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Biological Psychiatry

Infection Polygenic Factors Account for a Small Proportion of the Relationship Between Infections and Mental Disorders

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ABSTRACT

BACKGROUND: Several recent studies have suggested a role for infections in the development of mental disorders; however, the genetic contribution to this association is understudied.

METHODS: We use the iPSYCH case-cohort genotyped sample (n = 65,534) and Danish health care registry data to study the genetic association between infections and mental disorders. To test the hypothesis that these associations are due to genetic pleiotropy, we estimated the genetic correlation between infection and mental disorders. Polygenic risk scores (PRSs) were used to assess whether genetic pleiotropy of infections and mental disorders was mediated by actual infection diagnoses.

RESULTS: We observed that schizophrenia, attention-deficit/hyperactivity disorder, major depressive disorder, bipolar disorder, and posttraumatic stress disorder (r_g ranging between 0.18 and 0.83), but not autism spectrum disorder and anorexia nervosa, were significantly genetically correlated with infection diagnoses. PRSs for infections were associated with modest increase in risk of attention-deficit/hyperactivity disorder, major depressive disorder, and schizophrenia in the iPSYCH case-cohort (hazard ratios = 1.04 to 1.10) but was not associated with risk of anorexia, autism, or bipolar disorder. Using mediation analysis, we show that infection diagnoses account for only a small proportion (6%–14%) of the risk for mental disorders conferred by infection PRSs.

CONCLUSIONS: Infections and mental disorders share a modest genetic architecture. Infection PRSs can predict risk of certain mental disorders; however, this effect is moderate. Finally, recorded infections partially explain the relationship between infection PRSs and mental disorders.

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Several studies have shown that individuals with mental disorders have a higher risk of infections over their lifetime (1–8). The associations between mental disorders and inflammatory diseases suggest that both genetic risk variants and exposure to infectious agents may be involved in an abnormal response of the immune system, which confers a higher risk for mental disorders. However, it has been difficult to disentangle the causal nature of the relationships between these traits. Are infectious agents or inflammation from an infection disrupting neurological development and increasing the risk of mental disorders? Could people with mental disorders be more prone to infections due to lifestyle and behavior, or might these traits be correlated for other reasons? Understanding the potentially shared genetic basis for infections and mental disorders may help identify the directionality of this association and the extent that it is driven by biological mechanisms.

A potential source of phenotypic correlation between infections and mental disorders lies in overlapping genetic causes, i.e., pleiotropy. Genome-wide association studies (GWASs) for multiple common infections have identified the human leukocyte antigen/major histocompatibility complex region on chromosome 6 as a major common susceptibility locus (9). Many GWASs of mental disorders have identified loci implicated in the immune response. For example, the locus most significantly associated with schizophrenia (SCZ) is also located in the human leukocyte antigen/major histocompatibility complex region (10–13). One possible explanation for this association comes from *C4* within the human leukocyte antigen locus since the C4 protein is localized to neuronal synapses, dendrites, axons, and cell bodies (14). It is possible that other genetic loci are pleiotropic and therefore have effects on both mental disorders and immune system functioning. One common approach to quantifying the amount of correlated genetic liability would be to estimate the genetic correlation via linkage disequilibrium (LD) between the two traits (8,15–19). Polygenic risk scores (PRSs) can be used in similar ways to estimate genetic overlaps (20). An advantage of PRSs is that they summarize a particular individual's genetic liability to develop a specific disease and can be used as variables in statistical models to probe the nature of the

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relationship between shared genetic risk and phenotypic outcomes.

If infection PRS is a significant predictor for being diagnosed with an infection, and infections subsequently increase the risk of being diagnosed with a mental disorder, then the shared genetic risk of infections and mental disorders could be at least partially due to the mediating effects of actual infections. This would be considered vertical pleiotropy, meaning that the genetic factor increases the risk of the disease by influencing a separate trait that is, in turn, associated with an increased risk of the disease. In contrast, a scenario where the same genetic factor influences two different traits directly would be considered horizontal pleiotropy. Shared genetic liability, or genetic correlation, indicates pleiotropy. However, a lack of genetic correlation does not indicate a lack of pleiotropy because the directions of effect of many variants could potentially lead to a small or zero correlation, even though these variants might be involved in the two traits in question. Therefore, estimating genetic overlap and assessing the type of relationship between the traits are both needed to elucidate the potential pleiotropy between them. Here, we estimate the genetic correlations between infections and mental disorders to investigate the degree to which they are driven by shared genetic factors. We then further probe any observed pleiotropy using PRSs for infection and mental disorders. The aims of this study are thus 1) to estimate the genetic correlation of infections and specific mental disorders, 2) to estimate the impact of genetic risk for infections on the hazard for infection diagnoses, and 3) to determine the degree to which genetic correlations between infections and mental disorders are attributable to the mediational effect of infection diagnoses on the hazard for psychiatric diagnoses.

METHODS AND MATERIALS

Study Populations

We use the iPSYCH 2012 case-cohort population consisting of six case groups and a population-based cohort for this study (21). Individuals who are part of the population-based cohort were chosen at random among the 1,472,762 individuals born in Denmark between May 1, 1981, and December 31, 2005, who were alive and resided in Denmark on their 1-year birthday and had a known mother. For this study, control subjects were defined as individuals who were part of the population-based cohort that did not have the corresponding mental disorder diagnosis. Each iPSYCH case group includes individuals born in the same period (1981–2005) who had been diagnosed with the following disorders by December 31, 2016: SCZ cases were identified with an ICD-10 code of F20; single and recurrent depressive disorder cases, hereafter referred to as major depressive disorder (MDD), with code F32 or F33; bipolar disorder (BPD) cases with F30 or F31; autism spectrum disorder (ASD) cases with F84.0, F84.1, F84.5, F84.8, or F84.9; anorexia cases with F50.0; and attention-deficit/hyperactivity disorder (ADHD) with F90.0 (Table 1). For individuals diagnosed prior to 1994, equivalent ICD-8 codes were used.

Information on history of any infection was collected from Danish National Patient Registry hospital contacts in Denmark (both inpatient and outpatient), combining multiple types of infections. In this study the following 12 types were included: bacterial, central nervous system, gastrointestinal, genital, hepatitis, other, otitis, respiratory, sepsis, skin, urological, and viral. As each person may have a history of multiple infections, the age at infection was set to the date of first contact with any of the reported infection ICD codes within each category (Table S1). The population-based cohort contains a non-ascertained collection of infection and mental disorder cases. Control subjects were defined as individuals in the iPSYCH random sample without a recorded infection.

Genetic Analysis, GWA Data Cleaning, and PRS Calculation

For each GWAS summary statistic, we used a cleaning protocol to retain only reliable or useful annotation. To infer the genome build, all variants' positions were mapped to dbSNP build 151 using reference positions for GRCh35, GRCh36, GRCh37, and GRCh38. A variant was removed if it had any of the following characteristics: insertion-deletion, multiallelic, allele mismatched, strand ambiguous, multiple base pair positions, missing test statistics, and variants mapping nonuniquely to GRCh37 or GRCh38 positions and having nonunique rs-ids in dbSNP 151. All variant-effect alleles were flipped to be the reference allele o/f GRCh37. In addition, the cleaned summary statistics only contained autosomal single nucleotide polymorphisms (SNPs). The GWAS summary statistics on infection from FinnGen excluded variants with info

Table 1. Characteristics of the Case-Cohort Study Population

Characteristics	iPSYCH Cases, *n*	Population Cohort (*N* = 21,706), *n* (%)	Recorded Infections Among iPSYCH Cases, *n* (%)	Age at First Psychiatric Diagnosis, Years, Mean (SD)
Sex				
Female	–	10,644 (49.04%)	–	–
Male	–	11,062 (50.96%)	–	–
ADHD	15,060	441 (2.03%)	7050 (46.81%)	13.88 (6.54)
Autism	12,884	385 (1.77%)	5576 (43.28%)	11.22 (5.37)
Anorexia	2980	80 (0.37%)	1296 (43.49%)	16.89 (3.98)
Bipolar Disorder	1722	57 (0.26%)	860 (49.94%)	23.36 (4.44)
MDD	19,170	621 (2.86%)	9705 (50.63%)	20.25 (4.28)
Schizophrenia	2867	110 (1.32%)	1455 (50.75%)	21.87 (4.01)

ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder.

score <0.95, excluded variants with missingness >0.01, and excluded variants with a minor allele frequency <0.05.

We used Ldpred (22) to create PRSs for infection and mental disorders using publicly available GWAS summary statistics cleaned by the protocol described above. Ldpred adjusts the effect of each SNP allele for those of other SNP alleles in LD with it and also takes into account the likelihood of a given allele to have a true effect according to a user-defined P-parameter corresponding to the fraction of SNPs assumed to have a true effect on the trait. SNP inclusion criteria required a minimum minor allele frequency of >5%, a minimum imputation info score of 0.98, and a Hardy-Weinberg disequilibrium test p value $>1 \times 10^{-5}$ in the iPSYCH-imputed genotype dataset. We used Ldpred settings for P-parameter set to 1 because PRSs for highly polygenic traits usually perform best when assuming that all SNPs have a true effect. Polygenic scores were then computed using the "score" function in PLINK (version 1.9beta) (23).

Statistical Methods

In analyses of the association between infection and risk of mental disorder diagnosis, hazard ratios (HRs) were estimated using Cox proportional hazard (CPH) regression in R 3.6.1 [coxph function from the R package survival 3.2-7 (24)]. CPH longitudinal analysis uses infections as exposure and mental disorders as the outcome. The CPH analyses included as covariates sex, year of birth, and the first 10 genetic principal components. We report on two models, the first where there is no exclusion of individuals based on the ordering of infection and mental disorder diagnosis censoring, and the second where individuals with a recorded infection after a recorded mental disorder were excluded. Genetic principal components were standardized (centered at zero and with unit variance). The function "survConcordance" was used to estimate the Harrell's index (C-index), a measure of goodness-of-fit equivalent to the area under the receiver operating characteristic curve, with a range from 0.5 to 1 (25). A value of 0.5 means that the model is no better than predicting an outcome than random chance, and a value of 1 indicates perfect discrimination power (26).

Genetic correlations (r_g) were estimated using bivariate LD score regression (LDSC) with default settings (27). LDSC produces a statistic, referred to as the bivariate LDSC slope, interpreted as the genetic correlation between the two sets of summary statistics. All mental disorder summary statistics used for genetic correlation analysis were the full versions available from the Psychiatric Genomics Consortium. The major histocompatibility complex region (chr6: 26–34 M) was excluded from the analysis due to complex LD structure. In addition, CPH models were used to estimate the association between infection PRS and infection diagnosis. CPH analyses included as covariates sex, birth year, PRS, and the first 10 genetic principal components. PRSs and genetic principal components were centered at zero with a variance of 1. The proportional hazards assumption was assessed by visual inspection of survival curves. Mediation analyses (i.e., the indirect effects of infection PRS on time to first mental disorder diagnosis testing via its impact on infection diagnoses) were performed with the R package mediation using linear regression using 1000 bootstrap replications to obtain standard errors (28). Moderated mediation was performed using the same package to determine if PRSs for mental disorder moderated this mediating relationship.

See the Supplement for data and summary statistics sources.

RESULTS

Individuals With Any Infection Have a Higher Risk of Being Diagnosed With a Mental Disorder

We first estimated the effect of infection on time to onset of any mental disorder (ICD-10 codes: F00–F99, ICD-8 codes: 290–315). Using a study sample consisting of iPSYCH cases with any mental disorder and the population-based cohort, we observed that infections were associated with an increased risk of being diagnosed with a mental disorder (HR = 1.30; 95% CI = 1.27–1.32; $p < 2 \times 10^{-16}$) (Figure 1). Next, we subdivided mental disorders and focused on six major disorders, ADHD, ASD, anorexia, BPD, MDD, and SCZ, to determine if all disorders shared this significant association. Each comparison was done, one at a time, including each case group and the population-based cohort, with the case group corresponding only to the tested disorder (i.e., ADHD cases + population cohort). We observed a significant risk of being diagnosed with all six mental disorders following an infection (Figure 1). Infection was associated with ADHD with an HR of 1.43 (95% CI = 1.38–1.48, $p < 2 \times 10^{-16}$), with ASD of 1.30 (95% CI = 1.26–1.35, $p < 2 \times 10^{-16}$), with anorexia of 1.25 (95% CI = 1.16–1.34, $p = 2.11 \times 10^{-9}$), with BPD of 1.51 (95% CI = 1.38–1.67, $p \leq 2 \times 10^{-16}$), with MDD of 1.37 (95% CI = 1.33–1.41, $p < 2 \times 10^{-16}$), and with SCZ of 1.56 (95% CI = 1.45–1.68, $p < 2 \times 10^{-16}$). We also repeated this analysis where individuals with their first recorded infection occurring after a mental illness diagnosis were excluded (Table S1), and we observed similar effects of infection on mental disorder risk with the exception that infection no longer had a significant risk on anorexia (HR = 1.00; 95% CI = 0.92–1.08; $p = .98$). Overall, these results confirm previous findings of a link between an infection diagnosis and risk of developing a mental disorder in our study population (7,8).

Genetic Correlation Analysis Shows Genetic Overlap Between Infections and Mental Disorders

To explore a genetic overlap between infection and mental disorders, we performed a genetic correlation analysis using GWA summary statistics for infection and psychiatric traits (Figure 2). Genetic correlations (r_g) and heritability (h^2) (Table S2) were estimated using bivariate LDSC. Posttraumatic stress disorder (PTSD) is not part of the ascertained cases in iPSYCH but was included in the genetic correlation analysis because of its previously reported strong associations with infection (29). We observed that the genetic propensity for infection is significantly correlated with PTSD ($r_g = 0.88$, $p < 2.7 \times 10^{-10}$), MDD ($r_g = 0.37$, $p = 9.4 \times 10^{-11}$), ADHD ($r_g = 0.34$, $p = 1.0 \times 10^{-6}$), BPD ($r_g = 0.19$, $p = 2 \times 10^{-4}$), and SCZ ($r_g = 0.16$, $p = 5 \times 10^{-4}$) (Figure 2). Neither anorexia ($r_g = 0.12$, $p = .0804$) nor ASD ($r_g = -0.01$, $p = .935$) had a significant genetic correlation with genetic propensity for infection. After

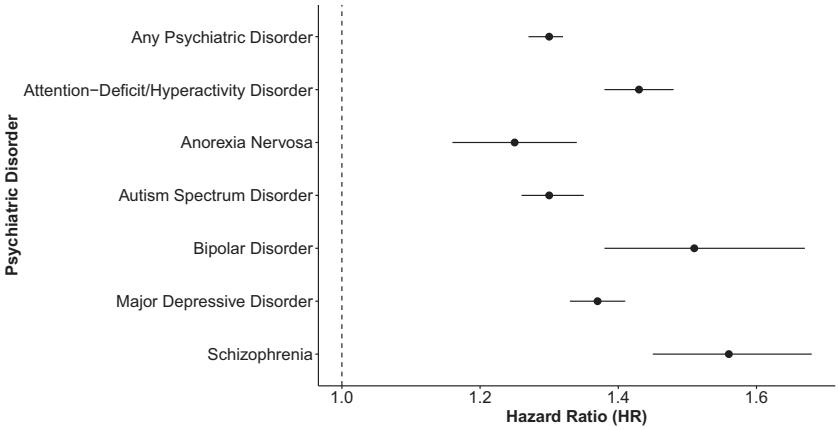

Figure 1. The predictive ability of infection on mental illness risk. Hazard ratios with error bars as 95% confidence intervals.

Bonferroni correction for seven tests, genetic correlations for PTSD, MDD, ADHD, BPD, and SCZ remained significant. These results demonstrate the existence of substantial pleiotropy between infections and certain mental disorders considering the low heritability of infection (0.0172) in FinnGen.

Infections Have a Small but Significant Mediating Effect on the Relationship Between Infection PRSs and the Risk of Mental Disorders

First, we verified whether PRSs are predictive of their respective disorder. The infection PRS significantly predicted any infection diagnosis in the iPSYCH random sample population (HR = 1.06; 95% CI = 1.04–1.09, $p = 3.1 \times 10^{-10}$) (Table S3). For each mental disorder PRS, we determined the predictive power in the iPSYCH case-cohort (Figure S1 and Table S3), and as expected, we observed that each PRS significantly predicts the corresponding disorder.

Next, we estimated the effect of infection PRS on age at first mental disorder diagnosis using CPH models. We observed that increased PRS for infection confers increased risk of any mental disorder (HR = 1.04; 95% CI = 1.03–1.05, $p \leq 2 \times 10^{-16}$) (Figure 3). When examining specific mental disorders, the PRS for infection significantly increased the risk of ADHD (HR = 1.08, 95% CI = 1.07–1.10, $p < 2 \times 10^{-16}$), ASD (HR = 1.02, 95% CI = 1.00–1.04, $p = .02$), MDD (HR = 1.04, 95% CI = 1.03–1.06, $p = 1.2 \times 10^{-7}$), and SCZ (HR = 1.08, 95% CI = 1.04–1.13, $p = 4.02 \times 10^{-5}$), but not of anorexia (HR = 1.01, 95% CI = 0.97–1.05, $p = .66$) or BPD (HR = 1.04, 95% CI = 0.99–1.09, $p = .13$). After Bonferroni correction for six tests, ASD was no longer significant. We performed a sex-stratified analysis and observed nearly identical results, with the exception that infection PRS significantly predicted SCZ in females but did not predict SCZ in males (Table S4). Overall, this result shows that there is a small but significant effect of the genetic liability of infections for some mental disorders, but not all.

We performed a mediation analysis to quantify the indirect mediation of infections between infection PRS and a mental disorder diagnosis (Figure 4 and Table 2). We applied two different approaches, the first using average causal mediation effects and the second using moderated mediation analysis with the corresponding mental disorder PRS as the moderating variable. In the first model, including, in turn, each mental

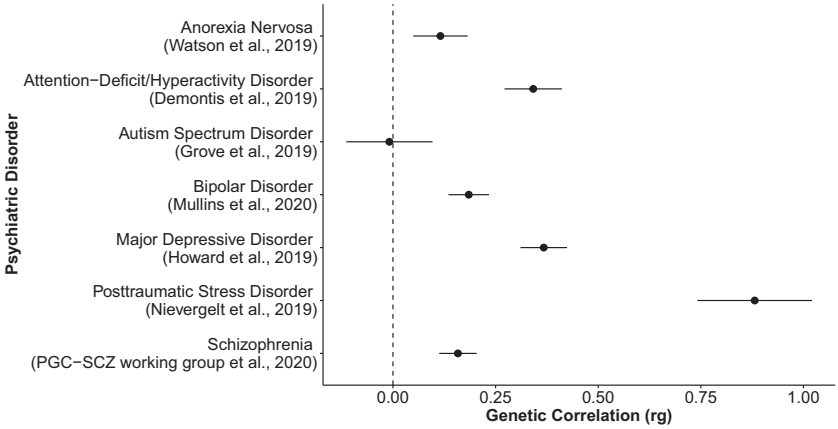

Figure 2. Genetic correlations between recorded infections and seven mental disorders. Genetic correlations (r_g) with standard error. PGC-SCZ, Psychiatric Genomics Consortium-Schizophrenia.

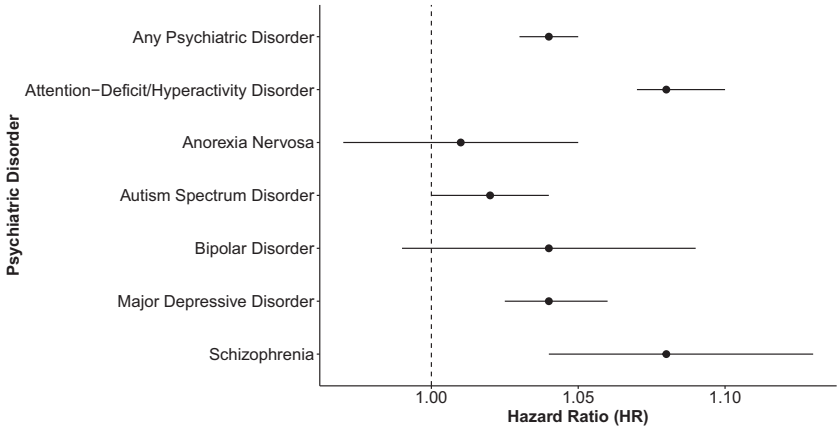

Figure 3. The predictive ability of infection polygenic risk scores on mental illness risk. Hazard ratios with error bars as 95% confidence intervals.

diagnosis as an independent outcome and infection as the mediator, only a small proportion of the effect of the infection PRS was mediated through infection. Although significant for ADHD, ASD, MDD, and SCZ ($p < 2 \times 10^{-16}$), only between 7% and 14% of the total effect of infection PRS was mediated by recorded infections. There was no significant effect from the mediation of infection on BPD or anorexia. The moderated mediation analysis, where the mediator and outcome models contain the moderator and its interaction terms with mental disorder PRS, showed a similarly small proportion of the mediating effect from infections (6%–12%) for ADHD, ASD, MDD, and SCZ. These results indicate that the recorded infections play only a minor role in the genetic propensity for infections and mental disorders.

When Compared With Other Risk Factors, Infection and Infection Polygenic Risk Perform Poorly at Predictive Mental Disorder Risk

Finally, we compared different models of PRS, infection history, and parental history of mental disorders to determine their overall concordance for each psychiatric diagnosis. In sex-stratified CPH regression models for all psychiatric diagnoses, models that added infection PRS or infection diagnosis did not significantly improve the overall explained variation (Figure 5). Models combining infection PRS and infections had a C-index range between 0.54 and 0.58, while models with parental history of mental disorders had a C-index range between 0.57 and 0.66. However, none of the models, when combined with all the aforementioned variables, obtained a C-index of 0.7.

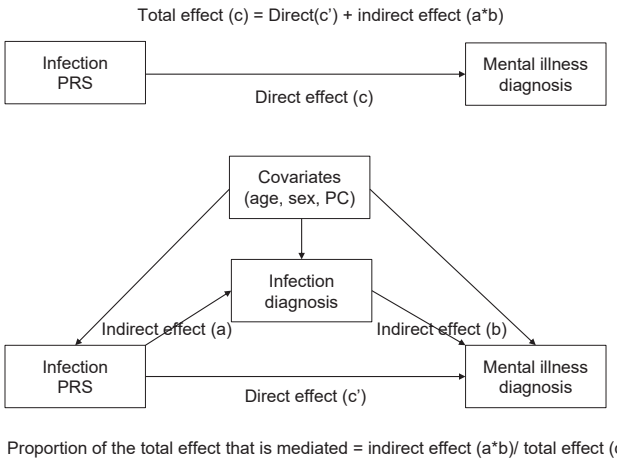

Figure 4. Mediation analysis flowchart. PC, principal component; PRS, polygenic risk score.

DISCUSSION

Here, we demonstrated that infections can be significant, but modest, predictors for most mental disorders, in line with previous studies (1,2,6,8,30). Most notably Nudel *et al.* (8) reported a high degree of genetic correlation between having any severe infection and having a psychiatric diagnosis. In this study, we extended the work of Nudel *et al.* by calculating PRSs to estimate the genetic overlap between infections and specific mental disorders. The shared additive genetic effect between infection and mental disorders was estimated using genetic correlation analysis, revealing several significant positive correlations for PTSD, MDD, ADHD, BPD, and SCZ. Furthermore, we reported that infection PRSs can predict the risk of ADHD, MDD, and SCZ in this Danish population. This suggests that there is a minor additive genetic contribution associated with infection risk that is involved in a liability to certain mental disorders. To test if reported infections explained the connection between infection PRS and a mental disorder diagnosis, a mediation analysis was performed, where recorded infections were the mediator between infection PRSs and mental disorder diagnosis. While PRS for infection does predict a small amount of risk for psychiatric illness, only a modest portion of the risk was mediated by actual history of infection (potentially suggesting other mechanisms, such as horizontal pleiotropy) (Table 2). Infections have a low heritability (1.7%) (Table S2), which is the result of environmental exposure. This low heritability may also explain the minor contribution of recorded infections in the mediation analysis.

While the genetic correlation results for ADHD, MDD, and SCZ were consistent with the significant effect of infection

Table 2. Mediation Analysis of Infection PRS Through Infection Diagnosis on Mental Illness Diagnosis

Proportion Mediated	Basic Mediation Estimate (95% CI)	*p* Value	Moderated Mediation Estimate (95% CI)	*p* Value
ADHD	0.078 (0.052 to 0.111)	$<1 \times 10^{-10}$	0.084 (0.053 to 0.121)	$<1 \times 10^{-10}$
Autism	0.127 (0.059 to 0.375)	$<1 \times 10^{-10}$	0.111 (0.056 to 0.251)	$<1 \times 10^{-10}$
Anorexia	0.258 (−2.336 to 2.017)	.472	0.130 (−1.19 to 1.16)	.218
Bipolar Disorder	0.158 (0.050 to 1.025)	.05	0.143 (0.062 to 0.692)	.02
MDD	0.098 (0.064 to 0.14)	$<1 \times 10^{-10}$	0.093 (0.058 to 0.143)	$<1 \times 10^{-10}$
Schizophrenia	0.091 (0.053 to 0.167)	$<1 \times 10^{-10}$	0.074 (0.045 to 0.126)	$<1 \times 10^{-10}$

Proportion mediated is the proportion of the effect that goes through the infection mediator.
ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder; PRS, polygenic risk score.

PRS on mental disorder risk, infection PRS did not have a significant effect on BPD. This was surprising because BPD does have a significant overlap with SCZ, both at a genetic level and at a diagnostic level. Given the relatively small number of BPD cases, the iPSYCH case-cohort (n = 1722) might lack the power to detect a significant effect from infection PRSs. While PTSD was not an ascertained case group in iPSYCH, we were able to analyze summary statistics from a recent independent GWAS (31), and we observed a substantially higher genetic correlation with infection (r_g = 0.88, $p < 2.7 \times 10^{-10}$) than other disorders. While it remains unclear why the genetic correlation is high, others have identified a similar epidemiological relationship in another Danish cohort (29).

Finally, we tested the predictive performance of different models that included variables associated with infection on disease risk using CPH models reported with a C-index. We observed that models including infection and infection PRSs did not increase the prediction accuracy compared with models containing solely principal components. Other factors such as psychiatric PRS and family history are only slightly better predictors of mental disorder risk because none of the factors combined have a C-index over 0.7.

Previous studies have investigated different genetic interactions between infections and mental disorders. One study found no evidence that PRS for SCZ had a significant effect on infection risk in SCZ cases and control subjects (32). Other studies have shown a significant genetic overlap for immune-related disorders and mental disorders (8,33). However, PRSs for autoimmune diseases were only slightly associated with increased risk of mental disorders. The results of these studies are consistent with our findings on PRSs for infections and mental disorders. To our knowledge, our study is the first to find evidence for a shared genetic contribution between infection PRS and specific mental disorders. This effect is observed for ADHD, MDD, and SCZ, but not anorexia and BPD (Figure 3). The effect of infection PRS was marginally significant for ASD but was not significant after correction for multiple testing. The connection of infection to certain mental health disorders could be due to biological mechanisms related to inflammation and immune response. Several studies have shown that severe infections could have a higher proportion of sepsis or inflammatory response, which could in turn cause encephalitis (34–36). Inflammatory mechanisms can affect the brain, especially during critical developmental windows, through various pathways to increase the risk of developing mental disorders.

Identifying the effects of specific mental disorders may help inform the biological mechanism that leads to increased risk of a mental disorder diagnosis following an infection. Combining multiple disorders together may mask the individual effects of one or the other. When we measure genetic liability for infections, we see the strongest associations to risk of ADHD, MDD, and SCZ, while infection PRS has a marginally significant effect on ASD risk. Further subdividing the major mental disorders into subtypes may help pinpoint the effect of infections on disease risk.

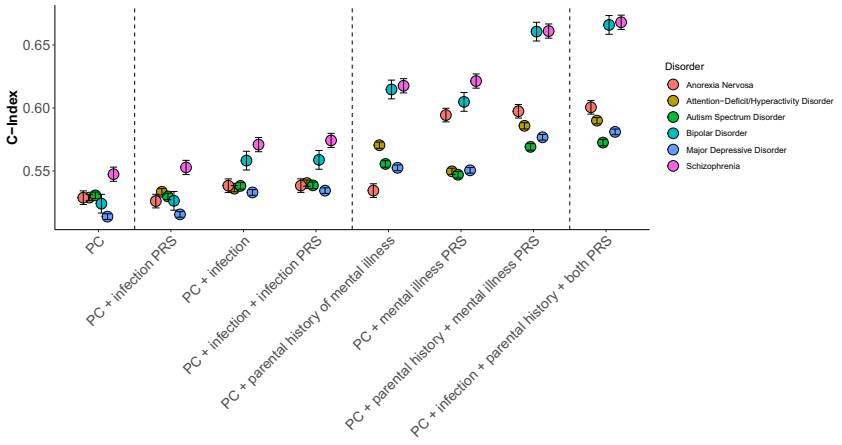

Figure 5. Concordance index analysis comparing different models that predict risk of mental illness diagnosis. The concordance index (C-index) of models with different exposures (PC, infection PRS, history of infections, mental disorder PRS, and parental history of mental illness) on six mental disorder outcomes. PC, principal component; PRS, polygenic risk score.

Limitations

While using lifetime hospital register data increases accuracy over other methods, such as self-reported data, we are limited to gathering only the most severe cases of infection that require hospital visits. Other less severe infections could be treated by a primary care physician or through privatized health care and would have not been captured by our analysis. Our knowledge about the severity of infections or additional health complications is also limited. The infection GWAS also combines many different types of infections together, each of which elicits different but overlapping aspects of an immune response. Relationships between particular types of infections were not examined and will require further studies with well-powered GWAS data. Despite the complexity in the infection GWAS, we do see that infection PRSs can significantly predict infection risk with available hospital register data. However, hospital record data could be biased in other ways as well, such as selection bias. Other studies have shown that children with ASD are taken to the hospital more often overall than children without ASD (37,38). This occurs both before and after children are diagnosed with ASD. It is not clear why this happens to children that have been or will be diagnosed with ASD or if individuals with other mental disorders also have more (or less) hospital contact in general.

Conclusions and Perspectives

Overall, the effect of infection PRSs on risk for a mental disorder diagnosis, while statistically significant, was relatively small. We see that this effect may be mediated by direct effects and may involve horizontal pleiotropy but could also be explained by unmeasured third variable effects. It is likely that the significant effects we observe on infections and mental disorders are driven by environmental nongenetic factors or nonadditive genetic factors owing to the small proportion of the variance explained by PRSs. It is also possible that there are genetic factors not captured by PRSs that drive this connection. Rare variants are not included in summary statistics and later downstream analysis due to uncertainty of effect estimates (27). There may still be genetic factors that could be important in clinical settings to help understand mental disorder risk; however, we failed to find compelling evidence that infection PRSs should be included in risk prediction in this context.

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The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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