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BIDIRECTIONAL TWO-SAMPLE MENDELIAN RANDOMIZATION STUDY OF AUTOIMMUNE HEPATITIS AND PREMATURE OVARIAN INSUFFICIENCY

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Abstract: **Objective**: To explore the bidirectional causal relationship between autoimmune hepatitis (AIH) and premature ovarian insufficiency (POI) by bidirectional Mendelian randomization (MR). **Methods**: Bidirectional MR analysis was used to explore the causal effect of AIH as the exposure factor and POI as the outcome index in the forward direction, and POI as the exposure factor and AIH as the outcome index in the reverse direction. Genome-wide association study (GWAS) data for AIH and POI were obtained from the IEU Open GWAS database. Single nucleotide polymorphisms (SNPs) that were strongly associated and independent were selected as instrumental variables (IVs) according to a predefined threshold. The causal association between AIH and POI was evaluated using inverse variance weighted (IVW), MR-Egger regression, weighted median, simple mode, and weighted mode methods. Heterogeneity among SNPs was assessed using Cochran's Q test. The MR-PRESSO test was applied to detect potential outlier SNPs. Horizontal pleiotropy was examined using the MR-Egger intercept test. A leave-one-out sensitivity analysis was performed to determine whether the MR results were driven by any single SNP. **Results**: The IVW analysis in the forward MR revealed no causal relationship between AIH and the onset of POI (OR = 1.06, 95% CI:0.88-1.29, P = 0.54). In the reverse MR, the IVW analysis indicated a statistically significant association between genetically predicted POI and a reduced risk of AIH (OR = 0.94, 95% CI:0.89-0.99, P = 0.02). No evidence of horizontal pleiotropy or heterogeneity was detected for any instrumental variable in the bidirectional MR analysis. **Conclusion**: The forward MR analysis does not support a causal effect of AIH on POI. The reverse MR analysis suggests that POI may reduce the risk of AIH. However, the observed effect size is small. This causal inference requires cautious interpretation. Future studies with larger sample sizes are needed for validation.
Keywords: Autoimmune hepatitis; Premature ovarian insufficiency; Bidirectional Mendelian randomization

1 INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic progressive liver disease of unknown etiology. It is primarily characterized by positive circulating autoantibodies, elevated serum globulin levels, and histological evidence of T-lymphocyte-mediated interface hepatitis [1-3]. AIH predominantly affects women. The female-to-male ratio is approximately 4:1. The age of onset exhibits a bimodal distribution. Peak incidences occur during adolescence and middle age [4]. Without effective immunosuppressive treatment, such as corticosteroids combined with azathioprine, the disease may progress. It can lead to advanced fibrosis, cirrhosis, or even liver failure [5]. Premature ovarian insufficiency (POI), formerly termed premature ovarian failure (POF), is defined as ovarian function decline occurring in women before the age of 40. Clinical manifestations include amenorrhea, elevated follicle-stimulating hormone (FSH) levels (>25 or 30 IU/L), and decreased estrogen levels [6,7]. The global prevalence of POI among women is 3.5%. Its incidence is approximately 1% in women under 40 years of age and 0.1% in those under 30. POI is a major cause of female infertility [8,9].

In recent years, growing evidence has suggested a close association between AIH and ovarian function.Patients with AIH often present with reproductive endocrine abnormalities, including menstrual disturbances and ovulatory dysfunction [10,11]. Furthermore, the prevalence of autoimmune diseases, such as autoimmune liver disease, is notably higher among patients with POI [12-14]. However, the causal relationship between the two and its clinical significance are still controversial, and traditional observational studies are susceptible to confounding factors and reverse causality, making it difficult to draw reliable conclusions.

Mendelian randomization (MR) uses genetic variation as an instrumental variable, which can effectively overcome confounding bias and reverse causality, and provides a new methodological means for causal inference [15]. In recent years, many scholars have used two-way MR method to explore the genetic causal relationship between multiple autoimmune diseases and POI. Luo et al. analyzed the two-way relationship between 10 autoimmune diseases and POI [16], and found that genetic prediction of Addison 's disease and systemic lupus erythematosus (SLE) are risk factors for POI, while POI genetic susceptibility is associated with a slight increase in the risk of type 1 diabetes and autoimmune thyroid disease, suggesting that there may be a two-way association between autoimmune diseases and POI. Lang et al. analyzed the two-way relationship between 13 autoimmune diseases and POI [17], and confirmed that SLE increased the risk of POI, while myasthenia gravis (MG) showed a protective effect, and found that there was a reverse causal relationship between POI and Crohn 's disease (CD), which further supported the complex two-way

effect between the two. Du et al. analyzed the relationship between 20 autoimmune diseases and POI [18], and found that celiac disease, vitiligo, SLE and Addison 's disease increased the risk of POI, while selective IgA deficiency (SIgAD) was a protective factor. It is worth noting that AIH was not included in the above studies, and the genetic causal relationship between AIH and POI was still blank.

To this end, this study used a two-way two-sample Mendelian randomization method to systematically evaluate the two-way causal association between AIH and POI for the first time, in order to provide new genetic evidence for the etiology understanding and clinical management of the two diseases.

2 MATERIALS AND METHODS

2.1 Research Design

This study was a two-way two-sample MR analysis using single nucleotide polymorphism (SNP) as an instrumental variable (IV). In order to ensure a stable effect estimation, IV must satisfy three core assumptions: 1 correlation hypothesis: genetic variation used as IV is related to exposure; 2.Independence hypothesis: IV is not related to confounding factors; 3 Exclusive hypothesis: IV only affects the outcome through exposure rather than other factors [19].

2.2 Data Source

The data of this study were from the IEU Open GWAS database website (https://gwas.mrcieu.ac.uk), AIH data was derived from ebi-a-GCST90018785, the total sample size was 485,234, and the number of SNPs was 24,198,482. The POI data was derived from finn-b-E4 _ OVARFAIL, with a sample size of 118,482 and a SNP number of 16,379,677. Both data are from the European population and meet the basic requirements of two-way MR. See Table 1 for details.

Table 1 Summary of GWAS included in MR Studies

Disease	GWAS ID	Cases	Controls	Number of participants	Number of SNPs	Population
AIH	ebi-a-GCST90018785	821	484,413	485,234	24,198,482	European
POI	finn-b-E4_OVARFAIL	254	118,228	118,482	16,379,677	European

2.3 Selection of Instrumental Variables

The appropriate instrumental variables were selected for MR analysis, and the threshold $P < 5 \times 10\text{-}8$ was used to screen SNPs related to exposure factors. When the number of instrumental variables was insufficient, the screening threshold was adjusted to $P < 5 \times 10\text{-}6$ according to the methodological recommendations of similar studies [17]. To ensure the independence of the selected SNPs, linkage disequilibrium (LD) ($r2 < 0.001$, $kb = 10000$) was performed to trim the SNPs. The tools obtained through the above screening process can effectively avoid the interference of confounding factors on exposure and outcome, and reduce the potential risk of bias. In this study, the strength of each SNP was calculated by F statistics. The calculation formula of F is : $F = [(n-k-1) / k] \times R2 / (1-R2)$, where r2 represents the exposure variance explained by each SNP, n represents the number of exposed data samples, k represents the number of SNPs, and SNPs with F statistics > 10 are selected to control instrumental variable bias.

2.4 MR Analysis and Sensitivity Analysis

Two Sample and MRMR-PRESSO package in R 4.4.3 software were used for statistical analysis. MR-Egger, weighted median estimator (WME), inverse variance weighted (IVW), simple mode (SM), and weighted mode (weighted) were used for statistical analysis. Mode (WM) Five methods were used to analyze the two-way causal relationship between POI and AIH. Among them, IVW has the highest statistical efficiency under the premise of assuming that the instrumental variables (SNP) are valid, and is determined as the main analysis method [20]. Sensitivity analysis was performed using multiple statistical methods. In this study, Cochrane 's Q test was used to test the heterogeneity of the results. The horizontal pleiotropy was analyzed by MR Egger regression method, and $P < 0.05$ was considered statistically significant. The odds ratio (OR) and 95 % confidence interval (CI) were used to quantify the intensity of causality. Leave-one-out test was used to analyze whether a single SNP had an effect on MR results to further verify the stability of the results. The potential horizontal pleiotropy was examined by observing the symmetry of the funnel plot to measure the reliability of the current MR analysis results.

3 RESULT

3.1 Instrument Variable Selection Status

Using the criteria of $P < 5\times10^{-8}$, $r^2 = 0.001$, and $kb = 10,000$, only one SNP was identified from the AIH GWAS. This number was insufficient for conducting MR analysis. Therefore, the P-value threshold was relaxed to 5×10^{-6}. This adjustment yielded thirteen independent SNPs significantly associated with AIH.After intersecting with the POI

outcome data and removing palindromic SNPs, twelve SNPs were retained for the forward MR analysis. The mean F-statistic was 26.01 (21.39 -56.32).In the reverse MR analysis, thirteen independent SNPs were selected from the POI GWAS using the same threshold. The mean F-statistic was 22.59(20.84 - 26.02. All instrumental variables had F-statistics greater than 10. This indicates a low risk of weak instrument bias.

3.2 Forward MR Analysis of AIH and POI

The forward MR analysis revealed no significant causal relationship between genetically predicted AIH and POI.The IVW method yielded an OR of 1.06 (95% CI: 0.88–1.29, P = 0.536). Results from MR-Egger, weighted median, simple mode, and weighted mode methods were all non-significant (all P > 0.05). These findings were consistent with the IVW estimate (Table 2). Notably, the MR-Egger intercept approached the significance threshold (intercept = 0.148, P = 0.099). Moreover, the point estimates from IVW and MR-Egger pointed in opposite directions (IVW OR > 1, MR-Egger OR < 1). This suggests the possible presence of weak directional horizontal pleiotropy. Nevertheless, the IVW result still supports the absence of a causal relationship.Cochran's Q test indicated no heterogeneity among the included SNPs (IVW Q = 8.06, P = 0.71). The leave-one-out analysis demonstrated that the effect estimates derived from the remaining SNPs overlapped with the overall estimate after any single SNP was removed. No individual SNP drove the result (Figure 1). The funnel plot exhibited general symmetry, although the directional effects of all SNPs on POI were not entirely consistent. Four SNPs showed positive effects, while eight showed negative effects (Figure.2).

Table 2 Bidirectional Mendelian Randomization Analysis Results based on Five Analysis Methods

Exposure	Outcome	Method	nSNP	OR（95%CI）	P-value
AIH	POI	MR Egger	12	0.75（0.49-1.15）	0.21
		Weighted median	12	1.12（0.86-1.45）	0.42
		Inverse variance weighted	12	1.06（0.88-1.29）	0.54
		Simple mode	12	1.15（0.89-1.48）	0.30
		Weighted mode	12	1.16（0.65-2.09）	0.62
POI	AIH	MR Egger	13	0.93（0.84-1.04）	0.23
		Weighted median	13	0.93（0.87-1.00）	0.07
		Inverse variance weighted	13	0.94（0.89-0.99）	0.02
		Simple mode	13	0.93（0.86-1.00）	0.05
		Weighted mode	13	0.93（0.83-1.04）	0.25

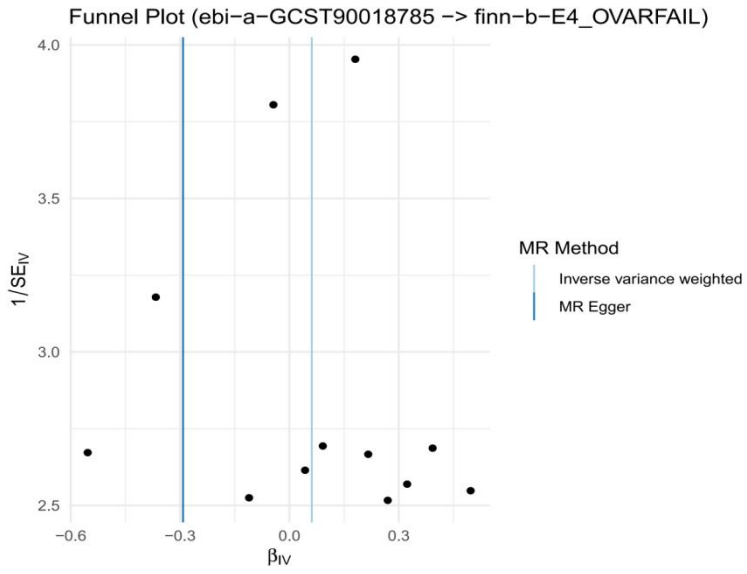

Figure 1 Funnel Plot of the Forward MR Analysis for AIH and POI

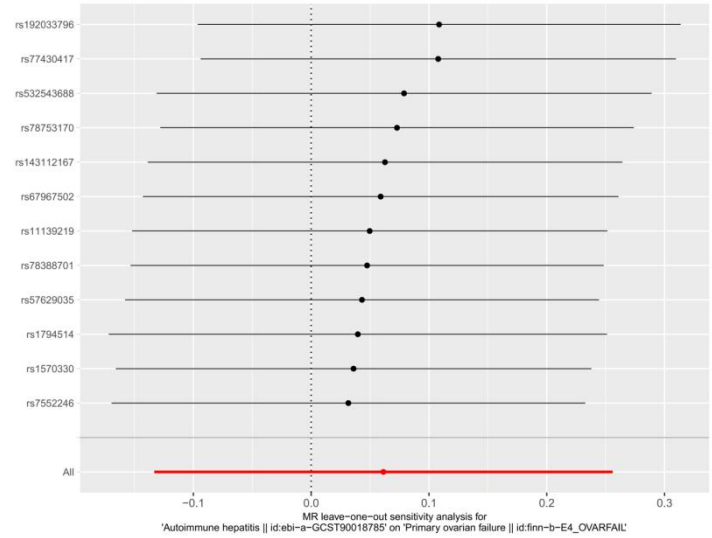

Figure 2 Leave-one-out Plot of the Forward MR Analysis for AIH and POI

3.3 Reverse MR Analysis of POI and AIH

Reverse MR analysis showed that there was a statistical correlation between genetic predicted POI and AIH risk reduction. The OR value estimated by the IVW method was 0.94 (95 % CI : 0.89-0.99, P = 0.023), suggesting that POI may reduce the risk of AIH by about 6 %. The OR point estimates of the other four methods (MR-Egger, weighted median, simple median, and weighted mode) were 0.93 in the same direction, but only the simple median method reached critical significance (P = 0.05), and the remaining P values were between 0.07 and 0.25 (Table 2). The results suggest that the effect size is weak and may be limited by statistical power. No heterogeneity was detected by Cochran 's Q test (IVW Q = 8.00, P = 0.79). There was no evidence of horizontal pleiotropy in MR-Egger intercept test (intercept = 0.006, P = 0.90). No significant outliers were found in the MR-PRESSO global test (P > 0.05). The funnel plot showed a certain asymmetry, among the thirteen SNPs, ten showed negative effects on AIH (β<0),and three showed positive effects (β>0) (Figure 3). Despite the visual asymmetry, the Egger intercept and PRESSO results did not support bias, and the leave-one-out analysis showed that the IVW estimates of the remaining SNPs remained negative after removing any SNP (all < 0), suggesting that a single SNP did not dominate the causal conclusion (Figure 4). However, this asymmetry still needs to be carefully interpreted, and the potential impact of small research effects is not ruled out.

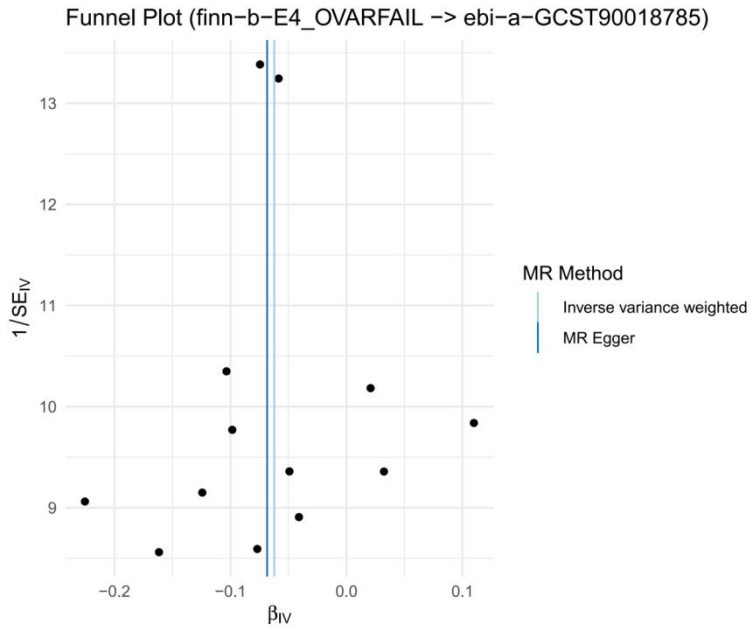

Figure 3 Funnel Plot of the Reverse MR Analysis of POI and AIH

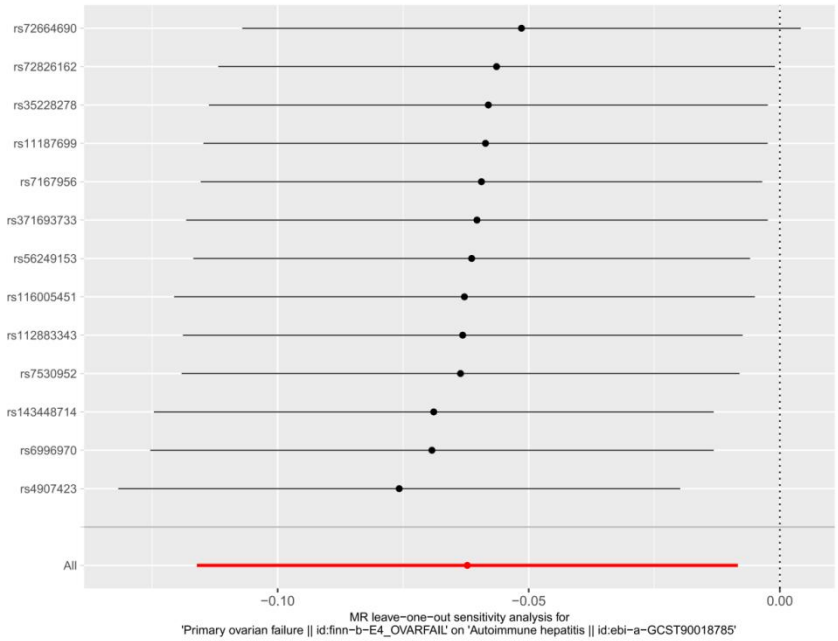

Figure 4 Leave-one-out Plot of the Reverse MR Analysis of POI and AIH

4 DISCUSSION

In this study, a two-way two-sample MR was used to explore the genetic causal relationship between AIH and POI for the first time. Positive analysis showed that there was no evidence that genetic susceptibility to AIH increased the risk of POI. Reverse analysis suggested that there was a statistical correlation between POI predicted by genetic prediction and the risk of AIH, that is, women with POI genetic tendency may have a relatively low risk of AIH. However, the effect size is weak (only 6 % risk reduction), and there is a certain asymmetry in the funnel plot. Although the sensitivity test does not detect horizontal pleiotropic or outliers, the causal inference should still be interpreted cautiously.

AIH is associated with a variety of extrahepatic autoimmune manifestations [21], but the results of this study do not support AIH as a direct genetic risk factor for POI. This result is similar to the recent MR studies on hyperthyroidism, Hashimoto 's thyroiditis and other thyroid diseases and AIH, which showed that thyroid diseases significantly increased the risk of AIH, but the reverse correlation was not significant [21]. In addition, other MR studies have shown heterogeneity in exploring certain autoimmune diseases and POI, such as no causal association between depression and POI [22], while Addison disease and systemic lupus erythematosus significantly increase the risk of POI [16,18]. It is worth noting that the MR-Egger intercept of positive MR in this study is close to the significance threshold ($P = 0.099$), and the point estimation directions of IVW and MR-Egger are opposite (IVW OR > 1, MR-Egger OR < 1), suggesting that there may be weak directional horizontal pleiotropicity. Although the main analysis showed no causal relationship between AIH and POI, this finding suggests that the results need to be interpreted cautiously.Although AIH and POI both belong to the autoimmune spectrum disorders, their target organs differ. AIH targets the liver. POI affects the ovaries. Fundamental differences exist in their antigenic epitopes and local immune microenvironments.The autoimmune attack in AIH is primarily confined to the liver [23,24]. Circulating autoantibodies associated with AIH include antinuclear antibodies (ANA) and smooth muscle autoantibodies (SMA)[25-27]. These autoantibodies may not directly target steroidogenic cells within ovarian tissue. This may explain why the genetic background of AIH does not directly translate into a pathogenic effect on ovarian function.

The reverse MR analysis identified a statistically significant association between POI and a reduced risk of AIH. The effect size was modest. Some funnel plot asymmetry was observed. Nevertheless, the direction of effect was consistent across multiple MR methods. Tests for heterogeneity and horizontal pleiotropy revealed no evidence of substantial bias.Its potential biological mechanism is worth exploring, but the following explanations are speculative hypotheses, which need to be further verified. Estrogen, especially estradiol, is widely considered as an immunopotentiator, which can promote B cell activation, antibody production and Th2 immune deviation [28]. The core pathophysiological change of POI is the long-term severe estrogen deficiency caused by premature ovarian failure. There is evidence that the incidence and severity of AIH are higher in women and are associated with fluctuations in estrogen levels [29]. Therefore, the low estrogen environment caused by POI may weaken the intensity of autoimmune response against the liver, thereby reducing the clinical dominant risk of AIH. POI not only means early reproductive aging, but also may be accompanied by accelerated aging or functional remodeling of the overall immune system [30]. Long-term low estrogen status may induce immune tolerance or change the distribution of T cell subsets, such as enhanced regulatory T cell function, thereby inhibiting abnormal immune attacks against the liver. The protective effect revealed in this study suggests that some genetic variants associated with POI may also have the function of inhibiting other autoimmune responses, reflecting the complexity of genetic pleiotropy. This finding is similar to the results of Du et al. ' s MR study,

which found that selective IgA deficiency (another immunodeficiency state) also had a protective effect on POI [18]. This suggests that certain genetic backgrounds that seem to lead to an immune-related disease may act as ' antagonists ' for another immune-related disease under specific physiological or pathological conditions.

The use of MR design in this study effectively avoids the confounding and reverse causal bias of traditional observational studies ; the reliability of the results was verified by a variety of sensitivity analysis methods.However, this study has certain limitations. The GWAS data were derived exclusively from European populations. Therefore, extrapolation of the conclusions to other populations requires caution. Funnel plot asymmetry was observed. The MR-Egger intercept test and MR-PRESSO global test detected no horizontal pleiotropy or outliers. Nonetheless, the possibility of small-study effects or residual confounding cannot be entirely excluded. Although multiple methods were employed to detect pleiotropy, the influence of unknown potential pleiotropic pathways cannot be fully ruled out. The sample sizes for AIH and POI were relatively modest. This may have limited statistical power for detecting small effect sizes. This study represents a population-level genetic inference. The observed protective effect (OR = 0.94) has limited predictive value in individual clinical practice. Its greater significance lies in revealing new directions for biological mechanism research.

5 CONCLUSION

In summary, this bidirectional Mendelian randomization study did not identify an increased risk of POI conferred by AIH. The inverse association between POI and a reduced risk of AIH was statistically significant. However, the observed effect was weak. There are some problems such as asymmetry of funnel plot and relaxation of P value threshold. It is not yet concluded that POI is a protective factor of AIH. In the future, larger sample size, multi-population GWAS and functional verification studies are needed to further clarify the causal relationship between the two conditions.

COMPETINGINTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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