Observational Study

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The causal relationship of colorectal cancer on schizophrenia

A Mendelian randomization study

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Abstract

Comorbidities associated with psychiatric disorders often occur in patients with cancer. A causal effect of schizophrenia on cancer was observed using Mendelian randomization (MR) analysis. However, the causal effect of colorectal cancer on schizophrenia has not been studied using MR analysis. Therefore, we performed MR analysis to investigate the causal effects of colorectal cancer on schizophrenia. We performed "two-sample summary-data Mendelian randomization" using publicly available genome-wide association studies data to investigate the causal relationship between colorectal cancer (as exposure) and schizophrenia (as outcome). The inverse variance weighted method was used to calculate causal estimates. In 2 TSMR analyses, we reported that the odds ratios for schizophrenia per log odds increase in colorectal cancer risk were 6.48 (95% confidential interval [CI] of OR 1.75–24.03; $P = .005$) and 9.62×10^6 (95% CI of OR 1.13–8.22×10^{13}; $P = .048$). Pleiotropic tests and sensitivity analysis demonstrated minimal horizontal pleiotropy and robustness of the causal relationship. We provide evidence for a causal relationship between the incidence of colorectal cancer and the development of schizophrenia through TSMR analysis.

Abbreviations: CI = confidential interval, ER = estrogen receptor, GWAS = genome-wide association study, IEU = integrative epidemiology unit, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, OR = odds ratio, SNP = single nucleotide polymorphism, TSMR = two-sample summary-data Mendelian randomization.

Keywords: colorectal cancer, Mendelian randomization, schizophrenia

1. Introduction

Schizophrenia is a neurological disorder with a multifaceted pathogenesis and pathophysiology.[1] This condition is identified by its chronic nature, recurrent episodes, and gradual deterioration leading to neurodegeneration over time.[1] Disease onset and clinical manifestation are significantly influenced by genetic predisposition, individual and environmental factors, and specific immune responses.[1]

Recent studies have suggested a possible association between cancer and schizophrenia, although the nature of this relationship is not yet fully understood.[1,2] Research on schizophrenia through genome-wide association studies (GWASs) has uncovered genetic similarities and some immune-related features that overlap with breast carcinoma.[1] Possible factors contributing to this association are shared genetic risk factors and similar lifestyles between the 2 conditions.[1,3] In addition, certain medications used to treat schizophrenia, such as antipsychotics, have been associated with an increased risk of breast cancer and colorectal cancer.[3–5] However, the evidence for this association is limited and conflicting,[3] and further research is needed to better understand the link between these 2 conditions.

Recently, Mendelian randomization (MR) studies have investigated the causal relationship between cancer and psychiatric disorders.[6–8] A statistically significant causal effect of depression on cancer has been reported.[8] Also, statistically significant causal effects of schizophrenia on cancers were indicated.[6,7] Other causal effects of schizophrenia on colon-related diseases (i.e., Crohn disease, inflammatory bowel disease, and ulcerative colitis) have also been established.[9]

Recently, bidirectional associations between schizophrenia and breast cancer were discovered, indicating shared genetic and biological contributions to the 2 diseases.[10] The study revealed not only that patients with schizophrenia were at high

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

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risk of breast cancer, but also that patients with breast cancer elevated risk of schizophrenia.[10] Like breast cancer, colorectal cancer can progress through estrogen and estrogen receptor (ER), which are also involved in colorectal cancer cell proliferation and tumor progression.[11] Considering the involvement of ER in colorectal cancer as well as in breast cancer,[12,13] colorectal cancer may be associated with schizophrenia. However, to date, the causal effect of colorectal cancer on schizophrenia has not been reported.

In this study, we aimed to explore the causal effect of colorectal cancer on schizophrenia through "two-sample summary-data MR analysis" (TSMR)[14,15] and observed genetic instrumental variables (IVs) that clarify the causal relationship between colorectal cancer and schizophrenia. Understanding this association may help clinicians better manage the health of patients with schizophrenia and identify potential risks for colorectal cancer.

2. Materials and methods

2.1. Data sources, exposure, and outcome

In this study, we set colorectal cancer as exposure and schizophrenia as outcome. A colorectal cancer GWAS was used as an exposure cohort and 2 schizophrenia GWASs were used as outcome cohorts. The colorectal cancer GWAS summary data from the UK BioBank[16] were used as exposure GWAS. Summary statistics of the colorectal cancer GWAS (a total of 377,673 European subjects; 5657 cases and 372,016 controls) were retrieved for 11,738,639 single nucleotide polymorphisms (SNPs) from the MRC integrative epidemiology unit (IEU) Open GWAS (IEU GWAS study accession ieu-b-4965).[17] The 2 schizophrenia GWAS[18,19] summary data were obtained through the IEU Open GWAS (IEU GWAS study accessions ebi-a-GCST90016624 and finn-b-F5_SCHZPHR).[17] The schizophrenia GWAS (accession ebi-a-GCST90016624) of the EMBL-EBI GWAS Catalog[20] included 45,494 subjects (40,675 cases and 4819 controls) and 4494,157 SNPs. The other schizophrenia GWAS (accession finn-b-F5_SCHZPHR) of the FinnGen project[18] included 214,236 subjects (5562 cases and 208,674 controls) and 16,380,456 SNPs.

Since 2 outcome GWAS cohorts were available for 1 exposure GWAS cohort, 2 TSMR analyses were performed: the first TSMR analysis for accession ieu-b-4965 as exposure (i.e., colorectal cancer) and accession ebi-a-GCST90016624 as outcome (i.e., schizophrenia); and the second TSMR analysis for accession ieu-b-4965 as exposure (i.e., colorectal cancer) and accession finn-b-F5_SCHZPHR as outcome (i.e., schizophrenia).

2.2. Selection of SNPs as instrumental variables (IVs)

We selected SNPs as IVs in the colorectal cancer GWAS. We performed linkage disequilibrium clumping in R (version 4.1.0) by setting a window size of 10,000 kb and $R^2 < 0.001$ through the "TwoSampleMR" package (version 0.5.6).[17]

For the first TSMR analysis (i.e., accession ieu-b-4965 as exposure and accession ebi-a-GCST90016624 as outcome), we selected linkage disequilibrium-independent SNPs that were significantly associated with colorectal cancer ($P < 5 \times 10^{-8}$). Subsequently, the SNPs with effect allele frequency (EAF) < 0.01 were excluded.[21] After harmonization in the 2 GWASs, 6 SNPs (rs72746180, rs12135286, rs16892766, rs6066825, rs6983267, and rs33087967) were selected as IVs (Supplementary Table S1, http://links.lww.com/MD/K155).

In the second TSMR analysis (i.e., accession ieu-b-4965 as exposure and accession finn-b-F5_SCHZPHR as outcome), 8 SNPs (rs114717436, rs3087967, rs6983267, rs16892766, rs6066825, rs72746180, rs58658771, and rs12135286) were selected as IVs through the same process as the first MR analysis (Supplementary Table S2, http://links.lww.com/MD/K156).

2.3. Measurement of instrument strength

We calculated *F*-statistic to evaluate the instrument strength of the selected SNPs as IVs.[22] First, for each SNP, we calculated r^2, proportion of phenotypic variation explained by the SNP.[23] The formula is as follows: $r^2 = 2 \times \beta^2 \times EAF \times (1 - EAF) \div (2 \times \beta^2 \times EAF \times [1 - EAF] + SE^2 \times 2 \times N \times EAF \times [1 - EAF])$,[23,24] where *EAF* is effect allele frequency for each SNP, *SE* the standard error of β, and *N* the sample size. Then, we calculated *F*-statistic of each SNP as follows: $F = (N - 2) \times r^2 \div (1 - r^2)$. *F*-statistic >10 indicates that the SNPs are sufficient to reduce the bias in MR analysis, while *F*-statistic <10 regarded the SNPs as "weak instruments."[22]

2.4. TSMR

We performed TSMR[14,15] in R (version 4.1.0) using the "TwoSampleMR" package (version 0.5.6)[17] to estimate the causal effect of colorectal cancer on schizophrenia. The TSMR scheme between colorectal cancer and schizophrenia is indicated in Figure 1. We set colorectal cancer as exposure, and schizophrenia as the outcome. SNPs significantly associated with colorectal cancer were used as IVs. TSMR utilizes the inverse-variance weighted (IVW) method because IVW returns unbiased estimates.[25]

2.5. Sensitivity analysis and horizontal pleiotropy test

Leave-one-out sensitivity analysis was performed on SNPs to evaluate whether the causal effect of each SNP on the outcome was biased. Finally, the horizontal pleiotropy test was performed to determine whether IVs associated with colorectal cancer may affect schizophrenia through pathways other than colorectal cancer.

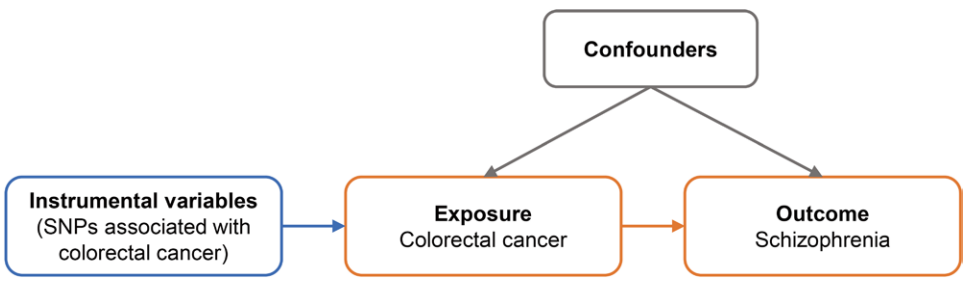

Figure 1. Study design of two-sample summary-data Mendelian randomization (TSMR) between colorectal cancer and schizophrenia. Single nucleotide polymorphism (SNPs), as genetic instrumental variables (IVs), control confounding effects and establish a causal relationship between exposure and outcome.

2.6. Statistical power

The power calculation web tool for MR[26,27] (https://sb452.shinyapps.io/power/) was used to obtain the minimum required sample size of the outcome cohort for each MR analysis. In the tool, power, and significance level α were set to 80% and 0.05, respectively.

2.7. Additional validation

For additional validation, through the IEU Open GWAS,[17] the summary statistics of both colorectal cancer (study accession: finn-b-CD2_BENIGN_COLON_EXALLC; a total of 183,354 subjects; 7435 cases and 175,919 controls) and schizophrenia (study accession: finn-b-F5_SCHIZO; a total of 218,792 subjects; 10,118 cases and 208,674 control) were obtained from the same FinnGen project.[18] Four SNPs (rs10505477, rs12143541, rs2427295, and rs78378222) were selected as IVs (Supplementary Table S3, http://links.lww.com/MD/K157). The subsequent analysis followed the same procedures above.

3. Results

3.1. IV selection and instrument strength of the selected SNPs as IVs

In this study, we set colorectal cancer as exposure and schizophrenia as outcome: the first TSMR analysis for accession ieu-b-4965 (a total of 377,673 subjects; 5657 cases and 372,016 controls) as exposure (i.e., colorectal cancer) and accession ebi-a-GCST90016624 (a total of 45,494 subjects; 40,675 cases and 4819 controls) as outcome (i.e., schizophrenia); and the second TSMR analysis for accession ieu-b-4965 (a total of 377,673 subjects; 5657 cases and 372,016 controls) as exposure (i.e., colorectal cancer) and accession finn-b-F5_SCHZPHR (a total of 214,236 subjects; 5562 cases and 208,674 controls) as outcome (i.e., schizophrenia).

To evaluate the instrument strength of the selected SNPs as IVs, *F*-statistics of the 6 selected SNPs (rs72746180, rs12135286, rs16892766, rs6066825, rs6983267, and rs33087967) were shown in Supplementary Table S1, http://links.lww.com/MD/K155. In the second MR analysis, *F*-statistics of the 8 selected SNPs (rs114717436, rs3087967, rs6983267, rs16892766, rs6066825, rs72746180, rs58658771, and rs12135286) were shown in Supplementary Table S2, http://links.lww.com/MD/K156. Since *F*-statistic for each SNP is >10, the 2 TSMR analyses are unlikely to yield biased results.

3.2. TSMR

We performed TSMR[14,15] to demonstrate that colorectal cancer may be a risk factor for schizophrenia. The 2 TSMR analyses were performed because we had 1 colorectal cancer GWAS cohort (as exposure) and 2 schizophrenia GWAS cohorts (as outcomes). The scatter plot in Figure 2A and B illustrates the estimated causal relationship between colorectal cancer and schizophrenia using IVW method.[28] And the results of each MR analysis investigating the causal relationship between colorectal cancer and schizophrenia are shown (Table 1).

In the first MR analysis (i.e., accession ieu-b-4965 as exposure and accession ebi-a-GCST90016624 as outcome), we identified 6 SNPs (i.e., rs72746180, rs12135286, rs16892766, rs6066825, rs6983267, and rs3087967) as IVs. The causal effect size of each SNP is shown (Fig. 2C). The analysis revealed that IVW MR estimates suggest a significant increase in the risk of schizophrenia in patients with colorectal cancer (odds ratio [OR] = 6.48; 95% confidential interval [CI] of OR 1.75–24.03; $P = .005$).

In the second MR analysis (i.e., accession ieu-b-4965 as exposure and accession finn-b-F5_SCHZPHR as outcome), we identified 8 SNPs (i.e., rs72746180, rs12135286, rs16892766, rs6066825, rs6983267, rs3087967, rs114717436, and rs58658771) as IVs. The causal effect size of each SNP is shown (Fig. 2D). The analysis revealed that IVW MR estimates suggest a significant increase in the risk of schizophrenia in patients with colorectal cancer (OR = 9.62×10^6; 95% CI of OR 1.13–8.22×10^{13}; $P = .048$).

3.3. Sensitivity analysis

Leave-one-out sensitivity analysis was performed to evaluate whether the estimated causal effects in the 2 MR analyses were biased. We performed leave-one-out sensitivity analysis in the first (Fig. 3A) and second (Fig. 3B) MR analyses. We did not find any single SNP with strong effects that could dominate the results.

3.4. Pleiotropy tests

We additionally performed horizontal pleiotropy tests to determine if the SNPs as IVs have a horizontal pleiotropic effect. In both MR analyses, no statistical significances for horizontal pleiotropy ($P = .61$ and $P = .45$ for the first and second ones, respectively) were observed. This suggests that the SNPs as IVs influence schizophrenia only through colorectal cancer.

3.5. Statistical power

Through the power analysis,[27] the minimum sample sizes for the first and second MR analyses under power 80 % and significance level (α) 0.05 were 29,400 and 1200, respectively. Since the actual sample sizes of the outcome cohorts in the 2 MR analyses met the minimum required sample size, our 2 MR analyses had sufficient statistical power.

3.6. Additional validation

We found that, in IEU Open GWAS, the exposure and outcome were measured in the same cohort (i.e., the FinnGen project). When the exposure and outcome are both measured in the same cohort or dataset, 1-sample MR is usually used.[29] However, since only summary statistics of the exposure and outcome are available in IEU Open GWAS, TSMR using IVW is feasible for MR. Reportedly, TSMR using IVW, which we used in our study, can be performed for 1-sample MR within a large cohort.[29] In the line, we obtained the summary statistics of the exposure (IEU GWAS study accession: finn-b-CD2_BENIGN_COLON_EXALLC) and outcome (IEU GWAS study accession: finn-b-F5_SCHIZO) from the same FinnGen project and performed TSMR using IVW.

Regarding unbiased IV selection, the *F*-statistics of the 4 selected SNPs (rs10505477, rs12143541, rs2427295, and rs78378222) were >10 (Supplementary Table S3, http://links.lww.com/MD/K157), indicating non-significance of bias. The scatter plot (Supplementary Fig. S1A, http://links.lww.com/MD/K154) illustrates the estimated causal relationship between colorectal cancer and schizophrenia using IVW method (Supplementary Table S4, http://links.lww.com/MD/K158). The IVW MR estimate suggests a statistically significant increase in the risk of schizophrenia in patients with colorectal cancer (OR = 1.26; 95% CI of OR 1.00–1.57; $P = .045$). The causal effect size of each SNP is shown in Supplementary Fig. S1B, http://links.lww.com/MD/K154. We performed the leave-one-out sensitivity analysis, indicating robustness of our conclusion (Supplementary Fig. S1C, http://links.lww.com/MD/K154). No

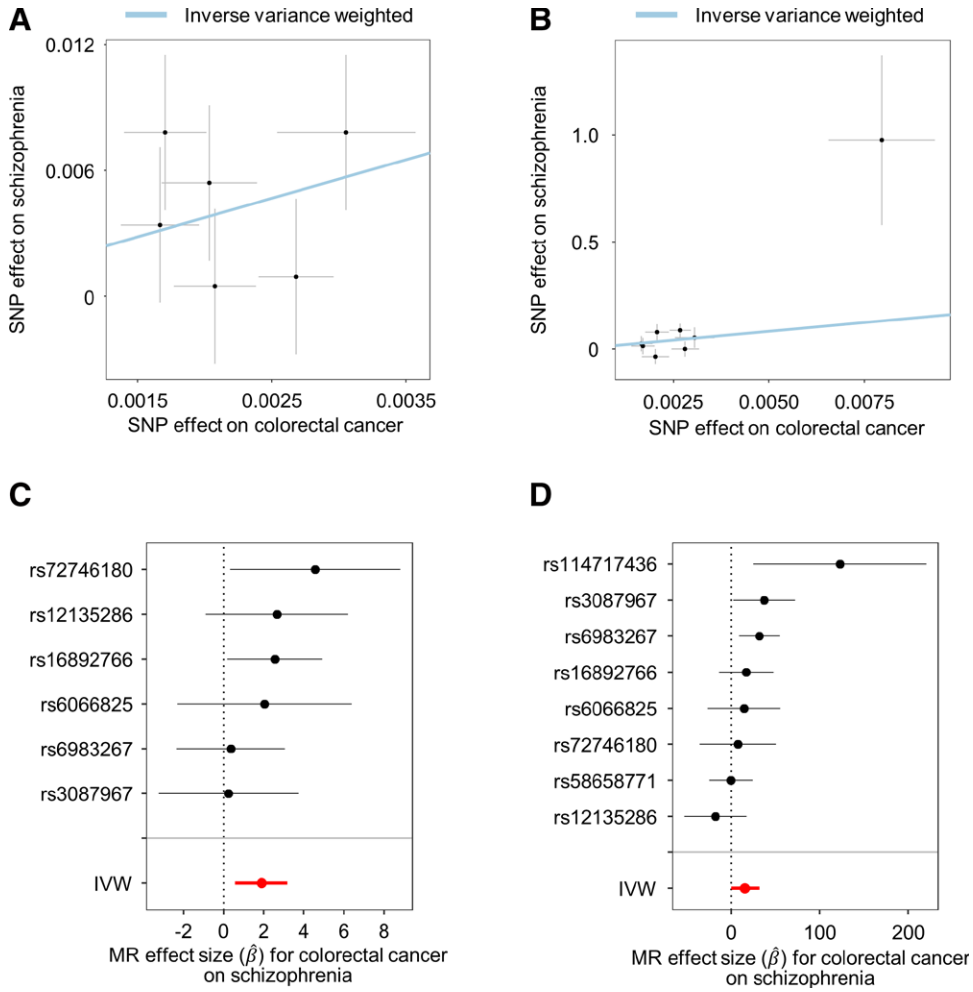

Figure 2. IVW method estimates a positive causal relationship of colorectal cancer on schizophrenia in 2 TSMR analyses. The associations of genetic markers for colorectal cancer (the effect size shown as X axis) with schizophrenia (Y axis) were plotted based on the GWAS summary statistics in the first (A) and second (B) TSMR analyses. The slope of the light blue line is the MR estimate of the causal effect obtained using the IVW method. Each black point represents the causal effect size of each of the SNPs as genetic IVs using the Wald ratio test in the first (C) and second (D) MR analyses. The red point is the effect size for the causality of the combined SNPs using IVW method. Error bars indicate 95% confidence intervals (CIs). GWAS = genome-wide association study, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, SNP = single nucleotide polymorphism, TSMR = two-sample summary-data Mendelian randomization.

Table 1

Mendelian randomization estimates from inverse variance weighted method of assessing the causal effect of colorectal cancer (as exposure) on schizophrenia (as outcome).

Exposure cohort	Outcome cohort	# of SNPs	β	SE	*P*	OR (95% CI)
ieu-b-4965	ebi-a-GCST90016624	6	1.87	0.67	.005	6.48 (1.75–24.03)
ieu-b-4965	finn-b-F5_SCHZPHR	8	16.08	8.14	.048	9.62×10^{6} ($1.13–8.22 \times 10^{13}$)

CI = confidence interval, OR = odds ratio, SE = standard error of β, SNPs = single-nucleotide polymorphisms.

statistical significance for horizontal pleiotropy ($P = .97$) were observed.

4. Discussion

In this study, we utilized GWAS summary data for colorectal cancer and schizophrenia to investigate the causal relationship between the 2 diseases. Through the 2 MR analyses, we showed significant causal relationships between the risk of colorectal cancer and schizophrenia.

Regarding the first MR analysis, we inspected the genes adjacent to the 6 SNPs: *LINC00604* for rs72746180, *LINC01705* for rs16892766, eukaryotic translation initiation factor 3 subunit H (*EIF3H*) for rs16892766; phosphatidylinositol-3,4,5-trisphosphate dependent rac exchange factor 1 (*PREX1*) for rs6066825, cancer susceptibility 8 (*CASC8*) for rs6983267, and POU class 2 homeobox associating factor 2 (*POU2AF2*) for rs3087967.[30,31] Interestingly, the mRNA and protein expression of *PREX1* was highly expressed in the brain,[32] and *PREX1* was overexpressed in colorectal cancer.[33] A recent study found that *PREX1* knockdown in the CA1 region of the hippocampus of mice induced autism-like behavior.[34] Moreover, overexpression of *PREX1* has been observed in cancer (e.g., ER-positive breast cancer).[35] In

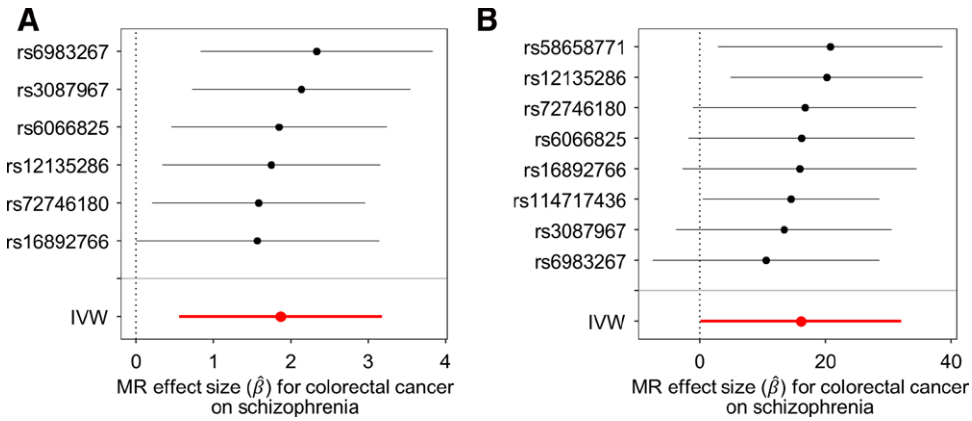

Figure 3. The estimated effect size of each single nucleotide polymorphism (SNP) is not biased. The results of the leave-one-out sensitivity analysis are shown on the forest plot. Each black point represents the estimated causal effect size using all SNPs except for the SNP listed on the y-axis. The red point represents inverse variance weighted (IVW) estimates using all SNPs. Error bars indicate 95% CIs in the first (A) and second (B) two-sample summary-data Mendelian randomization (TSMR) analysis.

addition, psychosis-related behaviors were observed in mice overexpressing *PREX1* in the medial prefrontal cortex.[36] The SNP (rs6066825) in *PREX1* may regulate gene expression in specific regions of the brain and may be functionally related to psychiatric disorders.[37] In the second MR analysis, we identified the 8 SNPs as IVs. Interestingly, when we compared the IVs used in the 2 MR analyses, the 6 SNPs were shared. Presumably, the shared IVs in the 2 MR analyses may be associated with an increased risk of schizophrenia among patients with colorectal cancer. In particular, rs6066825 near *PREX1* may be a new candidate for an increased risk of schizophrenia.[37]

This study has limitations. First, our MR analyses were applied to specific populations, the Europeans. For the study results to be applicable to other populations, GWAS data on schizophrenia and colorectal cancer in various populations are still required. Second, the underlying biological mechanisms of increased schizophrenia risk in patients with colorectal cancer remain unclear. We inspected the functional roles of the SNP (i.e., rs6066825 near *PREX1*) among IVs to provide biological causality for comorbidity. Further studies are warranted to clarify whether colorectal cancer contributes to the development of schizophrenia. Third, there are 2 main types of MR: 1-sample MR and 2-sample MR.[29,38] In 1-sample MR, the exposure and outcome are both measured in the same cohort or dataset.[29,38] In 2-sample MR, the exposure and outcome are measured in 2 different cohorts or datasets.[29,38] In this study, we used 2-sample MR, as we had data from 2 different cohorts. We believe that the summary statistics of the SNP-exposure and SNP-outcome were derived from separate non-overlapping samples.[29,39] Last, due to unknown confounding factors, the credibility of our results may be reduced and the results should be carefully interpreted.

5. Conclusion

In conclusion, our MR study supports the comorbidity of colorectal cancer and schizophrenia.

Author contributions

Conceptualization: Seungyoon Nam.
Data curation: Sungyeon Kim.
Formal analysis: Sungyeon Kim.
Investigation: Sungyeon Kim.
Methodology: Sungyeon Kim.
Project administration: Seungyoon Nam.
Resources: Seungyoon Nam.
Validation: Sungyeon Kim, Seungyoon Nam.
Visualization: Sungyeon Kim.
Writing – original draft: Sungyeon Kim.
Writing – review & editing: Seungyoon Nam.

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