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The association of metabolic syndrome with rotator cuff tendinopathy: a two-sample Mendelian randomization study

Ziqin Cao[1,2], Qiangxiang Li[2,3,4], Yajia Li[2,5*] and Jianhuang Wu[1,2*]

Abstract

Background Observational research reported the underlying correlation of metabolic syndrome (MetS) and its components with rotator cuff tendinopathy (RCT), but their causality remained unclear. This study aimed to investigate whether genetically predicted MetS was related to the risk of RCT.

Methods Both univariable and multivariable Mendelian randomization (MR) analysis was applied using summary-level data from the most comprehensive genome-wide association studies to estimate the associations of MetS and its component with RCT, with the inverse variance weighted (IVW) as the primary method, and the method of Causal Analysis Using Summary Effect Estimates (CAUSE) as a supplement for false positives detection. The mediation analysis was furtherly used for the assessment of direct and indirect effects.

Results Univariable analysis revealed that genetically predicted MetS (OR: 1.0793; 95% CI 1.0311 to 1.1297), body mass index (BMI) (OR 1.2239; 95% CI 1.1357 to 1.3189), and waist circumference (WAC) (OR 1.3177; 95% CI 1.2015 to 1.4451) had a significant positive association with the risk of RCT. Triglycerides and systolic blood pressure were suggestively associated with RCT risk. These associations were also identified by CAUSE. There was independent causality of BMI (OR: 1.1806; 95% CI 1.0788 to 1.2920) and WAC (OR 1.3716; 95% CI 1.2076 to 1.5580) on RCT after adjustment for confounders. No mediator was found in the causal associations.

Conclusion Our study revealed the genetic causality of MetS and its components, especially BMI and WAC, with RCT risk. Early prevention and diagnosis of excess central adiposity contributing to MetS are significant in the RCT risk management.

Keywords Metabolic syndrome, Rotator cuff tendinopathy, Body mass index, Waist circumference, Mendelian randomization

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Introduction

Shoulder pain ranks third among primary care musculo-skeletal consultations and has a self-reported prevalence ranging from 16% to 26%[1–3]. Rotator cuff syndrome (RCS), also called rotator cuff tendinopathy (RCT) produces major clinical signs of pain and weakness during external rotation and elevation and is considered to account for over 70% of conditions of shoulder pain[2]. The condition involves subacromial structures, such as rotator cuff tendinitis/tendinosis, subacromial bursitis, and shoulder impingement syndrome[4–6]. RCT is commonly refractory to treatment, leading to restriction of daily activities and considerable socio-economic burden[7]. Extrinsic and inherent mechanisms associated with RCT are multifactorial and understanding of the condition is limited as a result.

Metabolic syndrome (MetS), is known as a complex group of metabolic disorders including central obesity, elevated blood pressure, hyperglycemia, and hyperlipidemia. The condition affects billions of the worldwide population and shows a rising global prevalence[8, 9], contributing to a serious health burden and mortality[10–12]. Epidemiological studies have indicated a potential relationship between MetS and RCT. Pooled meta-analyses have shown that diabetes [13] and dyslipidemia [14] are associated with a respective 1.24 and 1.17-fold increased risk of RCT. Hyperglycemia, hypertension, and excess body weight have also been found to be linked with symptomatic rotator cuff tears[15]. It has also been shown that hypertension [16] and excessive waist circumference [17] were associated with increased RCT risks in different observational studies. However, associations of MetS or its components with RCT identified by traditional observational studies are likely to be affected by confounders, limited sample capacity, short follow-up time, and reverse causation[18]. Thus, any causal effects of MetS in determining RCT risk remain unclear.

This study has applied Mendelian randomization (MR) analysis, an approach of causal inferences with relative robustness, to investigate associations of MetS with RCT to overcome the limitations in traditional study designs. Genetic variants closely related to exposure were used as instrumental variables (IVs) to eliminate the effects of confounders or reverse causality[18–20]. Genome-wide association studies (GWAS) have provided IVs associated with the target phenotype. The IVs associated with 10 predominant ingredients for MetS were identified, including body mass index (BMI), waist circumference (WAC), serum triglycerides (TC), high-density lipoprotein (HDL) cholesterol, fasting serum insulin (INS), fasting serum glucose (GLU), type 1 and type 2 diabetes (T1D and T2D), diastolic blood pressure (DBP), and systolic blood pressure (SBP). Additional mediators, such as alcohol and cigarette consumption, were also taken into consideration. A two-sample MR method, including both univariable MR (UVMR) and multivariable MR (MVMR), was used to explore genetic causal associations of MetS or its component conditions with RCT.

Methods

Data sources and instrumental variables selection

This study was guided by the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) Statement.The following principal assumptions were made (Additional file 1: Figure S1): genetic variables should be strongly related to the exposure and variables could only have effects on the outcome through exposure with effects being independent of any confounding factors. Publicly available summary-level data was used and no additional ethical approval was needed. RCT summary data was obtained from the FinnGen Biobank Analysis Consortium database (Release 8, https://finngen.gitbook. io/documentation/) with diagnosis according to ICD-10 (International Classification of Diseases) criteria. A total of 274320 participants, including 21998 cases and 253122 controls, of European ancestry, were analyzed. The MetS dataset was obtained from a large GWAS study [21] using the UK biobank cohort, including 291107 participants aged 40–69 years of European ancestry. BMI (mg/kg^2) data was obtained from a large GWAS meta-analysis which included 681275 individuals of European ancestry[22], WAC (462,166 individuals), HDL (403,943 individuals), and TC (441,016 individuals) were obtained from the UK biobank database[23]. Recent GWAS datasets for T1D (n=24840)[24] and T2D (n= 655666)[25] patients of European ancestry were also used. GLU and INS were obtained from two European GWAS cohorts with 200622 and 151013 participants, respectively[26]. SBP and DBP were obtained from a European cohort of the International Consortium of Blood Pressure with 757601 individuals. MVMR and a two-step mediation MR model were constructed for the component conditions of MetS to adjust the mediation effect for potential confounders. Five mediators were adjusted for BMI, WAC, HDL, and TC, including alcohol intake, cigarette consumption, age at recruitment, genetic sex, and level of physical activity (moderate or vigorous). BMI was additionally adjusted as a mediator for the other six components of MetS. All mediators were obtained from different databases than the one used for the outcome to avoid the influence of sample overlap. A strict genome-wide significant threshold of $p < 5 \times 10^{-8}$ was set to filter out all strongly related SNPs and a process of the clump with a window of kb = 10000 and $r^2 = 0.001$ was performed to avoid linkage disequilibrium (LD). The

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phenome-wide association studies database (pheWAS) was also matched to prevent the potential linkage between SNPs and confounders with the threshold of p-value $< 5 \times 10^{-6}$. All the estimates are given per one SD unit increase and the effect size is presented as the odds ratio (OR) with a 95% confidence interval (CI).

Statistical approach

UVMR was performed using R packages MRPRESSO (version 1.0) and Two-Sample MR (version 0.5.6). Six different statistical methods were combined to evaluate the causal effects of MetS on RCT and a Bonferroni correction was applied to the UVMR to avoid multiple comparison errors. A post-correction p threshold < 0.0083 was considered statistically significant and $0.0083 < p < 0.05$ was considered suggestively significant.

The inverse-variance weighted method (IVW) produces a relatively accurate assessment by combining all the Wald values of causality for each IV, with the assumption of invalid genetic instruments [27, 28]. The MR-Egger and MR pleiotropy residual sum and outlier (MR-PRESSO) methods were used to test the violation caused by directional pleiotropy. The intercept of the MR-Egger regression quantified pleiotropy across IVs, and the MR-Egger method could estimate a relatively robust value independent of IV validity, and obtain an adjusted result via the regression slope and intercept [29, 30]. MR-PRESSO was used for the detection of distorted effects related to horizontal pleiotropy and provided a corrected causal effect. The weighted model allowed the generation of a valid MR result even when the majority of IVs were invalid [31]. The weighted-median estimator method could give a consistent valid inference under the condition of over 50% of valid IVs [32]. MR-Robust Adjusted Profile Score (MRAPS) was applied to obtain an accurate estimate for the causality when there was ideally independent of IVs [33]. However, other methods produced wider confidence intervals (CI) than the IVW method and were only considered complements [34]. Thus, the MR-Egger Regression Model would be applied when significant pleiotropy was detected, and the MR-PRESSO model was applied to detect final outliers. Otherwise, the results by the IVW result method were given priority.

MVMR and two-step mediation MR were performed using the R packages, Two-Sample MR (version 0.5.6), MVMR (version 0.3.0), and MendelianRandomization (version 0.5.1). Random-effect IVW and MR-Egger models were constructed in MVMR and selected IVs were further analyzed by the two multi-variable models with an independent significance level of $p < 0.05$. MR-Egger results were prioritized under the condition of significant pleiotropy (p-value < 0.05). A two-step mediation MR analysis based on the difference method [35] was conducted to measure the mediation effects and mechanisms for each mediator. The total effect was estimated by the IVW method without correction of heterogeneity or pleiotropy and the direct effect was estimated using the multivariable IVW method. The indirect effect of MetS on RCT via the mediator was generated from the differences between total and direct estimates and the proportion mediated was calculated if the indirect effect was significant [36]. A value of $p < 0.05$ was considered statistically significant in the MVMR and mediation MR analysis.

Sensitivity analysis

F-statistics were used to test the first assumption, calculated according to the formula: $F = \left(\frac{n-k-1}{k} \right) \left(\frac{R^2}{1-R^2} \right)$ (n: sample size; k: number of instrumental variables; R2: variance of exposure explained by selected instrumental variables generated by the MR Steiger directionality test). The conditional F-statistic was generated using the R package, MVMR, and was used to measure the instrument strength in MVMR to test whether the SNP strongly predicts each exposure conditional on the other exposures. Both an F or conditional F < 10 suggested significant weak instrument bias. Cochran's Q-statistic was used to assess the heterogeneity caused by invalid IVs and a p-value < 0.05 was considered to indicate significant heterogeneity [38] in which case, a random-effect IVW model was adopted. The Causal Analysis Using the Summary Effect Estimates (CAUSE) method which utilizes the full genome-wide summary results rather than genome-wide significant loci only was used to correct the bias due to correlated and uncorrelated horizontal pleiotropy. Sample overlap was corrected by combining the largest sample sizes available for both exposure and outcome and improving the statistical power. Those associations inconsistent with the results of CAUSE were likely to have a false-positive error [39]. An arbitrary value of $p < 1 \times 10^{-3}$ for SNPs was set for the CAUSE analysis. If the pareto-k-diagnostic test reported a high-risk k value, a more strict p threshold would be adopted. A value of $p < 0.05$ was considered statistically significant for CAUSE analysis. The proportion of phenotypic variance explained by all SNPs (R2xy) was calculated by MR Steiger methods and was used to measure heritability. A binary-outcome-model from the mRnd tools was used to evaluate the statistical power of the current study (https://shiny.cnsgenomics.com/mRnd/). A power lower than 80% would be considered insufficient and the minimum sample size required at 80% power calculated. Leave-one-out analysis was performed to detect an unstable SNP which showed a disproportionately large individual influence on IVW regression coefficients. The

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Table 1 Sensitivity analysis of the UVMR

Exposure	Number of IVs	Heterogeneity test		MR-Egger pleiotropy test		MR-PRESSO global and distorted outlier test			R2xz	F statistics	Statistics power		Minimum number of participants at 80% power
		Q value	P-value	Intercept	P-value	RSSobs	P-value	Number of outliers			Power	NCP	
Metabolic syndrome	77	656.4696	5.13E-08	0.0021	2.16E-01	659.3605	3.00E-04	2	11.96%	75.6922	97%	14.53	NA
Body mass index	475	486.6747	5.04E-07	0.0000	9.83E-01	512.8289	2.00E-04	7	4.91%	73.9818	100%	46.67	NA
Waist circumference	344	466.5209	1.08E-08	−0.0029	3.28E-02	479.2033	2.00E-04	6	4.49%	63.0433	100%	84.94	NA
HDL cholesterol	308	336.4586	2.20E-03	0.0024	7.07E-02	363.4878	1.00E-04	7	11.76%	174.6032	6%	0.07	32,989,842
Triglycerides	267	44.7670	1.78E-01	−0.0033	3.88E-01	57.3322	1.04E-01	5	9.63%	175.9911	83%	8.46	NA
Type 1 diabetes	38	148.4480	1.20E-02	0.0072	1.85E-02	164.9014	5.00E-03	0	17.93%	142.5518	7%	0.16	NA
Type 2 diabetes	113	96.4514	1.51E-03	−0.0030	3.99E-01	108.7939	3.00E-04	2	13.95%	940.3147	51%	3.96	544,383
Fasting glucose	60	50.3129	5.70E-02	−0.0014	8.53E-01	52.8547	5.90E-02	3	4.40%	153.7989	43%	3.17	678,174
Fasting insulin	37	556.1044	1.85E-05	−0.0017	3.15E-01	603.9387	1.00E-04	0	1.75%	51.6940	84%	8.81	NA
Systolic blood pressure	426	614.9849	8.85E-09	−0.0014	3.99E-01	629.4504	1.00E-04	4	4.63%	86.3792	5%	0.02	113,387,310
Diastolic blood pressure	430	99.0027	3.94E-02	0.0053	1.25E-01	104.7258	4.87E-02	8	4.80%	88.7655	5%	0.02	1,599,783,962

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identification of such an SNP indicates that conclusions should be drawn with caution[31].

Results

Genetic instruments

A total of 77 SNPs were identified as IVs for MetS, 475 were for BMI, 344 were for WAC, 308 were for HDL, 267 were for TC, 38 were for T1D, 113 were for T2D, 60 were for GLU, 37 were for INS, 426 were for SBP and 430 were for DBP (Additional file 2:Table S1-S11). The sensitivity analysis is shown in Table 1. MetS (11.96%), HDL (11.76%), TC (9.63%), T1D (17.93%), and T2D (13.95%) showed relatively high heritability but BMI (4.91%), WAC (4.49%), GLU (4.40%), INS (1.75%), SBP (4.63%) and DBP (4.80%) showed relatively low heritability. F-statistics indicated high instrumental strength for all exposures, ranging from 63.04 to 940.31. HDL (6%), T1D (7%), T2D (51%), GLU (43%), SBP (5%), and DBP (5%) all generated insufficient statistical power, perhaps due to insufficient sample size and low heritability.

UVMR analysis

All traits showed significant heterogeneity except for INS (Q=50.313; p=0.057) while only T2D (intercept=0.0072; p=0.0185) and HDL (intercept= 0.003; p=0.033) showed pleiotropy. No distorted effect outliers were detected by MR-PRESSO analysis.

MetS (OR: 1.0793; 95% CI 1.0311 to 1.1297; p=1.57E-03), BMI (OR:1.2239; 95% CI 1.1357 to 1.3189; p=1.82E-07) and WAC (OR: 1.3177; 95% CI 1.2015 to 1.4451; p=1.05E-08) were all causally related to RCT while TC (OR 1.3177; 95% CI 1.2015 to 1.4451; p=1.94E-02) and SBP (OR 1.0045; 95% CI 1.0003 to 1.0089; p=3.59E-02) had a suggestively significant association with RCT. T2D also showed a significant positive effect on RCT (IVW OR: 1.10534; 95% CI 1.0172 to 1.0909; p=3.57E-03). However, after the MR-Egger correction, no significant association between T2D and RCT remained (MR-Egger OR: 0.9620; 95% CI 0.8864 to 1.0441; p=3.56E-01) (Fig. 1).

The CAUSE models gave similar results (Additional file 1:Figure S4). A genetically determined causal association was found for MetS-RCT (CAUSE OR 1.0408; 95% CI 1.0202 to 1.0725; p=0.023), BMI-RCT (CAUSE OR 1.1503; 95% CI 1.0618 to 1.2461; p=0.024) and WAC-RCT (CAUSE OR 1.2214; 95% CI 1.1504 to 1.2840; p=0.001) and a suggestively significant association for TC (CAUSE OR: 1.0101; 95% CI 0.7558 to 1.3100; p=0.859) and SBP (CAUSE OR: 1.0202; 95% CI 0.9900 to 1.0513; p=0.520) were caused by horizontal pleiotropy.

The Wald ratio estimates for individual SNPs are described in Additional file 2: Table S12-S22. Leave-one-out plots are shown in Additional file 1: Figure S3 and indicated that no individual genetic variants appeared to significantly affect the results under the Bonferroni corrected threshold. Scatter plots are presented in Additional file 1: Figure S2.

MVMR and mediation effect analysis

MVMR models were built for MetS components to avoid the influence of other confounders (Fig. 2 and Additional file 2: Table S23). Weak instrumental strength was only found for T1D (conditional F=2.5323) and INS (conditional F=3.5613). Heterogeneity remained significant across all components.

Five mediators were controlled for BMI, WAC, HDL, and TC. Significant pleiotropy was only found in the MVMR models of HDL (intercept= 0.003, p=0.045) and TC (intercept=0.003, p=0.024). There was strong evidence for a causal effect of BMI (OR: 1.1806; 95% CI 1.0788 to 1.2920; p=0.000) and WAC (OR: 1.3716; 95% CI 1.2076 to 1.5580; p=0.000) on the increased risk of RCT. T2D, GLU, INS, SBP, and DBP gave no significant pleiotropy in the MVMR models of T1D. No direct causal association was identified after controlling for six mediators.

Details of mediation MR analysis are shown in Fig. 3. The directions of the total effect were mainly consistent with the UVMR results. BMI (total OR 1.2237; 95% CI 1.1298 to 1.3255; p=7.20E-07), WAC (total OR 1.3208; 95% CI 1.1943 to 1.4606; p=6.00E-08), HDL (total OR: 0.9259; 95% CI 0.8661 to 0.9898; p=2.38E-02), TC (total OR: 1.090; 95% CI 1.0250 to 1.1583; p=5.93E-03), T1D (total OR: 1.0184; 95% CI 1.0050 to 1.0319; p=6.96E-03) and T2D (total OR: 1.0536; 95% CI 1.0157 to 1.0930; p=5.24E-03) all had a significant effect on RCT occurrence. The direct effects of these components also remained significant while no significant indirect effect was identified. No mediator was thus found to influence the causal associations identified from UVMR.

Discussion

UVMR during the current MR study revealed that genetically predicted MetS, BMI, and WAC had a significant positive association with the risk of RCT. TC and SBP were suggestively associated with RCT risk. The associations of MetS-RCT, BMI-RCT, and WAC-RCT were identified by CAUSE models. There was strong evidence for independent causal associations between both BMI and WAC and RCT after adjustment for confounders. No mediator was found in the causal associations identified from UVMR. Our study unveils a genetic predisposition to RCT in patients with MetS, and we hope that the insights gained will contribute to the enhancement of early diagnosis and monitoring of RCT risk in MetS populations. Given the rising

Rotator cuff sydrome

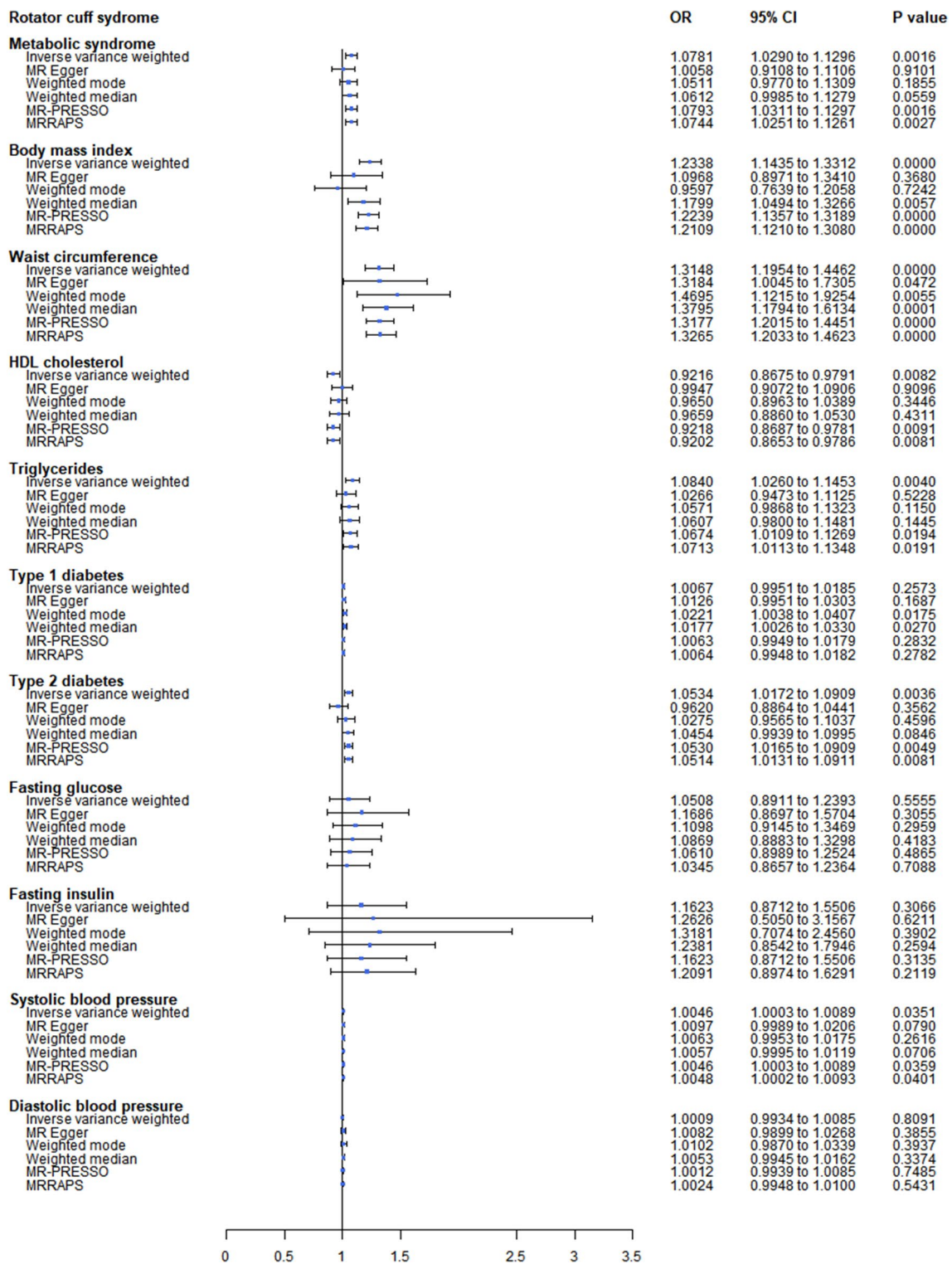|	OR	95% CI	P value
Metabolic syndrome			
Inverse variance weighted	1.0781	1.0290 to 1.1296	0.0016
MR Egger	1.0058	0.9108 to 1.1106	0.9101
Weighted mode	1.0511	0.9770 to 1.1309	0.1855
Weighted median	1.0612	0.9985 to 1.1279	0.0559
MR-PRESSO	1.0793	1.0311 to 1.1297	0.0016
MRRAPS	1.0744	1.0251 to 1.1261	0.0027
Body mass index			
Inverse variance weighted	1.2338	1.1435 to 1.3312	0.0000
MR Egger	1.0968	0.8971 to 1.3410	0.3680
Weighted mode	0.9597	0.7639 to 1.2058	0.7242
Weighted median	1.1799	1.0494 to 1.3266	0.0057
MR-PRESSO	1.2239	1.1357 to 1.3189	0.0000
MRRAPS	1.2109	1.1210 to 1.3080	0.0000
Waist circumference			
Inverse variance weighted	1.3148	1.1954 to 1.4462	0.0000
MR Egger	1.3184	1.0045 to 1.7305	0.0472
Weighted mode	1.4695	1.1215 to 1.9254	0.0055
Weighted median	1.3795	1.1794 to 1.6134	0.0001
MR-PRESSO	1.3177	1.2015 to 1.4451	0.0000
MRRAPS	1.3265	1.2033 to 1.4623	0.0000
HDL cholesterol			
Inverse variance weighted	0.9216	0.8675 to 0.9791	0.0082
MR Egger	0.9947	0.9072 to 1.0906	0.9096
Weighted mode	0.9650	0.8963 to 1.0389	0.3446
Weighted median	0.9659	0.8860 to 1.0530	0.4311
MR-PRESSO	0.9218	0.8687 to 0.9781	0.0091
MRRAPS	0.9202	0.8653 to 0.9786	0.0081
Triglycerides			
Inverse variance weighted	1.0840	1.0260 to 1.1453	0.0040
MR Egger	1.0266	0.9473 to 1.1125	0.5228
Weighted mode	1.0571	0.9868 to 1.1323	0.1150
Weighted median	1.0607	0.9800 to 1.1481	0.1445
MR-PRESSO	1.0674	1.0109 to 1.1269	0.0194
MRRAPS	1.0713	1.0113 to 1.1348	0.0191
Type 1 diabetes			
Inverse variance weighted	1.0067	0.9951 to 1.0185	0.2573
MR Egger	1.0126	0.9951 to 1.0303	0.1687
Weighted mode	1.0221	1.0038 to 1.0407	0.0175
Weighted median	1.0177	1.0026 to 1.0330	0.0270
MR-PRESSO	1.0063	0.9949 to 1.0179	0.2832
MRRAPS	1.0064	0.9948 to 1.0182	0.2782
Type 2 diabetes			
Inverse variance weighted	1.0534	1.0172 to 1.0909	0.0036
MR Egger	0.9620	0.8864 to 1.0441	0.3562
Weighted mode	1.0275	0.9565 to 1.1037	0.4596
Weighted median	1.0454	0.9939 to 1.0995	0.0846
MR-PRESSO	1.0530	1.0165 to 1.0909	0.0049
MRRAPS	1.0514	1.0131 to 1.0911	0.0081
Fasting glucose			
Inverse variance weighted	1.0508	0.8911 to 1.2393	0.5555
MR Egger	1.1686	0.8697 to 1.5704	0.3055
Weighted mode	1.1098	0.9145 to 1.3469	0.2959
Weighted median	1.0869	0.8883 to 1.3298	0.4183
MR-PRESSO	1.0610	0.8989 to 1.2524	0.4865
MRRAPS	1.0345	0.8657 to 1.2364	0.7088
Fasting insulin			
Inverse variance weighted	1.1623	0.8712 to 1.5506	0.3066
MR Egger	1.2626	0.5050 to 3.1567	0.6211
Weighted mode	1.3181	0.7074 to 2.4560	0.3902
Weighted median	1.2381	0.8542 to 1.7946	0.2594
MR-PRESSO	1.1623	0.8712 to 1.5506	0.3135
MRRAPS	1.2091	0.8974 to 1.6291	0.2119
Systolic blood pressure			
Inverse variance weighted	1.0046	1.0003 to 1.0089	0.0351
MR Egger	1.0097	0.9989 to 1.0206	0.0790
Weighted mode	1.0063	0.9953 to 1.0175	0.2616
Weighted median	1.0057	0.9995 to 1.0119	0.0706
MR-PRESSO	1.0046	1.0003 to 1.0089	0.0359
MRRAPS	1.0048	1.0002 to 1.0093	0.0401
Diastolic blood pressure			
Inverse variance weighted	1.0009	0.9934 to 1.0085	0.8091
MR Egger	1.0082	0.9899 to 1.0268	0.3855
Weighted mode	1.0102	0.9870 to 1.0339	0.3937
Weighted median	1.0053	0.9945 to 1.0162	0.3374
MR-PRESSO	1.0012	0.9939 to 1.0085	0.7485
MRRAPS	1.0024	0.9948 to 1.0100	0.5431

Fig. 1 Forest plot of the univariable Mendelian randomization analyses exploring associations between childhood sunburn to skin carcinoma risk using different Mendelian randomization statistical models. OR: odds ratio; CIs: confidence intervals
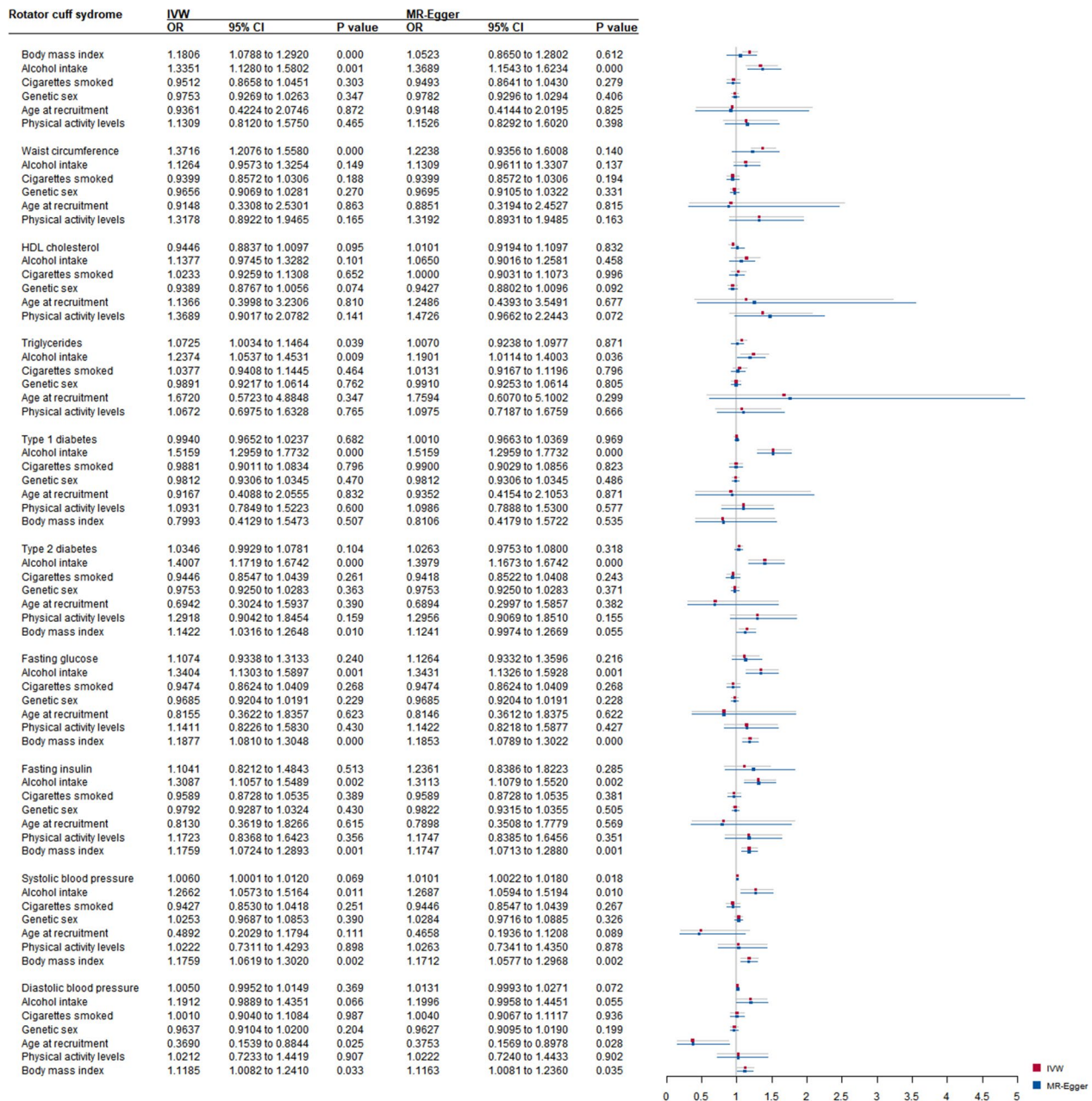
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Rotator cuff sydrome	IVW OR	95% CI	P value	MR-Egger OR	95% CI	P value
Body mass index	1.1806	1.0788 to 1.2920	0.000	1.0523	0.8650 to 1.2802	0.612
Alcohol intake	1.3351	1.1280 to 1.5802	0.001	1.3689	1.1543 to 1.6234	0.000
Cigarettes smoked	0.9512	0.8658 to 1.0451	0.303	0.9493	0.8641 to 1.0430	0.279
Genetic sex	0.9753	0.9269 to 1.0263	0.347	0.9782	0.9296 to 1.0294	0.406
Age at recruitment	0.9361	0.4224 to 2.0746	0.872	0.9148	0.4144 to 2.0195	0.825
Physical activity levels	1.1309	0.8120 to 1.5750	0.465	1.1526	0.8292 to 1.6020	0.398
Waist circumference	1.3716	1.2076 to 1.5580	0.000	1.2238	0.9356 to 1.6008	0.140
Alcohol intake	1.1264	0.9573 to 1.3254	0.149	1.1309	0.9611 to 1.3307	0.137
Cigarettes smoked	0.9399	0.8572 to 1.0306	0.188	0.9399	0.8572 to 1.0306	0.194
Genetic sex	0.9656	0.9069 to 1.0281	0.270	0.9695	0.9105 to 1.0322	0.331
Age at recruitment	0.9148	0.3308 to 2.5301	0.863	0.8851	0.3194 to 2.4527	0.815
Physical activity levels	1.3178	0.8922 to 1.9465	0.165	1.3192	0.8931 to 1.9485	0.163
HDL cholesterol	0.9446	0.8837 to 1.0097	0.095	1.0101	0.9194 to 1.1097	0.832
Alcohol intake	1.1377	0.9745 to 1.3282	0.101	1.0650	0.9016 to 1.2581	0.458
Cigarettes smoked	1.0233	0.9259 to 1.1308	0.652	1.0000	0.9031 to 1.1073	0.996
Genetic sex	0.9389	0.8767 to 1.0056	0.074	0.9427	0.8802 to 1.0096	0.092
Age at recruitment	1.1366	0.3998 to 3.2306	0.810	1.2486	0.4393 to 3.5491	0.677
Physical activity levels	1.3689	0.9017 to 2.0782	0.141	1.4726	0.9662 to 2.2443	0.072
Triglycerides	1.0725	1.0034 to 1.1464	0.039	1.0070	0.9238 to 1.0977	0.871
Alcohol intake	1.2374	1.0537 to 1.4531	0.009	1.1901	1.0114 to 1.4003	0.036
Cigarettes smoked	1.0377	0.9408 to 1.1445	0.464	1.0131	0.9167 to 1.1196	0.796
Genetic sex	0.9891	0.9217 to 1.0614	0.762	0.9910	0.9253 to 1.0614	0.805
Age at recruitment	1.6720	0.5723 to 4.8848	0.347	1.7594	0.6070 to 5.1002	0.299
Physical activity levels	1.0672	0.6975 to 1.6328	0.765	1.0975	0.7187 to 1.6759	0.666
Type 1 diabetes	0.9940	0.9652 to 1.0237	0.682	1.0010	0.9663 to 1.0369	0.969
Alcohol intake	1.5159	1.2959 to 1.7732	0.000	1.5159	1.2959 to 1.7732	0.000
Cigarettes smoked	0.9881	0.9011 to 1.0834	0.796	0.9900	0.9029 to 1.0856	0.823
Genetic sex	0.9812	0.9306 to 1.0345	0.470	0.9812	0.9306 to 1.0345	0.486
Age at recruitment	0.9167	0.4088 to 2.0555	0.832	0.9352	0.4154 to 2.1053	0.871
Physical activity levels	1.0931	0.7849 to 1.5223	0.600	1.0986	0.7888 to 1.5300	0.577
Body mass index	0.7993	0.4129 to 1.5473	0.507	0.8106	0.4179 to 1.5722	0.535
Type 2 diabetes	1.0346	0.9929 to 1.0781	0.104	1.0263	0.9753 to 1.0800	0.318
Alcohol intake	1.4007	1.1719 to 1.6742	0.000	1.3979	1.1673 to 1.6742	0.000
Cigarettes smoked	0.9446	0.8547 to 1.0439	0.261	0.9418	0.8522 to 1.0408	0.243
Genetic sex	0.9753	0.9250 to 1.0283	0.363	0.9753	0.9250 to 1.0283	0.371
Age at recruitment	0.6942	0.3024 to 1.5937	0.390	0.6894	0.2997 to 1.5857	0.382
Physical activity levels	1.2918	0.9042 to 1.8454	0.159	1.2956	0.9069 to 1.8510	0.155
Body mass index	1.1422	1.0316 to 1.2648	0.010	1.1241	0.9974 to 1.2669	0.055
Fasting glucose	1.1074	0.9338 to 1.3133	0.240	1.1264	0.9332 to 1.3596	0.216
Alcohol intake	1.3404	1.1303 to 1.5897	0.001	1.3431	1.1326 to 1.5928	0.001
Cigarettes smoked	0.9474	0.8624 to 1.0409	0.268	0.9474	0.8624 to 1.0409	0.268
Genetic sex	0.9685	0.9204 to 1.0191	0.229	0.9685	0.9204 to 1.0191	0.228
Age at recruitment	0.8155	0.3622 to 1.8357	0.623	0.8146	0.3612 to 1.8375	0.622
Physical activity levels	1.1411	0.8226 to 1.5830	0.430	1.1422	0.8218 to 1.5877	0.427
Body mass index	1.1877	1.0810 to 1.3048	0.000	1.1853	1.0789 to 1.3022	0.000
Fasting insulin	1.1041	0.8212 to 1.4843	0.513	1.2361	0.8386 to 1.8223	0.285
Alcohol intake	1.3087	1.1057 to 1.5489	0.002	1.3113	1.1079 to 1.5520	0.002
Cigarettes smoked	0.9589	0.8728 to 1.0535	0.389	0.9589	0.8728 to 1.0535	0.381
Genetic sex	0.9792	0.9287 to 1.0324	0.430	0.9822	0.9315 to 1.0355	0.505
Age at recruitment	0.8130	0.3619 to 1.8266	0.615	0.7898	0.3508 to 1.7779	0.569
Physical activity levels	1.1723	0.8368 to 1.6423	0.356	1.1747	0.8385 to 1.6456	0.351
Body mass index	1.1759	1.0724 to 1.2893	0.001	1.1747	1.0713 to 1.2880	0.001
Systolic blood pressure	1.0060	1.0001 to 1.0120	0.069	1.0101	1.0022 to 1.0180	0.018
Alcohol intake	1.2662	1.0573 to 1.5164	0.011	1.2687	1.0594 to 1.5194	0.010
Cigarettes smoked	0.9427	0.8530 to 1.0418	0.251	0.9446	0.8547 to 1.0439	0.267
Genetic sex	1.0253	0.9687 to 1.0853	0.390	1.0284	0.9716 to 1.0885	0.326
Age at recruitment	0.4892	0.2029 to 1.1794	0.111	0.4658	0.1936 to 1.1208	0.089
Physical activity levels	1.0222	0.7311 to 1.4293	0.898	1.0263	0.7341 to 1.4350	0.878
Body mass index	1.1759	1.0619 to 1.3020	0.002	1.1712	1.0577 to 1.2968	0.002
Diastolic blood pressure	1.0050	0.9952 to 1.0149	0.369	1.0131	0.9993 to 1.0271	0.072
Alcohol intake	1.1912	0.9889 to 1.4351	0.066	1.1996	0.9958 to 1.4451	0.055
Cigarettes smoked	1.0010	0.9040 to 1.1084	0.987	1.0040	0.9067 to 1.1117	0.936
Genetic sex	0.9637	0.9104 to 1.0200	0.204	0.9627	0.9095 to 1.0190	0.199
Age at recruitment	0.3690	0.1539 to 0.8844	0.025	0.3753	0.1569 to 0.8978	0.028
Physical activity levels	1.0212	0.7233 to 1.4419	0.907	1.0222	0.7240 to 1.4433	0.902
Body mass index	1.1185	1.0082 to 1.2410	0.033	1.1163	1.0081 to 1.2360	0.035

Fig. 2 Forest plot of the multivariable Mendelian randomization analyses exploring genetically determined metabolic syndrome and its ingredients with rotator cuff syndrome risk-adjusted for confounding traits (alcohol intake, cigarettes consumption, age at recruitment, genetic sex, moderate to vigorous physical activity levels, and body mass index). OR: odds ratio; CIs: confidence intervals

adoption of sedentary lifestyles and physical inactivity, coupled with the increasing prevalence of metabolic syndrome with age, recognizing the heightened genetic risk of RCTs in patients with metabolic syndrome is crucial. This awareness is essential for ensuring appropriate early prevention and management of shoulder pain, especially among overweight MetS patients or those with excess WAC, in real-life medical practice.

Additionally, these findings could suggest a subcategory of metabolic shoulder pain, thereby introducing new concepts for management and prognosis.

Epidemiological data have consistently suggested an association of RCT with cardiometabolic risk factors, such as obesity, BMI, and body fat [17, 31, 40–42]. Several meta-analyses have also indicated that blood glucose and body mass are potential risk factors for MetS,
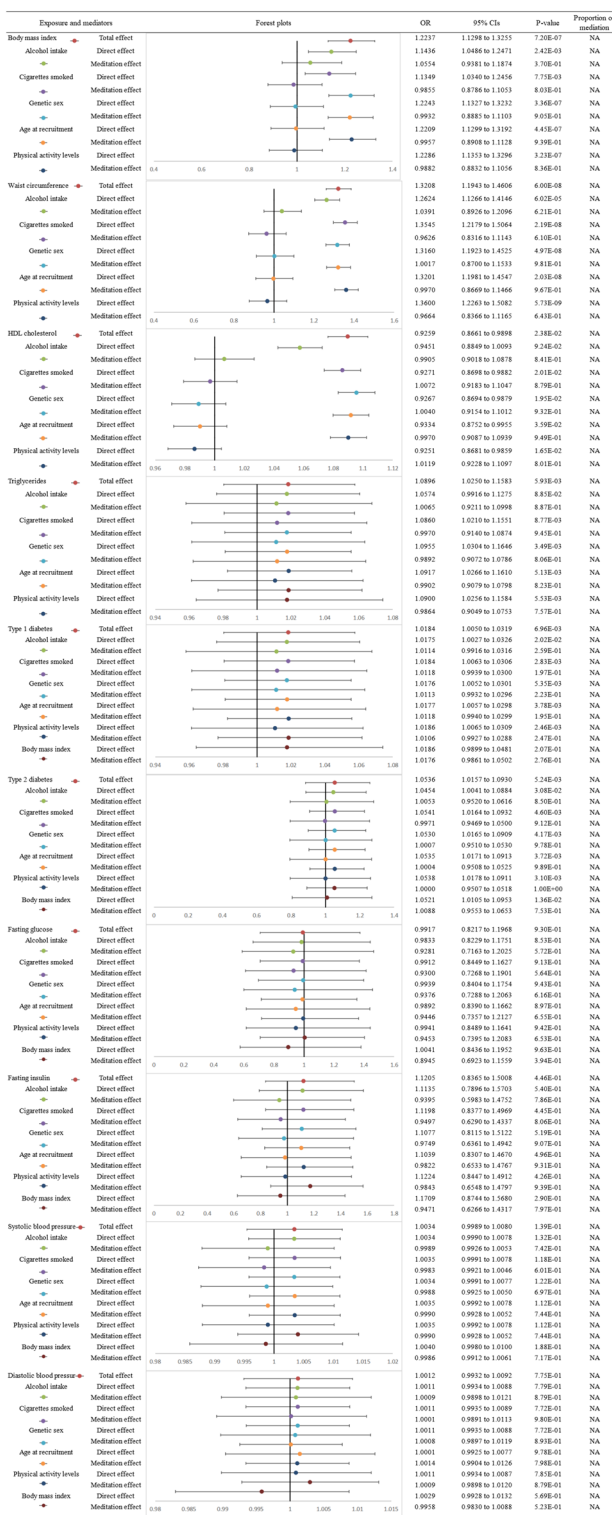
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Fig. 3 The forest plot of the mediation MR analyses. Causal estimates were given as odds ratio (OR) and 95% confidence intervals (CIs) for the effect of metabolic syndrome and its ingredients with rotator cuff syndrome risk. Red: total effect; Green: effect of alcohol intake; Purple: effect of cigarettes smoked; Blue: effect of genetic sex; Orange: effect of age at recruitment; Cyan: effect of physical activity levels; Brown: effect of body mass index

largely consistent with the current results[15]. However, previous observational design data for the impact of MetS on RCT risk have been inconclusive. Some MetS components, such as diabetes, hypertension, and dyslipidemia, have been proposed a significant positive association with RCT risk, [43, 44] but the possibility of bias existed for the three morbidities evaluated due to a lack of high-quality studies [45]. Obesity, hypertension, DM, and dyslipidemia are interrelated MetS components, making it hard to distinguish the contributions of the individual component versus the combination. The current MR analysis presents evidence supporting a determinate causal effect of some components of MetS, such as BMI and WAC on RCT. Suggestively significant associations found for TC and SBP may be false positives with observed associations being due to horizontal pleiotropy or confounders.

The underlying pathogenesis and mechanisms of RCT cannot be fully illustrated based on the available studies. Low-grade inflammatory biomarkers have been reported to be associated with RCT progression, although causality is unclear. MR analyses indicated that the genetically predicted risk of RCT is associated with high WAC (an indicator of central obesity) and BMI. Excess central adiposity has been considered a key component of MetS and adipose tissue may produce circulating proinflammatory cytokines (adipokines), such as tumor necrosis factor (TNF)-α, interleukin (IL)-1/6/1β, leptin and adiponectin. Elevated levels of cytokines IL-1 and IL-6 have been shown in the structure of subacromial bursa and partial thickness rotator cuff tear tissue [46–48]. Increased serum TNF-α has also been reported in the specimens of subacromial bursa extracted during symptomatic rotator cuff tendon surgery [49]. Decreased levels of the anti-inflammatory IL-10 have been found in obesity, insulin resistance, and dyslipidemia patients [50]. Increased proinflammatory and decreased anti-inflammatory adipokine expression may be a risk factor for RCT development [51]. However, these observations are speculative since no study has revealed appropriate biomarkers that

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might be possible regulatory factors between MetS and RCT. It should be noted that adipokines do not operate in isolation but interact with many other factors within a complex system.

The current MR study has the key strength of avoiding reverse causality and minimizing residual confounders. In addition, the summary-level dataset with predominant comprehensiveness and extensiveness for both RCT and MetS was utilized in this analysis, which provides high power in the causality investigation, as well as accurate estimated effect values. However, we also acknowledge some limitations. Firstly, the functions of the IVs and the pathway of their actual effects on the risk factors are not fully understood. Secondly, as weak instrumental strength was still found in T1D and INS in the MVMR results, these results should be interpreted with caution. Third, it is acknowledged that the pleiotropy effect could not be eliminated and may be obscured by potential confounders. Although we have adjusted for several significant common confounders in the MVMR and mediation MR models, considering the complex clinical and genetic backgrounds of both RCT and MetS, achieving complete avoidance of pleiotropy in MR analysis is nearly impossible. While significant covariates like occupational activity and concomitant tendinopathy could potentially influence the results, the absence of available high-quality datasets for these specific phenotypes currently hinders the verification of their potential pleiotropy. However, we believe that the bias in our results caused by pleiotropy is minimal, as several robust MR methods were employed. These methods can yield reliable inferences even if some genetic variants violate the IV assumptions. Last but not least, to mitigate biases stemming from population stratification and sample overlap, we strategically selected datasets from the FinnGen and UKB databases, confining our study to participants of European ancestry for exposure and outcomes, respectively. As a result, the findings of this study should be generalized to other populations with caution. Future investigations will necessitate the inclusion of high-quality GWAS datasets from diverse racial groups to determine the validity of our conclusions across varied genetic backgrounds. Furthermore, the absence of raw individual-level data limits our ability to conduct further stratified analysis on population subgroups.

Conclusion

In conclusion, the current MR study revealed the genetic causality of MetS and its components, especially BMI and WAC, with the risk of RCT. The current findings indicate that the prevention, management, and treatment of RCTs need to be strengthened in a clinical setting by controlling the excess central adiposity that contributes to MetS.

Abbreviations

RCS	Rotator cuff syndrome
RCT	Rotator cuff tendinopathy
Mets	Metabolic syndrome
MR	Mendelian randomization
IVs	Instrumental variables
GWAS	Genome-wide association studies
WAC	Body mass index (BMI), waist circumference
TC	Triglycerides
HDL	High-density lipoprotein
INS	Insulin
GLU	Fasting serum glucose
T1D	Type 1 diabetes
T2D	Type 2 diabetes
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
UVMR	Univariable MR
MVMR	Multivariable MR
STROBE-MR	Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization
pheWAS	Phenome-wide association studies database
IVW	Inverse-variance weighted method
MR-PRESSO	MR pleiotropy residual sum and outlier
MRAPS	MR-Robust Adjusted Profile Score
CI	Confidence intervals
CAUSE	Causal Analysis Using the Summary Effect Estimates
TNF	Tumor necrosis factor
IL	Interleukin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-023-01189-5.

Additional file 1: Figure S1. Diagram for key assumptions of MR analyses. MR study relies on three assumptions: (I) the instrumental variables (IVs) should be associated with the exposure (MetS). (II) the IVs should not be related to confounders. (III) the IVs should influence the outcome (RCT) risk via the exposure, not through other pathways. Line with arrows indicate that the genetic instruments (SNPs) are associated with the exposure and could only affect the outcome via the exposure. Dashed lines indicate that the genetic instruments (SNPs) are independent of any confounding variables between the results. MR: mendelian randomization; MetS:metabolic syndrome; RCT: rotator cuff tendinopathy. **Figure S2.** Scatter plots of the univariable mendelian randomisation analyses. The slope of each line corresponding to the estimated MR effect in different models, including the conventional IVW, WM, WMM, MR-Egger, MR-RAPS and MR-PRESSO methods. The effect of A: MetS on RCT; B: BMI on RCT; C: WAC on RCT; D: HDL on RCT; E: TC on RCT; F: T1D on RCT; G: T2D on RCT; H: GLU on RCT; I: INS on RCT; J: SBP on RCT; K: DBP on RCT. BMI: body mass index; WAC: waist circumference; HDL: serum HDL cholesterol; TC: triglycerides; T1D: type 1 diabetes; T2D: type 2 diabetes; GLU: fasting serum glucose; INS: fasting serum insulin; SBP: systolic blood pressure; DBP: diastolic blood pressure. **Figure S3.** Leave-one-out stability tests of the univariable mendelian randomisation analyses. Calculate the MR results of the remaining IVs after removing the IVs one by one. The effect of A: MetS on RCT; B: BMI on RCT; C: WAC on RCT; D: HDL on RCT; E: TC on RCT; F: T1D on RCT; G: T2D on RCT; H: GLU on RCT; I: INS on RCT; J: SBP on RCT; K: DBP on RCT. BMI: body mass index; WAC: waist circumference; HDL: serum HDL cholesterol; TC: triglycerides; T1D: type 1 diabetes; T2D: type 2 diabetes; GLU: fasting serum glucose; INS: fasting serum insulin; SBP: systolic blood pressure; DBP: diastolic blood pressure. **Figure S4.** The forest plot of the CAUSE method MR analysis. Causal estimates were given as beta and 95% confidence intervals (CIs).

Additional file 2. Table S1. Information of identified SNPs in exposure (metabolic syndrome) and outcomes(rotator cuff syndrome). **Table S2.** Information of identified SNPs in exposure (body mass index) and outcomes(rotator cuff syndrome). **Table S3.** Information of identified SNPs in exposure (waist circumference) and outcomes(rotator cuff syndrome).

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Table S4. Information of identified SNPs in exposure (HDL cholesterol) and outcomes(rotator cuff syndrome). **Table S5.** Information of identified SNPs in exposure (triglycerides) and outcomes(rotator cuff syndrome). **Table S6.** Information of identified SNPs in exposure (type 1 diabetes) and outcomes(rotator cuff syndrome). **Table S7.** Information of identified SNPs in exposure (type 2 diabetes) and outcomes(rotator cuff syndrome). **Table S8.** Information of identified SNPs in exposure (fasting glucose) and outcomes(rotator cuff syndrome). **Table S9.** Information of identified SNPs in exposure (fasting insulin) and outcomes(rotator cuff syndrome). **Table S10.** Information of identified SNPs in exposure (systolic blood pressure) and outcomes(rotator cuff syndrome). **Table S11.** Information of identified SNPs in exposure (diastolic blood pressure) and outcomes(rotator cuff syndrome). **Table S12.** Wald ratio estimate results of individual SNPs in exposure (metabolic syndrome) and outcomes(rotator cuff syndrome). **Table S13.** Wald ratio estimate results of individual SNPs in exposure (body mass index) and outcomes(rotator cuff syndrome). **Table S14.** Wald ratio estimate results of individual SNPs in exposure (waist circum) and outcomes(rotator cuff syndrome). **Table S15.** Wald ratio estimate results of individual SNPs in exposure (HDL cholesterol) and outcomes(rotator cuff syndrome). **Table S16.** Wald ratio estimate results of individual SNPs in exposure (triglycerides) and outcomes(rotator cuff syndrome). **Table S17.** Wald ratio estimate results of individual SNPs in exposure (type 1 diabetess) and outcomes(rotator cuff syndrome). **Table S18.** Wald ratio estimate results of individual SNPs in exposure (type 2 diabetes) and outcomes(rotator cuff syndrome). **Table S19.** Wald ratio estimate results of individual SNPs in exposure (fasting glucose) and outcomes(rotator cuff syndrome). **Table S20.** Wald ratio estimate results of individual SNPs in exposure (fasting insulin) and outcomes(rotator cuff syndrome). **Table S21.** Wald ratio estimate results of individual SNPs in exposure (systolic blood pressure) and outcomes(rotator cuff syndrome). **Table S22.** Wald ratio estimate results of individual SNPs in exposure (diastolic blood pressure) and outcomes(rotator cuff syndrome). **Table S23.** Detailed result of the MVMR analysis.

Author contributions
YJL and JHW conceived the study, participated in its design and coordination, and critically revised the manuscript. YJL and ZQC searched the databases. ZQC, QXL, and YJL reviewed the GWAS datasets and finished the data collection. ZQC and YJL finished the data analysis. YJL and ZQC drafted the manuscript. YJL, JHW, and ZQC had full access to all the data collection, analysis, and interpretation. YJL and JHW contributed equally to this work. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Publicly available summary-level data was used and no additional ethical approval was needed.

Competing interests
The authors declare no competing interests.

References
1. Harkness EF, Macfarlane GJ, Nahit ES, Silman AJ, McBeth J. Mechanical and psychosocial factors predict new onset shoulder pain: a prospective cohort study of newly employed workers. Occup Environ Med. 2003;60(11):850–7. https://doi.org/10.1136/oem.60.11.850.
2. Mitchell C, Adebajo A, Hay E, Carr A. Shoulder pain: diagnosis and management in primary care. BMJ. 2005;331(7525):1124–8. https://doi.org/10.1136/bmj.331.7525.1124.
3. Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Ann Rheum Dis. 1998;57(11):649–55. https://doi.org/10.1136/ard.57.11.649.
4. Desmeules F, Boudreault J, Dionne CE, Frémont P, Lowry V, MacDermid JC, et al. Efficacy of exercise therapy in workers with rotator cuff tendinopathy: a systematic review. J Occup Health. 2016;58(5):389–403. https://doi.org/10.1539/joh.15-0103-RA.
5. Lewis J, McCreesh K, Roy JS, Ginn K. Rotator cuff tendinopathy: navigating the diagnosis-management conundrum. J Orthop Sports Phys Ther. 2015;45(11):923–37. https://doi.org/10.2519/jospt.2015.5941.
6. Neer CS 2nd. Impingement lesions. Clin Orthop Relat Res. 1983;173:70–7.
7. Jeong JY, Song SY, Yoo JC, Park KM, Lee SM. Comparison of outcomes with arthroscopic repair of acute-on-chronic within 6 months and chronic rotator cuff tears. J Shoulder Elbow Surg. 2017;26(4):648–55. https://doi.org/10.1016/j.jse.2016.09.032.
8. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2010;375(9710):181–3. https://doi.org/10.1016/s0140-6736(09)61794-3.
9. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):12. https://doi.org/10.1007/s11906-018-0812-z.
10. Gonzalez-Chávez A, Chávez-Fernández JA, Elizondo-Argueta S, González-Tapia A, León-Pedroza JI, Ochoa C. Metabolic syndrome and cardiovascular disease: a health challenge. Arch Med Res. 2018;49(8):516–21. https://doi.org/10.1016/j.arcmed.2018.10.003.
11. Hildrum B, Mykletun A, Dahl AA, Midthjell K. Metabolic syndrome and risk of mortality in middle-aged versus elderly individuals: the Nord-Trøndelag Health Study (HUNT). Diabetologia. 2009;52(4):583–90. https://doi.org/10.1007/s00125-009-1271-5.
12. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care. 2004;27(5):1182–6. https://doi.org/10.2337/diacare.27.5.1182.
13. Leong HT, Fu SC, He X, Oh JH, Yamamoto N, Hang S. Risk factors for rotator cuff tendinopathy: a systematic review and meta-analysis. J Rehabil Med. 2019;51(9):627–37. https://doi.org/10.2340/16501977-2598.
14. Lai J, Gagnier JJ. The effect of lipid disorders on the risk of rotator cuff disease: a systematic review and meta-analysis. JB JS Open Access. 2018;3(3):e0018. https://doi.org/10.2106/jbjs.Oa.18.00018.
15. Zhao J, Luo M, Liang G, Pan J, Han Y, Zeng L, et al. What factors are associated with symptomatic rotator cuff tears: a meta-analysis. Clin Orthop Relat Res. 2022;480(1):96–105. https://doi.org/10.1097/corr.0000000000001949.
16. Applegate KA, Thiese MS, Merryweather AS, Kapellusch J, Drury DL, Wood E, et al. Association between cardiovascular disease risk factors and rotator cuff tendinopathy: a cross-sectional study. J Occup Environ Med. 2017;59(2):154–60. https://doi.org/10.1097/jom.0000000000000929.
17. Rechardt M, Shiri R, Karppinen J, Jula A, Heliövaara M, Viikari-Juntura E. Lifestyle and metabolic factors in relation to shoulder pain and rotator cuff tendinitis: a population-based study. BMC Musculoskelet Disord. 2010;11:165. https://doi.org/10.1186/1471-2474-11-165.

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18. Smith GD, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003;32(1):1–22. https://doi.org/10.1093/ije/dyg070.

19. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23(R1):R89-98. https://doi.org/10.1093/hmg/ddu328.

20. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. Bmj. 2018;362:k601. https://doi.org/10.1136/bmj.k601.

21. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med. 2008;27(8):1133–63. https://doi.org/10.1002/sim.3034.

22. Lind L. Genome-wide association study of the metabolic syndrome in UK biobank. Metab Syndr Relat Disord. 2019;17(10):505–11. https://doi.org/10.1089/met.2019.0070.

23. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in ∼700000 individuals of European ancestry. Hum Mol Genet. 2018;27(20):3641–9. https://doi.org/10.1093/hmg/ddy271.

24. Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G, et al. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable Mendelian randomisation analysis. PLoS Med. 2020;17(3):e1003062. https://doi.org/10.1371/journal.pmed.1003062.

25. Forgetta V, Manousaki D, Istomine R, Ross S, Tessier MC, Marchand L, et al. Rare genetic variants of large effect influence risk of type 1 diabetes. Diabetes. 2020;69(4):784–95. https://doi.org/10.2337/db19-0831.

26. Xue A, Wu Y, Zhu Z, Zhang F, Kemper KE, Zheng Z, et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. Nat Commun. 2018;9(1):2941. https://doi.org/10.1038/s41467-018-04951-w.

27. Chen J, Spracklen CN, Marenne G, Varshney A, Corbin LJ, Luan J, et al. The trans-ancestral genomic architecture of glycemic traits. Nat Genet. 2021;53(6):840–60. https://doi.org/10.1038/s41588-021-00852-9.

28. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658–65. https://doi.org/10.1002/gepi.21758.

29. Staley JR, Burgess S. Semiparametric methods for estimation of a nonlinear exposure-outcome relationship using instrumental variables with application to Mendelian randomization. Genet Epidemiol. 2017;41(4):341–52. https://doi.org/10.1002/gepi.22041.

30. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25. https://doi.org/10.1093/ije/dyv080.

31. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32(5):377–89. https://doi.org/10.1007/s10654-017-0255-x.

32. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol. 2017;46(6):1985–98. https://doi.org/10.1093/ije/dyx102.

33. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–14. https://doi.org/10.1002/gepi.21965.

34. Zhao Q, Wang J, Hemani G, Bowden J, Small DS. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. Ann Stat. 2018. https://doi.org/10.48550/arXiv.1801.09652.

35. Slob EAW, Burgess S. A comparison of robust Mendelian randomization methods using summary data. Genet Epidemiol. 2020;44(4):313–29. https://doi.org/10.1002/gepi.22295.

36. Sanderson E. Multivariable Mendelian randomization and mediation. Cold Spring Harb Perspect Med. 2021. https://doi.org/10.1101/cshperspect.a038984.

37. Burgess S, Thompson DJ, Rees JMB, Day FR, Perry JR, Ong KK. Dissecting causal pathways using Mendelian randomization with summarized genetic data: application to age at menarche and risk of breast cancer. Genetics. 2017;207(2):481–7. https://doi.org/10.1534/genetics.117.300191.

38. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. Stat Med. 2015;34(21):2926–40. https://doi.org/10.1002/sim.6522.

39. Morrison J, Knoblauch N, Marcus JH, Stephens M, He X. Mendelian randomization accounting for correlated and uncorrelated pleiotropic effects using genome-wide summary statistics. Nat Genet. 2020;52(7):740–7. https://doi.org/10.1038/s41588-020-0631-4.

40. Gaida JE, Ashe MC, Bass SL, Cook JL. Is adiposity an under-recognized risk factor for tendinopathy? A systematic review. Arthritis Rheum. 2009;61(6):840–9. https://doi.org/10.1002/art.24518.

41. Gumina S, Candela V, Passaretti D, Latino G, Venditto T, Mariani L, et al. The association between body fat and rotator cuff tear: the influence on rotator cuff tear sizes. J Shoulder Elbow Surg. 2014;23(11):1669–74. https://doi.org/10.1016/j.jse.2014.03.016.

42. Rechardt M, Shiri R, Lindholm H, Karppinen J, Viikari-Juntura E. Associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: a cross-sectional study. BMJ Open. 2013;3(8):e003036. https://doi.org/10.1136/bmjopen-2013-003036.

43. Lin TT, Lin CH, Chang CL, Chi CH, Chang ST, Sheu WH. The effect of diabetes, hyperlipidemia, and statins on the development of rotator cuff disease: a nationwide, 11-year, longitudinal, population-based follow-up study. Am J Sports Med. 2015;43(9):2126–32. https://doi.org/10.1177/0363546515588173.

44. Park HB, Gwark JY, Na JB. Risk factors of chronic subscapularis tendon tear. Clin Shoulder Elb. 2022;25(4):257–64. https://doi.org/10.5397/cise.2021.00710.

45. Giri A, O'Hanlon D, Jain NB. Risk factors for rotator cuff disease: a systematic review and meta-analysis of diabetes, hypertension, and hyperlipidemia. Ann Phys Rehabil Med. 2023;66(1):101631. https://doi.org/10.1016/j.rehab.2022.101631.

46. Voloshin I, Gelinas J, Maloney MD, O'Keefe RJ, Bigliani LU, Blaine TA. Proinflammatory cytokines and metalloproteases are expressed in the subacromial bursa in patients with rotator cuff disease. Arthroscopy. 2005;21(9):1076. https://doi.org/10.1016/j.arthro.2005.05.017.

47. Blaine TA, Kim YS, Voloshin I, Chen D, Murakami K, Chang SS, et al. The molecular pathophysiology of subacromial bursitis in rotator cuff disease. J Shoulder Elbow Surg. 2005;14(1):S84–9. https://doi.org/10.1016/j.jse.2004.09.022.

48. Chung SW, Choi BM, Kim JY, Lee YS, Yoon JP, Oh KS, et al. Altered gene and protein expressions in torn rotator cuff tendon tissues in diabetic patients. Arthroscopy. 2017;33(3):518–26. https://doi.org/10.1016/j.arthro.2016.08.017.

49. Dean BJ, Franklin SL, Carr AJ. A systematic review of the histological and molecular changes in rotator cuff disease. Bone Joint Res. 2012;1(7):158–66. https://doi.org/10.1302/2046-3758.17.2000115.

50. Aroor AR, McKarns S, Demarco VG, Jia G, Sowers JR. Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance. Metabolism. 2013;62(11):1543–52. https://doi.org/10.1016/j.metabol.2013.07.001.

51. Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population. Int J Med Sci. 2016;13(1):25–38. https://doi.org/10.7150/ijms.13800.

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