Bioinformatics Reveals the Potential Mechanisms Underlying the Co-occurrence of Anorexia Nervosa and Exercise Addiction

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Anorexia Nervosa (AN) has no definitive cure exists and leads to a high mortality rate due to multiple organs failure and brain damage resulting from emaciation and malnutrition. Although approximately 50% of AN patients exhibited **increased levels of exercise about one year before the onset of AN**, no studies definitively conclude that exercise is a causative factor of AN, and the mechanisms of Activity-Based Anorexia **(ABA)** remain poorly understood. To address this issue, we conducted bioinformatics analyses using public Genome-Wide Association Studies **(GWAS)** and single-cell RNA-sequencing **(scRNA-seq)** data. Our findings suggest that individuals with high levels of **exercise are 13 times more likely to develop AN, but AN does not necessarily lead to excessive exercise**. Our analysis identified a **Single Nucleotide Polymorphism (SNP)** in the ***CTBP2*** gene, a **Transcription Factor (TF)**, that increases the risk of AN by at least 2.94 times in individuals who exercise frequently. According to the TFLink database, ***CTBP2*** regulates the expression of many genes related to **Perineuronal Nets (PNNs)**. Our further bioinformatics analysis from exercise mice data suggested that ***Ctbp2*** may contribute to AN by affecting Glutamine **(Glu)** receptors, potassium/sodium channels, and PNNs formation in the **Lateral Septal Complex (LSX)** of the **Striatum (STR)** through TFs including ***Tcf4***, ***Prdm11***, and ***Erbb4***. Intriguingly, certain inhibitors that target ***TCF4*** and ***ERBB4*** may potentially ameliorate ABA, according to our bioinformatics analysis. In conclusion, our bioinformatics analysis suggests that the co-occurrence of Anorexia Nervosa and exercise addiction may be driven by CTBP2-mediated regulation of neural pathways, including perineuronal nets and glutamatergic signaling, with potential therapeutic targets such as TCF4 and ERBB4.

Table 1. Bidirectional Mendelian randomization analysis between HPA and AN.

Exposure	Outcome	Method	SNP #	beta	SE	*P*-value	Odds Ratio (95% CI)
HPA id:ukb-b-3502	AN id:ieu-a-1186	Inverse variance weighted	2	2.54	1.08	*0.01867*	12.72 (1.53 to 105.95)
AN id:ieu-a-1186	HPA id:ukb-b-3502	Inverse variance weighted	2	0.01	0.03	0.61382	1.01 (0.96 to 1.07)

SE, Standard Error; **CI**, Confidence Interval; **SNP**, Single Nucleotide Polymorphism; **HPA**, Habitual Physical Activities; **AN**, Anorexia Nervosa.

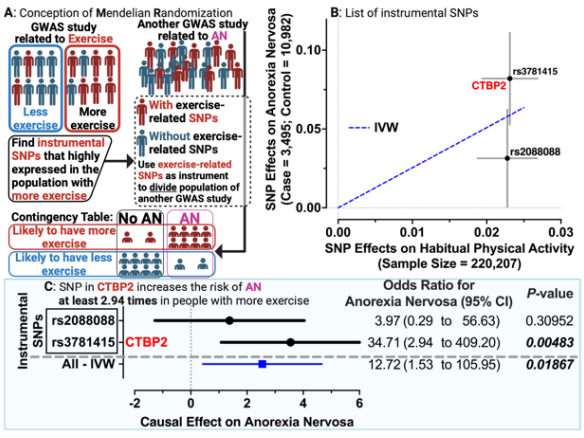

Figure 1. Exercise increases the risk of anorexia nervosa.