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ARTICLE

# Genetic Susceptibility of Thrombin Measurement Levels and the Risk of Colon Adenocarcinoma: A Mendelian Randomization Study

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## Abstract

**Aims/Background** This investigation sought to establish a possible correlation between thrombin measurement levels and the risk of developing colon adenocarcinoma (COAD).

**Methods** Thrombin measurement levels were sourced from a study by Pietzner M (2020, PMID: 33328453) and integrated into the IEU database. Data on COAD were obtained from the FinnGen database (2021, C3_COLON_ADENO). Various analytical methods were used to assess the relationship, including inverse variance weighting (IVW), mendelian randomization-Egger (MR-Egger) regression, as well as weighted median and mode techniques. Sensitivity analyses were performed, including Cochran's Q test, MR-Egger intercept test, mendelian randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO), along with leave-one-out analysis, to ensure the robustness of the results.

**Results** The IVW analysis indicated a significant inverse association between elevated thrombin levels and the risk of COAD (odds ratio (OR) = 0.76, 95% CI = 0.66–0.88, $p = 0.0003$). These findings were supported by the weighted median analysis (OR = 0.78, 95% CI = 0.68–0.90, $p = 0.0006$) and the weighted mode analysis (OR = 0.78, 95% CI = 0.68–0.88, $p = 0.0017$).

**Conclusion** This research identified an inverse causal relationship between thrombin measurement levels and the incidence of COAD, suggesting that higher thrombin levels are associated with a reduced risk of developing COAD.

**Key words: thrombin; colon adenocarcinoma; mendelian randomization**

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## Introduction

Colorectal cancer (CRC) (Sung et al, 2021) is a prevalent malignancy, ranking third in both incidence and mortality rates among all cancers. The predominant form of this disease is colon adenocarcinoma (COAD), which typically evolves from mucosal polyp hyperplasia, progresses through stages of colon adenoma, and ultimately culminates in malignancy (Benesch et al, 2023). In its advanced stages, COAD can present with symptoms such as hematochezia, iron deficiency anemia, abdominal discomfort, weight loss, and diminished appetite. Due to the absence of distinct clinical manifestations in the early stages, COAD is often diagnosed at an advanced phase, adversely impacting prognosis. Consequently, identifying innovative biomarkers and therapeutic targets is imperative to enhance the survival outcomes of patients with COAD (Yang et al, 2024).

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Thrombin, a critical coagulation factor, plays a pivotal role in the coagulation process by being activated in both the exogenous and endogenous pathways. Thrombin's influence extends to the progression of various cancers through multiple mechanisms. Research (Turpin et al, 2014) indicated that interactions between inflammation and the coagulation system can contribute to tumor progression. For instance, research (Lee et al, 2022) involving nude mice showed that thrombin-activated platelets aid vascular endothelial cells in preventing tumor cell invasion, thus acting as a protective factor against cancer. Although many observational studies have linked thrombin measurement levels with cancer, no research has yet examined the relationship between thrombin levels and COAD.

Mendelian randomization (MR) is a method extensively used in genetic epidemiology to infer causal relationships. MR provides a robust approach for genetic-level investigations and is increasingly applied to deduce associations in the pathogenesis of complex diseases. Several studies employed two-sample MR analyses, leveraging large-scale genome-wide association studies (GWAS), to investigate causal relationships between exposure and outcome.

In this study, we aimed to utilize GWAS data on thrombin measurement levels and COAD to analyze the pathogenic mechanisms at the genetic level. We examined the association between thrombin levels and COAD through a two-sample MR analysis. The aim of this study was to provide a foundational basis for the development of preventative strategies for COAD in clinical practice.

# Methods

## Study Design

In this investigation, a two-sample mendelian randomization analysis was employed to explore the causal nexus between thrombin measurement levels and COAD (Fig. 1). This mendelian randomization study was predicated on a comprehensive summary dataset derived from GWAS data.

## Data Source

The exposure variable, thrombin measurement levels, was extracted from the 2020 article by Pietzner et al (2020). This data was integrated into the IEU database, designated by the code GCST90019441, encompassing 10,708 samples and 15,567,527 SNPs (single nucleotide polymorphisms). The outcome variable, COAD, originated from the FinnGen database, denoted as C3_COLON_ADENO in 2021, comprising 218,792 samples and 16,380,466 SNPs. In the original investigations involving participants of European ancestry, all participants had provided informed consent, thus negating the necessity for additional ethical clearance in our study, which exclusively utilized aggregate data.

## Variables Screening for Genetic Tools

Firstly, genetic instrumental variables demonstrated a robust association with thrombin measurement levels (exposure factors) ($p < 5 \times 10^{-8}$). Secondly, these genetic instruments were not associated with confounders, warranting the exclusion of any instrumental variables linked to such confounders. Thirdly, the instrumental

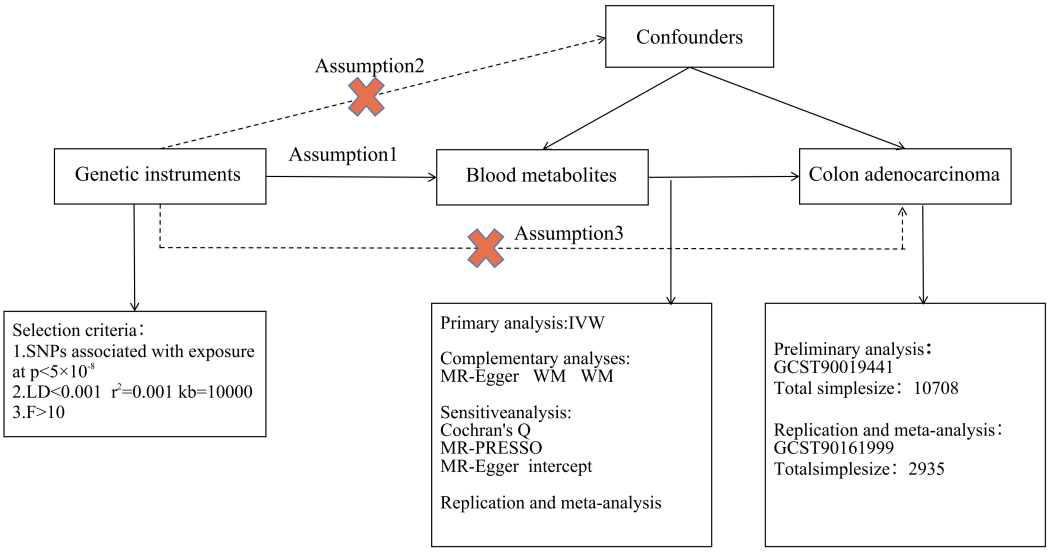


**Fig. 1. Flow chart of this mendelian randomization analysis.** LD, Linkage disequilibrium; WMWM, Weighted Median and Weighted Mode; SNPs, single nucleotide polymorphisms; MR, mendelian randomization; MR-PRESSO, mendelian randomization Pleiotropy RESidual Sum and Outlier; MR-Egger, mendelian randomization-Egger; IVW, inverse variance weighting.

variable influenced the outcomes solely through the exposure and was not directly correlated with the outcomes ($p > 5 \times 10^{-5}$).

## Mendelian Randomization Analysis

Mendelian randomization (MR) is an analytical technique in epidemiological research used to evaluate causal inferences. Genetic variants strongly associated with exposure factors are utilized as instrumental variables to assess the causal relationship between the exposure and the outcome.

### *Three Core Assumptions of Mendelian Randomization*

Relevance Assumption: The SNPs were strongly associated with the exposure factor, indicating a clear link between genetic variations and the exposure under investigation.

Independence Assumption: The SNPs remained unaffected by potential confounding factors, ensuring their independence and credibility as instrumental variables.

Exclusivity Assumption: The SNPs exerted their effect on the outcome solely through their association with the exposure factor, affirming a direct causal pathway without interference from other variables.

### *Mendelian Randomization Analysis Procedure*

Step 1: Researchers obtained GWAS data for both exposure and outcome from the IEU and FinnGen databases.

Step 2: Instrumental variables were selected from the exposure data. SNPs strongly associated with the exposure factor were identified through association analysis, employing a filtering criterion of $p$-value $< 5 \times 10^{-8}$.

Step 3: Linkage disequilibrium (LD) was addressed. LD refers to the non-random association of alleles at different loci. Genetic variants close together on a chromosome are likely to be inherited together. This was measured using kb (the genomic distance within which LD was assessed) and $r^2$ (the correlation coefficient between SNPs, ranging from 0 to 1). In this study, the KB was set to 10,000, and $r^2$ was set to 0.001, where $r^2 = 1$ indicated complete LD and $r^2 = 0$ indicated no LD.

Step 4: Weak instruments were removed using an F-test with a threshold of $F > 10$.

Step 5: Confounders were removed using resources such as Phenoscanner (https://doi.org/10.1093/bioinformatics/btw373).

Step 6: Mendelian randomization analysis was conducted.

Step 7: Heterogeneity analysis was performed using inverse variance weighting (IVW) and mendelian randomization-Egger (MR-Egger) tests. If the *p*-value was >0.05, the study was considered to have no heterogeneity.

Step 8: Pleiotropy analysis was conducted. If the instrumental variables affected the outcome through factors other than the exposure, they exhibited pleiotropy, which invalidated the independence and exclusivity assumptions. The MR-Egger intercept test could detect pleiotropy and assess result robustness. If the *p*-value was >0.05, the study was considered to have no pleiotropy.

Step 9: Results were visualized, including a scatter plot (Fig. 2). The x-axis depicted the effect of SNPs on the exposure, while the y-axis represented the effect of SNPs on the outcome. A positive slope indicated that the exposure was a risk factor for the outcome, whereas a negative slope suggested that the exposure was a protective factor.

Step 10: A leave-one-out sensitivity analysis (Fig. 3) was performed to evaluate the impact of each SNP on the MR analysis results. By removing outliers and repeating the analysis, the robustness of the findings was ensured.

For the mendelian randomization (MR) analysis, we employed IVW, MR-Egger regression, as well as the Weighted Median and Weighted Mode approaches as our effect size estimation strategies (Burgess and Thompson, 2017). The IVW method served as the principal estimator, consolidating individual Wald estimates from each SNP to derive a comprehensive estimate. MR-Egger regression was utilized to correct for Instrumental Variable bias in causal inference. It introduced an intercept term compared to the IVW method. The key idea behind MR-Egger regression was that by conducting a linear regression on a funnel plot of instrumental variable effects, directional bias of instrumental variables could be quantified and detected. When interpreting MR-Egger regression results, the main focus was on the following key points: the intercept value, the *p*-value associated with the intercept, the slope, and $I^2$.

If the intercept term was not significant, it suggested that no significant instrumental variable bias had been detected. The slope term represented the estimated causal effect corrected for bias. $I^2$ was used to quantify the proportion of heterogeneity among instrumental variables. A higher $I^2$ value (such as greater than 50%) indicated substantial heterogeneity. Weighted Median (WM) was a conceptual extension for finding the median in a dataset, applicable when data points had different

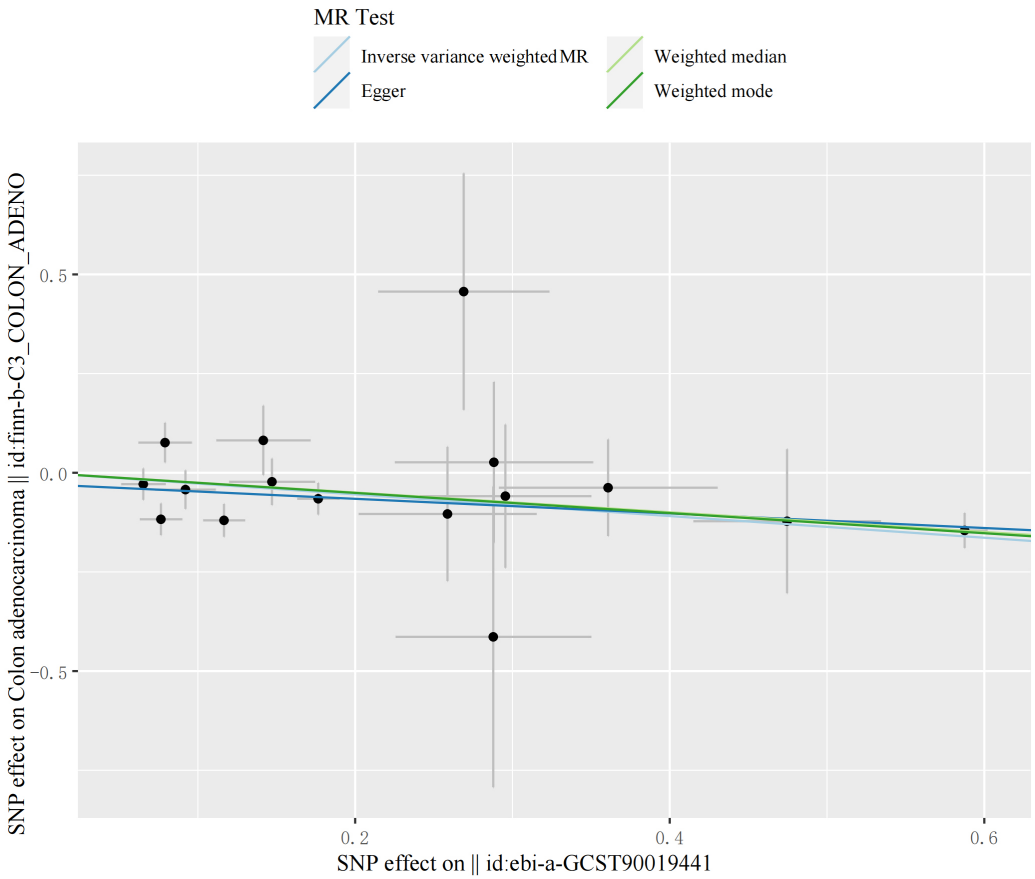


**Fig. 2. Scatter plot.**

weights. Weighted Mode (WM) was a statistical measure used to describe the most frequently occurring value in a dataset, being a form of weighted median (Chen et al, 2021, 2022).

## Sensitivity Analysis to Evaluate Biases

Conducting a sensitivity analysis was crucial for assessing potential biases in mendelian randomization studies. This comprehensive evaluation included tests for heterogeneity and pleiotropic effects. Inconsistencies within the IVW approach were investigated through Cochran's Q test. Furthermore, mendelian randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and the MR-Egger regression intercept were utilized to detect horizontal pleiotropy, where a *p*-value for the intercept below 0.05 signaled its presence. Additionally, MR-PRESSO was instrumental in identifying outliers (Bowden et al, 2018; Ong and MacGregor, 2019). The MR-PRESSO procedure involved three stages: (1) Using the MR-PRESSO global test to detect pleiotropy; (2) Re-establishing equilibrium by using MR-PRESSO's outlier-corrected method; (3) Conducting the test for distortion using MR-PRESSO to compare results before and after outlier correction. Finally, a leave-one-out approach was implemented, sequentially excluding each SNP to determine if the outcomes were influenced by any single variant.

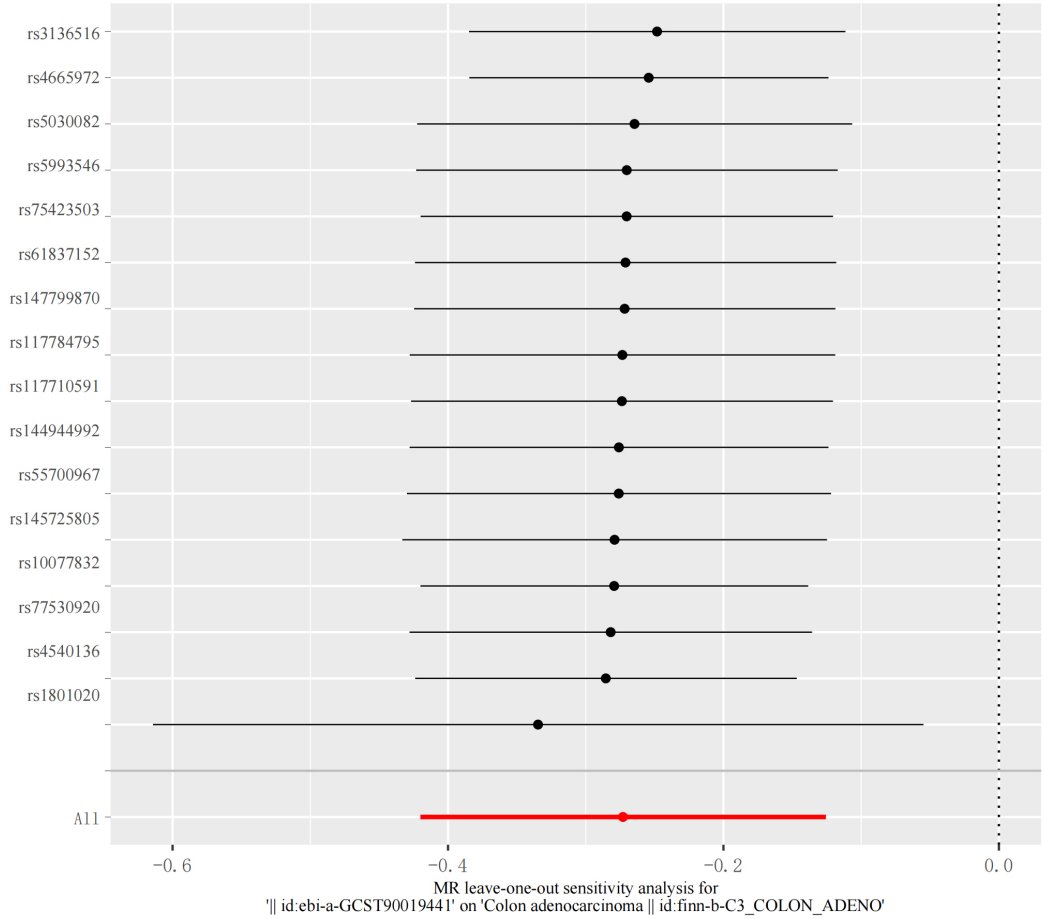


**Fig. 3. Leave-one-out analysis.**

### Statistical Analyses

Statistical analyses were conducted using R software (version 4.2.0, University of Auckland, Auckland, New Zealand), along with two-sample MR software (version 0.5.6, University of Auckland, Auckland, New Zealand) and RadialMR software (version 1.0, University of Auckland, Auckland, New Zealand). A threshold of *p*-value less than 0.05 was established as the criterion for statistical significance.

## Results

### Information of the Filtered Tool Variables

In this study, we extracted 18 genetic variants linked to thrombin measurement levels from the ebi-a-GCST90019441 dataset in the IEU database. After excluding one palindromic SNP (rs4253304) and one confounding SNP (rs9276689), a total of 16 SNPs were included in the analysis. Table 1 provides details of the instrumental variables used for thrombin quantification. All these variables exhibited an F-statistic value above 10, ranging from 20.92 to 446.21, validating the strength and reliability of the instruments used in the MR assessment. Details of the GWAS are provided in Table 2.

**Table 1. Instrument variables for thrombin measurement levels.**

| SNP | Effect allele | Other allele | Beta | eaf | se | *p*-value | Sample size |
|---|---|---|---|---|---|---|---|
| rs61837152 | T | C | –0.0653 | 0.3371 | 0.014 | $3.18 \times 10^{-6}$ | 10,708 |
| rs144944992 | T | C | 0.2882 | 0.0125 | 0.0629 | $4.68 \times 10^{-6}$ | 10,708 |
| rs147799870 | G | T | 0.2587 | 0.0168 | 0.0565 | $4.64 \times 10^{-6}$ | 10,708 |
| rs4665972 | C | T | –0.0765 | 0.5967 | 0.0134 | $1.18 \times 10^{-8}$ | 10,708 |
| rs5030082 | G | A | 0.1765 | 0.3987 | 0.0133 | $4.07 \times 10^{-40}$ | 10,708 |
| rs4540136 | T | C | –0.0791 | 0.8106 | 0.0169 | $2.98 \times 10^{-6}$ | 10,708 |
| rs10077832 | T | C | 0.269 | 0.0149 | 0.0543 | $7.26 \times 10^{-7}$ | 10,708 |
| rs55700967 | C | T | 0.1471 | 0.0678 | 0.0272 | $6.26 \times 10^{-8}$ | 10,708 |
| rs1801020 | G | A | 0.5875 | 0.7468 | 0.0144 | $1.00 \times 10^{-200}$ | 10,708 |
| rs117784795 | T | C | 0.4746 | 0.0132 | 0.0595 | $1.58 \times 10^{-15}$ | 10,708 |
| rs145725805 | A | G | 0.3608 | 0.01 | 0.0694 | $2.02 \times 10^{-7}$ | 10,708 |
| rs3136516 | A | G | –0.1166 | 0.5244 | 0.0132 | $8.75 \times 10^{-19}$ | 10,708 |
| rs117710591 | T | C | –0.2955 | 0.0167 | 0.0544 | $5.47 \times 10^{-8}$ | 10,708 |
| rs75423503 | G | C | –0.2878 | 0.0128 | 0.0621 | $3.56 \times 10^{-6}$ | 10,708 |
| rs77530920 | A | G | –0.1416 | 0.0573 | 0.0298 | $1.98 \times 10^{-6}$ | 10,708 |
| rs5993546 | A | G | –0.0921 | 0.1508 | 0.0191 | $1.40 \times 10^{-6}$ | 10,708 |

SNPs, single nucleotide polymorphisms.

**Table 2. Information about GWAS.**

| Trait | Ancestry | Consortium | Cases | Control | GWAS ID | Gender |
|---|---|---|---|---|---|---|
| Thrombin measurement levels | European | IEU | 10708 | | ebi-a-GCST90019441 | Both sex |
| Colon adenocarcinoma | European | FinnGen | 1396 | 217,396 | C3_COLON_ADENO | Both sex |

GWAS, genome-wide association studies.

We evaluated the causality between thrombin measurement levels and COAD using IVW, MR-Egger regression, Weighted Median, and Weighted Mode methods. The IVW result (Fig. 4) revealed a strong causal link between high serum thrombin measurement levels and a reduced risk of COAD (odds ratio (OR) = 0.76, 95% CI = 0.66–0.88, $p = 0.0003$). Similar risk estimates were obtained using the Weighted Median method (OR = 0.78, 95% CI = 0.68–0.90, $p = 0.0006$) and the Weighted Mode method (OR = 0.78, 95% CI = 0.68–0.88, $p = 0.0017$). The consistency across the three MR models enhances the reliability of the protective effect of high thrombin measurement levels against COAD prevalence (Fig. 2). Fig. 5 displays the MR estimate results.

To thoroughly assess possible biases and ensure the robustness of our MR study's outcomes, we conducted extensive sensitivity analyses employing diverse approaches. The absence of heterogeneity was confirmed by Cochran's Q test, with a Q statistic of 21.52 and a non-significant *p*-value ($p = 0.16$). MR-Egger analysis suggested no potential horizontal pleiotropy for the causal effect (intercept = –0.03, $p = 0.24$). Results of pleiotropy and heterogeneity tests are presented in Table 3.

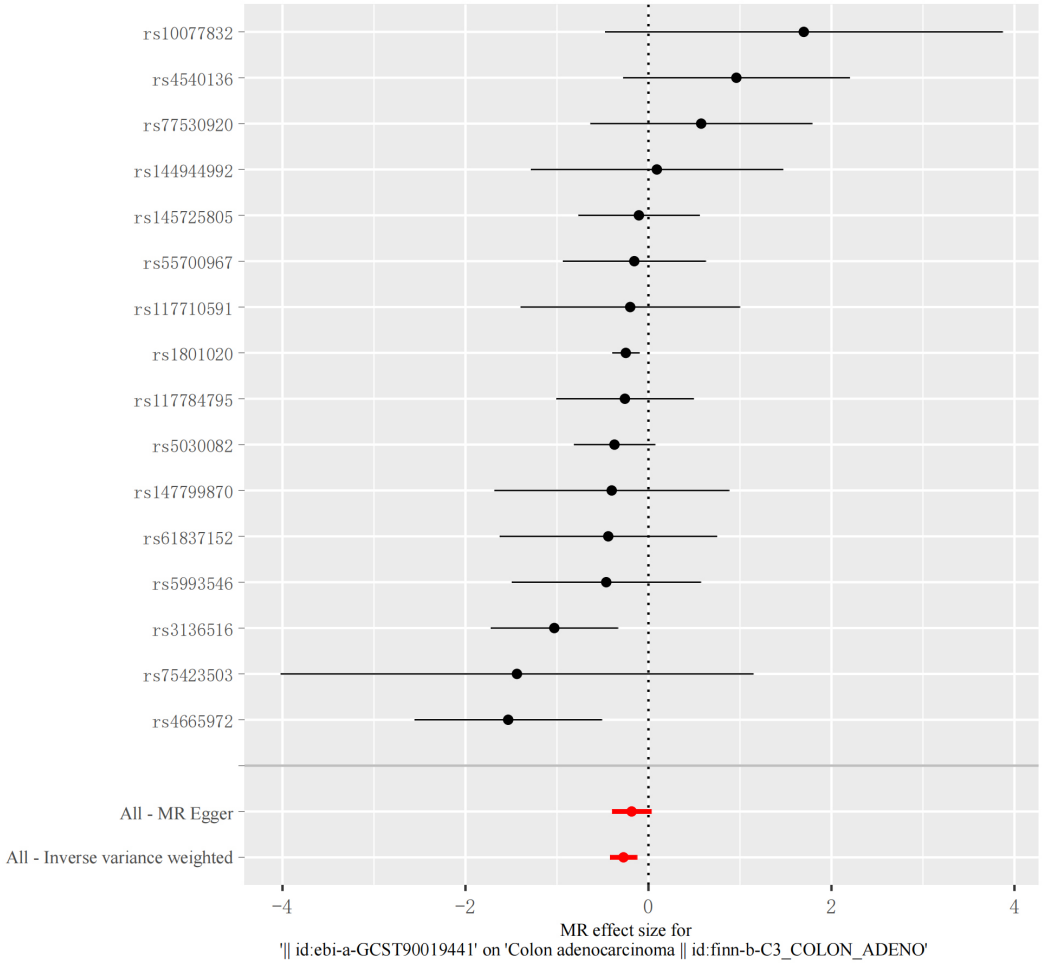


**Fig. 4. IVW and MR-Egger estimate of ebi-a-GCST90019441 on colon adenocarcinoma (COAD).**

| Exposure | No.of SNP | Method | OR(95% CI) | or | P |
|---|---|---|---|---|---|
| exposure | 16 | IVW | 0.76 (0.66 to 0.88) | 0.76 | 0.001 |
| | | MR Egger | 0.83 (0.67 to 1.03) | 0.83 | 0.114 |
| | | Weighted median | 0.78 (0.68 to 0.90) | 0.78 | 0.001 |
| | | Weighted mode | 0.78 (0.68 to 0.88) | 0.77 | 0.002 |

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**Fig. 5. Forest plots of the MR estimate of ebi-a-GCST90019441 on COAD.**

Furthermore, the MR-PRESSO examination revealed no outliers, ensuring the integrity of our data. A comprehensive leave-one-out assessment confirmed the influence of every single nucleotide polymorphism (SNP) on the collective causal inference. As depicted in Fig. 3, the exclusion of any single SNP did not result in the meta-effect of the other SNPs crossing zero, thereby demonstrating the stability and reliability of our findings. The funnel plot presented in Fig. 6 showed an absence of publication bias, further validating the reliability of the study.

**Table 3. MR for thrombin measurement levels on COAD.**

| MR methods | OR | 95% CI | *p*-value | MR-Egger intercept *p*-value | Cochran's Q test *p*-value |
|---|---|---|---|---|---|
| IVW | 0.76 | 0.66–0.88 | 0.001 | 0.24 | 0.16 |
| MR-Egger | 0.83 | 0.68–1.02 | 0.100 | | 0.19 |
| Weighted median | 0.78 | 0.68–0.90 | 0.001 | | |
| Weighted mode | 0.77 | 0.67–0.90 | 0.003 | | |

MR, mendelian randomization; COAD, colon adenocarcinoma; IVW, inverse variance weighting.

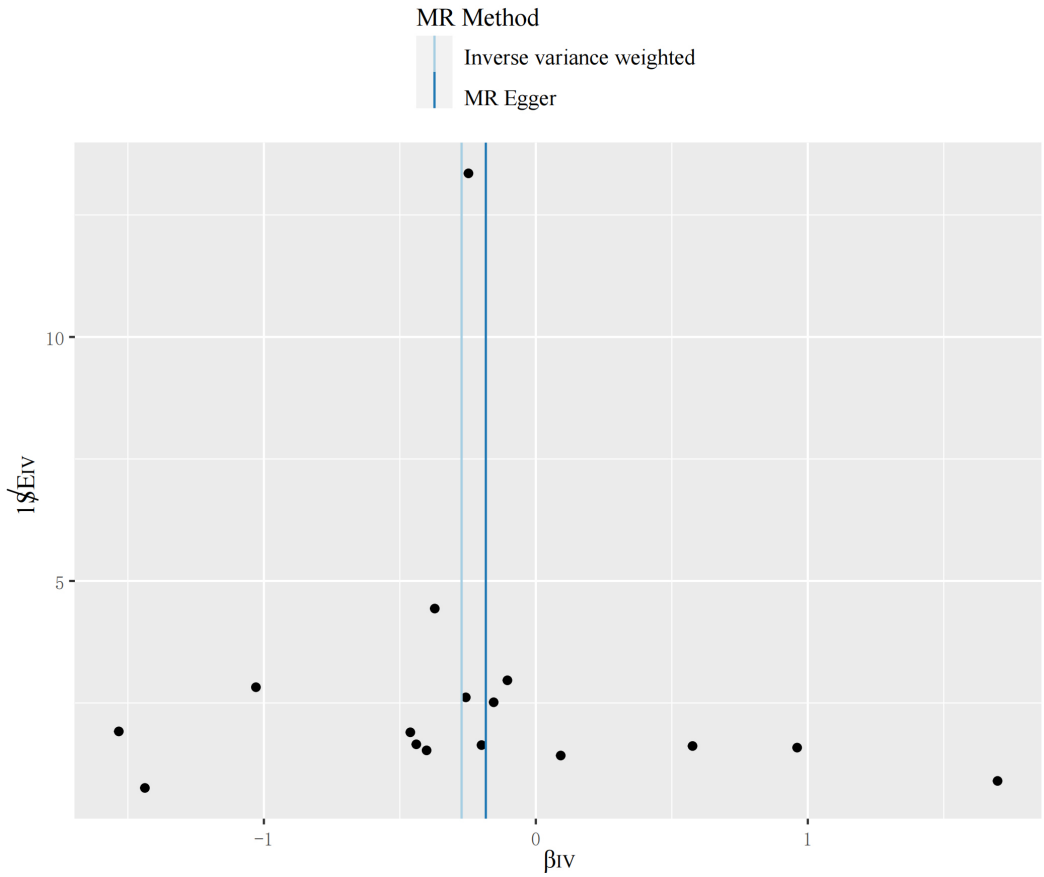


**Fig. 6. Funnel plots.**

## Discussion

Our research represents a pioneering effort in elucidating a negative causal association between thrombin measurement levels and the onset of COAD, utilizing the MR methodology. This suggests that a genetic predisposition for higher thrombin measurement levels corresponds to a reduced likelihood of developing COAD. MR, as an analytical technique, leverages genetic variation as an intermediary tool, effectively mitigating the effects of potential confounders and reverse causality. This methodology is based on three fundamental premises: The instrumental variables have a strong association with the exposure, they are not associated with confounding factors, and they are not directly linked to the outcome. Consequently, it has gained widespread application in various studies investigating the correlation

between exposures and outcomes, thereby enhancing our ability to more accurately dissect and comprehend the intricate relationships among diseases.

Previous studies have revealed that colon cancer can stem from a various factors, including familial history (Henry et al, 2023), physical inactivity (Slattery and Potter, 2002), smoking (Wong et al, 2007), red meat consumption (Sivasubramanian et al, 2023) and obesity (Giovannucci, 2002). However, COAD, a specific pathological manifestation of colon cancer, has received limited research attention regarding its correlation with thrombin measurement levels. According to previous study (Darmoul et al, 2004), thrombin functions as a potent growth factor in colon cancer cells, driving cancer development by activating the aberrantly expressed protease-activated receptor 1 (PAR1). Contrarily, a study (Virgilio et al, 2020) has identified thrombin's anti-proliferative properties, capable of inhibiting the abnormal proliferation of colon cancer cells. These findings, primarily derived from cellular experiments, present contradictory perspectives, thus necessitating further verification in human subjects to clarify the actual regulatory mechanisms.

Our study provided new insights into the protective role of high serum thrombin levels against the risk of COAD using MR methodology. We carefully selected 16 single nucleotide polymorphisms (SNPs) as instrumental variables, ensuring their robustness with F statistics ranging from 20.92 to 446.21, indicating the strength and reliability of our instruments for MR analysis. The IVW method unveiled a significant causal relationship between higher thrombin levels and a reduced risk of COAD (OR = 0.76, 95% CI = 0.66–0.88, $p$ = 0.0003). This result was consistently supported by the Weighted Median and Weighted Mode methods, demonstrating similar odds ratios (OR = 0.78, 95% CI = 0.68–0.90, $p$ = 0.0006, and OR = 0.78, 95% CI = 0.68–0.88, $p$ = 0.0017, respectively). The consistency of findings across these diverse analytical methods bolstered the validity of our conclusion.

Sensitivity analyses provided further validation of the robustness of our findings. The Cochran's Q test revealed no significant heterogeneity among the SNPs (Q value = 21.52, $p$ = 0.16), and MR-Egger regression indicated no horizontal pleiotropy (intercept = –0.03, $p$ = 0.24). Moreover, MR-PRESSO analysis detected no outliers, and leave-one-out analysis showed that no single SNP disproportionately influenced the overall causal estimate. The absence of publication bias was confirmed by funnel plot analysis.

The implications of our findings are significant. This study suggests that a genetic predisposition to higher thrombin measurement levels could serve as a protective factor against COAD. This novel insight opens potential avenues for COAD prevention strategies focusing on modulating thrombin measurement levels. Understanding the biological mechanisms through which thrombin exerts its protective effect could lead to the development of new therapeutic approaches targeting thrombin pathways.

Future research should explore the mechanistic pathways linking thrombin measurement levels and COAD risk. It would also be beneficial to replicate these findings in diverse populations to ensure generalizability. Furthermore, examining the interplay between thrombin and other coagulation factors or inflammatory

markers could provide a more comprehensive understanding of COAD pathogenesis.

The investigation boasts several prominent advantages. Firstly, the genome-wide association studies (GWAS) data for both thrombin quantifications and COAD originated from European participants, thereby mitigating the effects of population structure. Secondly, the chosen GWAS dataset, comprising millions of identified single nucleotide polymorphisms (SNPs), offered a substantial sampling population, significantly boosting statistical robustness. Ultimately, this study elucidates a reverse causal link between thrombin measurement and the incidence of COAD, paving the way for further investigation into the regulatory interplay between thrombin measurement levels and COAD. As this study was observational in nature, further mechanistic research is needed to elucidate the role of thrombin in colorectal adenocarcinoma.

This study conducted two-sample MR analyses using data from a comprehensive GWAS cohort, with results demonstrating robustness and independence from factors such as horizontal pleiotropy. While our research offers illumination, it is not devoid of limitations. Primarily, the study participants were solely of European descent, warranting prudent interpretation and generalization of our findings to populations beyond Europe. We acknowledged that the current study predominantly relied on data from individuals of European descent, while data from other ethnicities were still evolving. Therefore, we emphasized this limitation in our discussion and indicated our intent to further investigate diverse populations once comprehensive data became available, ensuring the broader applicability and generalizability of our findings. Additionally, reliance on summary-level statistical analysis precluded a nuanced, stratified examination.

## Conclusion

In conclusion, our study was the first to utilize MR methodology to uncover a negative causal association between thrombin measurement levels and COAD onset, suggesting that higher thrombin levels were associated with a decreased risk of developing COAD. This discovery not only advanced our understanding of COAD etiology but also laid the groundwork for potential preventive and therapeutic strategies targeting thrombin modulation.

### Key Points

- Higher thrombin measurement levels were causally linked to a decreased risk of COAD onset.
- Thrombin modulation was found to have significant potential in COAD prevention and therapeutic interventions.
- The study's findings were robust, supported by multiple MR methods and sensitivity analyses.

## Availability of Data and Materials

All data, models, and code generated or used during the study appear in the submitted article.

## Author Contributions

JJZ and YLL participated in the study design, data collection, analysis of data and preparation of the manuscript. JJZ drafted the manuscript. JJZ and YLL revised this paper critically for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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