Relationship of Major Depressive Disorder and Schizophrenia Polygenic Risk Scores to Suicide: A Comparison Between European and Asian Ancestry Populations

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Relationship of major depressive disorder and schizophrenia polygenic risk scores to suicide: a comparison between European and Asian ancestry populations

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ABSTRACT

Psychiatric diagnosis rates in suicide decedents appear higher in European ancestry populations compared with East Asians. Shared genetic components exist between major depressive disorder (MDD) /schizophrenia (SCZ) and suicide, but no study compared these shared polygenic architectures between Europeans and East Asians. We compared polygenic risk scores (PRSs) for MDD/SCZ determined from large datasets specific to each ancestry in European and East Asian suicide decedent samples, respectively. MDD/SCZ-PRSs appeared more prominent in European suicides compared with Japanese suicides. A greater coexistence of psychiatric disorders in European suicide than East Asians may be partly explained by genetics. Meanwhile, our results are limited by smaller sample size of our suicide decedents and sample size disparities between the European discovery dataset and the East Asian dataset for MDD/SCZ, resulting in less statistical power to detect robust difference between the two ancestries. (138 words)

Keywords: suicide; polygenic risk score; multi-ethnicity

HIGHLIGHTS

- Psychiatric diagnosis in suicides appears more common in European than East Asians.

- This is the first comparison of suicide GWASs between European and East Asians.
- MDD/SCZ-PRSs to suicide were more significant for Europeans than East Asians.

INTRODUCTION

Psychological autopsy studies find a psychiatric diagnosis in about 90% of European suicide decedents compared with about 60-65% of suicide decedents in China and Japan (Hirokawa et al., 2012; Phillips et al., 2002), but hitherto, the reason for this difference has been unknown. Though recent genome-wide association studies (GWASs) demonstrated that major psychiatric disorders such as major depressive disorder (MDD) and schizophrenia (SCZ) and suicide share genetic risk architecture (Docherty et al., 2020; Mullins et al., 2022; Otsuka et al., 2023), to our knowledge, there is no published study of multi-ethnic comparison of shared polygenic architecture between suicide death and psychiatric disorders.

Here we compared the relationship of MDD/SCZ-polygenic risk scores (PRSs) determined from large European and East Asians datasets in two different ethnic individual-level genotyped datasets for European and Japanese suicides, respectively.

METHOD

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the relevant

Institutional Review Boards at New York State Psychiatric Institute (No.4815/5760) and the Ethics Committee for Genetic Studies of Kobe University/RIKEN (No.180240).

Subjects

The demographics of our European and Japanese datasets are shown in **Supplementary Table S1** (details were previously published) (Galfalvy et al., 2015; Otsuka et al., 2019; Otsuka et al., 2023). The European ancestry samples for GWAS included 317 suicide decedents and 874 controls. Suicide status for all subjects was determined using the Columbia Classification Algorithm for Suicide Assessment, and psychological autopsies were conducted to determine DSM-IV diagnosis in 227 of the suicide cases. 874 unrelated controls were confirmed to be without psychiatric disorders or suicide attempt history. The Japanese samples for GWAS included 719 suicide decedents diagnosed by the Division of Legal Medicine at Kobe University and 14,049 non-suicide controls in the Biobank Japan (non-psychiatric disorders subjects and healthy volunteers). All study subjects or families of the decedents gave written informed consent to participate in this study.

Genotype and QC

Cases and controls were genotyped using the same genotyping platform in the European and Japanese dataset, respectively (HumanOmni1-Quad BeadChip for Europeans and HumanOmniExpress-24/ExpressExome-8 BeadChip for Japanese). Quality control (QC) was performed using PLINK 1.9; single nucleotide polymorphisms

(SNPs) with call rate < 0.98, minor allele frequency < 0.01, and those with $p < 1.0 \times 10^{-6}$ for Hardy-Weinberg equilibrium in controls were excluded. Then, we performed a principal component analysis (PCA) compared to HapMap Phase 3 population cluster, confirming all subjects were from the CEU (Northern Europeans from Utah) and the Japanese cluster, respectively (**Supplementary Fig. S1**). Hereafter, the European dataset is referred as EUR-SD (317 suicide decedents *vs*. 874 controls) and Japanese dataset as JPN-SD (719 suicide decedents *vs*. 14,049 controls).

PRS analysis

Using PRSice-2 (Choi and O'Reilly, 2015), PRSs of MDD and SCZ for Europeans and East Asians were generated based on the summary statistics from GWASs specific to each ancestry group (**Supplementary Table S2**). There was no overlap between the samples included in these GWAS summary statistics and our cohorts. The p threshold (P_t) for selecting 'risk' SNPs was sequentially set at 1×10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 and 1, excluding SNPs in the major histocompatibility complex region. Linkage disequilibrium (LD) clumping was used to select the eligible SNPs for PRS (clump-kb: 250, clump-p: 1.0, clump-r2: 0.1). Throughout, EUR-SD/JPN-SD was used as the target set with age, sex, and 10 PCs as covariates. The variance in the target datasets explained by the discovery set-based PRS was estimated based on Nagelkerke's R^2 from a logistic regression model and converted to R^2 on the liability scale (Lee et al., 2012). We assumed that the prevalence rate of suicide death is 0.002,

conservatively determined from previous estimates (Otsuka et al., 2019). The significance level for the PRS analysis was set at 0.001, a conservative threshold (Choi and O'Reilly, 2015). We used Cochran's Q test to detect difference between the odds ratios (ORs) of suicide risk based on MDD/SCZ-PRSs in the European suicides and in the Japanese suicides (the significance level was set at 0.05/2). For calculation of statistical power of the PRS analysis, we set $\alpha = 0.001$ and genetic correlation between suicidal behavior and MDD/SCZ = 0.2–0.5, an estimate based on recent findings from published papers (Docherty et al., 2023; Mullins et al., 2019; Mullins et al., 2022).

RESULTS

Within our psychological autopsied samples, our European suicide samples had higher comorbid rate of major psychiatric disorders (70.5%) and any psychiatric disorders (92.1%), compared with our Japanese suicide samples (49.8% for major psychiatric disorders and 60.2% for any psychiatric disorders) (Chi-squared $p = 2.2 \times 10^{-16}$ for major psychiatric disorders and 9.1×10^{-8} for any psychiatric disorders, respectively) (**Supplementary Table S1**).

Using European MDD/SCZ GWASs as the discovery dataset and our EUR-SD as the target dataset, PRS analysis demonstrated shared polygenic effects [EUR-MDD: maximum variance explained $R^2 = 1.19\%$, OR (95%CI) = 1.48 (1.27–1.72); EUR-SCZ: $R^2 = 1.26\%$, OR (95%CI) = 1.54 (1.31–1.80)] ($p < 0.001$) (**Fig. 1** and

Supplementary Table S3). Using East Asian MDD/ SCZ GWASs as the discovery dataset and our JPN-SD as the target set, PRS analysis did not show shared polygenic effects between EAS-MDD and JPN-SD [R^2 = 0.11%, OR (95%CI) = 1.10 (1.02–1.18)] ($p > 0.001$) but showed shared polygenic effects between EAS-SCZ and JPN-SD [R^2 = 0.27%, OR (95%CI) = 1.17 (1.08–1.25)] ($p < 0.001$) (**Fig. 1** and **Supplementary Table S4**). More significant polygenic effects of MDD/SCZ were observed in European suicides than Japanese suicides with all P_t for MDD and SCZ, respectively ($p_{diff} < 0.025$) (**Supplementary Table S5**).

To have statistical power > 0.8 based on our effect size shown here, the estimated minimum sample sizes to detect the effect size of MDD-PRS on suicide death would be approximately case N = 160-210 in European dataset and 2,060-2,630 in East Asian dataset, respectively. Similarly, the minimum sample size to detect the effect size of SCZ-PRS on suicide death are approximately case N = 140-170 in European dataset and 760-970 in East Asian dataset, respectively.

DISCUSSION

We found that the polygenic effects of MDD/SCZ on suicide were more significant for Europeans than East Asians. This may provide a part of genetic explanation for greater coexistence of psychiatric disorders with suicide in Europeans than East Asians (Hirokawa et al., 2012; Phillips et al., 2002). While a recent large GWAS for

suicide attempt showed ethnic variation of genetic architecture between Europeans and East Asians (Docherty et al., 2023), to our knowledge, our present study is the first multi-ethnic comparison of the relationship of PRSs for MDD/SCZ to suicide death between European and East Asian ancestries.

Our findings should be interpreted in the context of several limitations. First, our suicidal GWAS dataset was small and the findings require replication. While it is difficult to assemble a large series of multi-ethnic suicide decedent cases, consistent with a part of our results, European MDD/SCZ-PRSs explained similar amount of variance in a larger GWAS of European suicide decedents (Docherty et al., 2020). Second, multi-ethnic GWAS comparison could not exclude methodological limitations such as ethnic variations in LD patterns. In addition, genetic architecture of EUR-SD is more heterogeneous than JPN-SD from PCA plots; this might partially account for lower shared polygenic effects of MDD/SCZ on suicide in our Japanese sample, because Japan is an island population and may have different genetic structure and LD compared with other East Asian populations (Yamaguchi-Kabata et al., 2008). Our PRS results therefore require validation using genetic correlation analyses in a larger sample because that is less susceptible to differences in population genetics. Third, the sample size of European discovery dataset was larger than the East Asian dataset, perhaps resulting in more reliable PRS estimates. Furthermore, the sample sizes and suicide liability were different between the two target cohorts, potentially impacting

detection of a difference between two ancestries. Fourth, we did not have psychological autopsy data on our entire sample. Finally, since there is no publicly available East Asian GWAS data for other psychiatric traits or disorders other than MDD/SCZ, it limited the scope of comparison between these ethnicities.

In conclusion, we provided the first evidence that the polygenic overlap between suicide and MDD/SCZ may be more significant in European populations compared with East Asians. Meanwhile, our analyses are limited by small sample size of our suicide decedents and sample size disparities between the European discovery dataset and the East Asian dataset for MDD/SCZ. Larger multi-ethnic GWASs focusing on relationship between suicide and a variety of psychiatric traits will clarify more detailed ethnic differences in shared genetic architecture between psychiatric disorders and suicide.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit XXX.

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DISCLOSURE STATEMENT

Dr. Mann receives royalties for commercial use of the C-SSRS from the Research Foundation for Mental Hygiene. Dr. Galfalvy and her family hold equity in Illumina, Inc. All other authors report no financial interests or potential conflicts of interest.

AUTHOR NOTES

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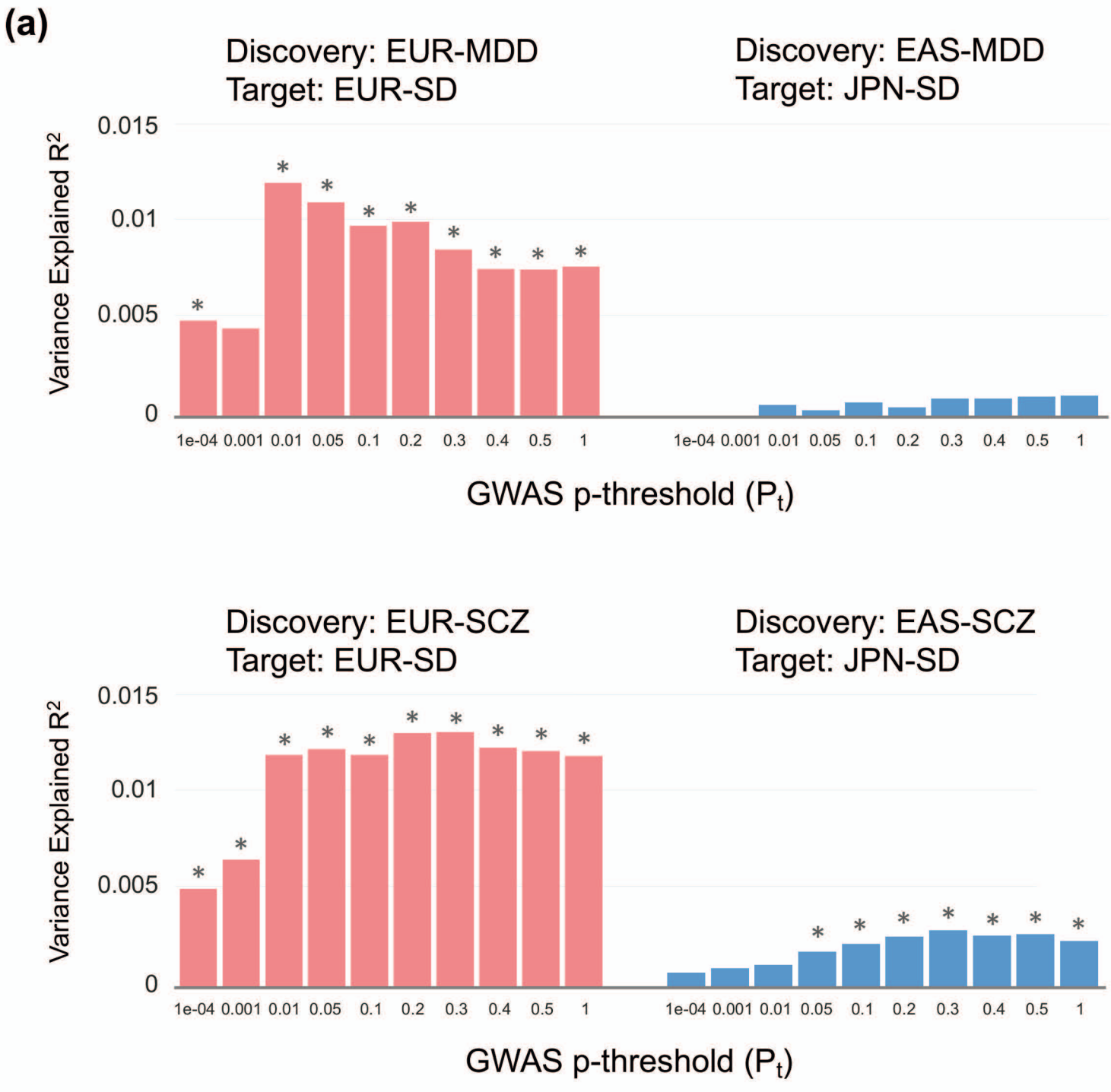
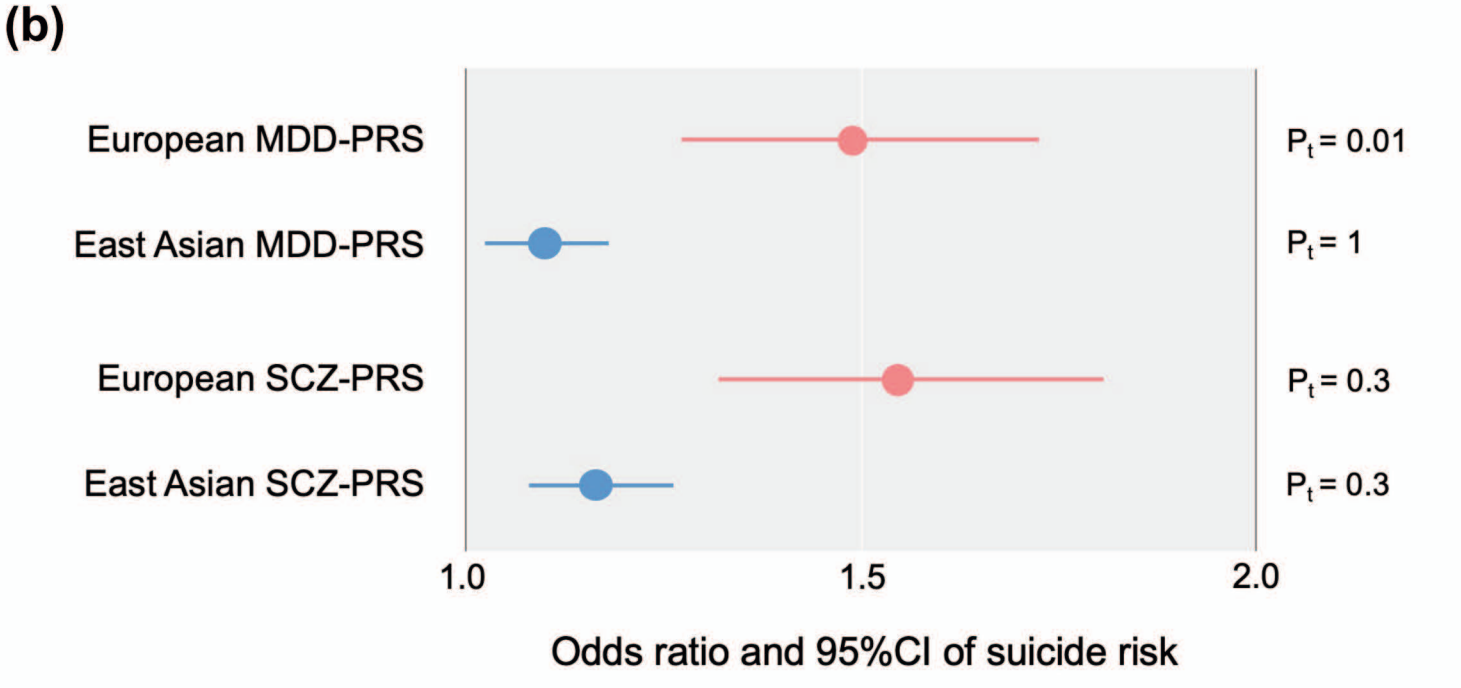
FIGURE LEGENDS

Fig. 1.

(a) Polygenic risk score (PRS) analysis using European (EUR) and East Asian (EAS) GWAS summary statistics of major depressive disorder (MDD) / schizophrenia (SCZ) as the specific discovery sets for each of the two ancestries and genotyped case-control GWAS data of European ancestry samples (EUR-SD; 317 suicides and 874 controls) and Japanese ancestry samples (JPN-SD; 719 suicides and 14,049 controls) as the respective same ancestry target sets. The x-axis illustrates the p threshold (P_t) used to select SNPs from the discovery GWAS. The y-axis illustrates the variance explained R^2 on the liability scale. Asterisk means the association reached the significance level for the PRS analysis ($p < 0.001$).

(b) Odds ratios (ORs) and 95% confidence interval (95%CI) of suicide based on polygenic risk scores for MDD/SCZ in Europeans and East Asians. Each OR (dot) and 95%CI (error bar) is shown at the P_t attaining the lowest p value, adjusted with age, sex and 10 PCs for EUR-SD (pink) and JPN-SD (blue) as the target set.


(a)
Discovery: EUR-MDD
Target: EUR-SD
Discovery: EAS-MDD
Target: JPN-SD
Variance Explained R2
0.015
0.01
0.005
0
1e-04 0.001 0.01 0.05 0.1 0.2 0.3 0.4 0.5 1
GWAS p-threshold (Pt)
Discovery: EUR-SCZ
Target: EUR-SD
Discovery: EAS-SCZ
Target: JPN-SD
Variance Explained R2
0.015
0.01
0.005
0
1e-04 0.001 0.01 0.05 0.1 0.2 0.3 0.4 0.5 1
GWAS p-threshold (Pt)


(b)
European MDD-PRS
East Asian MDD-PRS
European SCZ-PRS
East Asian SCZ-PRS
Pt = 0.01
Pt = 1
Pt = 0.3
Pt = 0.3
1.0
1.5
2.0
Odds ratio and 95%CI of suicide risk