associated at the genome-wide significant threshold with schizophrenia (b_{xy} = 33; $P = 7 \times 10^{-9}$), and bipolar disorder (b_{xy} = 48; P = .001) were associated with current population density (**Figure 4**). Apart from an observed association of autism spectrum disorder variants at the suggestive threshold 10^{-6} with current population density, the remaining results were not significant (eTable 13 in the Supplement).

Figure 3. Genetic Correlation Between 8 Psychiatric Disorders and Population Density



Standard adjustment includes the first 20 principal components, UK Biobank batch, age, and sex. Additional adjustments included the Townsend Deprivation Index and educational attainment. Genetic correlations are shown if they passed the Bonferroni-adjusted *P* value threshold of .002. Otherwise, the strength of the genetic correlation is indicated by the color bar and the significance of the correlation is indicated by the size of the circle. ADHD indicates attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASRD, anxiety and stress-related disorder; ASD, autism spectrum disorder, BIP, bipolar disorder; CUD, cannabis use disorder; MDD, major depressive disorder; and SCZ, schizophrenia.

Figure 4. Mendelian Randomization Analysis Testing Associations Between Schizophrenia and Bipolar Disorder as Exposure and Current Population Density as Outcome



Genetic instruments from genome-wide significant single-nucleotide variants (SNVs) ($P = 5 \times 10^{-8}$) and SNVs with suggestive significance ($P = 1 \times 10^{-6}$) for schizophrenia and bipolar disorder are shown in the plots. The blue line represents the slope (b_{xy}) of the SNV effect sizes for the exposure (b_{zx}) regressed on the SNV effect sizes for the outcome (b_{zy}).

Discussion

In this study we investigated genetic contributions to a person's environment. We first looked at the direct association between PRS for 8 psychiatric disorders and population density across lifetime and found that genetic liability to schizophrenia, bipolar disorder, autism spectrum disorder, and anorexia nervosa predispose individuals to living in more urban environments, whereas genetic liability to ADHD predisposes individuals to living in less densely populated areas. We also measured the association of PRS with population density at birth, hypothesizing an indirect genetic effect through the parents' genotype. We found an association of increased schizophrenia

PRS with birth in urban environments, which is consistent with recent evidence from the ALSPAC Birth Cohort that a higher schizophrenia PRS is associated with deprivation and social fragmentation at birth.[44] However, the magnitude of this association is small (explained variance of population density <0.1% in all age groups), which indicates that current estimates of genetic risk would not significantly attenuate the association of place of birth and upbringing with schizophrenia risk.[45]

The association of population density with schizophrenia PRS has been shown in another study that included the UKB cohort[18]; however, to our knowledge, the remaining associations are novel. These results are consistent with findings that the association of urbanicity with mental disorders is not specific to schizophrenia.[20] In sensitivity analyses excluding individuals diagnosed with a broad set of psychiatric disorders, the PRS results were largely unchanged. This finding provides evidence against the hypothesis that individuals with a diagnosed psychiatric disorder migrating to cities (eg, to seek treatment) solely accounts for the increased rates of psychiatric diagnoses.[46] Rather, our results suggest that selective migration occurs in individuals with high genetic risk even without a diagnosis of mental illness.

The genetic selection interpretation[13] was further supported by our results after estimating differences in PRSs across subsets of the UKB with different within-country migration patterns. We found significantly higher mean PRSs for schizophrenia, bipolar disorder, anorexia disorder, and autism spectrum disorder in those who moved into city centers from rural birthplaces compared with those who moved from the city to rural areas or those who stayed in rural areas. The association with schizophrenia PRS is consistent with a previous study from Sweden reporting that genetic liability to schizophrenia predicts subsequent residence in socioeconomically deprived neighborhoods, which tend to aggregate in cities.[14] The association of high liability to major depressive disorder with continuous residence in city centers needs further exploring.

People with lower ADHD PRSs preferentially moved to city centers. This finding exposes the complexity of formulating a universal model that explains movement into and out of urban environments. Beyond the treatment-seeking behavior or social drift already discussed, people move into cities for a variety of reasons, including higher education and certain employment choices, and these patterns of migration may change with time. The PRS for ADHD has been associated with a variety of behavioral traits,[47] and individuals at the low end of the ADHD PRS have higher cognitive performance and greater levels of educational attainment, which may affect their choice of environment.[48]

To measure genetic associations with population density directly, we performed GWASs and found significant but low SNV heritabilities, consistent with evidence from other studies.[18,49] Significant genetic correlations between psychiatric disorders and population density, largely in the same direction as the PRS analyses, further supported the notion of diverse genetic contribution to the choice of environment. Adjustment for TDI and educational attainment modified the associations but not the direction of the correlations; hence, we cannot fully attribute the associations to confounding by socioeconomic status. Major depressive disorder and anxiety and stress-related disorders showed a negative genetic correlation only when adjusted for TDI, which raises the possibility of spurious associations by TDI acting as a collider, as discussed in the Limitations subsection. Cannabis use disorder had null results in all analyses performed, indicating either lack of association or low power of the cannabis use disorder GWAS.[33]

From the MR analysis, population density was not associated with any of the psychiatric traits; however, we cannot refute the possibility of such an association as the power was compromised by the low heritability and the small number of genetic instruments available from the population-density GWASs. In the opposite direction, the liability to schizophrenia, bipolar disorder, and autism spectrum disorder was shown to have a significant association with current population density, which supports the hypothesis that liability to these disorders predisposes people to move into more urban environments.

Different mechanisms can explain the association between genetic liability to mental disorders and population density across the life span. It is possible that the observed associations are driven by pleiotropic variants directly affecting both risk to mental disorders and choice of residence, as suggested by the significant genetic correlations. Another possibility is that subtle psychotic symptoms or autistic traits in people with high genetic liability to schizophrenia, bipolar disorder, or autism spectrum disorder without a diagnosed disorder push them to move toward city centers, as indicated by the MR findings. An indirect association is also possible as it has been shown that genetic risk for psychiatric disorders correlates with a range of behaviors that may influence choice of residence, such as creativity, risk taking, and substance use.[50-52] The positive genetic correlations with population density after controlling for educational attainment (college/university degree) suggest that genetic effects on choice of environment are more complex than the movement into cities of people seeking higher education.

An additional complication in the interpretation of our findings is the complex matrix of correlations between population density, TDI, and educational levels (eTable 14 in the Supplement). Higher population density is associated with higher levels of deprivation, but also with higher educational levels in the UKB. People who move from a rural or suburban environment to cities have higher TDI but also up to double the rate of higher educational levels compared with those who move to or stay in urban areas (eTable 15 in the Supplement). These sociocultural factors, together with higher proximity to psychiatric services in cities, are relevant to the UK and possibly Northern Europe but cannot be generalized to other countries, which possibly explains the lack of observed association of urbanicity with psychosis in low- and middle-income countries.[4]

Limitations

This study has limitations. First, the home locations of the participants were distributed around the UKB assessment centers, mostly located in cities, so individuals living in remote

areas were underselected. Furthermore, there is evidence of selection bias on healthier and more educated individuals in the UKB,[53] not representing the general UK population. This discrepancy raises the possibility of collider bias (eMethods 10 in the Supplement), whereby selection into the UKB influences some of the observed associations or even generates spurious associations.[54] It is not possible to infer the direction of such associations; hence, caution is advised before any generalization of the findings beyond the discovery sample. Second, in our categorical analyses of migration patterns, a small number of participants may have been misclassified because the classification of postal regions into city or rural was based on a land cover map generated on remote sensing data from 2007, whereas birthplace population density for most participants was from 1950 to 1970. Third, these results are limited by the power of the PRS. The most predictive PRS in the present study was for schizophrenia, explaining approximately 8% of the liability,[26] but the variance explained for the other disorders was substantially lower. Given the dependence of results on the power of the training GWAS data set, no head-to-head comparison among the 8 psychiatric disorders we examined is appropriate. Fourth, these results may be confounded by subtle population structure due to the geographic nature of population density.[55] To address this, we used linear mixed models and adjusted for 20 principal components.[37,56,57] However, LD score[42] intercepts were inflated, indicating that some of the genetic associations may not have been due to population density per se but instead to other correlations between genetic variants and the environment and regional geography of the UK.

Conclusions

Urbanicity has traditionally been considered a proxy for unmeasured environmental risk for schizophrenia and other mental disorders. Possible underlying factors include diet, exposure to infections or toxins, household crowding, pollution, lack of green space, deprivation, and social fragmentation.[20,58,59] However, the possibility of genetic confounding, whereby genetically predisposed families and high-risk individuals are selected into more densely populated environments, remains open. Studies with familial design suggest possible genetic selection,[13] and our study provides further evidence that genetic liability to a variety of mental disorders may contribute to the choice of environment.

Our interpretation of the findings of this study is that high genetic risk for a variety of mental disorders may affect an individual's choice of residence. This selective migration partially accounts for the association between urbanicity and mental disorders. Our findings do not compromise the importance of the environment; however, the evidence for even small genetic associations supports more integrated approaches in exploring illness causation.

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Correction: This article was corrected on December 1, 2021, to fix the part label in Figure 2E and to correct wording in the last paragraph of the PRS Analyses subsection of the Results section.

Author Contributions: Dr Maxwell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Maxwell, Breen, Vassos.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Maxwell, Breen, Vassos.
Critical revision of the manuscript for important intellectual content: Coleman, Breen, Vassos.
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Disclaimer: The views expressed herein are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. UK Biobank cohort

The recruitment process was coordinated around 22 centres in the UK in 2006-2011.[1] Individuals within travelling distance of these centres were identified using NHS patient registers (response rate = 5.47%).[2] All participants provided written consent and the current study was approved by the UK Biobank Ethics and Governance Council (REC reference 11/NW/0382; UK Biobank application reference 18177).

The aim of this study was to explore genetic associations with migration patterns into or out of urban environments within the UK. Given the strong evidence that migration into the UK (including first- and second-generation migrants, in particular from African ethnicities) is strongly associated with risk of psychosis,[3–5] we restricted our analysis to individuals of European ancestry, to avoid confounding by ethnic minority status.

