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RESEARCH ARTICLE

Adiponectin and the risk of gastrointestinal cancers in East Asians: Mendelian randomization analysis

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Abstract

Background: Adiponectin is an important adipocytokine and has been associated with the risks of gastrointestinal cancers (GICs). Mendelian randomization (MR) analysis is needed to assess the causal relationships between adiponectin and GICs.

Methods: We retrieved the summary data of genome-wide association studies for adiponectin and six types of GICs in East Asians. A series of quality control steps were performed to select the eligible genetic instrumental tools. Horizontal pleiotropy and between-SNP heterogeneity were tested to choose the primary MR method. We also conducted sensitivity analyses to test the robustness of the main findings.

Results: We detected neither heterogeneity nor horizontal pleiotropy for the eligible SNPs in all of the MR analyses. Inverse variance weighted (IVW) was therefore used as the primary method, and suggested that per 10% increase in log-transformed adiponectin level was significantly associated with a decreased risk of gastric cancer (odds ratio [OR] = 0.88, 95% CI 0.81, 0.96), whereas with an increased risk of hepatocellular carcinoma (OR = 1.26, 95% CI 1.09, 1.44) and of biliary tract cancer (OR = 1.54, 95% CI 1.12, 2.12). However, only the association between adiponectin and HCC risk was statistically significant after correction for multiple testing. No statistically significant association was detected between adiponectin and esophageal (OR = 1.05, 95% CI 0.89, 1.23), pancreatic (OR = 1.04, 95% CI 0.78, 1.37), and colorectal cancers (OR = 1.00, 95% CI 0.93, 1.07). Sensitivity analyses did not find contradictory results.

Conclusion: High level of adiponectin may have a causal effect on and can serve as a biomarker for the carcinogenesis of gastric cancer, hepatocellular carcinoma, and biliary tract cancer.

KEYWORDS
adiponectin, East Asian, gastrointestinal cancer, Mendelian randomization

1 | INTRODUCTION

Gastrointestinal cancers (GICs), mainly including esophageal, gastric, pancreatic, liver, gallbladder, and colorectal cancers, are commonly diagnosed in East Asians and impose an increasing disease burden.[1,2] The risk factors for GICs have been widely investigated and are shared to a great degree.[3] Although enormous efforts have been made to combat GICs, there was still a long way to reduce the disease burden of GICs. One of the key points is early screening (and/or diagnosis) based on circulating biomarkers.

Adiponectin is one of the most important adipocytokines secreted by adipocytes and is deemed to play an important role in the carcinogenesis of GICs.[4] Previous epidemiological studies reported that the level of plasma adiponectin was associated with the risk of several types of GICs. For example, population-based studies reported that a low plasma adiponectin level was associated with an increased risk for gastric cancer (GAC), pancreatic cancer (PAC), and esophageal cancer (ESC).[5–7] On the contrary, in a nested case–control study, Aleksandrova et al. found that elevated level of adiponectin was associated with an increased risk of hepatocellular carcinoma (HCC).[8] The correlation between blood adiponectin and colorectal cancer (CRC) was inconsistent between studies.[9]

The findings from observational studies might be biased by several factors, such as incomplete adjustment for confounders, transient fluctuation of blood biomarker, and small sample size, and might subject to reverse causality. Mendelian randomization (MR) analysis that implemented genetic information is less susceptible to the aforementioned shortcomings because alleles are randomly assigned during meiosis and germline genetic variants are unaffected by environmental confounders.[10,11] Along with the accumulation of genetic data from genome-wide association study (GWAS), MR analysis has been widely used to detect causal relationships between exposures and outcomes.[12–15] For instance, Cornish et al. reported a nonsignificant correlation between circulating adiponectin and CRC risk.[16] The similar results were also reported by Nimptsch et al.[17] Dimou et al. found an inverse association between adiponectin and risk of CRC, while no association was found for adiponectin and risk of PAC.[18] The aforementioned studies were conducted among Europeans. However, the relationships between circulating adiponectin and GICs in East Asians have not been evaluated by MR. In the present study, based on genetic information from East Asians and leveraging MR methods, we aimed to assess the causal relationships between adiponectin and six types of GICs, that are ESC, GAC, PAC, HCC, biliary tract cancer (BTC), and CRC.

2 | METHODS

2.1 | GWAS of adiponectin

We retrieved the GWAS summary statistics of adiponectin from Asian Genetic Epidemiology Network (AGEN), which conducted a meta-analysis of GWAS for adiponectin in 7827 individuals of East Asian ancestry.[19] The details of the GWAS for adiponectin were shown in Wu et al.[19] Briefly, the GWAS consisted of 7827 Chinese, Korean, and Filipino individuals from SP2, the Korean Cancer Prevention Study II (KCPS-II), CLHNS and the Nutrition and Health of Aging Population in China (NHAPC). Within each study, adiponectin was natural logarithm transformed to approximate normal distribution. Multivariable linear regression models assuming an additive mode of inheritance were applied to test for association with genotyped or imputed SNPs by accounting for age, sex, and body mass index (BMI). In the meta-analysis of GWAS, approximately 2.5 million SNPs were used by an inverse variance weighted method implemented in METAL.[19] The proportion of variation in adiponectin that explained by SNPs was 2.65%.

2.2 | GWAS of gastrointestinal cancers

To ensure the comparability in participants' ancestry, we retrieved the GWAS summary data of the six types GICs from BioBank Japan (BBJ)[20] via IEU open GWAS project (https://gwas.mrcieu.ac.uk/). BBJ is a prospective biobank that collaboratively collected DNA and serum samples from 12 medical institutions in Japan and recruited ~200,000 participants, mainly of Japanese ancestry.[20] The BBJ participants were genotyped with the Illumina HumanOmniExpressExome BeadChip or a combination of the Illumina HumanOmniExpress and HumanExome BeadChip. Quality control of participants and genotypes was performed as described elsewhere.[21] The numbers of case and controls and SNPs used in the GWAS for GICs are shown in Table S1. A generalized linear mixed model implemented in SAIGE (v.0.37) was applied to perform the GWAS, in which age, age^2, sex, age×sex, age^2×sex, and the top 20 principal components were adjusted. In IEU open GWAS platform, the GWAS id corresponding to ESC, GAC, PAC, HCC, BTC, and CRC was "bbj-a-117", "bbj-a-119", "bbj-a-140", "bbj-a-158", "bbj-a-92", and "bbj-a-107", respectively.

2.3 | Genetic instrumental variables and GWAS summary statistics

We conducted a series of quality control steps to select eligible instrumental SNPs as performed elsewhere.[13] First,

we extracted the SNPs that reached the *p*-value threshold ($p < 5 \times 10^{-8}$) in the GWAS of adiponectin. Second, we assessed the linkage disequilibrium (LD) between SNPs based on the East Asians from the 1000 genomes project and then performed a clumping process ($R^2 < 0.1$, window size = 10,000 kb). Among those pairs of SNPs that had a LD estimate above the specified threshold (0.1), only the SNP with the lower *p*-value would be retained. Third, we removed SNPs with a minor allele frequency <5%.

We then extracted the GWAS summary statistics including beta coefficient and standard error of the eligible SNPs from GWAS of adiponectin and of the GICs. For instrumental SNPs that absent in the GWAS of GICs, we retrieved the data of a SNP proxy that had LD estimate $R^2 > 0.9$ with the requested SNP. The effects of ambiguous SNPs with inconsistent alleles and palindromic SNPs with ambiguous strand were either corrected or directly excluded in the subsequent two-sample MR analysis.

2.4 | Mendelian randomization estimates

The schematic representation of MR analysis is shown in Figure 1A and the methodological details have been shown in previous studies.[11,22] As displayed in Figure 1B, we constructed a flowchart to conduct MR step by step. First, we harmonized the GWAS summary data of adiponectin and of GICs using the selected SNP as matching index. Second, we used MR-Egger regression to test the horizontal pleiotropy. Third, we used Cochran's *Q* test in inverse variance weighted (IVW) method and MR-Egger regression to detect the between-SNP heterogeneity. We selected the primary MR method as follows:

1. if neither horizontal pleiotropy nor heterogeneity was detected, use fixed-effect IVW.
2. if no horizontal pleiotropy but heterogeneity, use IVW with multiplicative random effect or MR-PRESSO method.[23]
3. if horizontal pleiotropy was detected, use MR-Egger regression.[24]

We also checked the consistency of the directions in all four MR methods (i.e., IVW, MR-Egger regression, weighted median, and weighted mode methods). Finally, we conducted a leave-one-out analysis to detect the influential SNP. All estimates of MR analyses were multiplied by 1.1 and then converted to odds ratio (OR) to quantify the risk of GICs per 10% increase in log-transformed level of adiponectin. *F*-statistics was used to assess the strength of relationship between instrumental variables and phenotype, and calculated using the following Equation[25]:

$$F = \frac{R^2/k}{(1 - R^2)/(n - k - 1)}, \quad (1)$$
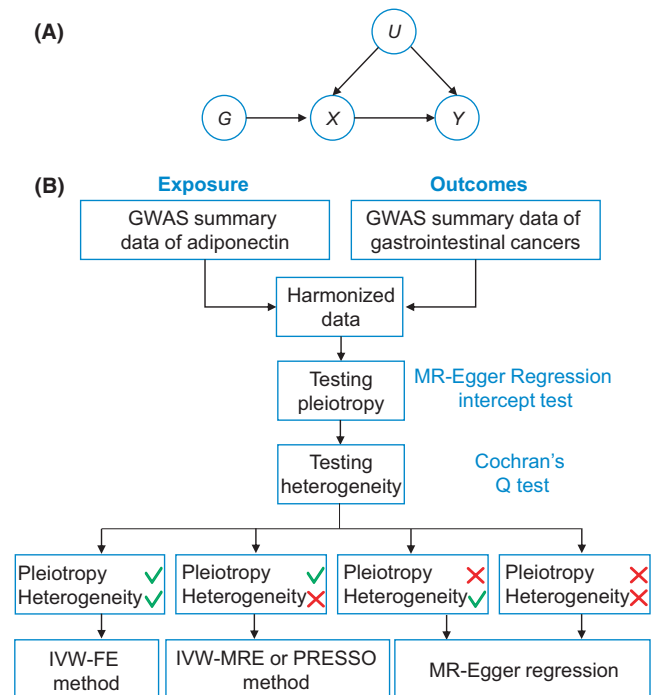

FIGURE 1 Mendelian randomization (MR) analysis used in this study. (A) The schematic representation of MR analysis. G, X, Y, and U Represents genetic instrumental tools, exposure of interest, outcome(s) of interest, and unobserved confounders, respectively. (B) The flowchart of MR analysis. The green √ means passing the test and the red × means not passing the test. FE, fixed effect; MRE, multiplicative random effects

where R^2 is the proportion of adiponectin variance, *k* is the number of instruments used in the model, and *n* is the sample size. We used the I^2-GX statistic that calculated from MR-Egger regression model to estimate the potential relative (dilution) bias due to measurement error.[26] All statistical analyses were implemented using TwoSampleMR and MRPRESSO packages in R program (v 4.1.1). We calculated the statistical power for MR analyses using *mRnd* website (https://shiny.cnsgenomics.com/mRnd/).[27] $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Validity of the instrumental variables

After quality control process, we included eight eligible SNPs in this analysis (Table S2). The mean F-statistics for the eight SNPs was 92.9, which satisfied the threshold of $F > 10$, typically recommended for MR analyses. The I^2-GX value was 96.9%, which was >95%, indicating a low probability of weak instrument bias and an acceptable collective

TABLE 1 Statistics of testing for heterogeneity and pleiotropy in Mendelian randomization analysis

| Outcomes | Between-SNP heterogeneity[a] | | Horizontal pleiotropy | | Odds ratio (95% CI)[b] | | Statistical power to identify OR >1.1 or <0.9[c] | Statistical power to identify OR >1.3 or <0.7[c] |
	Q statistics	p-value	Egger intercept	p-value		p-value		
Esophageal cancer	4.11	0.662	0.015	0.658	1.05 (0.89, 1.23)	0.631	0.10	0.42
Gastric cancer	8.02	0.237	−0.014	0.419	0.88 (0.81, 0.96)	0.009	0.25	0.97
Pancreatic cancer	2.86	0.826	−0.027	0.629	1.04 (0.78, 1.37)	0.823	0.06	0.18
Hepatocellular carcinoma	3.70	0.718	0.047	0.125	1.26 (1.09, 1.44)	0.003	0.11	0.56
Biliary tract cancer	5.22	0.516	−0.032	0.615	1.54 (1.12, 2.12)	0.016	0.06	0.15
Colorectal cancer	6.91	0.329	0.0003	0.983	1.00 (0.93, 1.07)	0.956	0.26	0.98

[a]Heterogeneity was tested by MR-Egger regression. The results from inverse variance weighted method were similar to that of the MR-Egger method, and therefore were not shown here.

[b]Odds ratios were derived from fixed-effect inverse variance weighted method.

[c]OR = odds ratio per genetically predicted SD unit increase in risk factor.

suitability of instrumental variables for MR analyses. As shown in Table 1, we detected neither between-SNP heterogeneity nor horizontal pleiotropy for the eligible SNPs in all of the MR analyses. These findings suggest the validity of the selected instrumental variables and fixed-effect IVW method was therefore used as the primary method.

3.2 | Causal relationships between adiponectin and gastrointestinal cancers

According to the IVW method, we found that per 10% increase in log-transformed adiponectin level was significantly associated with a decreased risk of GAC (OR = 0.88, 95% CI 0.81, 0.96), whereas with an increased risk of HCC (OR = 1.26, 95% CI 1.09, 1.44) and of BTC (OR = 1.54, 95% CI 1.12, 2.12) (Table 1). For the other three types of GICs, no statistically significant association was detected (Table 1). Of note only the association between adiponectin and HCC risk was statistically significant at the threshold of 0.0083 (adjusted p-value: 0.05/6). The MR analyses might be under-powered (<80%) in the current scenario (Table 1).

We conducted sensitivity analyses to check the robustness of the IVW estimates. As shown in Figure 2 and Table S3, the MR estimates calculated from the four different methods were highly consistent in terms of the direction. For GAC and BTC, the significant association with adiponectin was also detected in weighted median and weighted mode methods (Figure 3; Table S3). The significant association between adiponectin and HCC was only found in IVW method whereas not in the other three methods. For the rest three GICs, that are ESC, PAC, and CRC, all of the methods did not detect a significant correlation with adiponectin (Figure 3; Table S3).

Figures S1–S6 display the results of leave-one-out analysis for each GICs. The associations between adiponectin and GAC and HCC remained significant when excluding any one of the SNPs (Figures S2 and S4). However, the association of adiponectin with BTC was not statistically significant when leaving out the rs12051272 or rs11646213 (Figure S5). There was still no significant association of adiponectin with ESC, PAC, and CRC to be detected in this analysis.

4 | DISCUSSION

In the present study, we established a causal relationship of circulating adiponectin with the risk of GAC, HCC, and BTC leveraging MR analysis. Briefly, we reported that an elevated level of adiponectin was associated with a decreased risk of GAC, whereas with increased risks of HCC and BTC. We did not detect causal relationships between adiponectin and ESC, PAC, and CRC. These findings were to some extent robust due to the following reasons: (1) suitable genetic instrumental tools (F-statistics >10 and I^2-GX > 95%); (2) no horizontal pleiotropy and between-SNP heterogeneity was detected; (3) results calculated from the four methods were highly consistent, albeit the nuances in OR estimates; and (4) influential SNP was not detected in leave-one-out analysis for GAC and HCC, but for BTC.

The six major types of GICs were demonstrated to closely link with adiposity, and the risk of GICs were increased with the increment of BMI to a different degree.[28] However, debates still remained for this issue. Adiponectin inversely correlates with BMI and visceral adiposity.[4,29] The associations of adiponectin
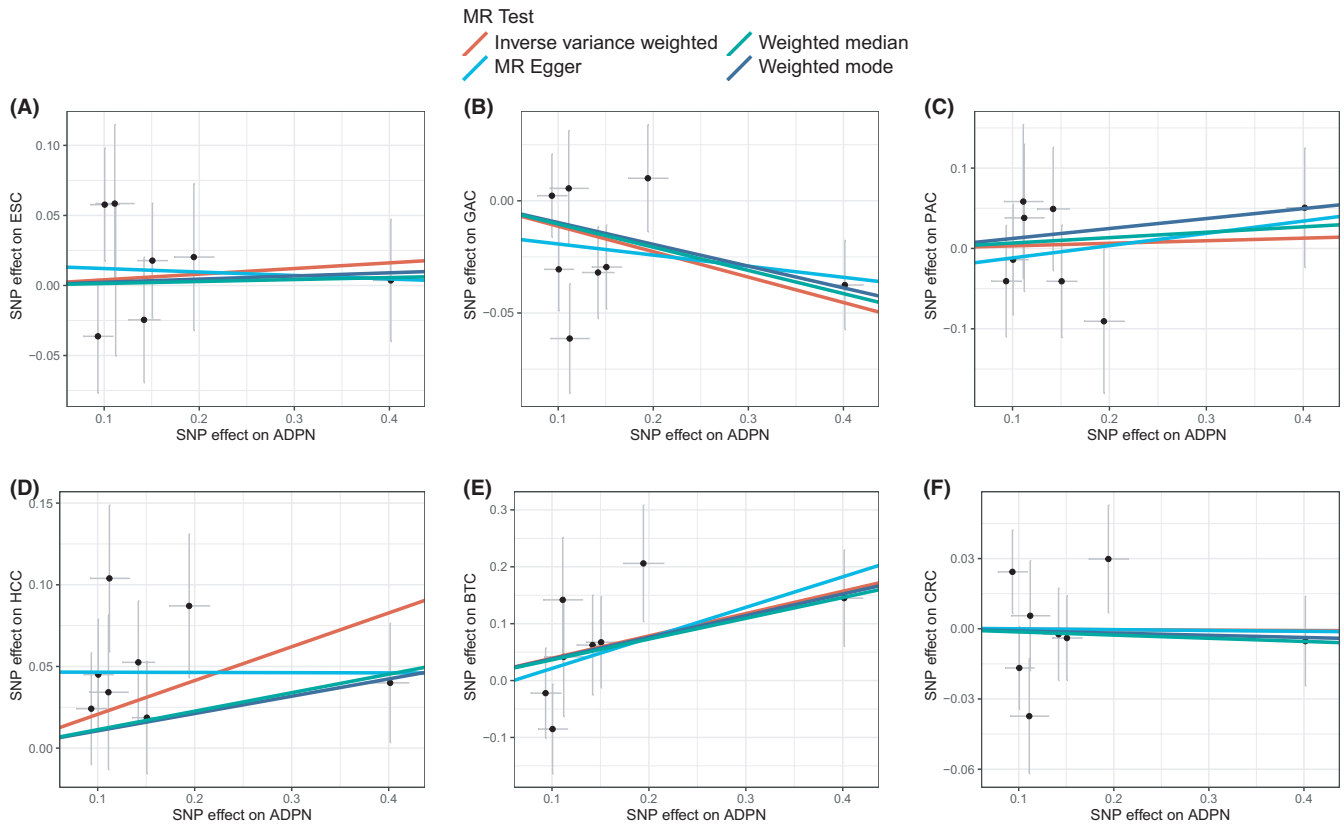
FIGURE 2 The scatter plots of associations between adiponectin (ADPN) and gastrointestinal cancers. The dots represent SNPs used in this analysis and the bars denote the 95% confidence intervals. (A) esophageal cancer (B) gastric cancer (C) pancreatic cancer (D) hepatocellular carcinoma (E) biliary tract cancer (F) colorectal cancer

FIGURE 3 The associations between adiponectin and gastrointestinal cancers according to different Mendelian randomization methods. ESC, esophageal cancer; GAC, gastric cancer; PAC, pancreatic cancer; HCC, hepatocellular carcinoma; BTC, biliary tract cancer; CRC, colorectal cancer
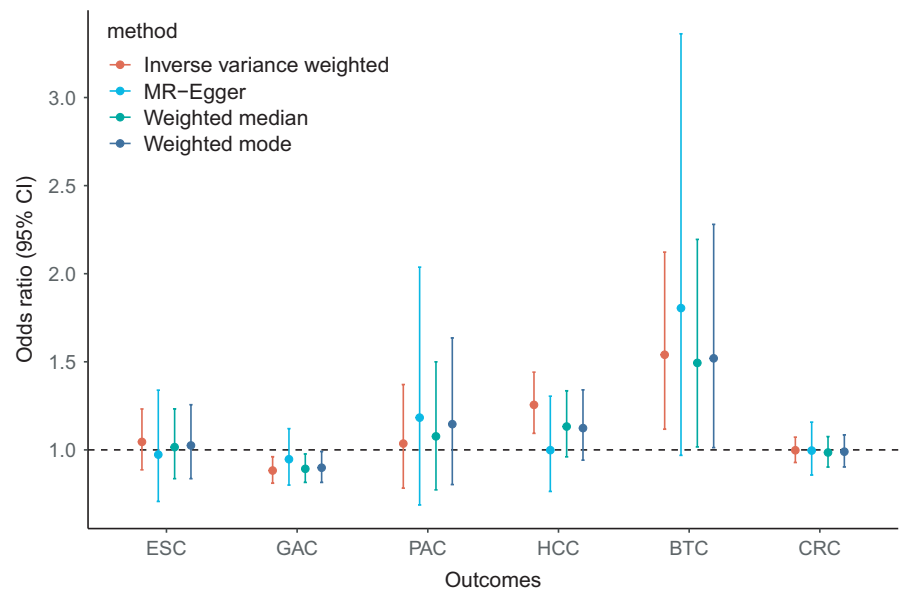
with GICs have been reported in previous studies, although the literature data were sometimes conflicting. Some studies reported that adiponectin might confer a protective effect on the development and progression of GICs due to its features of anti-inflammation and anti-proliferation.[5,29–32] On the other hand, there were evidences from population-based studies suggested no correlation between adiponectin and the risk of GICs[9,33,34] and that adiponectin conferred an increased risk for liver cancer.[35,36] The inconsistent findings of

the observational studies indicated a putative role of adiponectin in the carcinogenesis of GICs and greatly justified the necessity of our MR study. From the methodological perspective, MR analysis is less susceptible to confounders and inverse causality than observational study. We could draw a relatively robust conclusion if the MR assumptions are completely met.

In our study, we found that a low plasma adiponectin level might be causally associated with an increased risk for GAC. This finding was consistent with that of some epidemiological studies,[5,37] of which most were cross-sectional designs. On the contrary, we found that a high level of adiponectin might be causally related with an increased risk of HCC, which shares many risk factors with GAC. This result was highly in line with that of previous epidemiological studies,[8,36,38] indicating that adiponectin could serve as a risk factor for HCC, and more importantly, that GAC and HCC were distinct in physiopathologic process. Of note is that BMI was adjusted in the GWAS of adiponectin, suggesting the putative causal relationships between adiponectin and risks of GAC and HCC might be driven by mechanisms that were independent of obesity, and indicating multiple biological roles of adiponectin.

The protective effect of adiponectin was mainly related to its indirect antineoplastic actions, including insulin-sensitizing, immune-related, and angiogenesis-related effects.[39] For example, adiponectin has been demonstrated to inhibit B cells differentiation from bone marrow and elevate expression of a set of anti-inflammatory cytokines including IL-10, IL-6, TNF-α, and IFN-γ.[40] Moreover, adiponectin was deemed to be a strong inhibitor of the PI3K/Akt/mTOR pathway, thus limiting the tumor cell growth induced by insulin and by other growth factors.[41] Other underlying mechanisms have also been proposed.[4] On the other hand, the positive association between adiponectin and HCC risk is surprising and needs further investigations, given that adiponectin was reported to be protective against fatty liver disease and a low circulating adiponectin has been observed in patients with chronic hepatitis and hepatic steatosis.[42,43] However, Hui et al. reported that serum adiponectin levels were elevated in patients with advanced liver fibrosis.[44] Since adiponectin is majorly metabolized in the liver, circulating adiponectin may represent a biomarker of liver fibrosis, as it has been reported to negatively associated with the platelet count.[38] Moreover, elevated plasma adiponectin level has been associated with inflammatory diseases, such as arthritis, preeclampsia, and end-stage renal disease,[45–47] suggesting adiponectin may also have pro-inflammatory roles.

We also detected a positive association between adiponectin and the risk of BTC, which shares multiple aspects with HCC in terms of histological features, activation of pathways linked to disease development, and prognosis. However, this association disappeared in the leave-one-out analysis when excluding rs12051272 or rs11646213. The two polymorphisms are located in *CDH13* gene, which encodes a member of the cadherin superfamily. Previous studies reported that the two variants were associated with a set of traits, such as serum lipid levels, risk of hypertension and non-small cell lung cancer, and preeclampsia.[48–51] However, there was no evidence linked these variants to BTC. Future studies are warranted to further investigate the role of *CDH13* gene in the genesis of BTC.

The limitations of our study should be noted. First, we focused on study participants of East Asians ancestry, thus limiting the extrapolation of our findings to other populations. Second, the histological subtypes of GICs, such as esophageal squamous cell carcinoma and esophageal adenocarcinoma, were not considered in our study, and might bias the MR estimates because of the differences between cancer subtypes in many ways. Third, adiponectin exerts biological roles depending on its receptors, AdipoR1 and R^2, which might influence the association of adiponectin with diseases. Finally, due to the small proportions of the six types of GICs, our MR estimates might be under-powered. Future studies with larger sample size for cancer cases were warranted.

In summary, in the current MR study, we found that high level of adiponectin was associated with a decreased risk of GAC, whereas with increased risks of HCC and BTC. Adiponectin could serve as a biomarker for GAC, HCC, and BTC in clinical practice. Moreover, the heterogeneous associations between adiponectin and GICs connote a complex role of this adipocytokine in the onset of GICs. More investigations that pinpoint the underlying mechanisms are warranted.

CONFLICT OF INTEREST
The authors declare that they have no competing interest.

AUTHOR CONTRIBUTIONS
JN, CH, and HJ conceived the idea for the study. HJ and DH obtained the genetic data. HJ, BZ, and DH performed the data analyses. JN, CH, WJ, and HJ interpreted the results of the data analyses. HJ wrote the manuscript. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION
Not applicable.

ETHICS STATEMENT
This study was based on publicly available data and the ethics approvals are available in the original studies. All methods were carried out in accordance with relevant guidelines and regulations.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available in the following repository: GWAS summary data of adiponectin were available on the Asian Genetic Epidemiology Network website (AGEN; https://blog.nus.edu.sg/agen/). GWAS summary data of gastrointestinal cancer were available on IEU Open GWAS project website (https://gwas.mrcieu.ac.uk/).

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SUPPORTING INFORMATION

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