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Correlates of Risk for Disinhibited Behaviors in the Million Veteran Program Cohort

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IMPORTANCE Many psychiatric outcomes share a common etiologic pathway reflecting behavioral disinhibition, generally referred to as externalizing (EXT) disorders. Recent genome-wide association studies (GWASs) have demonstrated the overlap between EXT disorders and important aspects of veterans' health, such as suicide-related behaviors and substance use disorders (SUDs).

OBJECTIVE To explore correlates of risk for EXT disorders within the Veterans Health Administration (VA) Million Veteran Program (MVP).

DESIGN, SETTING, AND PARTICIPANTS A series of phenome-wide association studies (PheWASs) of polygenic risk scores (PGSs) for EXT disorders was conducted using electronic health records. First, ancestry-specific PheWASs of EXT PGSs were conducted in the African, European, and Hispanic or Latin American ancestries. Next, a conditional PheWAS, covarying for PGSs of comorbid psychiatric problems (depression, schizophrenia, and suicide attempt; European ancestries only), was performed. Lastly, to adjust for unmeasured confounders, a within-family analysis of significant associations from the main PheWAS was performed in full siblings (European ancestries only). This study included the electronic health record data from US veterans from VA health care centers enrolled in MVP. Analyses took place from February 2022 to August 2023 covering a period from October 1999 to January 2020.

EXPOSURES PGSs for EXT, depression, schizophrenia, and suicide attempt.

MAIN OUTCOME(S) AND MEASURE(S) Phecodes for diagnoses derived from the *International Statistical Classification of Diseases, Ninth* and *Tenth Revisions, Clinical Modification*, codes from electronic health records.

RESULTS Within the MVP (560 824 patients; mean [SD] age, 67.9 [14.3] years; 512 593 male [91.4%]), the EXT PGS was associated with 619 outcomes, of which 188 were independent of risk for comorbid problems or PGSs (from odds ratio [OR], 1.02; 95% CI, 1.01-1.03 for overweight/obesity to OR, 1.44; 95% CI, 1.42-1.47 for viral hepatitis C). Of the significant outcomes, 73 (11.9%) were significant in the African results and 26 (4.5%) were significant in the Hispanic or Latin American results. Within-family analyses uncovered robust associations between EXT PGS and consequences of SUDs, including liver disease, chronic airway obstruction, and viral hepatitis C.

CONCLUSIONS AND RELEVANCE Results of this cohort study suggest a shared polygenic basis of EXT disorders, independent of risk for other psychiatric problems. In addition, this study found associations between EXT PGS and diagnoses related to SUDs and their sequelae. Overall, this study highlighted the potential negative consequences of EXT disorders for health and functioning in the US veteran population.

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Supplemental content

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Group Information: The members of the Million Veteran Program (MVP) and the Cooperative Studies Program (CSP) #572 appear in Supplement 2.

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Psychiatric disorders have far-reaching consequences for affected individuals, their families, communities, and the broader society.[1-4] Many diagnoses are strongly comorbid and share, at least in part, a common etiology.[5] Disorders related to behavioral disinhibition, such as substance use disorders (SUDs) and antisocial personality disorder, have been labeled as externalizing (EXT) disorders.[6,7] Twin and family studies suggest that the common liability toward EXT is highly heritable (approximately 80%).[8-10] Recent multivariate genome-wide association studies (GWASs) have found robust evidence for a shared genomic factor for EXT,[11,12] composed of input GWASs related to SUDs, risky sexual behaviors, personality characteristics, and neurodevelopmental disorders. Importantly, genetic liability for EXT overlaps with other phenotypes of public health relevance, such as other psychiatric problems,[11,12] suicidal thoughts and behaviors,[11,13-15] other SUDs,[11,16-18] and a range of other medical conditions (eg, ischemic heart disease, liver disease, viral hepatitis).[11] The widespread impact of risk for EXT makes it a potential target for early intervention and prevention.

The proliferation of large-scale biobanks—such as All of Us,[19] the UK Biobank,[20] FinnGen,[21] and Biobank Japan[22]—linking individual-level genomic data with electronic health records (EHRs) presents opportunities to further explore the association between genetic liability for a given disorder (typically in the form of polygenic risk scores [PGSs]) and a wide range of outcomes. This hypothesis-free approach, referred to as a phenome-wide association study (PheWAS),[23] can aid in understanding pleiotropic effects. Recent PheWASs using PGSs for other psychiatric problems (eg, schizophrenia, bipolar disorder, and depression) have identified widespread associations between PGSs and a host of psychiatric and other medical diagnoses.[24,25]

In the current analysis, we applied a PheWAS of a PGS derived from a multivariate GWAS of EXT disorders[11] to the EHRs of the Department of Veterans Affairs Million Veterans Program (MVP) cohort.[26] A previous PheWAS of the EXT PGS in the Vanderbilt University Medical Center Biobank[27] identified over 250 associations with EHR-derived medical conditions[11] but was limited to individuals of European ancestries. We extended the PheWAS of EXT disorders to veterans of African, European, and Hispanic or Latin American ancestries. Additionally, EXT disorders are genetically correlated with other psychiatric problems (eg, depression, schizophrenia),[11] and any association with EXT disorders could be attributable to shared risk with these other phenotypes. We therefore compared results from our primary PheWAS of EXT PGS to results for the EXT PGS, controlling for PGSs of schizophrenia,[28] depression,[29] and suicide attempt.[13] Finally, we attempted to replicate associations from the primary PheWAS in a holdout sample of full siblings. Genetic differences between siblings are random; therefore, within-family associations between the EXT PGS and health outcomes cannot be attributed to between-family sources of confounding, such as environmental exposures.

Key Points

Question What are the correlates of risk for disinhibited behaviors in the US veterans population?

Findings In this cohort study including electronic health record data of 560 824 veterans, risk for disinhibited behaviors was associated with medical outcomes across all bodily systems, including substance use disorders, suicide and self-harm, liver disease, chronic airway obstruction, and viral hepatitis C. Many of these associations were significant across ancestry and after accounting for other comorbid problems.

Meaning Results suggest that risk for disinhibited behaviors was associated with many health outcomes of particular relevance within the veteran community.

Methods

MVP Cohort

The MVP cohort is a landmark endeavor that links genomic laboratory testing, survey-based self-report data, and EHRs, with the goal of creating a mega biobank and evidence base for precision medicine initiatives.[26] The 850 000 enrolled participants reflect the population that uses the Veterans Health Administration (VA), with overrepresentation of older and male individuals, as well as higher rates of multiple morbidities and chronic conditions related to EXT compared with the general population.[30,31] Participants are active users of the VA health care system and were recruited through invitational mailings or by MVP staff while receiving clinical care. Informed consent and authorization per the Health Insurance Portability and Accountability Act were the only other inclusion criteria. Once enrolled, participants' EHR data were linked. The current analysis, which took place from February 2022 to August 2023 using EHR data from the VA covering a period from October 1999 to January 2020, used release 4 of MVP data and was approved by the VA Central institutional review board. All participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Genotyping

MVP participants were genotyped on the MVP 1.0 Axiom array (Thermo Fisher Scientific).[32] Genetic ancestries of participants were classified using the harmonized ancestry and race-ethnicity (HARE) method,[33] which harmonizes the closest ancestral population with self-identified race and ethnicity. Genotypic data were imputed to the Trans-Omics for Precision Medicine (TOPMed) reference panel,[34] which specifically improves imputation quality in non-European and admixed ancestries.[35] As of release 4, there are 124 717 veterans of predominantly African ancestry, 8362 veterans of predominantly Asian ancestry, 467 101 veterans of predominantly European ancestry, and 52 416 veterans of predominantly Hispanic or Latin American ancestry. In the current analysis, we included data from the African, European, and Hispanic or Latin American groups, as these had sufficient statistical power. Within each of these HARE categories, we restricted analyses to unrelated individuals, excluding all those who were second-degree relatives or closer (KING software coefficient ≤0.177)[60] and limited to those whose primary self-identified race and ethnicity matched their HARE classification, so as to not introduce potential confounding driven by well-characterized health disparities related to racism and racial discrimination.[36,37]

EHRs

Our main outcomes were phecodes, which are clusters of *International Classification of Diseases, Ninth* and *Tenth Revision, Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*) codes in the EHR,[38,39] validated previously.[40,41] We considered individuals as having a diagnosis for any given phecode if there were 2 or more occurrences of that phecode in their EHR. Prior analyses have shown 2 or more phecodes to be good predictors of diagnosis.[24,25] We excluded phecodes for which there were fewer than 100 individuals with the diagnosis.

PGSs

We estimated PGSs derived from 4 large-scale GWASs: EXT (effective N = 1 492 085),[11] depression (effective N = 449 856),[29] schizophrenia (effective N = 117 498),[28] and suicide attempt (effective N = 91 230).[13] Internalizing (eg, depression) and thought (eg, schizophrenia) disorders are genetically correlated with EXT[11] and could confound associations with EXT. We used these additional PGSs as proxies to control for higher-order internalizing/thought disorder variance. Additionally, we included the suicide attempt PGS to explore the possibility that associations between EXT and suicide-related phenotypes were independent of risk for suicide attempt or other psychiatric problems. Although PheWAS is an agnostic approach, we included these additional PGSs to explore the robustness of associations between EXT and phenotypes of particular relevance to the veteran population (eg, suicidal behaviors). The additional PGSs contain variance related to both higher-order constructs (eg, internalizing) and phenotype-specific variance, all of which could be relevant to any associations observed between EXT and EHR outcomes. Although imperfect proxies for the corresponding higher-order constructs, these PGSs represent the most well-powered indicators currently available.

In European ancestries, we created PGSs using PRS-CS,[42] a bayesian regression and continuous shrinkage method that estimates the posterior effect sizes for each single-nucleotide variant in a given set of GWAS summary statistics. In the African and Hispanic or Latin American ancestries, we used a different approach. PGS accuracy decays continuously as target samples differ in ancestry from the discovery GWAS, even within relatively homogenous genetic clusters,[43] and we lacked ancestry-matched GWAS for EXT to use methods that boost power of PGS in underpowered samples, such as PRS-CSx.[44] Therefore, in the African and Hispanic or Latin American ancestries, we created EXT PGS using the 579 loci reported in the externalizing GWAS, as using genome-wide significant variants is more robust to population stratification.[45] We standardized all PGSs to *z* scores.

Statistical Analysis

We first conducted a PheWAS between the EXT PGS and phecodes within EUR ancestries, using logistic regression and covarying for age, sex, and 20 ancestry principal components. We conducted the same PheWAS for the depression, schizophrenia, and suicide attempt PGSs to compare the overlap of significant associations from the 4 independent PheWAS. Next, we attempted to replicate significant associations within African and Hispanic or Latin American ancestries. Third, we performed a PheWAS, including all PGSs in the same model, to test whether associations between EXT remained while controlling for depression, schizophrenia, and suicide attempt PGSs. We also included total comorbidity burden, a count of the top 600 phecode terms for which an individual met criteria transformed using an inverse normal transformation.[25] Lastly, we used a subset of full siblings identified through genetic data to test for associations between EXT and phecodes within family, using a linear probability model. Fixed-effects logistic regression can provide biased estimates when the number of observations per group is small.[25,46] We applied a multiple testing correction for tests across the 4 PGS included in the analyses for European ancestries. We used a less conservative approach to multiple testing in the African and Hispanic or Latin American ancestries given the expected reduction in predictive power of PGS, applying a false discovery rate (FDR)[47] of 5%. Data analyses were performed using R software, version 4.0.3 (R Project for Statistical Computing). All *P* values were 2-sided, and *P* values below the corresponding multiple testing corrected threshold were considered significant.

Results

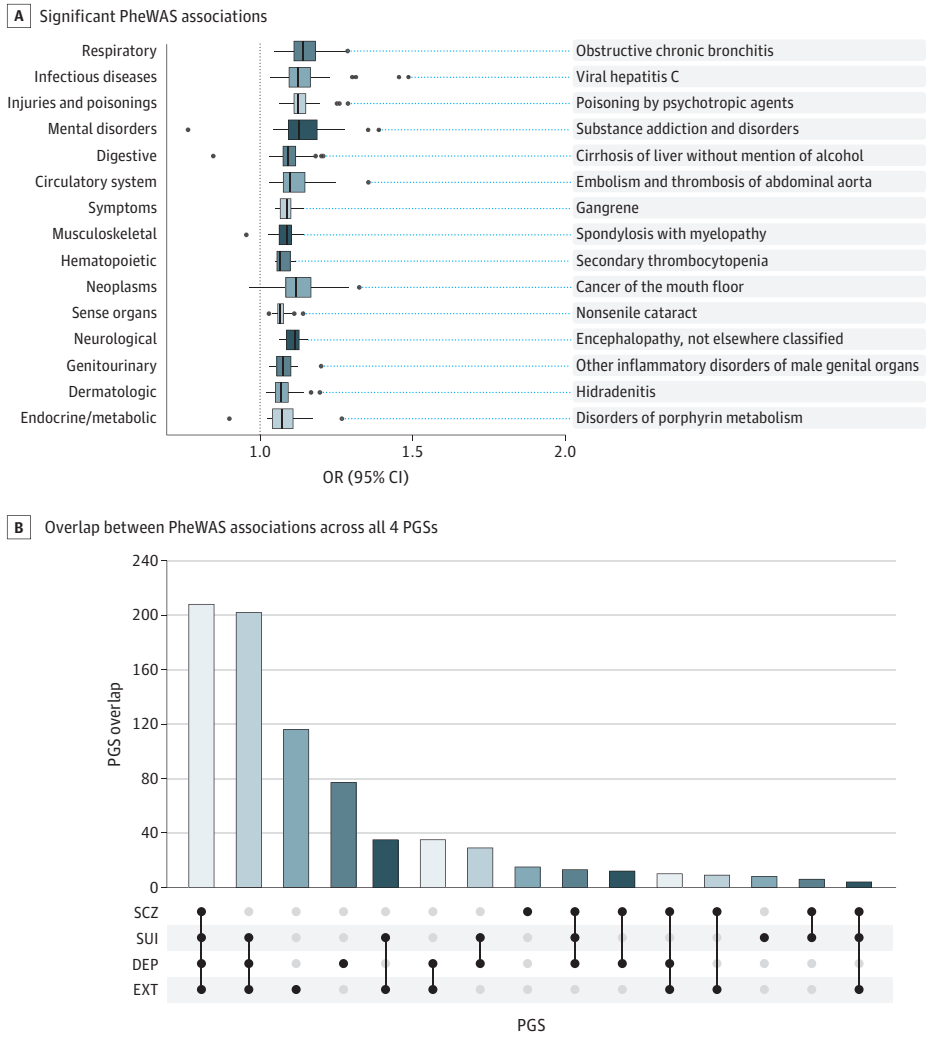
Main PheWAS of EXT PGS

After removing related individuals, those with any missing information, those without available EHR data, and those whose primary identity differed from their HARE classification within the MVP cohort were the data of 560 824 patients (mean [SD] age, 67.9 [14.3] years; 512 593 male [91.4%]; 48 231 female [8.6%]). A total of 406 255 participants of European ancestries were available for the initial PheWAS (mean [SD] age, 69.8 [14.1] years; 377 003 male [92.8%]; 29 251 female [7.2%]). We performed a similar process for veterans of African ancestries (112 390; mean [SD] age, 63.5 [12.6]; 96 993 male [86.3%]; 15 397 female [13.7%]) and Hispanic or Latin American ancestries (42 179; mean [SD] age, 60.5 [16.2]; 38 130 male [90.4%]; 4049 female [9.6%]). In total, there were 1436 phecodes for African veterans, 1652 phecodes for European veterans, and 1125 phecodes for Hispanic or Latin American veterans with 100 or more diagnoses available. eTable 1 in Supplement 1 presents all demographic statistics.

After correcting for multiple testing, 619 of the 1652 phecodes (37.5%) were significantly associated with EXT PGS. We observed associations with EXT across virtually all bodily systems, including the following associations being between EXT PGS and viral hepatitis C (odds ratio [OR], 1.49; 95% CI, 1.46-1.51), substance addiction and disorders (OR, 1.39; 95% CI, 1.37-1.40), embolism/thrombosis of the abdominal aorta (OR, 1.36; 95% CI, 1.22-1.51), tobacco use disorders (OR, 1.35; 95% CI, 1.34-1.36), and cancer of the mouth (OR, 1.33; 95% CI, 1.17-1.50).

Figure 1A presents the distribution in EXT effect sizes (ORs) for all 619 significant PheWAS associations by phecode domain, of which 188 were independent of risk for comorbid problems or PGSs. Across domains, there is a general enrichment for positive associations with EXT: the median effect sizes are generally above 1, and greater levels of EXT risk are generally

Figure 1. Phenome-Wide Association Study (PheWAS) of Externalizing Polygenic Risk in the Million Veterans Program (MVP)



PheWAS associations with externalizing (EXT) disorders polygenic risk scores (PGSs) in veterans of the primarily European ancestries (N = 406, 255). Phecodes are grouped into 17 categories: infectious diseases, neoplasms, endocrine/metabolic, hematopoietic, mental disorders, neurological, sense organs, circulatory system, respiratory, digestive, genitourinary, pregnancy complications, dermatologic, musculoskeletal, congenital anomalies, symptoms, and injuries & poisonings. A, Box plots of effect sizes (odds ratios [ORs]) for the 619 of 1652 significant PheWAS associations below the Bonferroni corrected *P* value threshold ($P < 7.57 \times 10^{-6}$). B, Upset plot of overlap between phenome-wide significant associations ($P < 7.57 \times 10^{-6}$) across all 4 PGSs (EXT, depression, schizophrenia, and suicide attempt).

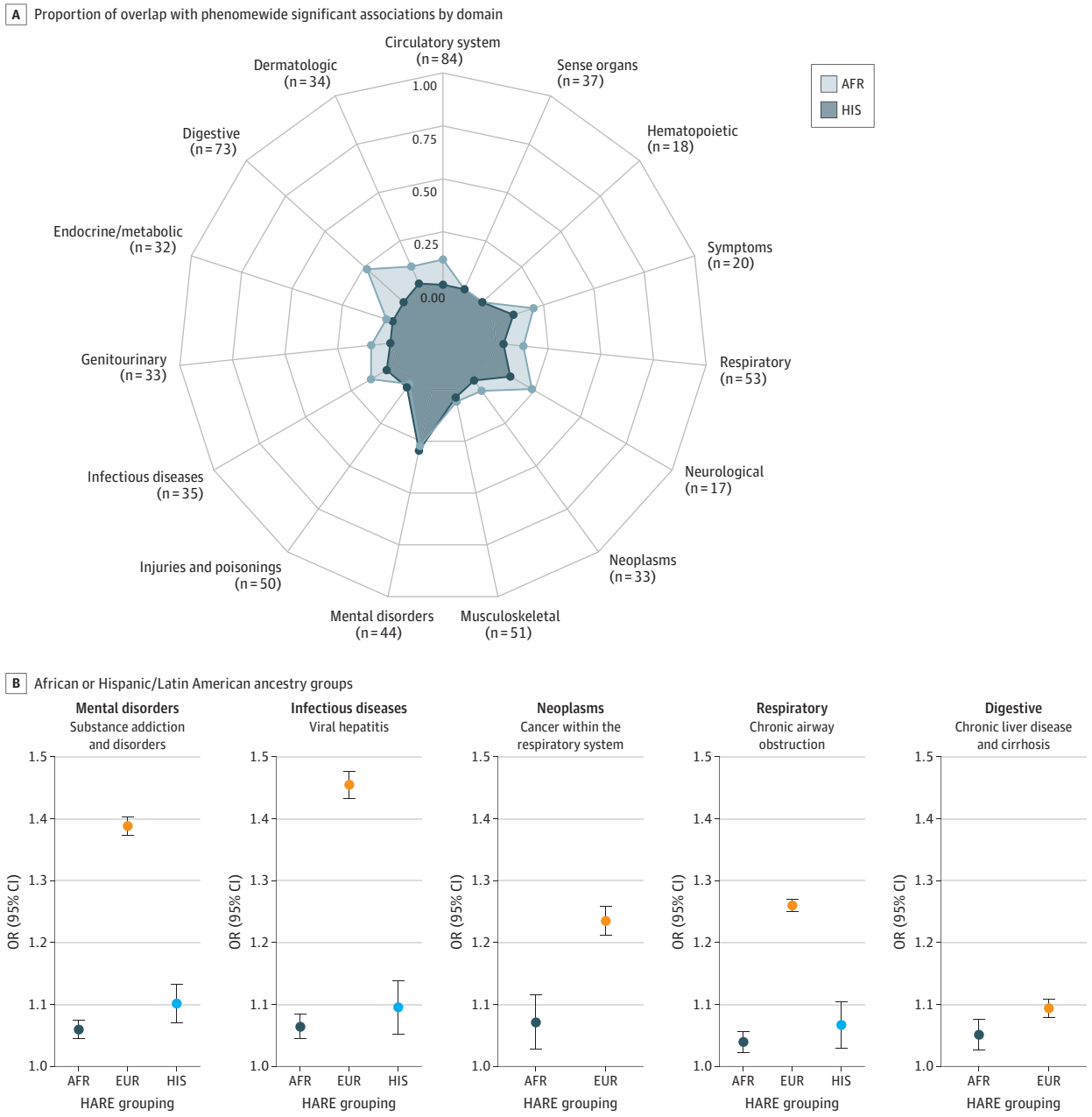
associated with increased risk of diagnoses. The 1 exception is pregnancy complications, which had no significant associations and is not unexpected given the predominantly male composition of this study sample. Although there was variation in effect sizes across groupings of phecodes, the largest associations, on average, were for phecodes related to respiratory issues (median OR, 1.14; IQR, 1.11-1.18), mental disorders (median OR, 1.13; IQR, 1.09-1.19), injuries and poisonings (median OR, 1.12; IQR, 1.11-1.15), and infectious diseases (median OR, 1.12; IQR, 1.10-1.16).

Figure 1B presents the breakdown of independent phenome-wide significant associations across the EXT, depression, schizophrenia, and suicide attempt PGSs.[48,49] Across all the 6608 tests (4 PGS with 1652 phecodes), 779 of the associations (11.78%) had *P* values below the Bonferroni corrected threshold ($P < 7.58 \times 10^{-4}$). The majority of these associations (437 [56.1%]) involved 3 of the 4 PGSs, and 561 (70%) involved 2 or more of the PGSs. The full results are in eTable 2 in Supplement 1.

Multiancestry Verification of EXT PGS

We next examined whether EXT PGS associations that were significant in the main European analyses were comparable in the African and Hispanic or Latin American MVP participants. After correction for multiple testing, among the 619 significant associations in veterans of European ancestries, 73 (11.9% of 614 available with >100 diagnoses) were significant in veterans of African ancestries, and 26 (4.5% of 584 associations were available) were significant in veterans of Hispanic or Latin American ancestries. **Figure 2**A presents the proportion of associations identified in the European PheWAS that replicated in either African or Hispanic or Latin American ancestries. Of all the domains, phecodes related to mental disorders had the highest proportion of associations that replicated across ancestry (approximately 25%). Figure 2B includes a subset of these replicated associations, which included SUDs (alcohol, tobacco, and other substances), viral hepatitis, and problems related to the respiratory system (eg, cancer, chronic airway obstruction, and respiratory

Figure 2. Multiancestry Results for Externalizing (EXT) Disorder Polygenic Risk in the Million Veterans Program (MVP)



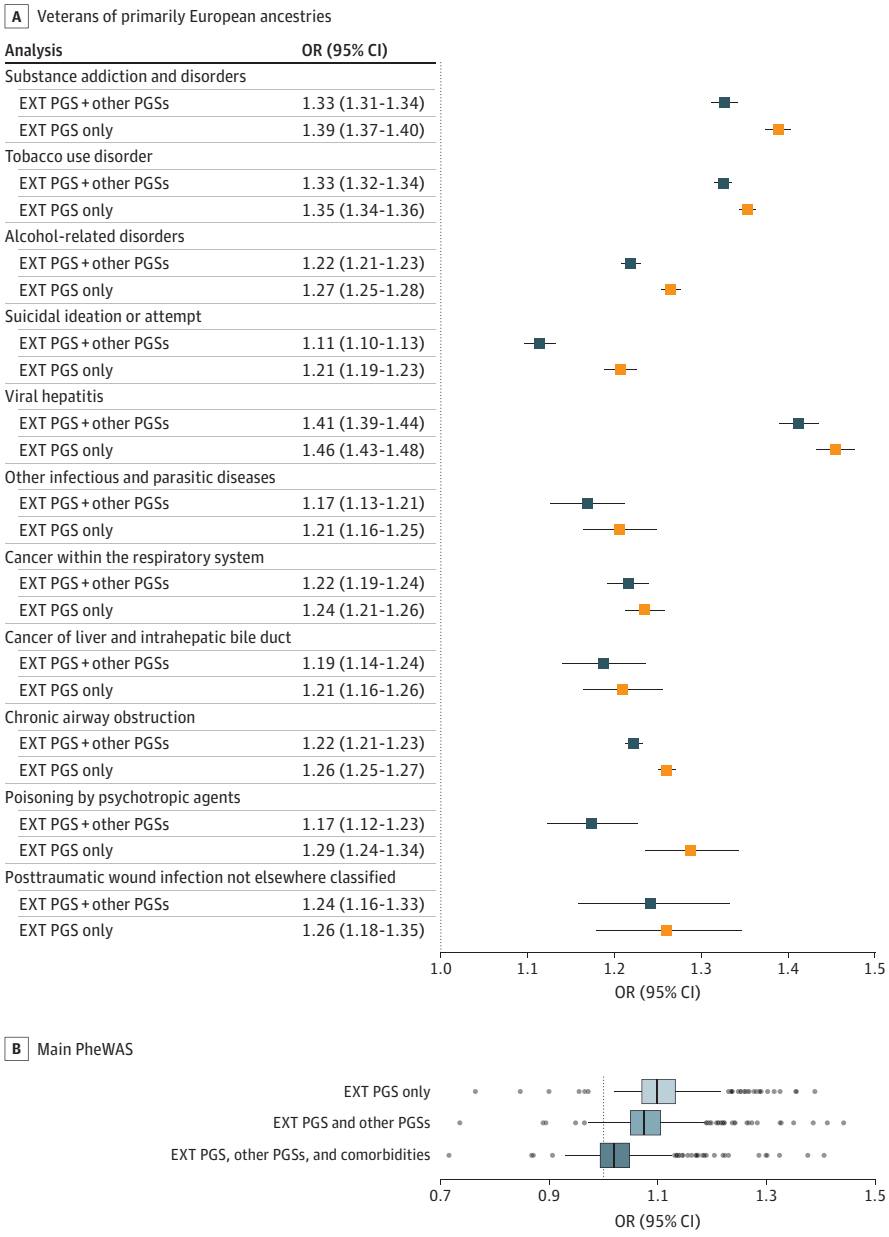
Overlap in associations across African (AFR), European (EUR), and Hispanic or Latin American (HIS) ancestries. A, Proportion of polygenic risk scores (PGSs) identified in EUR ancestries that were significant in the AFR and HIS groupings by phecode domain. Numbers in parentheses represent the total number of significant associations in EUR, per phecode domain. B, Selected associations and corresponding effect sizes (odds ratios [ORs]) of EXT PGS associations that replicated in either AFR or HIS ancestry groups. HARE indicates harmonized ancestry and race-ethnicity.

failure). As expected, although these associations were significant, there was a large attenuation in effect sizes[44,45] (full results in eTable 3 in Supplement 1).

Joint PheWAS of EXT, Depression, Schizophrenia, and Suicide Attempt PGSs

Of the 619 associations with EXT, 494 (79.8%) remained associated after conditioning on the depression, schizophrenia, and suicide attempt PGSs ($P < .05/619 = P < 8.08 \times 10^{-5}$). Effect sizes ranged from 1.02 for overweight/obesity (phecode = 278; 95% CI, 1.01-1.03) to 1.44 for viral hepatitis C (phecode 070.3; 95% CI, 1.42-1.47) for traits positively related to the EXT PGS. Associations that were no longer significant spanned all bodily systems, and included schizophrenia, rheumatoid arthritis, and chronic sinusitis, among many others. The median OR for the EXT PGS dropped from 1.10 in the mar-

Figure 3. Associations Between Externalizing Disorder (EXT) Polygenic Risk Score (PGS) and Selected Phecodes Accounting for Depression, Schizophrenia, and Suicide Attempt PGSs



A, Selected associations and their corresponding effect sizes from conditional phenome-wide association studies (PheWASs; EXT + depression, schizophrenia, and suicide attempt PGSs) in veterans of primarily European ancestries (N = 406 255) compared with models with the EXT PGS only (marginal). B, Box plots for the effect sizes from the 619 significant associations identified in the main PheWAS in (1) the PheWAS of EXT PGS only; (2) the PheWAS of EXT and other PGSs; and (3) the PheWAS of EXT, other PGSs, and the total comorbidity score.

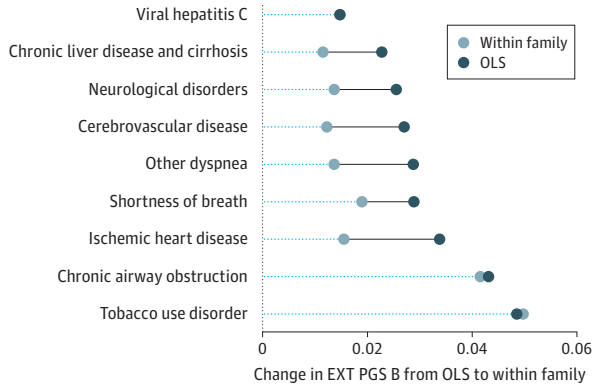
ginal associations with these phecodes to 1.08 after conditioning on the other PGSs. **Figure 3**A presents a subset of the larger associations (full results in eTable 4 in Supplement 1). Although there was attenuation in effect sizes, EXT remained associated with the various phecodes independent of risk for depression, schizophrenia, or suicide attempt.

To examine whether EXT was associated with outcomes due to an increased number of comorbidities, we ran the PheWAS including total comorbidity burden in European ancestries. Figure 3B includes box plots for the main PheWAS (EXT PGS only), the conditional PheWAS (EXT, depression, schizophrenia, and suicide attempt PGSs), and the model with all PGSs and the comorbidity score. There is an attenuation in median effect size across each set of analyses. Of the 619 significant associations, 188 remained associated with EXT after adjusting for total comorbidity burden and the additional PGSs, with the top associations remaining those for viral hepatitis, substance use disorders, and complications from smoking (full results in eTable 5 in Supplement 1). Of these 188 scores, 181 (96%) were not phenotypes directly related to EXT (eg, SUDs), and 165 (88%) were outside the domain of mental disorders.

Within-Family Replication of Main PheWAS Results

Finally, we investigated the 494 phecodes that remained significantly associated with EXT in the conditional PheWAS using

Figure 4. Change in Effect Sizes for Externalizing Disorder (EXT) Polygenic Risk Scores (PGSs) in Within-Family Models



Change in effect sizes for significant associations in a sample of related veterans of primarily European ancestries (N = 12 127). Estimates represent the change between ordinary least squares models (with clustered SEs) and family fixed-effects models. All associations significant after correcting for a false discovery rate (FDR) of 5%. OLS indicates ordinary least squares.

a sample of full siblings from the broader MVP (N = 12 127). Of these 494 phecodes, 439 had available information in the subset of related veterans. Within these remaining 439 associations, 77 were marginally significant (threshold $P < .05$), but only 13 (3.0%) of these associations remained after correcting for multiple testing using an FDR of 5%. **Figure 4** shows the relative effect sizes from the linear probability models the linear probability models with (within-family) and without (ordinary least squares) family fixed effects. For some of the associations, we noted a marked decrease in effect size. Therefore, a nontrivial portion of the association between the EXT PGS and these phenotypes may be due to some type of confounding. However, for viral hepatitis C, tobacco use disorder, and chronic airway obstruction, there was little or no attenuation (eTable 6 in Supplement 1). Although suicide ideation, attempt, and self-harm were associations in the PheWAS, they did not replicate on a within-family basis. This may have been due to the relatively few cases of suicidal ideation, attempt, or self-harm in the EHR of the smaller within-family sample (205 [1.7%]).

Discussion

Problems related to behavioral disinhibition, commonly referred to as EXT, may have detrimental consequences for health and well-being. We and others have shown that risk for EXT overlaps with a variety of key public health outcomes at both the genetic and phenotypic level.[11,13-18,50] In the current analysis, we leveraged these recent, novel insights into the underlying genetic basis of EXT, extended analyses to multiple ancestries, and evaluated their correlates in the largest integrated health care system in the US.

As expected, the largest associations across all models were in the phecode domain of mental disorders. Specifically, SUDs (alcohol, tobacco, and other substances) were among these, although other psychiatric problems, including conduct disorder, personality disorders, and attention-deficit/hyperactivity disorder (ADHD) were also associated. Some components, specifically problematic alcohol use, smoking, and ADHD, contributed to the multivariate GWAS used for creating the EXT PGS,[11] but analyses in the original EXT article showed that the latent factor was not driven by any single indicator; therefore, it is unlikely that associations are driven by any indicator-outcome similarity. Overall, these associations help to validate the EXT PGS within MVP and further demonstrate the utility of focusing on shared risk across psychiatric conditions.[7]

Results from the main PheWAS also replicated the diversity of bodily systems that were associated with risk for EXT.[11] For example, the EXT PGS remained associated with suicide-related phecodes (suicidal ideation, suicide attempt, and self-harm) even when conditioning on the suicide PGS and other comorbidities, suggesting that the association between externalizing and suicidal behaviors is independent of risk for the other forms of psychiatric problems (eg, depression), supporting the role of impulsivity in suicide risk.[51] In total, 181 (approximately 96%) of the associations that survived correction for multiple testing and covarying for other PGS and comorbidities were not phenotypes traditionally used to measure externalizing (eg, ADHD, SUDs). Overall, these results point to a robust pathway between risk for EXT and numerous medical conditions that (1) replicated across ancestry, (2) were not explained by risk for other common forms of psychiatric problems, and (3) could not be fully explained by documented comorbidities.

The expansive MVP cohort allowed us the opportunity to explore the possibility of confounding influences via a novel approach: leveraging an appreciable number of full siblings that comprise less than 2% of the overall cohort. The within-family analyses presented an additional test of whether EXT is simply a correlate or potentially causally related to various phecodes. In the holdout sample of full siblings, only a portion of the associations (13 of 439 [3.0%]) remained associated after correcting for multiple testing. In terms of SUDs, only tobacco use disorders remained significant after multiple testing correction. Moreover, many of the associations that replicated within family were likely consequences of SUDs. These included chronic airway obstruction (smoking related), chronic liver disease, cirrhosis (alcohol related), and viral hepatitis C (intravenous drug use related). The within-family associations point to the potential causal impact of risk for externalizing on these medical conditions, likely mediated through SUDs. However, within-family associations can be biased in the presence of genetic nurture and sibling effects.[52]

It is important to note that even though we detected a large number of significant associations with the EXT polygenic score, many of the effect sizes are too small to be clinically relevant. The utility of polygenic scores in clinical settings is an ongoing discussion.[53,54] Recent work in SUDs has shown that PGSs are not sufficiently powered to meaningfully identify individuals at increased risk of developing SUDs[55], especially when well-known social or clinical risk factors are included in the same model.[50]

Limitations

Our analysis has several important limitations. First, although we included large samples of multiple ancestries, PGSs were derived from a GWAS of primarily European ancestries. Consistent with recent observations of other PGSs in MVP,[25] the EXT PGS was associated with many of the traits within the African and Hispanic or Latin American samples, but the effect sizes were highly attenuated. Large-scale discovery GWASs in diverse cohorts are vital to ensuring that PGSs perform as well in these groups and that any benefit of precision medicine is shared equitably across the population.[56] Second, results from this sample may not be generalizable to the broader US population, as MVP is a selected subset comprising primarily male individuals. Additional work is needed to ensure that the study results generalize beyond the VA. Third, we did not examine PGSs in conjunction with social and environmental factors, which are both important for understanding key outcomes in veterans' health.[50,57,58] Many veterans are at risk for adverse environmental experiences due to poverty, minority status, and physical and psychiatric challenges.[59] Future work should endeavor to use integrated approaches. Lastly, although our results are largely robust to additional confounds and replicate within family, we cannot completely rule out noncausal reasons for the observed associations.

Conclusions

In this cohort study, risk for EXT disorders was correlated with many outcomes of serious public health concern. A predisposition toward greater levels of externalizing was associated with increased risk of substance use disorders, suicide-related behaviors, and other chronic medical conditions. Our analysis demonstrated that externalizing risk is equally important among the US veteran population who receive their health care within the VA system. Intervention and prevention efforts that identify ways to target and monitor the behavioral manifestations of externalizing risk could substantially improve morbidity and mortality outcomes.

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Author Contributions: Dr Barr 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. Drs Barr and Bigdeli contributed equally to this work.
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