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ORIGINAL ARTICLE

Association between IGFBP1 and Lung Cancer Risk: Evidence from a Mendelian Randomization Analysis

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ABSTRACT

Background: **Reliable biomarkers for lung cancer risk assessment remain limited. Insulin-like growth factor-binding proteins (IGFBPs) are involved in multiple biological processes and may have clinical relevance in tumor development. This study aimed to evaluate the association between IGFBP family members, with particular attention to insulin-like growth factor-binding protein 1 (IGFBP1), and lung cancer risk using a genetic approach.**
Methods: **Summary statistics from genome-wide association studies (GWAS) for IGFBPs and lung cancer were obtained from publicly available databases. A two-sample Mendelian randomization (MR) analysis was performed to explore potential associations. The inverse variance weighted (IVW) method was used as the primary analysis, with complementary approaches applied to ensure robustness. Sensitivity analyses were conducted to assess heterogeneity and potential pleiotropy.**
Results: **Genetically predicted IGFBP1 levels were significantly associated with lung cancer risk. Higher IGFBP1 levels were linked to a modest reduction in lung cancer risk (OR = 0.9989, 95% CI: 0.9981 - 0.9998, p = 0.0126). No significant associations were observed for other IGFBP family members. The results were consistent across analytical methods, and no evidence of heterogeneity or horizontal pleiotropy was detected.**
Conclusions: **Genetically predicted higher IGFBP1 levels were associated with a reduced risk of lung cancer. These findings provide supportive genetic evidence for the potential involvement of IGFBP1 in lung cancer susceptibility, although further mechanistic and clinical studies are needed for validation.**
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KEYWORDS

IGFBPs, lung cancer, biomarker, GWAS, Mendelian randomization

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide. Due to the lack of specific symptoms at early stages and the relatively high cost of screening, many patients are diagnosed at advanced stages, resulting in poor treatment outcomes and unfavorable prognosis [1,2]. According to recent epidemiological data, approximately 1.06 million new cases and over 730,000 deaths were reported in China in 2022, accounting for a substantial proportion of the global disease burden [3]. These chal-

lenges highlight the need for improved strategies in early detection and risk assessment, particularly through the identification of reliable and accessible biomarkers. Cigarette smoking is a well-established risk factor for lung cancer; however, a notable proportion of cases occur in never-smokers, suggesting that genetic susceptibility and molecular mechanisms also play important roles in disease development [4-8]. This highlights the importance of identifying novel biomarkers associated with lung cancer risk [9-11]. In this context, increasing attention has been directed toward circulating proteins that may serve as potential biomarkers. Insulin-like growth factor-binding proteins (IGFBPs) are a group of regulatory proteins that modulate the bioavailability and activity of insulin-like growth factors (IGFs). IGFBPs are involved in key biological processes, including cell proliferation, differentiation, and apoptosis, and have been implicated in various pathological conditions, including cancer [12,13]. Several studies have suggested that IGFBP family members may participate in tumor progression. For example, IGFBP3 has been associated with bone metastasis in lung cancer [14], while IGFBP7 has demonstrated anti-tumor effects through inhibition of angiogenesis and induction of cellular senescence and apoptosis [15]. In addition, IGFBP-2 and IGFBP3 have been proposed as potential therapeutic targets in breast cancer [16]. Nevertheless, the clinical relevance of IGFBPs in lung cancer risk, particularly as potential biomarkers, remains to be fully elucidated.

Genome-wide association studies (GWAS) have identified numerous genetic variants associated with lung cancer susceptibility, especially single-nucleotide polymorphisms (SNPs), providing important insights into disease etiology [17-19].

Mendelian randomization (MR), a genetic epidemiological approach, enables the assessment of potential associations by using genetic variants as instrumental variables, thereby reducing confounding and reverse causation [20-24]. Such approaches may complement traditional observational studies and provide supportive evidence for biomarker research.

Therefore, the present study aimed to investigate the association between IGFBP family members and lung cancer risk using a two-sample MR approach based on publicly available GWAS data. By integrating genetic evidence, this study seeks to further clarify the potential role of IGFBPs and to provide additional support for their application in laboratory-based risk assessment.

MATERIALS AND METHODS

Study design

A two-sample Mendelian randomization (MR) approach was applied to investigate the association between insulin-like growth factor-binding proteins (IGFBPs) and lung cancer risk.

This genetic approach utilizes variants associated with exposures as instrumental variables, which can help reduce bias from confounding factors and reverse causation.

A valid MR analysis is based on three key assumptions: 1) the selected single-nucleotide polymorphisms (SNPs) are significantly associated with IGFBP levels; 2) these genetic variants are independent of potential confounders; and 3) their effects on lung cancer risk are mediated through IGFBPs rather than alternative biological pathways. The overall study design is illustrated in Figure 1.

Data sources

All data were obtained from publicly available genome-wide association study (GWAS) summary statistics.

Genetic data for IGFBPs were retrieved from the IEU OpenGWAS database. GWAS datasets for IGFBP1, IGFBP2, IGFBP3, IGFBP6, and IGFBP7 (GWAS IDs: prot-a-1447, prot-a-1448, prot-a-1449, prot-a-1450, and prot-a-1451) were included. These data were derived from the study by Sun et al., which analyzed the human plasma proteome in 3,301 individuals of European ancestry and included over 10 million SNPs [25].

Summary-level data for lung cancer were obtained from the UK biobank through the IEU OpenGWAS database (GWAS ID: ieu-b-4954), comprising 374,687 individuals of European descent, including 2,671 cases and 372,016 controls, with more than 11 million SNPs available for analysis [26–28]. Additionally, two external datasets were retrieved for validation, including squamous cell lung cancer (GWAS ID: ieu-a-967) and lung adenocarcinoma (GWAS ID: ieu-a-965). The former contained 8,881,354 genotyped SNPs from 18,336 participants (3,442 cases and 14,894 controls), while the latter included 8,893,750 genotyped SNPs across 18,313 individuals (3,275 cases and 15,038 controls) [29].

Selection of instrumental variables

Instrumental variables associated with IGFBPs were selected through a multi-step procedure. First, SNPs significantly associated with IGFBP levels were identified. Given the limited number of SNPs at the conventional genome-wide significance threshold ($p < 5 \times 10^{-8}$), a relaxed threshold of $p < 1 \times 10^{-5}$ was adopted in accordance with previous studies [30].

To ensure independence among selected SNPs, linkage disequilibrium (LD) clumping was performed using PLINK (Version: b.7.11) with a threshold of $R^2 < 0.001$ and a clumping window of 10,000 kb, and 1,000 Genomes project European samples used as reference. To minimize weak instrument bias, the F-statistic for each SNP was calculated, and SNPs with $F > 10$ were considered sufficiently strong instruments. $F = [(N - K - 1) / K] \times [R^2 / (1 - R^2)]$, where K is the number of genetic variants, and N is the sample size [31].

Mendelian randomization analysis

The primary analysis was conducted using the inverse variance weighted (IVW) method to estimate the association between IGFBPs and lung cancer risk. Additional

Table 1. Characteristics of instrumental variables (SNPs) used in Mendelian randomization analysis.

Exposure	SNPs	R^2, median [25th - 75th percentile]	F-statistics, median [25th - 75th percentile]
IGFBP1	22	0.0790 [0.0782 - 0.0801]	1737.00 [1712.00 - 1757.00]
IGFBP2	27	0.0791 [0.0783 - 0.0801]	1410.00 [1386.00 - 1427.00]
IGFBP3	21	0.0794 [0.0783 - 0.0829]	1811.70 [1728.00 - 1837.00]
IGFBP6	25	0.0800 [0.0774 - 0.0822]	1506.00 [1462.00 - 1562.00]
IGFBP7	20	0.0797 [0.0784 - 0.0830]	1894.00 [1812.00 - 1927.00]

Table 2. Mendelian randomization analysis of insulin-like growth factor binding protein on the occurrence of lung cancer.

MR info							
Exposure	Snp (n)	Method	Beta	SE	OR [95% CI]	p-value	Adjusted p-value
IGFBP1	16	MR-Egger	-0.0011	0.0010	0.9989 [0.9968 - 1.0009]	0.2918	0.2918
		IVW	-0.0011	0.0004	0.9989 [0.9981 - 0.9998]	0.0126	0.0273
		Weighted median	-0.0010	0.0006	0.9990 [0.9978 - 1.0001]	0.0760	0.0950
		MR-RAPS	-0.0011	0.0005	0.9989 [0.9980 - 0.9998]	0.0164	0.0273
		MR-PRESSO	-0.0011	0.0003	0.9989 [0.9983 - 0.9995]	0.0021	0.0105
IGFBP2	23	MR-Egger	-0.0005	0.0010	0.9995 [0.9975 - 1.0015]	0.6206	0.7196
		IVW	0.0002	0.0004	1.0002 [0.9995 - 1.0009]	0.5818	0.7196
		Weighted median	-0.0002	0.0005	0.9998 [0.9989 - 1.0008]	0.7196	0.7196
		MR-RAPS	0.0002	0.0004	1.0002[0.9994 - 1.0010]	0.6083	0.7196
		MR-PRESSO	0.0002	0.0003	1.0002 [0.9996 - 1.0008]	0.5216	0.7196
IGFBP3	18	MR-Egger	0.0005	0.0008	1.0005 [0.9989 - 1.002]	0.5536	0.8876
		IVW	-0.0001	0.0004	0.9999 [0.9991 - 1.0006]	0.7815	0.8876
		Weighted median	-0.0002	0.0006	0.9998 [0.9988 - 1.0009]	0.7731	0.8876
		MR-RAPS	-0.0001	0.0004	0.9999 [0.9991 - 1.0008]	0.8876	0.8876
		MR-PRESSO	-0.0001	0.0004	0.9999 [0.9992 - 1.0006]	0.7739	0.8876
IGFBP6	22	MR-Egger	-0.0005	0.0009	0.9995 [0.9977 - 1.0013]	0.5712	0.7067
		IVW	-0.0001	0.0004	0.9999 [0.9991 - 1.0006]	0.6826	0.7067
		Weighted median	-0.0003	0.0005	0.9997 [0.9988 - 1.0006]	0.4716	0.7067
		MR-RAPS	-0.0003	0.0004	0.9997 [0.999 - 1.0005]	0.4892	0.7067
		MR-PRESSO	-0.0001	0.0003	0.9999 [0.9993 - 1.0004]	0.7067	0.7067
IGFBP7	19	MR-Egger	0.0002	0.0010	1.0002 [0.9983 - 1.0021]	0.8623	0.8623
		IVW	0.0004	0.0004	1.0004 [0.9997 - 1.0012]	0.2346	0.3161
		Weighted median	0.0006	0.0005	1.0006 [0.9996 - 1.0016]	0.2529	0.3161
		MR-RAPS	0.0005	0.0004	1.0005 [0.9998 - 1.0012]	0.1473	0.3161
		MR-PRESSO	0.0004	0.0004	1.0004 [0.9997 - 1.0012]	0.2500	0.3161
Outcome (IGFBP1 as exposure)	**Snp (n)**	**Method**	**Beta**	**SE**	**OR [95% CI]**	**p-value**	**Adjusted p-value**
Squamous cell lung cancer	12	MR-Egger	-0.0717	0.2033	0.9308 [0.6249 - 1.3864]	0.7315	0.7315
		IVW	-0.1348	0.0749	0.8739 [0.7546 - 1.012]	0.0718	0.0897
		Weighted median	-0.1986	0.0984	0.8199 [0.6761 - 0.9943]	0.0435	0.0897
		MR-RAPS	-0.1470	0.0792	0.8633 [0.7392 - 1.0082]	0.0633	0.0897
		MR-PRESSO	-0.1348	0.0522	0.8739 [0.7888 - 0.9681]	0.0256	0.0897

Table 2. Mendelian randomization analysis of insulin-like growth factor binding protein on the occurrence of lung cancer (continued).

Outcome (IGFBP1 as exposure)	Snp (n)	Method	Beta	SE	OR [95% CI]	p-value	Adjusted p-value
Lung adeno-carcinoma	12	MR-Egger	-0.1689	0.1982	0.8446 [0.5727 - 1.2454]	0.4139	0.9693
		IVW	-0.0029	0.0736	0.9971 [0.8631 - 1.1519]	0.9684	0.9693
		Weighted median	0.0349	0.0916	1.0355 [0.8653 - 1.2392]	0.7036	0.9693
		MR-RAPS	-0.0030	0.0769	0.997 [0.8575 - 1.1593]	0.9693	0.9693
		MR-PRESSO	-0.0029	0.0400	0.9971 [0.9219 - 1.0785]	0.9433	0.9693

SE: Standard error.

Table 3. Summary of Cochran's Q test, horizontal pleiotropy tests, and MR-PRESSO outlier test results in Mendelian randomization analysis.

Exposure	Method	Cochran's Q			Horizontal pleiotropy			MR-PRESSO outlier test	
		Q	df	Q_pval	intercept	SE	p	RSSobs	p-value
IGFBP1	MR-Egger	6.8013	14	0.9421	9.52e-06	0.0002	0.9623	7.7833	0.9680
	IVW	6.8036	15	0.9629	-	-	-	-	-
IGFBP2	MR-Egger	15.1789	21	0.8139	-0.0019	0.0069	0.7784	17.2207	0.7830
	IVW	15.7304	22	0.8290	-	-	-	-	-
IGFBP3	MR-Egger	17.8275	16	0.3341	-0.0001	0.0001	0.4053	20.4331	0.4340
	IVW	18.6416	17	0.3495	-	-	-	-	-
IGFBP6	MR-Egger	13.8644	20	0.8373	6.85e-05	0.0002	0.6570	15.57047	0.9050
	IVW	14.0676	21	0.8667	-	-	-	-	-
IGFBP7	MR-Egger	22.0604	17	0.1824	5.67e-05	0.0002	0.7659	24.11271	0.2660
	IVW	22.1793	18	0.2241	-	-	-	-	-
Outcome (IGFBP1 as exposure)	Method	Q	df	Q_pval	intercept	SE	p	RSSobs	p-value
Squamous cell lung cancer	MR-Egger	5.2440	10	0.8743	-0.0114	0.0341	0.7456	6.3872	0.9150
	IVW	5.3553	11	0.9127	-	-	-	-	-
Lung adeno-carcinoma	MR-Egger	2.4356	10	0.9917	0.0303	0.0335	0.3881	3.9472	0.9870
	IVW	3.2500	11	0.9869	-	-	-	-	-

Q: Cochran's Q statistic, Q_df: Degrees of freedom for Cochran's Q, Q_pval: p-value of Cochran's Q statistic, RSSobs: Observed Residual Sum of Squares.

MR methods, including MR-Egger, weighted median, and MR-RAPS, were applied as complementary approaches to assess the consistency of the results. Furthermore, the MR-PRESSO method was used to identify and correct potential outliers, thereby reducing bias related to horizontal pleiotropy. Additionally, the Steiger directionality test was conducted via the R package TwoSampleMR. And R package "gsmr2" package (Version: 1.1.1) was applied to perform HEIDI (Heterogeneity in Dependent Instruments) test.

Sensitivity analyses

Sensitivity analyses were performed to evaluate the robustness of the findings. Heterogeneity across instrumental variables was assessed using Cochran's Q test. Potential horizontal pleiotropy was examined using the MR-Egger intercept and applied the outlier test for the MR-PRESSO method. Lastly, funnel plots and leave-one-out sensitivity analysis were conducted to evaluate the stability of the results.

All statistical analyses were conducted using R software

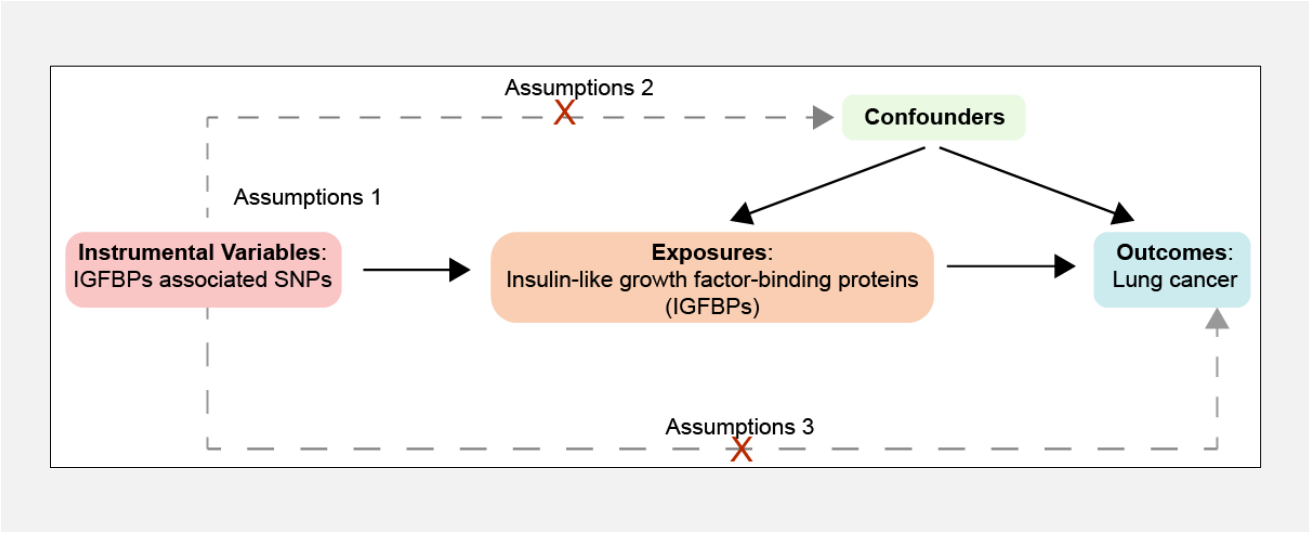

Figure 1. Three main hypotheses for Mendelian randomization analysis of insulin-like growth factor binding protein and lung cancer.

(version 4.5.3) with the TwoSampleMR (version 0.6.22) and MR-PRESSO (version 1.0) packages. A two-sided p-value < 0.05 was considered statistically significant. Benjamini-Hochberg (BH) correction was applied to the MR-derived p-values.

Ethics statement

This study used only publicly available, de-identified GWAS summary statistics from the IEU OpenGWAS database. No new individual-level data were collected, and no additional ethical approval or informed consent was required. All original studies contributing data to these GWAS datasets had obtained appropriate ethical approval and participant informed consent.

RESULTS

Selection of instrumental variables

Using the predefined threshold ($p < 1 \times 10^{-5}$), SNPs associated with IGFBP levels were initially identified from the exposure GWAS datasets. To ensure independence among variants, linkage disequilibrium (LD) clumping ($r^2 < 0.001$, window size = 10,000 kb) was performed, and SNPs potentially associated with lung cancer were excluded.

After these selection steps, independent SNPs were retained as instrumental variables for subsequent analyses. All selected instruments demonstrated adequate strength (F-statistics > 10), suggesting a low risk of weak instrument bias. Following harmonization and quality control procedures, the final numbers of SNPs included were 16 for IGFBP1 (Supplementary Table 1), 23 for IGFBP2, 18 for IGFBP3, 22 for IGFBP6, and 19 for IGFBP7 (Table 1).

Association between IGFBP1 and lung cancer risk

The association between IGFBPs and lung cancer risk was evaluated using multiple MR approaches. The primary inverse variance weighted (IVW) analysis indicated that genetically predicted higher levels of IGFBP1 were significantly associated with lung cancer risk. Specifically, increased IGFBP1 levels were linked to a modest reduction in lung cancer risk (OR = 0.9989, 95% CI: 0.9981 - 0.9998, p = 0.0126). Because circulating IGFBP1 levels in the source proteomic GWAS were analyzed on their original measurement scale rather than standardized to a one-standard-deviation increase, the reported OR represents the relative change in lung cancer risk per genetically predicted unit increase in IGFBP1. Therefore, its proximity to 1 should be interpreted in the context of the exposure scale. This association remained consistent in direction and significance in the MR-RAPS (OR = 0.9989, 95% CI: 0.9980 - 0.9998, p = 0.0164) and MR-PRESSO analysis (OR = 0.9989, 95% CI: 0.9983 - 0.9995, p = 0.0021), supporting the robustness of the finding (Table 2; Figure 2A, 2B). We additionally conducted the Steiger directionality test by R package TwoSampleMR, which verified the causal directionality between IGFBP1 and lung cancer (p < 0.0001). The results of the HEIDI (Heterogeneity in Dependent Instruments) test showed that there was no significant colocalization between the SNPs of IGFBP1 and lung cancer (p > 0.05).

In contrast, no significant associations were observed between other IGFBP family members (IGFBP2, IGFBP3, IGFBP6, and IGFBP7) and lung cancer risk across all analytical methods (Table 2; Figure 2C - F).

Furthermore, external validation was performed separately for the two lung cancer subtypes with IGFBP1 set as the exposure. The results indicated that IGFBP1 may

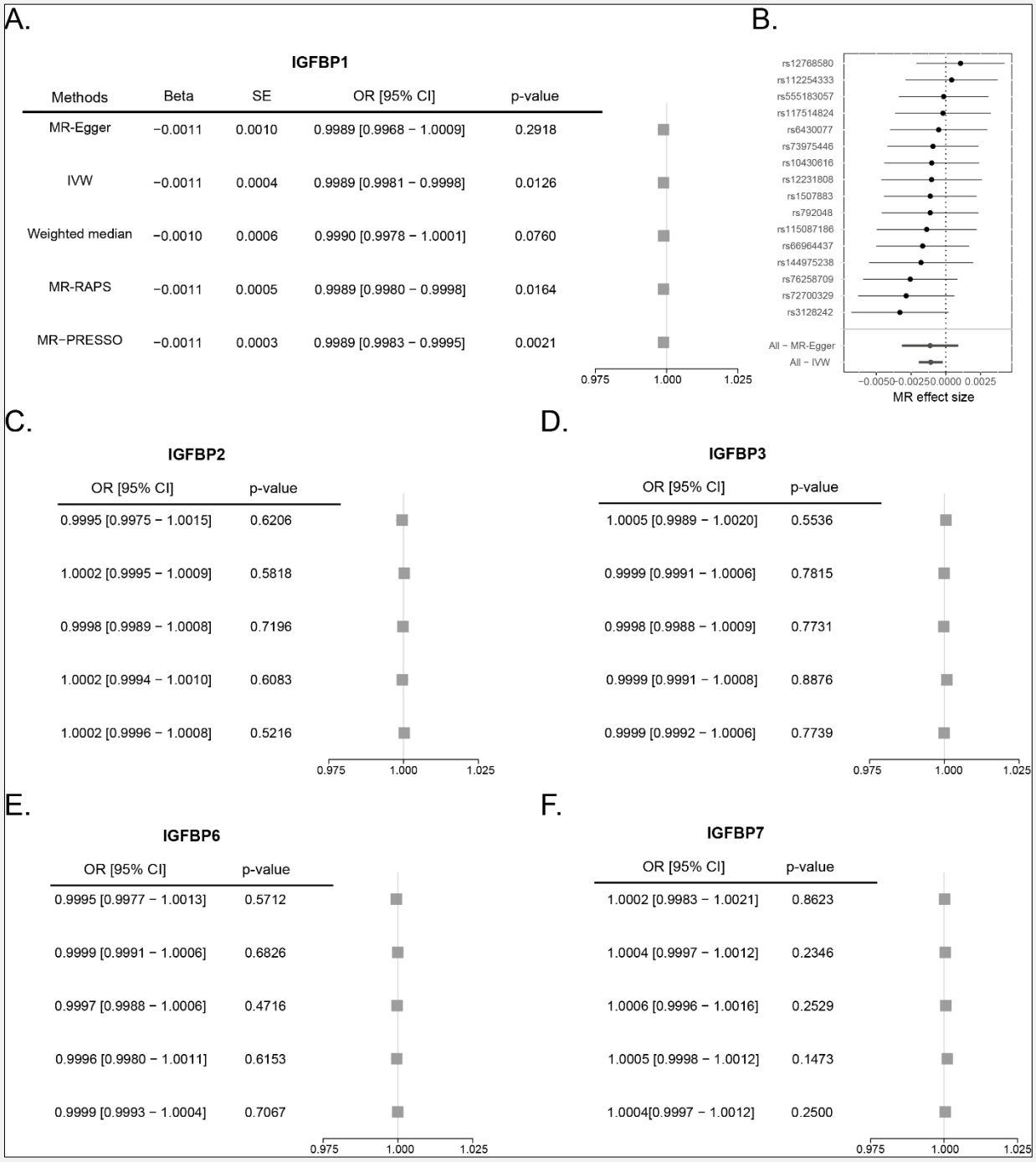

Figure 2. Results of Mendelian randomization analysis of insulin-like growth factor binding protein on lung cancer.

A: Main result of IGFBP1, B: MR effect size of IGFBP1 SNPs, C - F: result of IGFBP2, IGFBP3, IGFBP6 and IGFBP7.

serve as a potential protective factor for LUSC. The p-values of the weighted median and MR-PRESSO methods were 0.0435 and 0.0256, with the corresponding OR (95% CI) being 0.8199 (0.6761 - 0.9943) and 0.8739 (0.7888 - 0.9681), respectively. In contrast, no significant causal association was detected between IGFBP1 and LUAD (Table 2).

Sensitivity analyses

Sensitivity analyses were performed to evaluate the stability of the results (Table 3). Cochran's Q test showed no evidence of heterogeneity among the instrumental ($p = 0.4659$, 0.4053, 0.6570, and 0.7659, respectively). These findings support the absence of substantial directional pleiotropy, although the statistical power of the MR-Egger intercept test may be limited when the number of instrumental variables is relatively small.

The MR-PRESSO outlier test revealed no significant outliers ($p > 0.05$), indicating no evidence of outlier-induced bias and supporting the robustness of the causal estimates (Table 3). The funnel plots, depicting the causal relationships among these SNPs, revealed no evidence of asymmetry (Supplementary Figure 1). Through the leave-one-out analysis, systematically removing each SNP and re-evaluating the remaining SNPs, the results remained consistent (Supplementary Figure 2).

DISCUSSION

In this study, a two-sample Mendelian randomization approach was applied to evaluate the association between IGFBP family members and lung cancer risk. The results indicate that genetically predicted higher IGFBP1 levels are associated with a reduced risk of lung cancer, whereas no significant associations were observed for IGFBP2, IGFBP3, IGFBP6, or IGFBP7. Sensitivity analyses showed no evidence of heterogeneity or horizontal pleiotropy, supporting the stability of the findings. Although the primary effect estimate was numerically close to 1 (OR = 0.9989), this reflects the original measurement scale of IGFBP1 in the source proteomic GWAS rather than a standardized one-standard-deviation increase. Consistent with this interpretation, a stronger inverse association was observed in the lung squamous cell carcinoma subgroup (MR-PRESSO OR = 0.8739).

Previous studies have explored the relationship between IGFBPs and lung cancer, although the reported results have been inconsistent. Experimental data suggest that IGFBP3 may inhibit tumor cell survival in non-small cell lung cancer through a p53-dependent mechanism [32]. Clinical studies have also reported elevated circulating IGFBP-4 levels in patients with lung cancer [33]. In addition, a meta-analysis by Zhang et al. indicated that IGFBP1 may act as a protective factor in lung cancer, although its role may differ across cancer types [34]. However, these findings are largely derived from variables for any of the IGFBPs. For IGFBP1, the p-values for MR-Egger and IVW were 0.9421 and 0.9629, respectively. Similar results were observed for IGFBP2 (0.8139 and 0.8290), IGFBP3 (0.3341 and 0.3495), IGFBP6 (0.8373 and 0.8667), and IGFBP7 (0.1824 and 0.2241), indicating consistency across instruments.

In addition, the MR-Egger intercept test suggested no evidence of horizontal pleiotropy (Table 3). For IGFBP1, the intercept estimate was 9.52×10^{-6}, which was extremely close to zero, with a corresponding p-value of 0.9623. Similar non-significant results were observed for IGFBP2, IGFBP3, IGFBP6, and IGFBP7 observational or experimental studies and may be influenced by confounding factors or reverse causation. In this context, the present study provides complementary genetic evidence supporting an inverse association between IGFBP1 and lung cancer risk.

From a biological perspective, IGFBP1 is a dynamic regulator of the insulin-like growth factor (IGF) axis. By binding circulating IGF-1 with high affinity, IGFBP1 modulates the balance between free and bound IGF-1, thereby controlling the availability of biologically active IGF-1 to activate the IGF-1 receptor and downstream signaling pathways involved in cell proliferation, survival, and invasion [35,36]. IGFBP1 is synthesized predominantly in the liver and is tightly regulated by insulin, with hyperinsulinemia strongly suppressing hepatic IGFBP1 expression. Consequently, circulating IGFBP1 levels are closely linked to metabolic status and insulin sensitivity [37]. Smoking, a major risk factor for lung cancer, has also been associated with insulin resistance, chronic inflammation, and metabolic disturbances, which may alter IGFBP1 concentrations and indirectly affect IGF signaling. In addition to its effects on the IGF axis, IGFBP1 has been implicated in cell adhesion, inflammatory responses, and metabolic regulation [38]. Together, these mechanisms provide a biologically plausible explanation for the inverse association observed between genetically predicted IGFBP1 levels and lung cancer risk.

Importantly, from a clinical laboratory perspective, IGFBP1 may represent a potential circulating biomarker for lung cancer risk assessment. As IGFBPs are detectable in blood samples, the observed association may have implications for the development of non-invasive strategies for risk evaluation. Although the effect size observed in this study is modest, such biomarkers may still be valuable when combined with other clinical or laboratory indicators.

Several strengths of this study should be highlighted. First, the use of a genetic approach reduces bias from confounding and reverse causation. Second, multiple analytical methods were applied, and the consistency of findings across approaches enhances the robustness of the results. Third, the use of large-scale GWAS datasets improves statistical power and the reliability of the estimates.

Limitations

Several limitations should be acknowledged. First, no formal correction for multiple testing was applied; therefore, the association between IGFBP1 and lung cancer should be interpreted cautiously until confirmed in independent studies. Second, although the Steiger directionality test supported the hypothesized causal direction, independent external replication was not performed. Third, the use of a relaxed significance threshold ($p < 1 \times 10^{-5}$) for instrument selection may have introduced winner's curse. Fourth, because both the exposure and outcome datasets were derived primarily from individuals of European ancestry, partial sample overlap cannot be entirely excluded and the generalizability of the findings to other populations remains uncertain. Finally, the number of instrumental variables for some IGFBP family members was limited, and the subgroup analyses should be considered exploratory and require further validation.

CONCLUSION

In conclusion, this study provides genetic evidence supporting an association between higher IGFBP1 levels and a reduced risk of lung cancer, while no significant associations were observed for other IGFBP family members. These findings support a potential role of IGFBP1 in lung cancer susceptibility and provide a basis for future mechanistic and validation studies.

Declaration of Generative AI in Scientific Writing:

The authors declare that generative artificial intelligence tools were used solely to assist with language editing and grammatical refinement during the preparation of this manuscript. The artificial intelligence tools did not contribute to the study design, data collection, data analysis, data interpretation, or the generation of scientific conclusions. All content was reviewed and approved by the authors, who take full responsibility for the integrity and originality of the work.

Declaration of Interest:

The authors declare no conflicts of interest.

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