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Correspondence

Genetic confounding in the association between obesity-related phenotypes and neuropsychiatric disorders

Dear Editor,

Based on previous observational studies, obesity is commonly comorbid with several neuropsychiatric disorders (Simon et al., 2006). However, whether these associations show a causal relationship is difficult to explain, as confounding by genetic liability for neuropsychiatric disorders may play a critical role in resulting in observed associations. Particularly, the underlying genetic vulnerability for neuropsychiatric disorders not only increases risk for neuropsychiatric disorders, but could also elevate risk for body weight gain and obesity via various ways, such as altered dopaminergic reward circuits, changes in the sleep-wake cycle, and impulsivity of food intake via treatments (Opel et al., 2015). Therefore, we aimed to investigate the plausibility of this hypothesis by assessing the association between polygenic risk scores (PRSs) for 11 neuropsychiatric disorders and the risks of obesity-related phenotypes.

The study was designed using data from the Mass General Brigham (MGB) Biobank, a hospital-based cohort integrating electronic health records (EHR) with genomic information (Hao et al., 2022). A total of 4995 individuals of European genetic ancestry, all of whom were classified as White by race, were included after passing standard genotype quality-control procedures (Hao et al., 2022). PRSs for neuropsychiatric disorders, including attention-deficit/hyperactivity disorder [ADHD], Alzheimer's disease, anxiety disorder, autism spectrum disorder, bipolar disorder, eating disorder, major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, schizophrenia, and substance use disorder, were calculated using publicly available genome-wide association study summary statistics from the Psychiatric Genomics Consortium. Obesity-related phenotype was defined using the International Classification of Diseases (ICD), Tenth Revision codes E65-E68, which include overweight, obesity, and other hyperalimentation-related diagnoses (Garvey and Mechanick, 2020). Associations between each PRS and obesity-related phenotype were estimated using logistic regression adjusted for age, sex, and ethnicity, and results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). The present study protocol was approved by the MGB Institutional Review Board (#2009P002312) and was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Additional methodological details are provided in the Supplementary Methods.

A total of 4995 individuals of European genetic ancestry from the MGB biobank were included in the final study cohort (Fig. S1). During follow-up, 2408 participants developed obesity-related phenotype (mean [standard deviation, SD] age, 72.4 [10.4] years; 55.5% male) and 2547 served as controls (mean [SD] age, 74.6 [11.2] years; 61.3% male; Table S1). Adjusted analyses showed that 4 of the 11 neuropsychiatric PRSs were significantly associated with obesity-related phenotype (Fig. 1). Higher genetic liability for ADHD (aOR, 1.040 [95% CI, 1.004–1.077]), bipolar disorder (1.030 [1.004–1.057]), and major depressive disorder (1.095 [1.029–1.164]) was associated with increased odds of obesity-related phenotype, whereas higher genetic liability for eating disorders was associated with lower odds of obesity-related phenotype (0.964 [0.939–0.989]). Corresponding crude associations are presented in Fig. S2.

In this cohort study using genotype data from a large hospital-based cohort with EHRs, we found two distinct patterns in comorbid associations between neuropsychiatric disorders and obesity-related phenotype. First, positive associations were observed between odds of obesity-related phenotype and PRSs for ADHD, bipolar disorder, and major depressive disorder. These associations may reflect shared genetic architecture involving enhanced neural responsiveness to reward systems, as well as psychosocial mechanisms such as impulsive eating in ADHD, weight gain associated with treatments for bipolar disorder (including second-generation antipsychotics, mood stabilizers, and certain antidepressants), and stress-related hyperphagia and inflammatory dysregulation in depression (Opel et al., 2015). Second, the inverse association between obesity-related phenotype and the PRS for eating disorders aligns with evidence that anorexia nervosa is characterized by metabolic genetic variants linked to lower body mass index and increased energy expenditure (Biotteau et al., 2025).

Although part of these associations may be mediated by clinical manifestations of neuropsychiatric disorders that influence weight-related outcomes, our findings also suggest that the observed comorbidity may reflect confounding by shared genetic liability. To our knowledge, this is the first study to directly evaluate this possibility using polygenic risk scores. A study limitation is that the variance explained by current PRSs for neuropsychiatric disorders remains limited. Thus, while our findings strongly suggest the presence of confounding by genetic liability, they may not accurately represent the actual effect size (Ostergaard et al., 2025). In addition, our analysis was limited in determining whether genetic liability captured by PRSs operates across the continuum from overweight to obesity or through specific pathways leading to obesity-related outcomes.

Our findings suggested that confounding by genetic vulnerability for neuropsychiatric disorders could contribute to some of the associations between certain neuropsychiatric disorders and obesity-related phenotypes. Beyond etiologic implications, these findings also provided the possibility that PRS-based risk stratification could inform personalized prevention strategies for weight-related outcomes, warranting validation in future prospective research. Therefore, accounting for this underlying genetic liability is essential to prevent overstating causal interpretations in further studies.

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Source	aOR (95% CI)
PRS-ADHD	**1.040 (1.004-1.077)**
PRS-Alzheimer's disease	0.985 (0.938-1.034)
PRS-anxiety disorder	1.000 (0.994-1.006)
PRS-autism spectrum disorder	0.989 (0.962-1.017)
PRS-bipolar disorder	**1.030 (1.004-1.057)**
PRS-eating disorder	**0.964 (0.939-0.989)**
PRS-major depressive disorder	**1.095 (1.029-1.165)**
PRS-obsessive compulsive disorder	1.018 (0.988-1.050)
PRS-post traumatic stress disorder	1.005 (0.943-1.071)
PRS-schizophrenia	1.006 (0.986-1.027)
PRS-substance use disorder	1.222 (0.999-1.495)

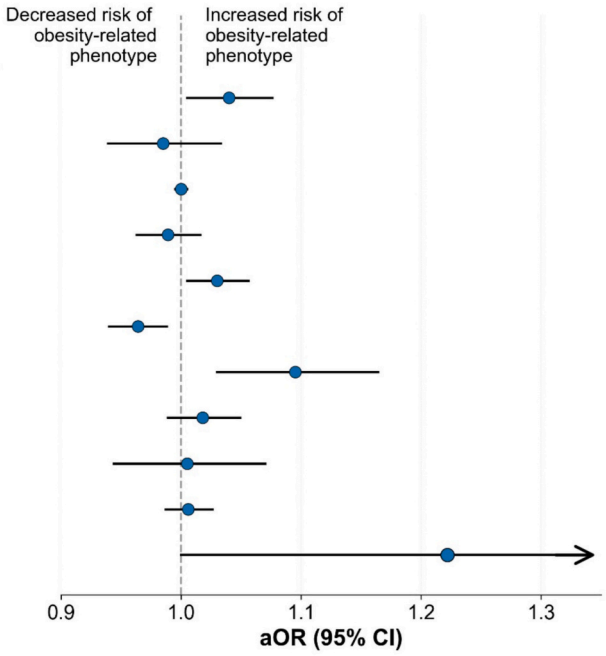


Fig. 1. Association between polygenic risk scores for ADHD, Alzheimer's disease, anxiety disorder, autism spectrum disorder, bipolar disorder, eating disorder, major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, schizophrenia, substance use disorder, and obesity-related phenotype.
Abbreviation: ADHD, attention-deficit/hyperactivity disorder; aOR, adjusted odd ratio; CI, confidence interval; PRS, polygenic risk score.
Bold indicates statistically significant associations ($p < 0.05$).
Adjusted model was adjusted for age, sex, and ethnicity (Hispanic, non-Hispanic, and not reported/unavailable).

CRediT authorship contribution statement

Jiseung Kang: Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hyeon Jin Kim:** Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yesol Yim:** Writing – review & editing. **Soyeon Kim:** Writing – review & editing. **Dong Keon Yon:** Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Christa J. Nehs:** Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Disclaimer

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Declaration of competing interest

The authors declare that they have no financial interests related to the material in the manuscript. This research was conducted independently of any business or financial relationships that could be construed as a potential conflict of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2026.121971.

Data availability

Dr. CJN had full access to the Mass General Brigham dataset in the study and took responsibility for the integrity of the data and accuracy of the data analysis. Data are available from the Mass General Brigham Human Research Office/Institutional Review Board at Mass General Brigham (contact located at https://www.partners.org/Medical-Research/Support-Offices/Human-Research-Committee-IRB/Default.aspx) for researchers who meet the criteria for access to confidential data.

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