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FIBP Gene Role in Elderly Anorexia: A Mendelian Study

Kai Deng[a] Yunwang Zhang[a] Zhongyun Li[a]
[a] *People's Hospital of Xishuangbanna Dai Autonomous Prefecture, Jinghong City, Yunnan Province, China*

Abstract *Introduction: This study aims to explore the causal relationship between the FIBP (FGF1-interacting protein) gene and elderly anorexia using Mendelian randomization (MR). Elderly anorexia is a serious public health issue, often accompanied by various physiological and pathological factors, significantly affecting the quality of life and health status of the elderly.Methods: The study utilized data from the IEU OpenGWAS project, including European male and female participants. Analytical methods such as MR-Egger regression, weighted median, and inverse variance weighting (IVW) were used to assess how genetic variations in the FIBP gene influence the risk of anorexia.Results: The analysis revealed a significant association between the FIBP gene and a reduced risk of anorexia. The MR-Egger regression method produced an odds ratio (OR) of 0.007 with a 95% confidence interval (CI) ranging from 4.12E-05 to 1.313. The weighted median method yielded an OR of 0.168 (95% CI: 0.046-0.619), and the IVW method yielded an OR of 0.166 (95% CI: 0.036-0.767). Further sensitivity analyses confirmed the reliability of these results, with no significant heterogeneity detected.Conclusion: The findings indicate that higher FIBP expression is significantly associated with a lower risk of developing anorexia in the elderly. This discovery provides a foundation for future research into the mechanisms by which the FIBP gene affects anorexia and could inform the development of targeted public health strategies and early intervention measures for this disorder. These methods provide new insights into the causal relationships between genetic variations and anorexia, highlighting the potential protective role of the FIBP gene in the prevention and treatment of anorexia.*

Abbreviations： *CI = Confidence Interval, GWAS = Genome-Wide Association Study, IVs = Instrumental Variables, IVW = Inverse Variance Weighted, MR = Mendelian Randomization, OR = Odds Ratio, SNP = Single Nucleotide Polymorphism.*

Keywords： *Anorexia, Mendelian Randomization, FIBP, Genetic Epidemiology, Public Health*

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I. Introduction

Anorexia significantly increases all-cause mortality and is an independent predictor of morbidity and mortality. [1,2] Research shows that aging involves various physiological and pathological factors such as declines in olfactory and gustatory senses, reduced gastric ghrelin, and decreased nitric oxide at the gastric base which influence food intake and accelerate malnutrition, leading to anorexia. [3,4] As the global population ages, the proportion of elderly individuals increases, and anorexia including appetite and food intake associated with weight loss and malnutrition,becomes more common. The prevalence of anorexia varies according to the environment, with incidence rates of 25%,62% and 85% in homes, hospitals, and nursing homes respectively. [5] Weight loss due to anorexia is common among elderly and serves as an independent predictor of morbidity and mortality in various clinical settings. [6,7] From its high incidence and mortality rates, anorexia imposes significant public health burdens, leading to economic losses, patient stress, and challenges for daily life, families, and healthcare.

Studies have indicated that olfactory and gustatory senses are crucial for pleasurable eating experiences. With age, these senses typically weaken and the rate of decline varies reducing food intake and leading to a monotonous and selective diet. A reduction in the number and function of taste buds, often exacerbated by diseases, medications, smoking, and environmental exposure, primarily affects the perception of salty and sweet taste. Consequently, less flavorful foods may fail to stimulate appetite, prompting the elderly to opt for more flavorful but potentially less healthy foods. Additionally, a reduction in saliva secretion decreases the ability to dissolve food, further limiting effective interaction with taste receptors on the tongue.

Ghrelin, known as the "hunger hormone," is the only known peripheral hormone that actively stimulates hunger and is released in pulses by gastric mucosal cells. The dynamics of ghrelin secretion change with age, and increased circulating levels of leptin and insulin may reduce ghrelin sensitivity in the elderly, affecting their appetite and energy intake. Similarly, changes in the dynamics of cholecystokinin (CCK), a satiety hormone, and higher levels of peptide YY (PYY) after meals in the elderly may suppress the desire to continue eating, thus prolonging fasting periods. The combined actions of CCK and PYY may send strong anorexic signals to the

hypothalamus, affecting dietary behavior and overall health. Leptin,which is crucial in the pathophysiology of aging anorexia, may indirectly regulate food intake by influencing satiety.

Gastrointestinal dysfunction, particularly gastroparesis, causes a premature feeling of fullness in the elderly, and is associated with reduced gastric compliance. Reduced nitric oxide production in the stomach leads to faster stomach filling and delayed gastric emptying, which is related to reduced gastric digestive capacity and age-related decline in gastric motility and can affect digestion and satiety. [4] Chronic low-grade inflammation, typical of aging, alters the response of specific brain regions to peripheral stimuli. Elevated circulating levels of interleukin (IL) 1, IL6, and tumor necrosis factor α (TNF-α) reduce food intake, contributing to weight loss and delayed gastric emptying. These cytokines can also directly stimulate leptin mRNA expression and increase circulating leptin levels, further influenced by pro-inflammatory cytokines that stimulate corticotropin-releasing factor (CRF) production in the hypothalamus, mediating the anorexic effects of leptin. [13]

Role of STAT 3 signaling in hypothalamic inflammation and anorexia following lipopolysaccharide (LPS) induction in mice. Activation of STAT 3, associated with inflammation-induced anorexia, and its regulation of appetite-related genes directly affect food intake. Negative feedback involves increased expression of Socs 3, regulating the intensity and duration of inflammatory signals. The interaction between peripheral and central inflammatory responses links LPS injection to anorexic behavior through STAT 3 activation. [15] Studies also show a close interaction between FIBP (FGF1-interacting protein) and STAT3, affecting gene expression regulation STAT3 nuclear localization and DNA-binding ability. [16 ,17 - 22]

Despite extensive research on the pathophysiology of anorexia, few studies have demonstrated a relationship between FIBP and anorexia. A Mendelian randomization (MR) study was conducted to investigate this causal relationship using genetic variations including single-nucleotide polymorphisms(SNPs) as instrumental variables (IVs). This study enhances our understanding of the causal connections between genetic variations and anorexia, as these variations are unaffected by confounding factors owing to their random allocation during gamete formation. [15,16]

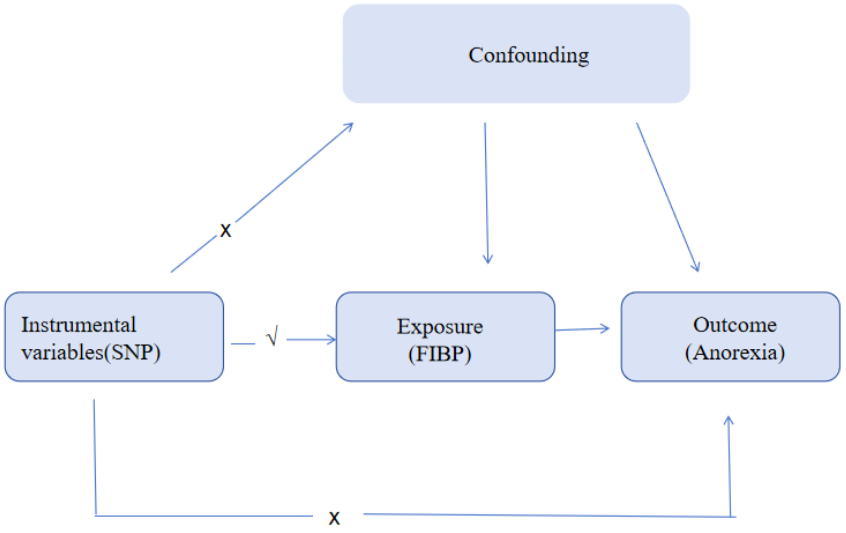

Figure 1.Schematic representation of Mendelian randomization analysis.
SNP=single-nucleotide polymorphism.

II. Data and Methods

2.1 Data Sources

The data for this study were obtained from genome-wide association studies (GWAS) of the FIBP gene and anorexia, available through the IEU OpenGWAS project at [https://www.decode.com/summarydata/]. This study included both male and female participants of European descent. The FIBP database (eqtl-a-ENSG00000172500) featured 16,118 single nucleotide polymorphisms (SNPs) across a sample of 31,684 individuals. The anorexia database (finn-b-R18_ANOREXIA) contained 16,380,466 SNPs(Table 1). This study, being a reevaluation of existing publicly available data, did not require additional ethical authorization.

Table 1

Table 1: Information from the GWAS Database for Two-Sample Mendelian Randomization

Trait	ID	Sample size	SNP	Population	Sex
FIBP	eqtl-a-ENSG00000172500	31,684	16,118	European	Males and Females
Arthritis	finn-b-M13_ARTHROSIS	37,233	16,380,382	European	Males and Females

GWAS = genome-wide association study, SNP= sigle-nucleotide polymorphism

2.2 Data Processing

Typically, a P-value threshold of less than 5.0×10^{-8} is regarded as statistically significant for confirming associations between SNPs and phenotypes. In this study, we used the TwoSample MR package of R software (R Development Core Team, Global Collaboration) to manage linkage disequilibrium, setting parameters at $P < 5.0 \times 10^{-6}$, $r^2 = 0.001$, and kb = 10000. Instrumental variables (IVs) with an F-value greater than 10 were excluded from analysis. We meticulously eliminated potential confounding factors to identify SNPs associated with FIBP accurately.

2.3 MR Analysis

The absence of horizontal pleiotropy was assumed when conducting the inverse variance weighted (IVW) test to calculate the causal effects and ensure unbiased estimates. Depending on whether heterogeneity was present, either a fixed or random-effects model was combined using the IVW method. The magnitude of the effect was represented by the odds ratio (OR) and the corresponding 95% confidence interval (CI). Additionally, the weighted median method and MR-Egger test were employed as supplementary methods.[11,12]

2.4 Sensitivity Analysis

Various analytical methods have been used for sensitivity analysis. Cochran's Q test was used to assess the heterogeneity among individual SNPs, with significant findings indicating notable heterogeneity. The leave-one-out method is used to assess the robustness of the findings. An SNP affecting the results would yield a P-value greater than 0.05 when excluded.

III. Results

Three studies retained three SNPs for the analysis (Table 2).

Table 2

Characteristics of SNPs Related to FIBP and Their Relationship with Osteoarthritis

			Exposure			Outcome		
SNP	EA	OA	β	SE	*p*	β	SE	*p*
rs11082304	T	G	-0.0942	0.008081	2.11E-31	0.0135573	0.00554548	0.0144954
rs1354034	C	T	0.0548	0.008277	3.57E-11	-0.00349834	0.00604967	0.563082

SNP = single nucleotide polymorphism

Mendelian Randomization analyses were performed using the MR-Egger (OR: 0.007, 95% CI: 4.12E-05–1.313), weighted mean (OR: 0.168, 95% CI: 0.046–0.619), and inverse variance weighted (IVW) (OR 0.166 95% CI 0.036–0.767) methods (Table 3).

Table 3

MR Regression Analysis for Three Methods

method	β	SE	pval	Or (95%CI)
MR Egger	-4.912740728	2.645378469	0.314458522	0.00735231
Weighted median	-1.781853338	0.664560696	0.007334771	0.168325893
Inverse variance weighted	-1.79745825	0.78203114	0.021536279	0.165719571

Cl=confidence interval, MR= mendelian randomization

The findings indicate that variations in FIBP are associated with a reduced risk of developing anorexia (see Figures 1).

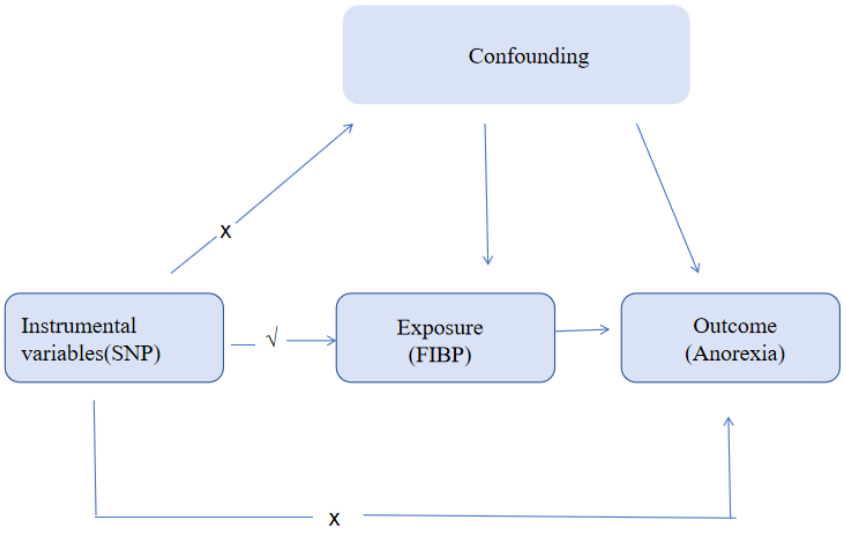

Figure 1.Schematic representation of Mendelian randomization analysis.
SNP=single-nucleotide polymorphism.

No significant heterogeneity was detected using the MR-Egger (P = 0.24) or IVW (P = 0.17) methods (Figure 2 and 3).

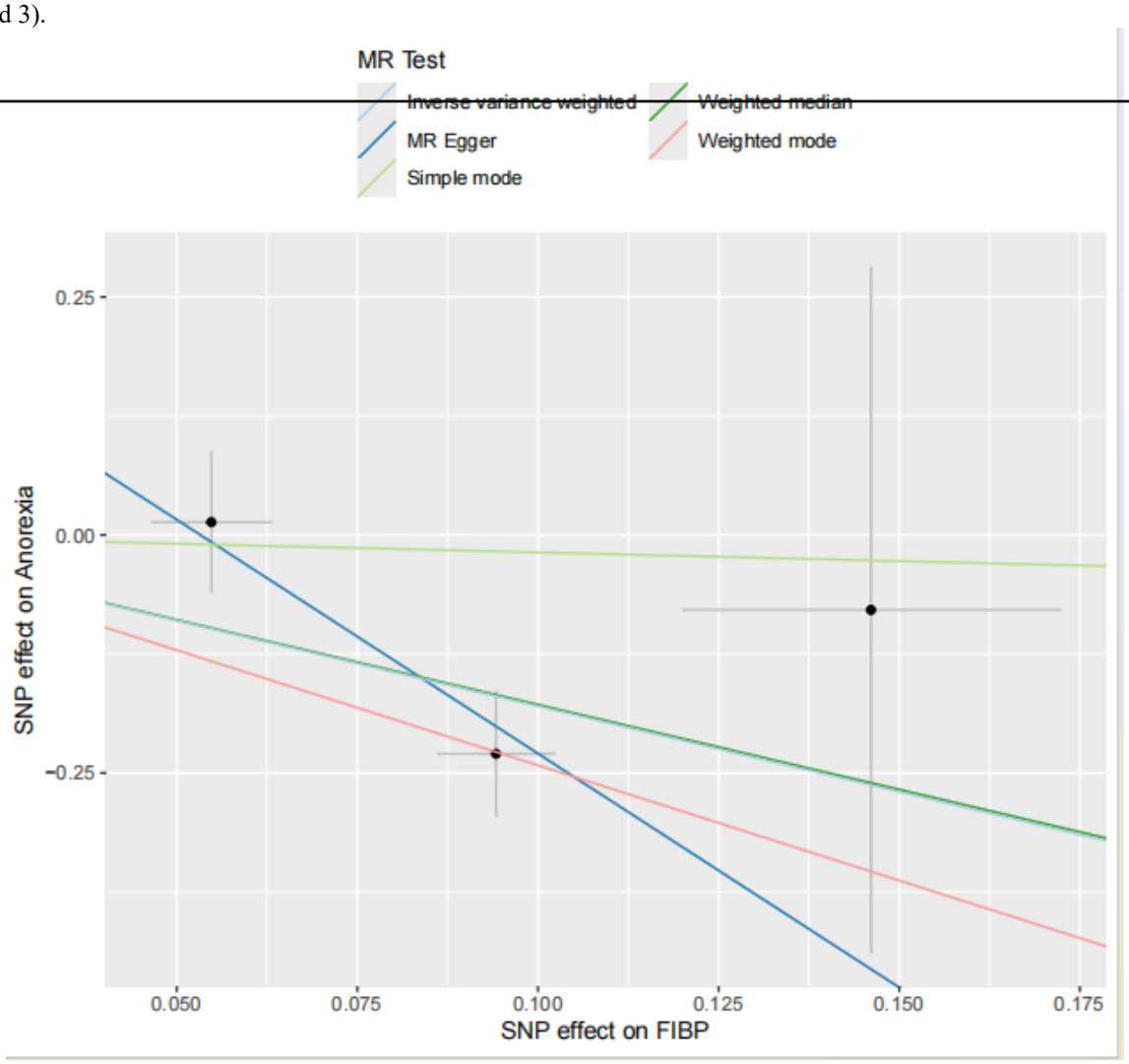

Figure 2: Scatter Plot of FIBP and Anorexia

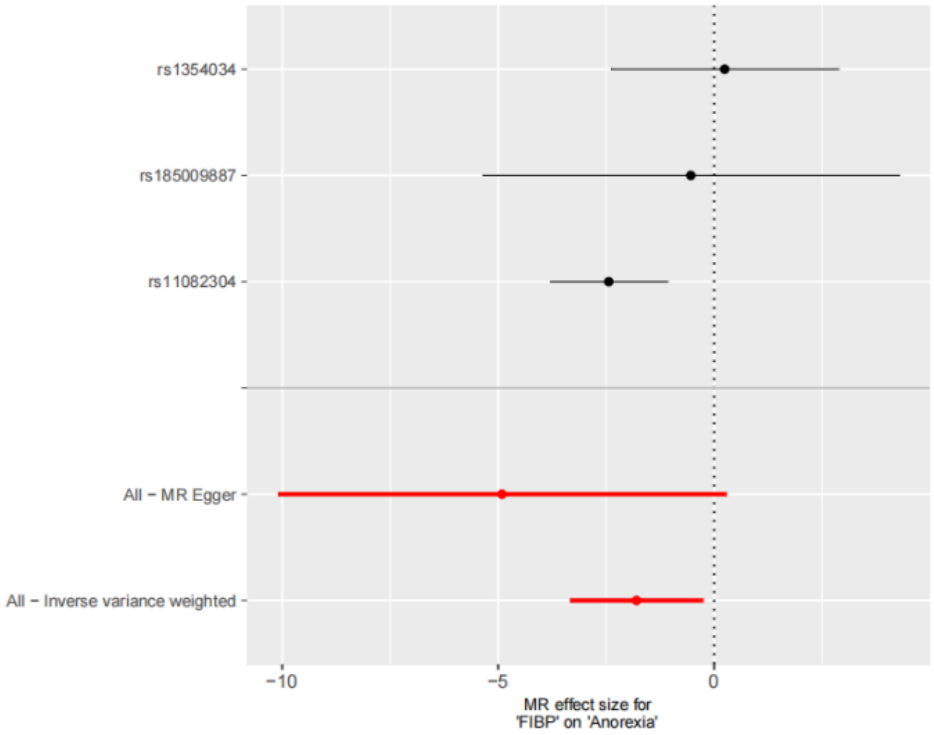

Figure 3: Forest Plot of FIBP and Anorexia

Leave-one-out analysis did not identify any SNP as having a significant impact on the results (Figure 4).

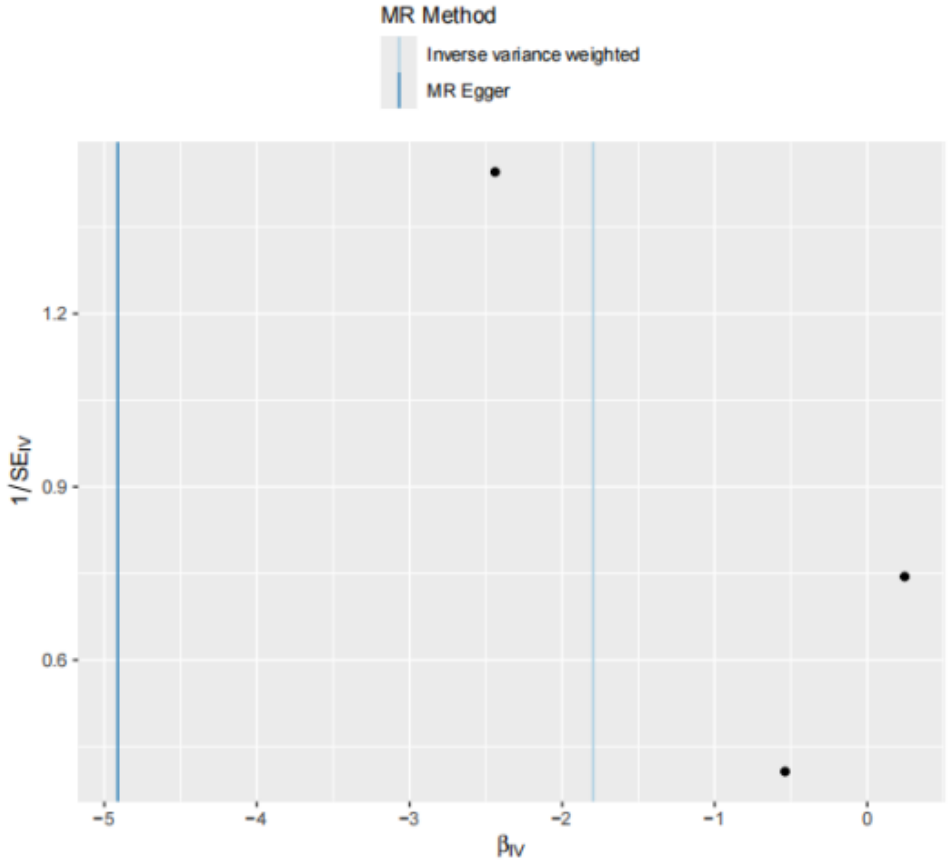

Figure 4: Funnel Plot of FIBP and Anorexia

We employed leave-one-out (LOO) sensitivity analysis to assess the robustness of our Mendelian Randomization (MR) analysis. This method involves sequentially excluding each single nucleotide polymorphism (SNP) and recalculating the MR analysis with the remaining SNPs. Using this approach, we observed that the effect estimates of the remaining SNPs did not differ significantly from the overall effect estimate when one SNP was excluded. This indicated that removing certain SNPs did not significantly affect our MR analysis results, thereby validating the stability and reliability of our findings. Specifically, LOO analysis showed that the effect values of the remaining SNPs after excluding any single SNP had relatively small variations compared to the effect values when including all SNPs. This finding further strengthens our confidence in the MR analysis results, as it demonstrates that the results are not driven by a single SNP but are the outcome of the combined effects of multiple SNPs. Therefore, we are confident that our study successfully passed the LOO test, indicating a high level of robustness of our analysis results(Figure 5).

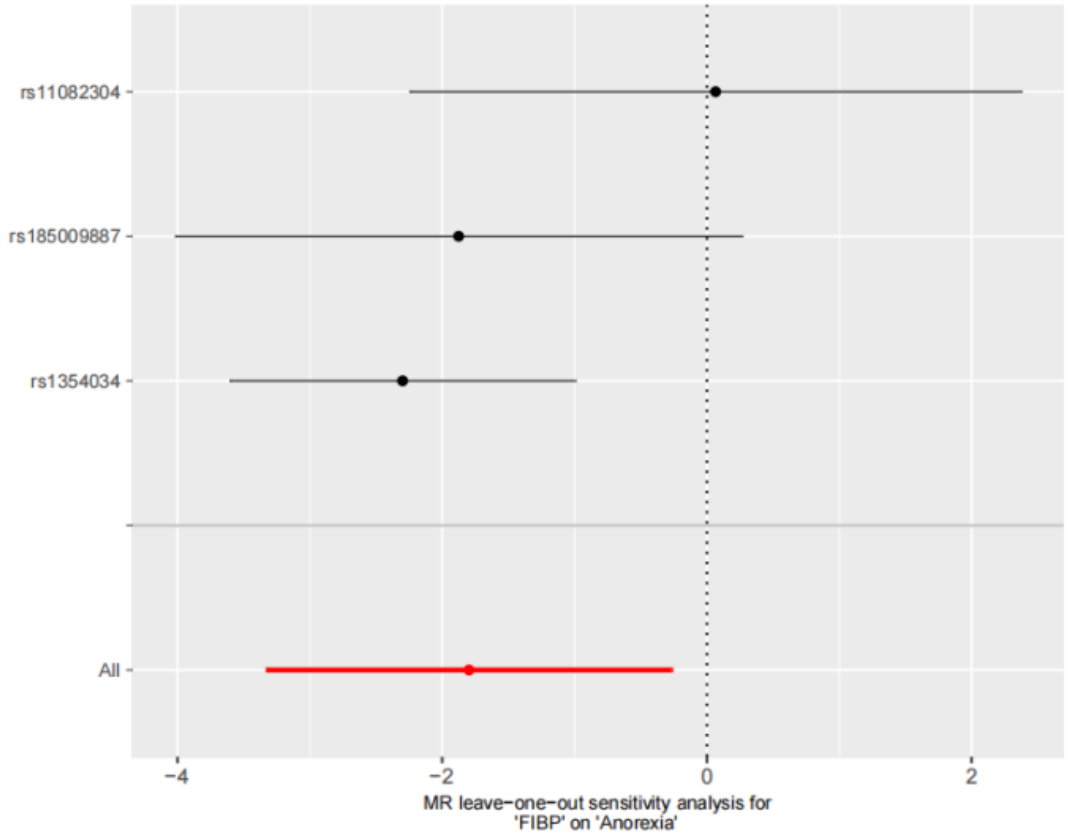

Figure 5: Leave-One-Out Analysis of FIBP and Anorexia

IV. Discussion

This study employed Mendelian Randomization (MR) to explore the relationship between FIBP and anorexia in the elderly, uncovering the potential protective role of FIBP. Utilizing data from the IEU OpenGWAS project,the findings suggest that FIBP expression is significantly associated with a reduced risk of anorexia in the elderly, highlighting its potential importance for future prevention and treatment strategies.

Anorexia in the elderly is a prevalent health issue that arises from diminished appetite and food intake with aging, leading to malnutrition and weight loss, which adversely affect the quality of life and health status. Previous studies identified factors that contribute to the onset of reduced olfactory and gustatory senses, decreased ghrelin levels, and lower nitric oxide levels at the gastric base. [4] Additionally, changes in leptin and insulin levels, along with elevated levels of inflammatory mediators such as interleukins and tumor necrosis factors associated with chronic low-grade inflammation, may also influence appetite centers and promote anorexia. [8]

Specifically, this study focused on how FIBP mitigates anorexia risk through its effects on these physiological pathways. MR analysis revealed that different FIBP expression levels significantly correlated with a reduced risk of anorexia, suggesting a potential role in regulating appetite and energy intake through an unknown mechanism. Although the precise mechanism remains to be elucidated, this discovery opens new avenues for functional research.

Furthermore, the interaction between the FIBP gene and aging-related changes in appetite-regulating

hormones such as ghrelin and cholecystokinin, which are crucial for food intake and satiety regulation, could also be significant. These hormones are vital for appetite control, and FIBP may affect the secretion or activity of their receptors, thereby indirectly influencing appetite. [13,14]

Understanding the intricate mechanisms of gene-disease relationships is crucial for developing treatment strategies for anorexia. Future research confirm that the FIBP gene impacts anorexia through specific biological pathways, targeting this gene could become a viable approach to mitigating anorexia in the elderly. For example, enhancing the expression of the FIBP gene through gene-editing techniques or developing small-molecule drugs targeting its protein products could enhance its protective role in appetite regulation.

However, this study had several limitations. Although Mendelian Randomization provides insights into the potential causal relationships between genes and complex diseases, the effects of a single gene may be obscured by other unmeasured or unknown variables. Additionally, because this study primarily analyzed data from European populations, the findings may not be fully generalizable to other ethnic and geographical groups. Therefore, further research involving more diverse populations is required.[9,10]

In summary, using MR methods, this study demonstrated a potential link between FIBP and reduced risk of anorexia in the elderly, offering a scientific basis for further investigation of the role of this gene in anorexia. Future studies should delve into the specific biological functions of FIBP and assess its effects across different populations to better understand its role in anorexia and develop more effective clinical interventions.

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The author has no conflicts of interest to disclose.

The datasets generated and/or analyzed during the current study are publicly available.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinkiand its later amendments or comparable ethical standards.

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