

Mendelian randomization analysis of Circulating adiponectin levels on prostate cancer

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Research Article

Keywords: adiponectin, prostate cancer, Mendelian randomization analysis, causality

Posted Date: March 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-319125/v1>

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Abstract

Background: Previous observational studies showed a conflict with the correlation between circulating adiponectin levels and prostate cancer.

Methods: In this study, we employed Mendelian randomization analysis to identify the causal effects between them. 14 single nucleotide polymorphisms were screened from the largest-scale genome-wide association study meta-analysis of adiponectin in a multi-ethnic population. The SNP outcome effects were obtained from Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome and Japanese Encyclopedia of Genetic Associations by Riken. Inverse variance weighted model with random-effects was the main effect estimation in our study, alongside weighted median, MR-Egger, and weighted mode models.

Results: The results showed no significant causal estimate but a potential protective effect of adiponectin on prostate cancer. In addition, two other research of adiponectin repeated the analysis to avoid the bias of human species showing the similar results.

Conclusion: Our study did not provide significant evidence to support the causal effects of circulating adiponectin levels on prostate cancer, but most of our results showed a potential protective effect requiring larger-scale MR analysis to confirm.

Introduction

Prostate cancer is one of the most common cancer in men around the world, which is estimated to own 191,930 new cases and 33,330 deaths in 2020 in the United States nationally by the American Cancer Society [1]. Although many risk factors of prostate cancer have been confirmed, such as age, obesity, heritage, ethnicity and smoking, its etiology and pathogenesis remain to be fully elucidated [2].

Adiponectin is a kind of endocrine factor secreted by adipose tissue, whose plasma concentrations are higher than other adipose-derived hormones constituting approximately 0.01% to 0.05% of total serum proteins. Adiponectin has been found to regulate specific physiological functions increasing insulin sensitivity and reducing inflammation [3, 4]. However, the impact of adiponectin on prostate cancer is conflicting from published studies. It has been demonstrated that adiponectin may play a protective role in prostate cancer from part of studies. The main reason for this opinion is that prostate cancer is related to obesity and circulating adiponectin level is lower in fat people. While others indicated that adiponectin had no significant association with prostate cancer [5-7].

Two-sample Mendelian randomization (MR) analysis is a new genetic method to determine whether an observed association between a risk factor and a kind of disease is consistent with a causal effect. The method is based on the natural assortment of genetic variants during meiosis, leading to a random distribution of genetic variants in a population. Compared with previous observational epidemiological studies, MR analysis is superior in cheaper cost, less time and easier methods [8, 9].

To identify the causal effect of adiponectin on prostate cancer, our study chose three large-scale genome-wide association study (GWAS) analyses of serum adiponectin concentrations and two different-ethnicity GWAS analyses of prostate cancer. Single nucleotide polymorphisms (SNPs) of adiponectin were used as instrumental variables (IVs), which were screened from GWAS of adiponectin. Then MR analysis generated unbiased causal estimates of adiponectin on prostate cancer.

Methods

Study design

We used two-sample MR analysis to identify the causal relationship between circulating adiponectin levels and prostate cancer. SNPs of adiponectin were selected as IVs from published GWAS analyses. For the MR study, three key assumptions must be met. First, the SNPs should be related to circulating adiponectin levels robustly. Second, the SNPs should be independent of confounders, such as body mass index (BMI), sex, age and so on. Third, the SNPs should affect prostate cancer only by adiponectin and the SNPs can't have a direct correlation with prostate cancer [10]. (**Figure 1**)

We chose a GWAS meta-analysis of adiponectin including 67,739 individuals of European, Hispanic, African American and East Asian ancestry from a published study [11]. Some SNPs related with adiponectin robustly were screened from the GWAS for MR analysis. And two GWAS of prostate cancer from Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) [12] and Japanese Encyclopedia of Genetic Associations by Riken (JENGER) [13] were used to estimate the causal relationship. Then we employed the inverse variance weighted (IVW) model with random-effects for our main effect estimation, alongside weighted median, MR-Egger and weighted mode models. In addition, leave-one-out and heterogeneity sensitivity analysis were performed to meet the key assumptions. Finally, two other GWAS of adiponectin whose individuals were European and East Asian respectively, were added into the study to avoid the bias of human species.

Exposure and outcome dataset

For the exposure dataset, we used the largest-scale GWAS meta-analysis of circulating adiponectin levels, which included 60,465 European, 1,435 Hispanic, 3,271 African American and 2,568 East Asian. The GWAS meta-analysis incorporated 28 data-sets from 25 previous studies (mean age: 20.0-73.9 years; mean BMI: 24.2-43.3 kg/m²; mean circulating adiponectin level: 2.8-29.7 ug/ml). The analysis of circulating adiponectin levels had been adjusted for age, sex, BMI and other study-specific covariates.

In addition, we chose two GWAS meta-analysis of adiponectin including 29,347 European and 12,125 East Asian ancestry respectively, for avoiding the bias of human species. The GWAS of European was compounded of 26 studies (mean age: 9.8-75.4 years; mean BMI: 24.2-43.3 kg/m²; mean circulating adiponectin level: 4.9-25.5 ug/ml) [14] and the GWAS of East Asian consisted with 10 data-sets including 5,403 Chinese, 3,973 Korean, 1,717 Filipino and 1,030 Japanese (mean age: 41.6-66.2 years; mean BMI: 17.2-29.0 kg/m²; mean circulating adiponectin level: 2.5-14.0 ug/ml) [15].

Considering the bias of human species, we employed two different-ethnicity larger-scale GWAS meta-analysis of prostate cancer. The GWAS accessed from PRACTICAL had 79,148 cases and 61,106 controls of European ancestry and JENGER dataset had 5,408 cases and 103,939 controls of East Asian ancestry. Unfortunately, we did not obtain the demographic data from two GWAS. (**Table 1**)

Statistical analysis

For the adiponectin, we extracted significant genome-wide SNPs (IVs) from the GWAS. Then each SNP calculates the R^2 indicating the proportion of phenotypic variance. And F-statistic of each SNP calculates based on R^2 to evaluate the strength of IVs in adiponectin [16]. The SNPs are remained if the result of F-statistic is larger than 10. Moreover, the SNPs on the same chromosome were assessed in linkage disequilibrium with each other. It can be calculated in a website (<https://ldlink.nci.nih.gov/>) [17-20]. The SNPs would be excluded if the result of linkage disequilibrium r^2 is larger than 0.01.

Two-sample MR analysis was performed to estimate the causal effect between serum adiponectin concentrations and prostate cancer. IVW method with multiplicative random effects is the main analysis to obtain the causal estimates [21]. Wald estimate is used to evaluate each genetic variant by the ratio of the SNP-outcome estimate over the SNP-exposure estimate, with standard error (SE) using Delta method. Furthermore, MR-Egger, weighted media and weighted mode methods were chosen as complementary analysis. The result of IVW is based on the hypothesis that there is no horizontal pleiotropy meaning no intercept in the axis of coordinate. But it is vulnerable if the hypothesis does not hold, which is against the assumption three of MR analysis. Therefore, MR-Egger model is utilized to estimate the precise intercept representing the average horizontal pleiotropy. And the slope of MR-Egger shows the pleiotropy-adjusted estimate [22]. Weighted media model is a greater choice if over 50% of the SNPs meet the hypothesis of no horizontal pleiotropy that each SNP is weighted equally to the inverse of its SD in the analysis.

As for the heterogeneity, the Cochran's Q statistics are used to evaluate the variance between SNPs in IVW model [23]. In addition, leave-one-out analysis calculates the causal estimates after excluding one SNP. It is visualized to assess whether some SNPs play a particularly significant role in the results among all the SNPs [24].

For avoiding the bias of confounders, the SNPs selected from the GWAS of adiponectin were checked whether they were related with any diseases or traits factors other than adiponectin by the PhenoScanner online dataset (<http://www.phenoscanter.medschl.cam.ac.uk/phenoscanter>, $p < 5 \times 10^{-8}$, $r^2 > 0.8$) [25, 26]. Then the SNPs associated with adiponectin only were chosen to estimate the causal effects by IVW.

In our study, We used RStudio software (version 4.0.2; <http://www.rproject.org>) and TwoSampleMR package of R (version 0.5.4; <https://github.com/MRCIEU/TwoSampleMR>) to accomplish the analysis. The threshold value of statistical significance is set as $P < 0.05$ (two-tailed).

Results

MR analysis of multiple-ethnicity individuals

We selected the SNPs related with adiponectin from the largest-scale GWAS meta-analysis for MR analysis. 18 genome-wide significant SNPs were extracted from the GWAS ($P < 5 \times 10^{-8}$), which had been adjusted for sex, age, BMI and other study-specific covariates. Then each SNP calculated the F-statistic based on the results of r^2 . Four SNPs were excluded from the study because the results of F-statistics were smaller than 10 meaning weak strength of SNPs in adiponectin. Furthermore, the remained SNPs calculated linkage disequilibrium and the results of SNPs on the same chromosome were all lower than 0.01, fortunately. Hence, we utilized 14 SNPs as IVs to estimate the causal effect, which explained 5.2% of the variability in circulating adiponectin levels. (**Supplementary Table 1**)

Two GWAS of prostate cancer were used to assess the relationship between adiponectin and prostate cancer. In the IVW analysis, similar results were showed in European (OR 0.978; 95% CI 0.928-1.030; $P = 0.407$) and East Asian (OR 0.939; 95% CI 0.824-1.069; $P = 0.340$) population that an inverse effect was found between adiponectin and prostate cancer, while it had no significant effects (**Figure 2**). MR-Egger, Weighted media and weighted mode analysis performed the consistent results (**Supplementary Figure 1 and 2**).

For the sensitivity analysis, horizontal pleiotropy is important for the assumption 3 of MR analysis. And it was represented by the intercept of MR-Egger showing no horizontal pleiotropy in European (intercept = -0.001; SE = 0.004; $P = 0.878$) and East Asian (intercept = 0.001; SE = 0.010; $P = 0.888$). In addition, Cochran's Q value performed no heterogeneity existing in European (Q-value = 14.231; $P = 0.358$) and East Asian (Q-value = 13.111; $P = 0.439$). Finally, two leave-one-out plots showed that no SNPs played an especially significant role in the analysis (**Supplementary Figure 1 and 2**).

MR analysis of simple-ethnicity individuals

For avoiding the bias of ethnical difference, we chose two other GWAS meta-analysis of adiponectin in European and East Asian, respectively. Firstly, MR analysis was performed in East Asian population. We extracted 11 target SNPs from the GWAS ($P < 1 \times 10^{-5}$). We lowered the threshold of P because of the small-scale population and less SNPs. F-statistic values of the whole SNPs were larger than 10 and no linkage disequilibrium was found in the SNPs. Therefore, we performed MR analysis using 11 SNPs, which explained 7.8% of the variability in adiponectin of East Asian (**Supplementary Table 2**). Next, JENGER GWAS of prostate cancer was employed to estimate the causal effects in East Asian population. It generated the similar results that there was an inverse effect in IVW (OR 0.931; 95% CI 0.838-1.033; $P = 0.177$) and other models, while it was not significant (**Figure 3A**).

As for the European, another GWAS was chose and 11 SNPs were selected ($P < 5 \times 10^{-8}$). One SNP was excluded because of the small F-statistic value. Hence, 10 SNPs explaining 0.75% of the variability in adiponectin were used to estimate the effect in PRACTICAL GWAS (**Supplementary Table 3**). However, IVW analysis showed a positive but insignificant effect (OR 1.014; 95% CI 0.896-1.147; $P = 0.830$) (**Figure 3B**).

MR-Egger analysis provided the estimates of no horizontal pleiotropy in East Asian (intercept = 0.003; SE = 0.008; P = 0.701) and European (intercept = -0.005; SE = 0.014; P = 0.723). And Cochran's Q statistics showed no heterogeneity in East Asian (Q-value = 9.887; P = 0.451) and European (Q-value = 7.065; P = 0.630). The leave-one-out plots also performed no significant IVs among all the SNPs. (**Supplementary Figure 3 and 4**)

Additional analysis

To minimize the bias of confounders, 14 SNPs selected from the largest-scale GWAS meta-analysis of multiple-ethnicity individuals were examined by the PhenoScanner online dataset. And three SNPs (rs17366568, rs4311394, rs11057353) were considered with no relationship with other diseases or traits factors. Then the results of IVW showed accordant effects in European (OR 0.977; 95% CI 0.922-1.037; P = 0.452) and East Asian (OR 0.933; 95% CI 0.804-1.085; P = 0.372) (**Figure 4**).

Discussion

Our study was aimed to reveal the relationship between circulating adiponectin levels and prostate cancer by a two-sample MR analysis. And we did not provide consistent evidence to support the causal effect of serum adiponectin levels on prostate cancer. While most results showed that adiponectin might play a potential protective role in prostate cancer, which was no significant in the analysis.

As for the relationship between circulating adiponectin and prostate cancer, there is a conflict in the previous studies. Some previous studies reported that adiponectin levels had an inverse correlation with prostate cancer, while others did not provide enough evidence of the relationship. A meta-analysis of 11 studies including 3565 cases and 2504 controls found that the adiponectin levels in patients with prostate cancer were lower than controls, and adiponectin had the potential biomarker for early detection [27]. Another cross-sectional study of 2,939 Japanese showed that it had a positive correlation between adiponectin levels and Prostate Specific Antigen (PSA) levels [28]. Hu et al. also provided rich evidence that adiponectin and its receptor were involved in the development and progression of prostate cancer, and adiponectin was expected to become a novel targeted therapy. However, a study aimed on the American male physicians reported that adiponectin levels were not associated with risk of overall prostate cancer [29]. Another case-control study also showed no association between adiponectin and prostate cancer [30]. In addition, the study between benign prostatic hyperplasia patients and prostate cancer patients showed no difference in adiponectin.

Recently, the largest-scale meta-analysis including 39 studies showed that adiponectin levels had no significant correlation with the incidence of prostate cancer, while it had an influence on mortality, implicating adiponectin was a bridge between obesity and prostate cancer advancement [31]. It has been recognized that inflammation is a risk factor of cancer. A novel opinion is that obesity is a state of inflammation leading to diseases [32, 33]. Moreover, adiponectin has been found to own the physiological function of reducing inflammation. Therefore, adiponectin may play a protective role in cancer by inflammation reduction. Adenosine Monophosphate-activated Protein Kinase (AMPK) is

speculated to be the most important signal-protein, which is influenced by adiponectin receptor. And the growth and apoptosis of cancer are changed by the pathway AMPK/mTOR or AMPK/PI3K/Akt [34].

In this study, we used a new genetic method to estimate the causal effects of circulating adiponectin levels on prostate cancer and multiple analysis was utilized to meet the key assumption of MR analysis. First, the largest-scale GWAS meta-analysis of adiponectin including 67,739 individuals were used to screen the significant genome-wide SNPs for meeting the assumption 1. Second, to meet the assumption 2, the SNPs were adjusted for sex, age, BMI and other study-specific covariates. And we also chose 2 other GWAS of adiponectin in European and East Asian to avoid the bias of human species. Another important method was that 3 SNPs only associated with adiponectin were selected by PhenoScanner online dataset. Third, horizontal pleiotropy and leave-one-out sensitivity analysis were used to meet the assumption 3. Furthermore, several models involving IVW, MR-Egger, weighted media and weighted mode were chosen to estimate the causal effects of adiponectin on prostate cancer. It may improve the robustness of results.

There are several advantages in our study compared with previous observational studies. First, our study contained a larger-scale population, which had the benefit to reduce the bias of statistics. Second, MR analysis is based on the random distribution of genetic variants in a population and observation biases can be avoided. Third, our study considered the influence of confounders and additional analysis estimated the causal effect by minimizing the confounders.

However, limitations are still subsistent in our study. The SNPs screened from the GWAS in European species had a low explanation of the variability in adiponectin, which did not meet the assumption 1 robustly. And it might be the reason of a positive correlation.

In conclusion, our study did not provide significant evidence to support the causal effects of circulating adiponectin levels on prostate cancer, but most of our results showed a potential protective effect requiring larger-scale MR analysis to confirm.

Abbreviations

MR: Mendelian randomization

GWAS: Large-scale genome-wide association study

SNP: Single nucleotide polymorphisms

IV: Instrumental variable

BMI: Body mass index

PRACTICAL: Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome

JENGER: Japanese Encyclopedia of Genetic Associations by Riken

IW: Inverse variance weighted

CI: Confidence interval

OR: Odds ratio

SE: Standard error

PSA: Prostate Specific Antigen

AMPK: Adenosine Monophosphate-activated Protein Kinase

Declarations

Acknowledgements: We would like to thank Mingxiao Jiang for his help in constructing the search strategy.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: RStudio software (version 4.0.2; <http://www.rproject.org>) and TwoSampleMR package of R (version 0.5.4; <https://github.com/MRCIEU/TwoSampleMR>) was used to accomplish the analysis.

All the dataset of GWASs are openly available. The dataset of GWAS from PRACTICAL can be downloaded from the FTP (ftp://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST006001-GCST007000/GCST006085). The dataset of GWAS from JENGER can be downloaded from the website (<http://jenger.riken.jp/en/result>; ID: 90; Study: Prostate cancer). The SNPs associated with adiponectin can be accessed from the GWAS catalog website (https://www.ebi.ac.uk/gwas/efotraits/EFO_0004502).

Competing interests: The authors declare that they have no competing interests.

Funding: GHL were supported by Joint construction project of Zhejiang Province and Ministry (grant number: 2020388200); Key R & D plan of Zhejiang Province (grant number: 2019C03089); National Natural Science Foundation of China (grant numbers: 81672520, 8187048).

Authors' contributions: LLR, CHY, ZWZ and GHL designed the study. LLR and CHY analysed the data. LLR and CHY drafted the paper. ZWZ and GHL critically revised the paper. All authors read and approved the final manuscript.

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Tables

Table 1. characteristics of exposure datasets and outcome datasets.

phenotype	consortium	Total population	cases	controls	ethnicity	references
Prostate cancer	PRACTICAL	140254	79148	61106	European	Schumacher et al (2018)
Prostate cancer	JENGER	109347	5408	103939	East Asian	Ishigaki et al (2020)
Adiponectin		67739			Multi-ethnic	Spracklen et al (2019)
Adiponectin		29347			European	Dastani et al (2012)
Adiponectin		12125			East Asian	Wu et al (2014)

Figures

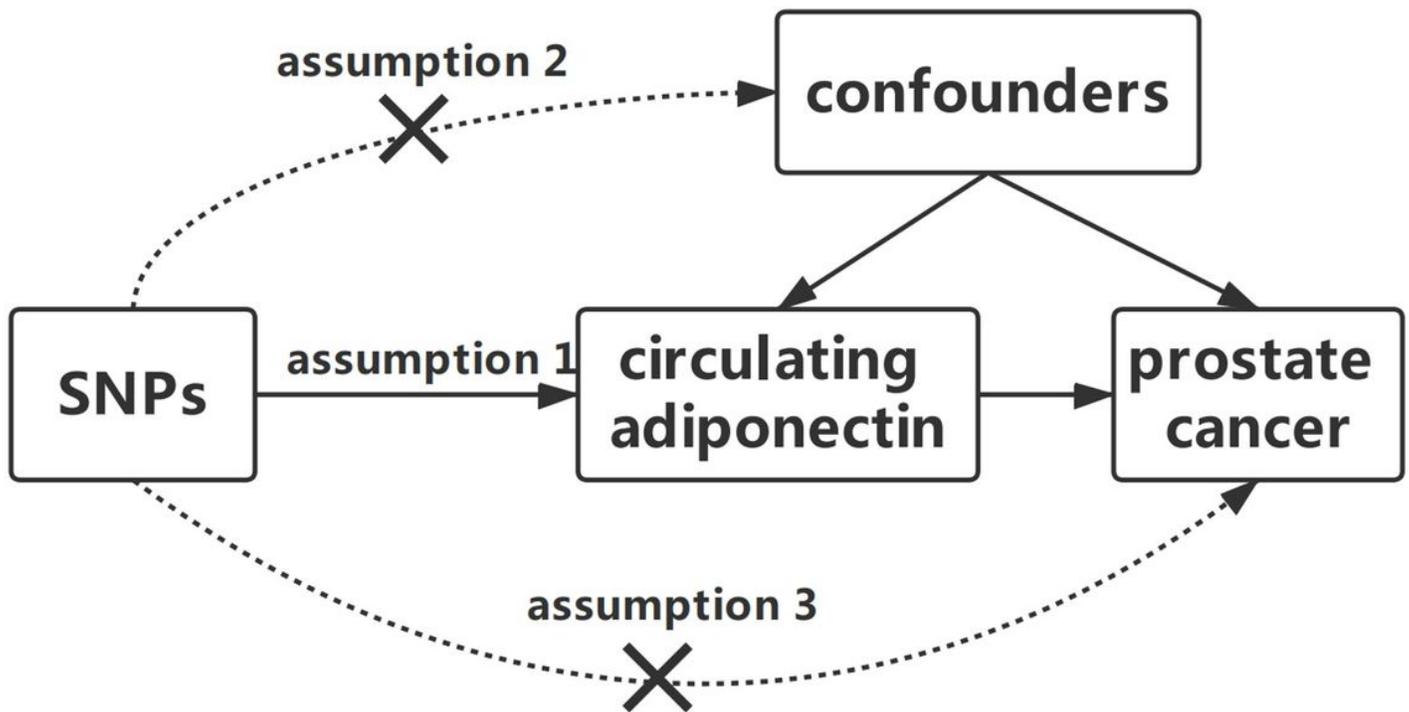
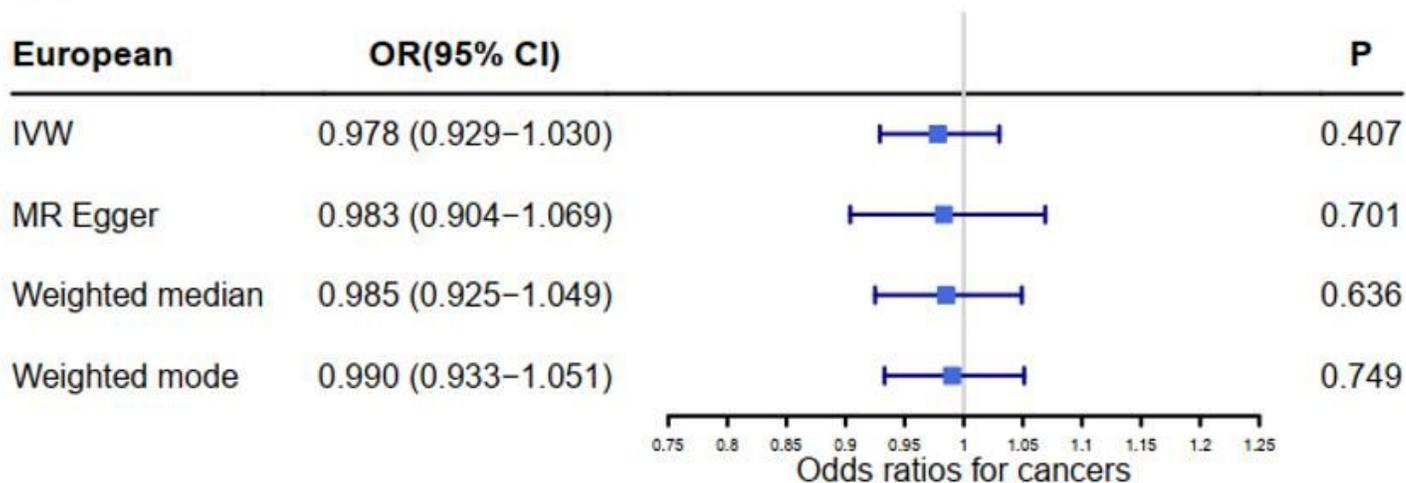
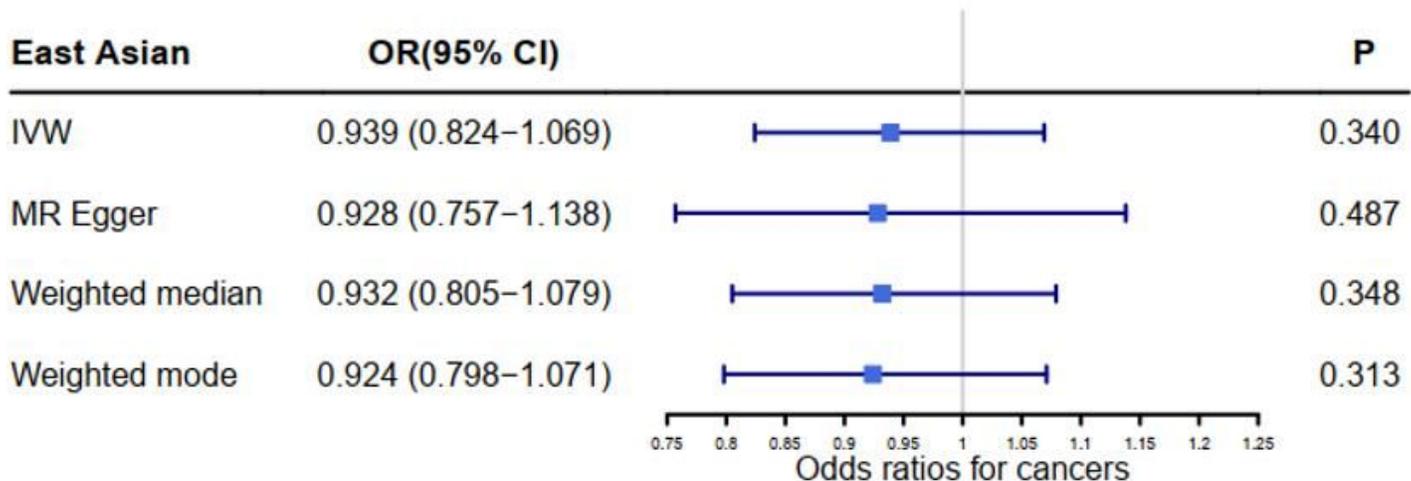
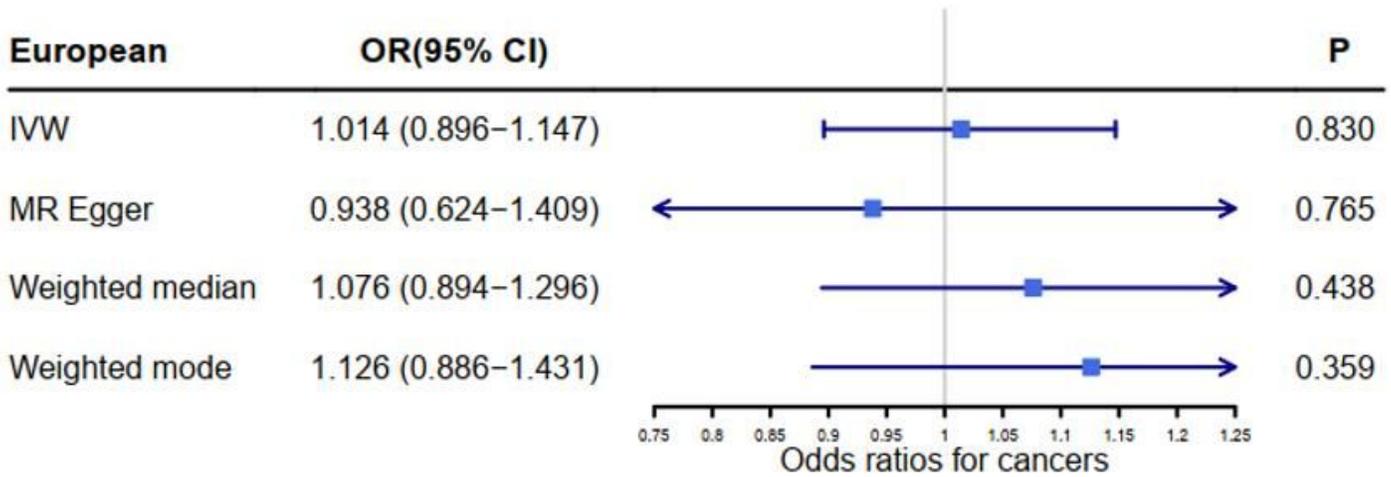
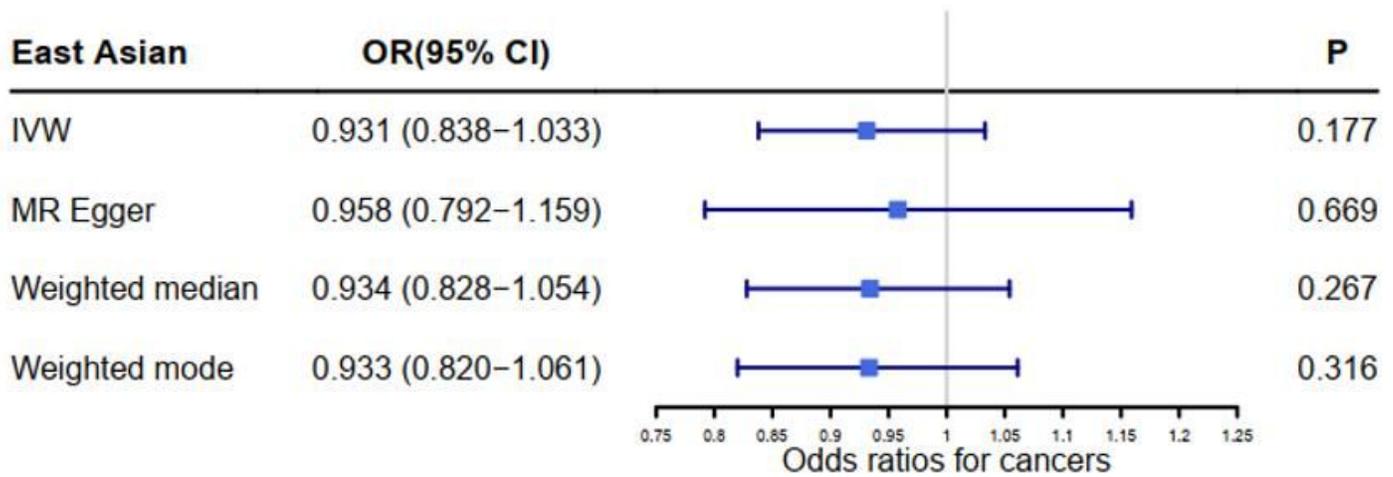


Figure 1

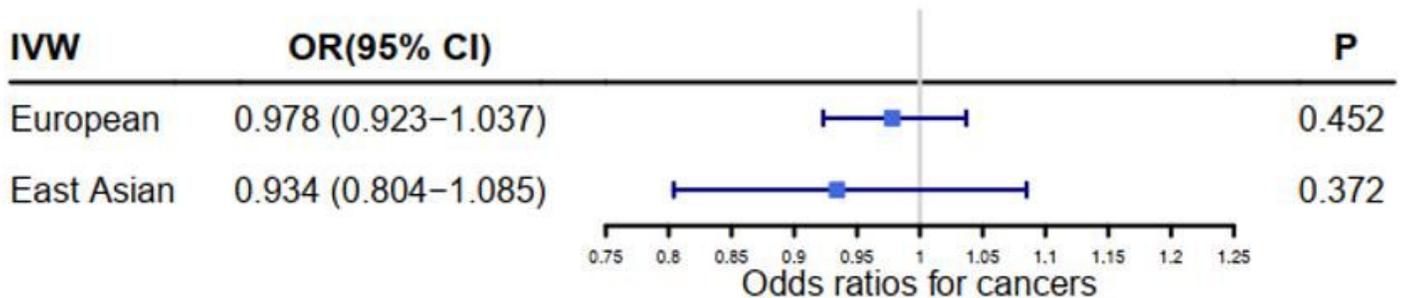
Diagram of two-sample Mendelian Randomization analysis of circulating adiponectin levels and prostate cancer risk. 3 key assumptions in Mendelian Randomization analysis are as follows: (1) the SNPs should be related to circulating adiponectin levels robustly, (2) the SNPs should be independent of confounders, (3) the SNPs should affect prostate cancer only by adiponectin and the SNPs can't have a direct correlation with prostate cancer.

A**B****Figure 2**

Mendelian Randomization analysis between circulating adiponectin levels of multiple-ethnicity individuals and prostate cancer of (A) European and (B) East Asian.

A**B****Figure 3**

Mendelian Randomization analysis between circulating adiponectin levels of simple-ethnicity individuals and prostate cancer of (A) European and (B) East Asian.

**Figure 4**

The forest plots of 3 SNPs selected by PhoneScanner calculating in European and East Asian.

Supplementary Files

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