Associations of Polygenic Risk Score, Environmental Factors, and Their Interactions with the Risk of Schizophrenia Spectrum Disorders

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Introduction

Schizophrenia (SZ) involves genetic and environmental factors, with over 80% heritability from twin studies. Environmental factors, like childhood adversity, are crucial in SZ development. Gene-environment interactions (GEIs) help discover new genetic/environmental effects and understand biological pathways, aiding personalized medicine. Polygenic risk scores (PRS) have enhanced the ability to identify GEIs. Recent studies show mixed GEI results using cumulative environmental scores.

Objectives

We investigated the associations of polygenic risk score for SZ (PRS-SZ), environmental measures, and their interactions with case-control status and clinical phenotypes among patients with schizophrenia spectrum disorders (SSD).

Method

The PRS-SZ for 717 SSD patients and 356 healthy controls (HCs) were calculated using the LDpred model. The Korea-Polyenvironmental Risk Score-I (K-PERS-I) and Early Trauma Inventory-Self Report (ETI-SR) were utilized as environmental measures. Logistic and linear regression analyses were performed to identify the associations of PRS-SZ and two environmental measures with case-control status and clinical phenotypes.

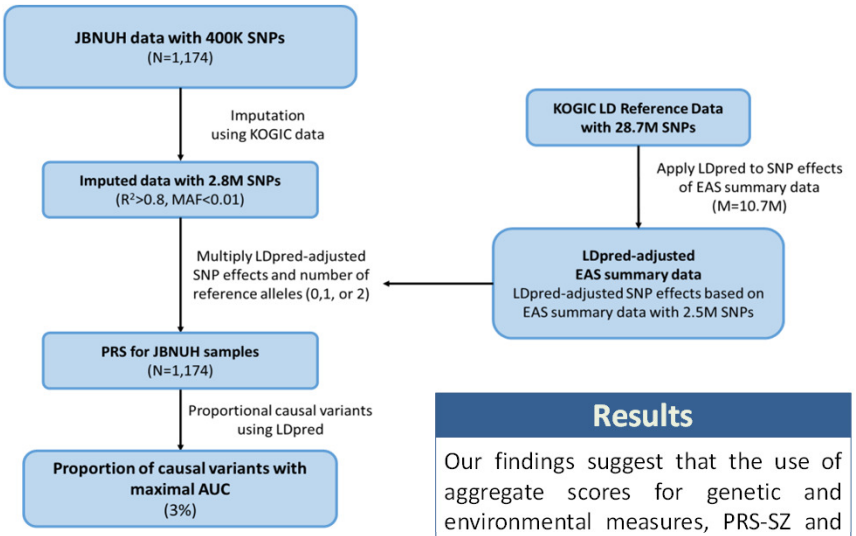

Figure 1. Flowchart of PRS calculation

Conclusions

The PRS-SZ explained 8.7% of SZ risk. We found greater associations of PRS-SZ and total scores of the K-PERS-I with case-control status than with the ETI-SR total score, but no interactions were present. However, when we analyzed the subdomains of the K-PERS-I and ETI-SR, we identified a significant interaction of PRS-SZ and parental socioeconomic status (pSES) in association with case-control status. Regarding associations with clinical phenotypes, we observed significant interactions between PRS-SZ and ETI-SR total score for negative-self and between PRS-SZ, and pSES and obstetric complications of the K-PERS-I for negative symptoms and negative-others, respectively.

Results

Our findings suggest that the use of aggregate scores for genetic and environmental measures, PRS-SZ and K-PERS-I, can more accurately predict case-control status and specific environmental measures may be more suitable for the exploration of GEIs. There is a need for additional research concerning GEIs and modifiable environmental factors.

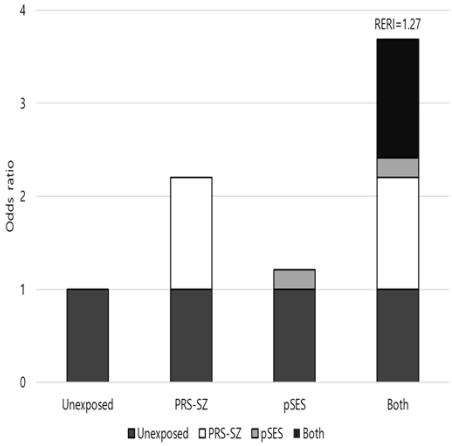

Figure 2. Synergistic effects of PRS-SZ and pSES

Table 1. Main and interaction effects of PRS-SZ and K-PERS-I/ETI-SR on case-control status

Models	Total (SSDs/HCs)	PRS-SZ		Environmental measures		Interaction		Nagelkerke's R^2
		Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	
PRS-SZ	615 (295/320)	2.20 (1.74-2.80)	1.68×10^{-11}	-	-	-	-	0.161
K-PERS-I		-	-	3.26 (2.66-4.05)	7.41×10^{-28}	-	-	0.350
PRS-SZ + K-PERS-I		2.43 (1.85-3.24)	1.28×10^{-10}	3.39 (2.73-4.25)	7.01×10^{-27}	-	-	0.417
PRS-SZ + K-PERS-I + PRS-SZ * K-PERS-I		2.43 (1.85-3.24)	1.33×10^{-10}	3.37 (2.71-4.25)	3.74×10^{-26}	0.98 (0.76-1.25)	0.849	0.417
PRS-SZ	830 (474/356)	2.31 (1.89-2.82)	3.76×10^{-16}	-	-	-	-	0.187
ETI-SR		-	-	1.93 (1.62-2.30)	1.47×10^{-13}	-	-	0.173
PRS-SZ + ETI-SR		2.40 (1.94-2.97)	4.38×10^{-16}	1.99 (1.65-2.38)	1.74×10^{-13}	-	-	0.273
PRS-SZ + ETI-SR + PRS-SZ * ETI-SR		2.40 (1.94-2.96)	6.06×10^{-16}	1.97 (1.64-2.38)	1.11×10^{-12}	0.97 (0.80-1.17)	0.731	0.273

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