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Metabolic syndrome and cancer risk: a two-sample Mendelian randomization study of European ancestry

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Background: The relationship between Metabolic Syndrome and cancer remains controversial. The authors aimed to assess the association between Metabolic Syndrome and cancer risk at different locations using a Mendelian randomization approach.

Methods: The authors extracted single nucleotide polymorphisms (SNPs) of MetS and its components from public databases for populations of European ancestry. Causal effects were estimated using inverse variance weighting, MR-Egger, weighted median, and MR-PRESSO. Sensitivity analyses were performed using Cochran's *Q* test, MR-Egger intercept test, MR-PRESSO, leave-one-out analysis, and funnel plots. In addition, the authors calculated the Statistical power. Finally, the authors applied the False Discovery Rate (FDR) to correct our results.

Results: IVW methods showed that Genetically predicted Metabolic Syndrome may be a potential risk factor for hepatocellular carcinoma ($P = 0.031$, P-FDR = 0.093). Metabolic Syndrome was not causally associated with cancers at other sites (lung, thyroid, breast, prostate, kidney, bladder, colorectal, esophagus, and stomach). In further analyses, WC may increase the risk of lung ($P = 0.003$, P-FDR = 0.018), and esophageal ($P = 0.011$, P-FDR = 0.066) cancers and decrease the risk of prostate cancer ($P = 0.006$, P-FDR = 0.001). Furthermore, hypertension may reduce the risk of Hepatic cancer ($P = 0.014$, P-FDR = 0.084).

Conclusion: Our study suggests that genetically predicted Metabolic Syndrome may increase the risk of some cancers. Prevention and treatment of Metabolic Syndrome may help to prevent the development of related cancers.

Keywords: cancer, Mendelian randomization, metabolic syndrome, obesity

Introduction

Metabolic Syndrome (MetS), also known as Syndrome X, is a disease with metabolic disorders as the main pathophysiological mechanism resulting in excessive obesity, which is widely prevalent in the world. The etiology of MetS has not yet been clearly defined, but it is currently believed to be the result of multigene and multiple environmental interactions and is closely related to genetics and immunity. Although much controversy still exists, ranging from the WHO glucose-centered definition to the International Diabetes Federation's (IDF) obesity-centered definition, the consensus is that obesity (large waist circumference), dyslipidemia, hypertension, and dysregulation of glucose homeostasis are the main components[1,2]. The MetS, although originating in developed countries, is also on the rise in the Asia-Pacific region[3]. The Asia-Pacific region is home to more than half of the world's population. Most are poor or developing countries, but patients with MetS are not uncommon, meaning that MetS is not just a disease of the rich. It is the lack of medical and economic conditions in these regions that results in huge socio-economic costs and high mortality rates[4].

In addition to cardiovascular disease, MetS increases the risk of cancer. The relationship between MetS and cancer has already been reported in various studies, and some evidence indicates that, although the association is weak, MetS is implicated in an increased risk of many types of cancer in adults[5]. Components of the MetS have also been shown to be associated with different tumors. Obesity or high BMI may increase the risk of cancers

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such as hepatic cancer[6], breast cancer[7], ovarian cancer[8], and colorectal cancer[9]; both men and women with hypertension appear to have a higher risk of developing renal malignancies[10]; cervical cancer patients with type 2 diabetes have a worse prognosis[11]; higher fasting glucose levels also increase mortality from various cancers[12] and low levels of HDL cholesterol levels are associated with an increased risk of lung cancer[13]. The association of certain cancers with MetS remains controversial. A multicentre cohort study in Africa suggests that obesity may increase the incidence of intermediate-risk prostate cancer[14]. Still, another study suggests that obesity at a young age may be associated with a reduced risk of prostate cancer[15].

Therefore, the association between MetS and its components with cancer remains unknown and controversial. To avoid confounding potential confounding and reverse causality effects, we used Mendelian randomization (MR) studies to explore the relationship between the MetS and its components with common cancers. MR is a data analysis method for etiologic inference in epidemiologic studies that uses single nucleotide polymorphisms (SNPs) from GWAS as instrumental variables to infer causal relationships between exposures and outcomes, yielding results that are more reliable than those from traditional observational studies[16].

HIGHLIGHTS

- The first Mendelian randomization study to comprehensively explore the relationship between metabolic syndrome and cancers.
- A total of 10 common cancers were included.

Methods

Data source: exposure and outcome

This study strictly followed the STROBE-MR guidelines. All GWAS cohorts were almost exclusively of European ancestry. There was no overlap between the exposure and outcome cohorts. GWAS Summary data for the MetS were obtained from the Complex Trait Genetics LAB (CTGLAB). Walree *et al.*[17] used the Genomic Structural Equation Model (SEM) approach to elucidate the genetic structure of the MetS in 461 920 individuals of European ancestry. We selected GWAS summary data for waist circumference (WC), hypertension, fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) from the IEU Open GWAS database to represent the five components of the MetS (https://gwas.mrcieu.ac.uk/). GWAS summary data for cancers are also derived from the IEU Open GWAS database. The project, supported by the University of Bristol's MRC Integrated Epidemiology Unit (IEU), collated and analyzed GWAS data from the UK Biobank, published articles, and the FinnGen Biobank. Proxy SNPs were used when there were insufficient SNPs or no statistically significant. Details of exposure and outcome data are provided in Table 1.

Instrumental variable selection

Mendelian randomization studies need to satisfy three major assumptions, (1) instrumental variables are strongly associated with exposure factors, (2) instrumental variables are not associated with confounders, and (3) instrumental variables are associated with exposure outcomes only. We chose SNPs significantly associated with exposure as instrumental variables, and to minimize the effect of confounders, we chose a threshold smaller than the genome-wide significance threshold as the criterion($P < 5*10^{-9}$). SNPs in high linkage disequilibrium ($r^2 > 0.001$ or clump windows <10 000 kb) were excluded. Additionally, coordination was implemented to harmonize the orientation of all SNPs and remove palindromic sequences, lastly, we also computed the F-test statistic ($F = \frac{R^2 \times (N-2)}{1-R^2}$, $R^2 = \frac{2 \times EAF \times (1-EAF) \times \beta^2}{2 \times EAF \times (1-EAF) \times (\beta^2 + N \times SE^2)}$) to ensure that all instrumental variables had an F-statistics > 10[18].

Statistical analysis

We use the inverse variance-weighted (IVW) method as the primary method for calculating causal effects. The IVW model is the most powerful method for detecting causality in two-sample MR analysis[19,20]. If the effect estimates in the IVW method were significant and no contradictory results were found in other methods, the causal effect of exposure on the outcome was considered significant. We supplemented our results with the weighted median and MR-Egger method. The weighted median method allows no more than 50% of invalid IVs, whereas the MR-Egger method allows all IVs to be invalid. Therefore, it is more convincing when the three models are consistent.

Sensitivity analysis

We perform sensitivity analysis using the following methods, Cochran's Q test was used to test for possible heterogeneity, and Cochran's Q test $P < 0.05$ indicates heterogeneity. However, the presence of heterogeneity does not mean that the IVW model is necessarily invalid[21]. When there is a high degree of heterogeneity in the results of the IVW method, we will adopt a random effects model; when the heterogeneity still cannot be eliminated, we will refer to the results of the Weighted Median, which reduces the weight of the genetic instrumental variables with heterogeneity and minimizes their impact on the results[22]. Funnel plots are also used to detect heterogeneity, and symmetry plots indicate the absence of heterogeneity. We also preliminarily assessed the potential level pleiotropy of IVs by MR-Egger regression intercepts; If the P-value is less than 0.05, there is horizontal pleiotropy[21]. In addition, the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test will be used to further identify and correct the effects of outliers. If outliers are present, we will remove them and then perform the MR analysis again until there are no outliers[23]. Leave-one-out analysis is used to detect the presence of SNPs that can have a significant impact on the results to ensure the robustness of the conclusions. Furthermore, we calculated the Statistical power of our results, and if the value of the Power is > 0.8, which implies that our results are significant[24]. Lastly, we applied the Benjamini–Hochberg (BH) method of false discovery rate (FDR) to avoid false-positive results. This study was designed to broadly explore the association between Metabolic Syndrome and cancer, so we used broader thresholds. A potential causal relationship between exposure and outcome is usually considered to exist when the corrected P-value is less than 0.1[25,26], and when the corrected

Table 1

Details of the GWASs included in the Mendelian randomization.

Exposure	Year	Sample size	Web sources	Population
Metabolic syndrome	2022	461 920	https://ctg.cncr.nl/software/summary_statistics	European
WC	2018	462 166	https://gwas.mrcieu.ac.uk/datasets/ukb-b-9405/	European
Hypertension	2021	484 598	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90038604/	European
FBG	2012	58 074	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005186/	European
Triglycerides	2013	177 861	https://gwas.mrcieu.ac.uk/datasets/ieu-a-302/	Mixed (96% European)
HDL-C	2013	187 167	https://gwas.mrcieu.ac.uk/datasets/ieu-a-299/	Mixed (96% European)
Outcome				
Thyroid cancer	2021	407 746	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90013863/	European
Breast cancer	2021	257 730	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018799/	European
Lung cancer	2021	492 803	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018875/	European
Colorectal cancer	2021	407 746	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90013862/	European
Hepatic cancer	2021	475 638	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018858/	European
Gastric cancer	2021	476 116	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018849/	European
Bladder cancer	2021	373 295	https://gwas.mrcieu.ac.uk/datasets/ieu-b-4874/	European
Prostate cancer	2021	211 227	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018905/	European
Malignant neoplasm of esophagus	2021	174 238	https://gwas.mrcieu.ac.uk/datasets/finn-b-C3_OESOPHAGUS_EXALLC/	European
Malignant neoplasm of kidney	2021	174 977	https://gwas.mrcieu.ac.uk/datasets/finn-b-C3_KIDNEY_NOTRENALPELVIS_EXALLC/	European

P-value is less than 0.05, this implies a significant causal association. A flowchart of Mendelian randomization is shown in Figure 1. All analyses were performed using the TwoSampleMR package and MR-PRESSO package in R software (version 4.3.2)[23,27].

Ethical approval

Our study involved only existing data and documents obtained from published studies approved by the Ethics Committee, therefore no further ethical approval was required for this study.

Results

Table 1 shows details of all the GWAS data involved. The results of the MR analysis, the Statistical power, and the sensitivity analysis are shown in Table 2. Details of the STROBE-MR checklist are in Supplementary Material 1 (Supplemental Digital Content 1, http://links.lww.com/JS9/D198) and information on

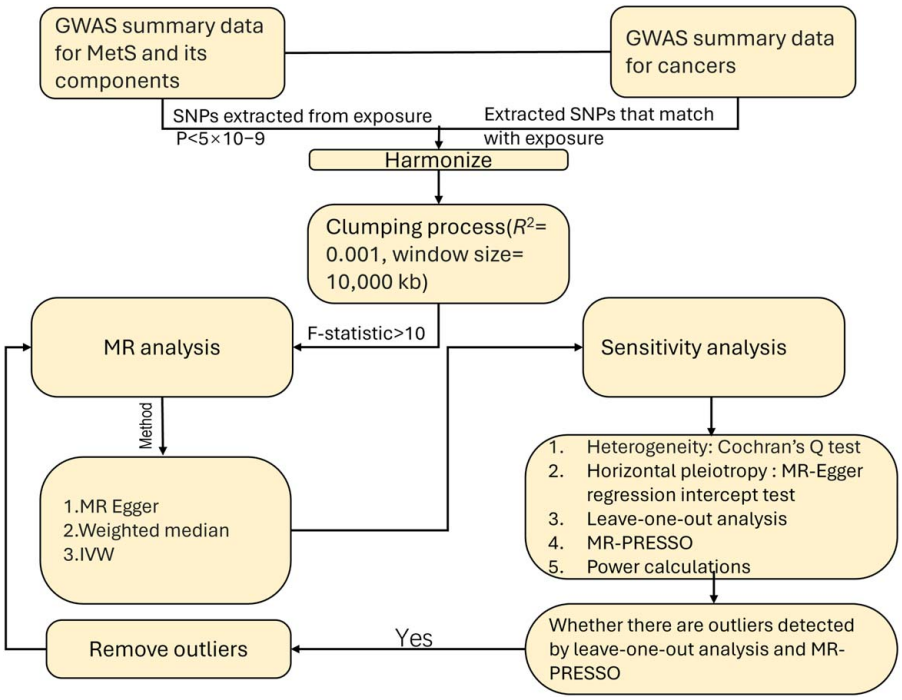

Figure 1. A flowchart of Mendelian randomization.

Table 2

Results of Mendelian randomization of metabolic syndrome and cancers.

Exposure	Outcome	Method	nSNP	*P*	P-FDR	OR	OR-lci95	OR-uci95	Cochran's Q-derived P	MR-Egger intercept	*P*	Power
Metabolic syndrome	Lung cancer	MR-Egger	122	0.929		0.978	0.597	1.600	0.216	5.43E-04	0.91	
		Weighted median	122	0.769		0.958	0.720	1.275				
		IVW	122	0.970		1.004	0.835	1.206	0.235			
FBG		MR-Egger	14	0.274		0.735	0.434	1.245	0.190	9.56E-03	0.44	
		Weighted median	14	0.931		0.987	0.737	1.323				
		IVW	14	0.351		0.886	0.687	1.143	0.204			
Hypertension		MR-Egger	84	0.169		2.420	0.695	8.424	0.307	−1.13E-02	0.10	
		Weighted median	84	0.803		0.928	0.517	1.666				
		IVW	84	0.606		0.895	0.587	1.364	0.260			
HDL-C		MR-Egger	71	0.754		1.033	0.846	1.260	0.123	2.02E-03	0.68	
		Weighted median	71	0.968		0.997	0.859	1.157				
		IVW	71	0.192		1.070	0.966	1.186	0.137			
TG		MR-Egger	44	0.838		0.982	0.830	1.163	0.102	−3.65E-03	0.47	
		Weighted median	44	0.480		0.950	0.825	1.094				
		IVW	44	0.229		0.936	0.841	1.042	0.110			
WC		MR-Egger	277	0.499		1.170	0.743	1.841	0.007	1.44E-03	0.70	
		Weighted median	277	0.209		1.165	0.918	1.478				
		IVW	277	0.003	0.018	1.270	1.086	1.486	0.007			1.00
Metabolic syndrome	Thyroid cancer	MR-Egger	119	0.234		2.814	0.517	15.314	0.912	−1.52E-02	0.36	
		Weighted median	119	0.207		1.954	0.690	5.530				
		IVW	119	0.349		1.330	0.732	2.418	0.913			
FBG		MR-Egger	13	0.959		0.942	0.105	8.492	0.748	−2.27E-02	0.59	
		Weighted median	13	0.904		0.919	0.234	3.615				
		IVW	13	0.221		0.538	0.200	1.450	0.791			
Hypertension		MR-Egger	74	0.840		1.534	0.025	95.607	0.605	3.40E-03	0.88	
		Weighted median	74	0.817		1.280	0.158	10.368				
		IVW	74	0.323		2.064	0.490	8.700	0.636			
HDL-C		MR-Egger	71	0.706		0.884	0.467	1.672	0.296	1.70E-02	0.28	
		Weighted median	71	0.451		1.220	0.727	2.048				
		IVW	71	0.297		1.194	0.855	1.668	0.289			
TG		MR-Egger	44	0.886		0.958	0.534	1.719	0.708	−2.53E-04	0.99	
		Weighted median	44	0.459		0.813	0.470	1.407				
		IVW	44	0.798		0.954	0.668	1.363	0.745			
WC		MR-Egger	251	0.823		1.176	0.283	4.892	0.150	3.94E-04	0.97	
		Weighted median	251	0.148		1.912	0.795	4.600				
		IVW	251	0.475		1.203	0.725	1.995	0.160			
Metabolic syndrome	Breast cancer	MR-Egger	124	0.337		0.830	0.569	1.212	0.067	2.68E-03	0.46	
		Weighted median	124	0.137		0.883	0.750	1.040				
		IVW	124	0.416		0.952	0.846	1.072	0.071			
FBG		MR-Egger	14	0.454		0.892	0.669	1.191	0.979	1.58E-03	0.81	
		Weighted median	14	0.340		0.916	0.765	1.097				
		IVW	14	0.256		0.921	0.800	1.061	0.988			
Hypertension		MR-Egger	81	0.354		0.675	0.295	1.543	0.030	3.99E-03	0.38	
		Weighted median	81	0.492		0.871	0.587	1.292				
		IVW	81	0.748		0.955	0.719	1.267	0.031			
HDL-C		MR-Egger	71	0.741		0.975	0.839	1.133	0.00001	3.94E-03	0.29	

		Weighted median	71	0.375		1.044	0.950	1.148				
		IVW	71	0.268		1.045	0.966	1.130	0.00001			
TG		MR-Egger	43	0.462		0.959	0.859	1.071	0.085	– 1.36E-03	0.67	
		Weighted median	43	0.293		0.955	0.876	1.041				
		IVW	43	0.084		0.941	0.879	1.008	0.099			
WC		MR-Egger	277	0.691		0.934	0.665	1.310	0.000001	1.34E-03	0.63	
		Weighted median	277	0.546		0.960	0.840	1.097				
		IVW	277	0.832		1.011	0.911	1.123	0.000001			
Metabolic syndrome	Gastric cancer	MR-Egger	129	0.410		1.223	0.759	1.971	0.642	– 7.39E-03	0.12	
		Weighted median	129	0.970		1.006	0.752	1.345				
		IVW	129	0.087		0.858	0.720	1.022	0.606			
FBG		MR-Egger	14	0.673		1.113	0.685	1.810	0.266	– 2.72E-03	0.82	
		Weighted median	14	0.901		1.017	0.773	1.339				
		IVW	14	0.627		1.058	0.843	1.328	0.331			
Hypertension		MR-Egger	82	0.415		0.583	0.160	2.120	0.350	2.46E-03	0.73	
		Weighted median	82	0.101		0.593	0.318	1.107				
		IVW	82	0.137		0.724	0.472	1.109	0.376			
HDL-C		MR-Egger	71	0.087		0.824	0.662	1.025	0.022	9.94E-03	0.07	
		Weighted median	71	0.990		1.001	0.858	1.168				
		IVW	71	0.784		0.984	0.878	1.103	0.012			
TG		MR-Egger	44	0.503		1.054	0.904	1.230	0.170	– 7.38E-03	0.13	
		Weighted median	44	0.470		0.951	0.831	1.089				
		IVW	44	0.463		0.963	0.869	1.066	0.132			
WC		MR-Egger	278	0.499		0.858	0.550	1.337	0.177	2.59E-03	0.49	
		Weighted median	278	0.928		0.989	0.773	1.265				
		IVW	278	0.942		0.994	0.854	1.158	0.182			
Metabolic syndrome	Hepatic cancer	MR-Egger	130	0.208		1.861	0.711	4.872	0.046	– 4.88E-03	0.61	
		Weighted median	130	0.347		1.273	0.770	2.104				
		IVW	130	0.031	0.093	1.472	1.036	2.093	0.051			1.00
FBG		MR-Egger	14	0.347		1.639	0.610	4.403	0.117	– 2.87E-02	0.24	
		Weighted median	14	0.747		1.087	0.655	1.803				
		IVW	14	0.853		0.955	0.585	1.557	0.090			
Hypertension		MR-Egger	84	0.729		0.646	0.055	7.593	0.153	– 6.50E-03	0.63	
		Weighted median	84	0.207		0.472	0.147	1.515				
		IVW	84	0.014	0.084	0.364	0.162	0.817	0.167			1.00
HDL-C		MR-Egger	70	0.360		1.215	0.803	1.837	0.008	– 1.17E-02	0.25	
		Weighted median	70	0.808		1.040	0.757	1.429				
		IVW	70	0.895		0.986	0.798	1.218	0.007			
TG		MR-Egger	40	0.370		1.285	0.748	2.208	0.001	2.15E-03	0.88	
		Weighted median	40	0.193		1.285	0.881	1.875				
		IVW	40	0.059		1.332	0.989	1.794	0.001			
WC		MR-Egger	279	0.255		1.607	0.711	3.631	0.117	– 6.69E-03	0.33	
		Weighted median	279	0.486		0.848	0.533	1.349				
		IVW	279	0.520		1.096	0.828	1.450	0.117			
Metabolic syndrome	Colorectal cancer	MR-Egger	119	0.927		1.032	0.523	2.039	0.278	2.18E-03	0.74	
		Weighted median	119	0.873		1.032	0.702	1.518				
		IVW	119	0.255		1.149	0.905	1.460	0.298			
FBG		MR-Egger	13	0.205		0.557	0.238	1.306	0.680	2.34E-02	0.16	
		Weighted median	13	0.575		0.861	0.510	1.453				
		IVW	13	0.970		0.993	0.676	1.457	0.565			

Table 2

(*Continued*)

Exposure	Outcome	Method	nSNP	*P*	P-FDR	OR	OR-lci95	OR-uci95	Cochran's Q-derived P	MR-Egger intercept	*P*	Power
Hypertension		MR-Egger	74	0.782		0.796	0.160	3.976	0.636	−1.80E-03	0.84	
		Weighted median	74	0.764		0.879	0.380	2.036				
		IVW	74	0.177		0.680	0.389	1.190	0.666			
HDL-C		MR-Egger	70	0.437		0.897	0.682	1.179	0.041	9.75E-04	0.89	
		Weighted median	70	0.717		1.037	0.852	1.262				
		IVW	70	0.205		0.912	0.791	1.051	0.049			
TG		MR-Egger	43	0.960		0.993	0.760	1.297	0.070	−3.04E-03	0.67	
		Weighted median	43	0.529		0.933	0.753	1.157				
		IVW	43	0.532		0.949	0.806	1.118	0.082			
WC		MR-Egger	124	0.226		1.601	0.750	3.418	0.360	−3.57E-03	0.58	
		Weighted median	124	0.026		1.601	1.058	2.422				
		IVW	124	0.054		1.311	0.996	1.726	0.376			
Metabolic syndrome	Malignant neoplasm of esophagus	MR-Egger	129	0.096		11.541	0.663	200.980	0.021	−2.79E-02	0.32	
		Weighted median	129	0.006		9.297	1.908	45.302				
		IVW	129	0.041	0.123	2.994	1.047	8.561	0.021			0.99
FBG		MR-Egger	14	0.579		0.452	0.029	6.955	0.850	2.40E-02	0.69	
		Weighted median	14	0.821		0.814	0.136	4.874				
		IVW	14	0.667		0.744	0.194	2.854	0.887			
Hypertension		MR-Egger	80	0.807		2.356	0.003	2204.046	0.780	−2.16E-04	1.00	
		Weighted median	80	0.439		3.932	0.122	126.259				
		IVW	80	0.472		2.311	0.235	22.689	0.804			
HDL-C		MR-Egger	69	0.308		1.733	0.608	4.940	0.304	−1.86E-02	0.48	
		Weighted median	69	0.613		1.238	0.542	2.827				
		IVW	69	0.417		1.255	0.725	2.170	0.319			
TG		MR-Egger	39	0.344		0.622	0.235	1.643	0.625	3.25E-02	0.25	
		Weighted median	39	0.821		0.909	0.398	2.078				
		IVW	39	0.937		0.976	0.533	1.787	0.607			
WC		MR-Egger	274	0.103		6.308	0.693	57.448	0.464	−1.48E-02	0.42	
		Weighted median	274	0.031		3.864	1.131	13.207				
		IVW	274	0.011	0.066	2.709	1.252	5.865	0.470			0.92
Metabolic syndrome	Malignant neoplasm of kidney	MR-Egger	130	0.343		1.840	0.525	6.451	0.848	−4.45E-03	0.72	
		Weighted median	130	0.085		1.889	0.916	3.897				
		IVW	130	0.093		1.484	0.936	2.352	0.860			
FBG		MR-Egger	14	0.889		0.906	0.233	3.519	0.850	1.25E-02	0.67	
		Weighted median	14	0.851		1.088	0.450	2.630				
		IVW	14	0.634		1.176	0.603	2.291	0.886			
Hypertension		MR-Egger	83	0.392		0.200	0.005	7.811	0.108	1.02E-02	0.61	
		Weighted median	83	0.188		0.320	0.059	1.743				
		IVW	83	0.251		0.492	0.146	1.651	0.118			
HDL-C		MR-Egger	71	0.562		1.159	0.706	1.904	0.637	−5.54E-03	0.65	
		Weighted median	71	0.676		1.092	0.723	1.650				
		IVW	71	0.704		1.052	0.811	1.364	0.662			
TG		MR-Egger	44	0.492		1.186	0.732	1.919	0.379	1.90E-03	0.89	
		Weighted median	44	0.408		1.195	0.784	1.822				
		IVW	44	0.188		1.219	0.908	1.636	0.420			
WC		MR-Egger	275	0.447		1.537	0.508	4.649	0.346	−2.09E-03	0.82	

		Weighted median	275	0.082		1.769	0.930	3.367				
		IVW	275	0.115		1.364	0.927	2.006	0.361			
Metabolic syndrome	Bladder cancer	MR-Egger	128	0.712		0.999	0.995	1.003	0.051	2.86E-06	0.94	
		Weighted median	128	0.612		0.999	0.997	1.002				
		IVW	128	0.406		0.999	0.998	1.001	0.058			
FBG		MR-Egger	14	0.319		1.002	0.998	1.006	0.414	– 1.42E-05	0.87	
		Weighted median	14	0.119		1.002	0.999	1.005				
		IVW	14	0.061		1.002	1.000	1.004	0.493			
Hypertension		MR-Egger	82	0.720		0.998	0.988	1.008	0.143	3.24E-05	0.57	
		Weighted median	82	0.520		1.002	0.997	1.007				
		IVW	82	0.586		1.001	0.997	1.004	0.154			
HDL-C		MR-Egger	69	0.171		1.001	1.000	1.003	0.165	– 6.12E-05	0.12	
		Weighted median	69	0.852		1.000	0.999	1.001				
		IVW	69	0.936		1.000	0.999	1.001	0.133			
TG		MR-Egger	43	0.059		0.998	0.997	1.000	0.743	7.05E-05	0.09	
		Weighted median	43	0.133		0.999	0.998	1.000				
		IVW	43	0.387		1.000	0.999	1.001	0.653			
WC		MR-Egger	266	0.832		1.000	0.997	1.004	0.455	1.38E-05	0.61	
		Weighted median	266	0.035		1.002	1.000	1.004				
		IVW	266	0.047	0.183	1.001	1.000	1.002	0.468			1.00
Metabolic syndrome	Prostate cancer	MR-Egger	119	0.296		0.810	0.547	1.200	0.010	2.67E-03	0.49	
		Weighted median	119	0.283		0.882	0.702	1.109				
		IVW	119	0.272		0.921	0.795	1.067	0.011			
FBG		MR-Egger	14	0.554		1.137	0.752	1.717	0.137	– 5.48E-03	0.56	
		Weighted median	14	0.959		1.006	0.805	1.256				
		IVW	14	0.863		1.017	0.836	1.239	0.162			
Hypertension		MR-Egger	81	0.380		0.605	0.198	1.846	0.0003	3.18E-03	0.61	
		Weighted median	81	0.853		0.958	0.608	1.509				
		IVW	81	0.235		0.796	0.547	1.160	0.0003			
HDL-C		MR-Egger	69	0.692		0.969	0.827	1.134	0.010	2.77E-03	0.48	
		Weighted median	69	0.683		0.977	0.874	1.092				
		IVW	69	0.689		1.017	0.937	1.104	0.011			
TG		MR-Egger	42	0.837		0.985	0.850	1.141	0.006	2.21E-03	0.62	
		Weighted median	42	0.629		0.971	0.863	1.093				
		IVW	42	0.763		1.014	0.926	1.111	0.007			
WC		MR-Egger	274	0.165		0.787	0.561	1.103	0.0002	7.94E-04	0.78	
		Weighted median	274	0.028		0.821	0.688	0.979				
		IVW	274	0.001	0.006	0.823	0.732	0.925	0.0003			1.00

the visualization of scatter plots, funnel plots, leave-one-out analyses, and forest plots is shown in Supplementary Material 2 (Supplemental Digital Content 2, http://links.lww.com/JS9/D199). Detailed information on the SNPs for Metabolic Syndrome can be found in Supplementary Material 3 (Supplemental Digital Content 3, http://links.lww.com/JS9/D200) and all SNPs for the components of Metabolic Syndrome are shown in Supplementary Material 4 (Supplemental Digital Content 4, http://links.lww.com/JS9/D201).

Lung cancer

For lung cancer, we did not detect a causal relationship between MetS and lung cancer (OR, 1.004; 95% CI: 0.835–1.206; $P = 0.970$), but WC appeared to increase the risk of lung cancer, even after correction, the results are still significant (OR, 1.270; 95% CI: 1.086–1.486; $P = 0.003$, P-FDR = 0.084). We removed all outliers and it is unlikely that there was pleiotropy (Table 2).

Thyroid cancer

Our findings suggest a causal relationship between MetS and thyroid cancer is unlikely (OR, 1.330; 95% CI: 0.732–2.418; $P = 0.349$). On further investigation, we also did not find a causal association between the five major components of MetS (FBG, Hypertension, HDL-C, TG, and WC) and thyroid cancer. The MR-PRESSO test did not reveal any outliers, and Cochran's Q test and MR-Egger regression INTERCEPT results also showed no heterogeneity or pleiotropy, which is sufficient to demonstrate the robustness of our results (Table 2).

Breast cancer

Our results show no causal relationship between MetS and breast cancer (OR, 0.952; 95% CI: 0.846–1.072; $P = 0.416$). In the same way, no causal association was found between the five components of the MetS and breast cancer. The results of the MR-Egger regression intercept suggest the unlikely presence of horizontal pleiotropy that can influence the results of MR analysis (Table 2).

Gastric cancer

Our Mendelian randomization study found no causal relationship between genetically predicted MetS and gastric cancer (OR, 0.858; 95% CI: 0.720–1.022; $P = 0.087$). When we performed component analyses, we did not find a causal relationship between any component and gastric cancer. Although we found some heterogeneity when analyzing HDL-C and gastric cancer, pleiotropy tests did not show any level of pleiotropy (Table 2).

Hepatic cancer

Our MR analysis found that MetS could increase the risk of hepatic cancer, which, corrected with the FDR method, still showed potential causality (OR, 1.472; 95% CI: 1.036–2.093; $P = 0.031$, P-FDR = 0.093), with all three main analyses showing the same trend. The test of heterogeneity and pleiotropy of MR results suggested no heterogeneity and no pleiotropy. Interestingly, when we performed an analysis between components of the MetS and hepatic cancer, we found that hypertension appeared to reduce the risk of hepatic cancer (OR, 0.364; 95% CI: 0.162–0.817; $P = 0.014$, P-FDR = 0.084), with sensitivity analyses showing no heterogeneity and no pleiotropy (Table 2).

Colorectal cancer

Our results indicate that there is no causal relationship between MetS and colorectal cancer (OR, 1.472; 95% CI: 1.036–2.093; $P = 0.031$). Similarly, we likewise did not find a causal relationship between the components of MetS and colorectal cancer, and the results of the test of heterogeneity and pleiotropy attest to the reliability of our conclusions (Table 2).

Esophagus cancer

For esophagus cancer, we observed a weak causal association between Metabolic Syndrome and esophagus cancer, but after we corrected for this using the FDR method, no association was detected (OR, 2.994; 95% CI: 1.047–8.561; $P = 0.041$, P-FDR = 0.123). The MR-Egger intercept test did not detect horizontal pleiotropy. There was a positive correlation between WC and esophagus cancer among the components of MetS (OR, 2.709; 95% CI: 1.252–5.865; $P = 0.011$, P-FDR = 0.066), and sensitivity analysis did not reveal any heterogeneity with horizontal pleiotropy (Table 2).

Kidney cancer

We did not find any causal relationship between either the MetS or its components and kidney cancer (OR, 1.484; 95% CI: 0.936–2.352; $P = 0.093$), and sensitivity analyses indicated no heterogeneity or pleiotropy in our results (Table 2).

Bladder cancer

Our study shows that MetS is not associated with the risk of bladder cancer (OR, 0.999; 95% CI: 0.998–1.001; $P = 0.406$). No factors that increase the risk of bladder cancer were identified in the components of the MetS. Although heterogeneity was present, the results of our test of pleiotropy showed that no pleiotropy bias was introduced (Table 2).

Prostate cancer

Our findings suggest that no causal relationship has been observed between MetS and prostate cancer (OR, 0.921; 95% CI: 0.795–1.067; $P = 0.272$), Cochran's Q test and MR-Egger regression intercept showed no heterogeneity or pleiotropy. In addition, we found that WC reduced the risk of prostate cancer (Table 2), and this association was significant with or without correction for the FDR method (OR, 0.823; 95% CI: 0.732–0.925; $P = 0.001$, P-FDR = 0.006).

Sensitivity analysis

We performed sensitivity analyses using Cochran's Q test, Funnel plot, MR-Egger regression intercept, MR-PRESSO, and Leave-one-out analysis. Although heterogeneity was detected in some of the results, it did not invalidate the IVW using a random effects model of MR results, which may balance the combined heterogeneity. Furthermore, the MR-Egger intercept did not detect any pleiotropy either, suggesting that MR estimation does not introduce pleiotropy bias in the presence of a heterogeneous background. The funnel plot is symmetric. We also used Leave-one-out analysis to test the stability of our results.MR-PRESSO was

used to detect outliers, and all outliers were removed for all instrumental variables involved in our study. In addition, the values of the Statistical power of our main results are all greater than 0.8, which means that we are unlikely to make a Type II error.

Discussion

As far as we know, this is the first Mendelian randomization study to comprehensively explore MetS and cancers. From a genetic perspective, we found that MetS may increase the risk of hepatic cancer. In further analyses of the components of the MetS, WC appeared to have a significant effect on cancer. As WC increased, the risk of lung cancer increased. WC may reduce the risk of prostate cancer. Interestingly, we also observed that hypertension may reduce the risk of hepatic cancer.

MetS has been reported to be associated with an increased risk of several commonly occurring cancers[28,29]. From simple steatosis to steatohepatitis, it then evolves to liver fibrosis, cirrhosis, and eventually to the end stage – hepatic cancer. Nonalcoholic fatty liver disease (NAFLD) serves as a bridge between the MetS and hepatic cancer. Insulin resistance and triglyceride accumulation are the main pathogenic mechanisms of NAFLD[30], and this has commonalities with the features of MetS (i.e. hypertension, dyslipidemia, central obesity, and dysglycaemia)[31,32]. The relationship between MetS and hepatic cancer may be mediated through lipid metabolism and glucose metabolism. Few studies have been conducted on the etiology of hypertension in hepatic cancer. Raffetti *et al*.[33] reported that hypertension does not affect the survival of patients with hepatic cancer. A clinical trial in Japan showed that patients with hepatocellular carcinoma and hypertension who received angiotensin II blockers had significantly better liver function[34], highlighting the fact that hypertension does not appear to be a risk factor for hepatic cancer. The mechanism of hypertension and cirrhosis was reported as early as 2006, and it is rare for arterial hypertension to show up in cirrhotic patients, even in the presence of renal vascular disease and high circulating renin activity[35]. A possible reason for this is that antihypertensive drugs commonly used in hypertensive patients can also be used in the treatment of cirrhosis and portal hypertension, which may reduce the risk of hepatic cancer[36].

Although Metabolic Syndrome appeared to increase the risk of esophagus cancer, this causality disappeared when we performed a false discovery rate correction. The number of studies on Metabolic Syndrome and esophagus cancer is small, with one Korean study suggesting that MetS was shown to increase the risk of squamous esophagus cancer[37]; By analyzing data from the SEER database, Drahos *et al*.[38] demonstrated that patients with MetS have a greater than normal risk of developing esophagus adenocarcinoma, which is not consistent with the results of our study. This may be because these studies were on tumor subtypes, whereas our GWAS summary data included all types of esophagus cancer. Another reason that cannot be ignored is the limitation of retrospective studies. WC may increase the risk of esophagus cancer in a component analysis, a finding in agreement with the results of a meta-analysis of prospective studies[39], which could be explained by the fact that increased intra-abdominal pressure in patients with large WC and abdominal fat contributes to gastro-esophageal reflux disease (GERD), transient relaxation of the lower esophageal sphincter, and hiatal hernia, leading to an increased risk of developing Barrett's esophagus[40–42]. A further potential reason is that people with large WC and obesity are more likely to trigger a systemic inflammatory response, which can accelerate the development of precancerous lesions[43]. Similarly, we did not detect a causal association between WC and bladder cancer after FDR correction. Roswall *et al*.[44] conducted a comprehensive analysis of anthropometric measures and bladder cancer and did not find an association between WC and bladder cancer; another meta-analysis, which included 25 cohort studies, also showed that no statistically significant associations were observed between overweight or obesity and bladder cancer[45], providing support for our conclusions.

In addition to the above, WC has been found to be positively correlated with the risk of lung cancer. A meta-analysis suggests that abdominal obesity may contribute to the development of lung cancer, with a greater WC to waist-to-hip ratio associated with a higher risk of lung cancer[46], and this may be due to an inflammatory response in adipose tissue. Our research suggests that WC may reduce the risk of prostate cancer. Actually, the relationship between WC and prostate cancer has been controversial. In a large-scale prospective cohort study, Jochems *et al*.[47] found that both BMI and WC were negatively associated with limited prostate cancer. Another study suggests that abdominal obesity may be associated with an increased risk of prostate cancer, a trend that is more significant in aggressive prostate cancer[48]. Several meta-analyses have focused on BMI, but the results have mostly been invalid or weak[49–51]. The advantage of our approach is that we can minimize the interference of confounding factors and the conclusions are more reliable.

What is surprising is that we found our findings to be different from the conclusions of some earlier studies. Interestingly, a recently performed meta-analysis of prospective studies showed that Metabolic Syndrome increased the risk of colorectal cancer and hepatic cancer and was not associated with gastric cancer[29]. This seems to be a different conclusion from ours. Still, Zhan *et al*. additionally did a comprehensive Mendelian randomization, and the results of their Mendelian randomization study were consistent with ours. They did not find any significant causal association between Metabolic Syndrome and colorectal or gastric cancer[29].

We are the first study to conduct a Mendelian randomization analysis of Metabolic Syndrome and multiple cancers. Many previous studies have shown that Metabolic Syndrome may increase the risk of some cancers[52–54], but most of these studies were retrospective or prospective. Although there have been some meta-analyses[5,45,55,56], as mentioned earlier, the insufficient number of RCT studies may affect the accuracy of the meta-analysis results to some extent.

In summary, our study supports the promotional role of the MetS and its constituents in certain cancers. Both MetS and cancer are the main public health burdens worldwide, whereas the occurrence of MetS can be avoided, and interventions in lifestyle and dietary habits can be effective in preventing the occurrence of MetS and cancer[57].

There are several limitations in our study. Firstly, as this study only included a sample of Europeans, the results may not apply to other racial groups with different lifestyles and cultural backgrounds. Second, because MR analyses extrapolated causal

hypotheses by using random assignment of genetic variants, it is difficult to fully distinguish between mediation and pleiotropy using MR methods. Instrumental variables in our genome may influence one or more phenotypes. Finally, we aim to comprehensively explore the relationship between Metabolic Syndrome and cancer in a broad sense, and more research is needed in the future to unlock the links between Metabolic Syndrome and the histological subtypes of various cancers.

Conclusion

Genetically predicted Metabolic Syndrome may increase the risk of some cancers. Our study strengthens the evidence for a causal relationship between MetS and cancer. Prevention and management of MetS may serve to reduce the public health burden of cancer.

Ethical approval

All data analyzed in the article were taken from public database and no further ethical approval is required.

Consent

Not applicable.

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Author contribution

L.Z.: conceptualization; J.Z. and Y.Z.: data curation; H.G., L.W., and J.Z.: formal analysis; T.W.: funding acquisition; L.Z., Z.L., J.Z., X.C., and W.S.: investigation; L.Z., L.W., H.S., and X. D.: methodology; X.C.: project administration; Y.Z. and W.S.: resources; Q.X., H.G., Q.W., and Y.T.: software; X.D. and T.W.: supervision; L.Z., Q.X., J.Z., Q.W., and H.S.: validation; L.Z. and Q.X.: visualization; L.Z.: writing – original draft; L.Z. and T.W.: writing – review and editing.

Conflicts of interest disclosure

All authors have no conflicts of interest or financial ties to disclose.

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Data availability statement

All data analyzed in the article were taken from public database. The data presented in the article may be requested by consulting the correspondence author.

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