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Genetic Insights into the Risk of Metabolic Syndrome and Its Components on Dementia: A Mendelian Randomization

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Abstract.
Background: The role of metabolic syndrome (MetS) on dementia is disputed.
Objective: We conducted a Mendelian randomization to clarify whether the genetically predicted MetS and its components are casually associated with the risk of different dementia types.
Methods: The genetic predictors of MetS and its five components (waist circumference, hypertension, fasting blood glucose, triglycerides, and high-density lipoprotein cholesterol [HDL-C]) come from comprehensive public genome-wide association studies (GWAS). Different dementia types are collected from the GWAS in the European population. Inverse variance weighting is utilized as the main method, complemented by several sensitivity approaches to verify the robustness of the results.
Results: Genetically predicted MetS and its five components are not causally associated with the increasing risk of dementia (all $p > 0.05$). In addition, no significant association between MetS and its components and Alzheimer's disease, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and dementia due to Parkinson's disease (all $p > 0.05$), except the association between HDL-C and dementia with Lewy bodies. HDL-C may play a protective role in dementia with Lewy bodies (OR: 0.81, 95% CI: 0.72–0.92, $p = 0.0010$).
Conclusions: From the perspective of genetic variants, our study provides novel evidence that MetS and its components are not associated with different dementia types.

Keywords: Alzheimer's disease, causal association, components, dementia, Mendelian randomization, metabolic syndrome, types

INTRODUCTION

Dementia is characterized by a chronic and progressive decline affecting cognitive function in aged adults [1]. Generally, the main types of dementia consist of Alzheimer's disease (AD), vascular

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dementia, frontotemporal dementia, dementia with Lewy bodies, and dementia in Parkinson's disease. It is estimated that there have 50 million patients around the world [2]. More seriously, the number of cases is dramatically increasing due to the increasing life expectancy and risk factors [3], which puts a heavy burden on individuals, families, health care, and society. Therefore, strategies for preventing and alleviating dementia are priorities in healthcare.

Metabolic syndrome (MetS) is a cluster of pathological conditions based on the World Health Organization's (WHO) definition, including glucose abnormalities, hyperlipidemia, central obesity, and hypertension [4]. At present, the incidence of MetS is increasing rapidly, and approximately 25% adults have MetS [5]. Some studies have shown that MetS has a positive association with the risk of dementia [6, 7], while no association is observed, even the inverse relationship in other studies [8, 9]. In addition, obvious confounding factors such as the study design and retrospective features are inherent shortcomings in these observational studies, which may interfere with the understanding of these conclusions.

Mendelian randomization (MR), as a genetic approach, is a robust statistical analysis using genetic variants to make a causal inference, which can overcome the limitation of observational studies [10]. During gestation, single nucleotide polymorphism (SNP), a genomic variant at a single base position in the deoxyribonucleic acid (DNA), is assorted randomly in forming a zygote [11]. However, no study has been conducted to investigate the causal association of MetS and its five components on dementia. Therefore, we performed this MR analysis to illustrate their causal links.

METHODS

Study design

The overview of our MR study is shown in Fig. 1. In our study, we explored the causal relationship between MetS, waist circumference (WC), hypertension, fasting blood glucose (FBG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and different dementia types, including AD, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and dementia due to Parkinson's disease. No ethical approval is required due to the analysis of the public summary-level datasets.

Date sources of exposures and outcomes

All exposure datasets are originated from public databases. MetS ($N = 291{,}107$ samples), WC ($N = 462{,}166$ samples), hypertension ($N = 463{,}010$ samples), TG (441,016 samples), and HDL-C (403,943 samples) are obtained from the UK biobank [12, 13]. Genetic predictors for FBG (281,416 participants) are available from the Meta-Analyses Glucose and Insulin-related traits Consortium (MAGIC) [14]. The detailed sources of these datasets utilized in our MR study are described in Table 1.

All outcome datasets are derived from European ancestry. The summary-level dataset for AD are taken from the MR study including 954 cases and 487,331 controls [15]. The dataset for vascular dementia is extracted from the FinnGen consortium, consisting of 212,389 samples (881 cases and 211,508 controls). As to frontotemporal dementia, its dataset includes 515 cases and 2,509 controls [16]. Summary statistics for dementia with Lewy bodies are collected from an independent GWAS multicenter study with 2,591 cases and 4,027 controls [17]. Dementia due to Parkinson's disease consists of 212,389 samples (267 cases and 216,628 controls) from the FinnGen consortium. The detailed resources of our datasets are visualized in Table 1.

Genetic instrument selection

Genetic instruments are usually collected as those having statistically robust associations with the risk factor in a MR analysis [18]. The genetic instrument selection undertaken the following procedures. All the genetic instrumental variables (IVs) associated with MetS and its five components must meet a significance level at a genome-wide statistical threshold of $p < 5 \times 10^{-8}$. Then, the independent SNPs are identified using the linkage disequilibrium (LD) with the threshold of LD $r^2 < 0.05$ at a window size of 10,000 Kb [19, 20]. In addition, Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis is used to detect the potential outlier SNPs accounting for possible pleiotropy [21]. The SNPs will be removed when the outlier SNPs are detected. The qualified SNPs of MetS and its five components are displayed in Table 1.

Main statistical analyses

The inverse variance weighting (IVW) approach is deemed as the main method in our MR study because

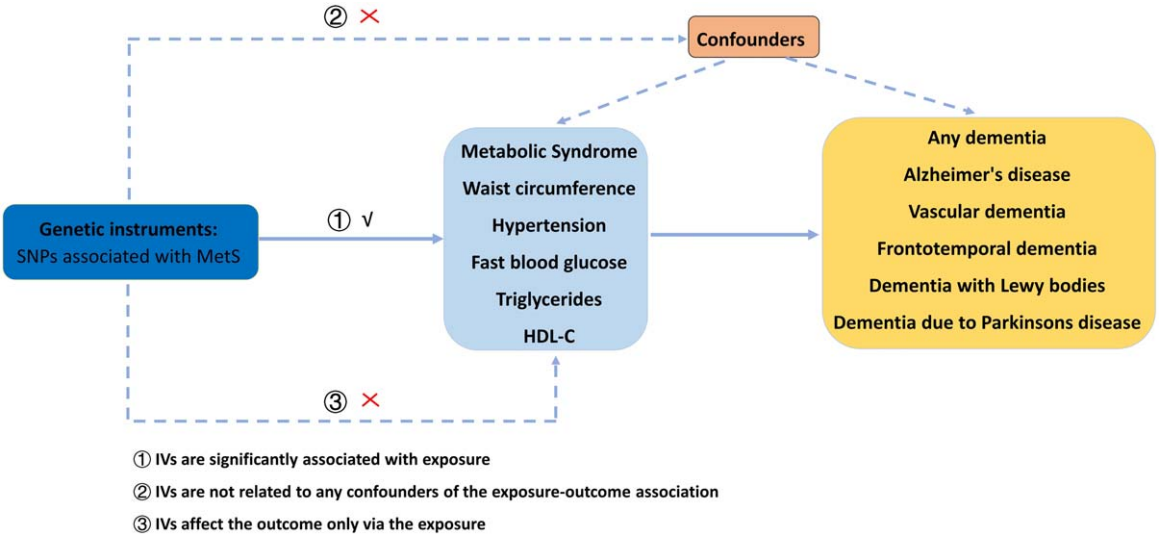

Fig. 1. The flow chart of our MR analysis. MetS, metabolic syndrome; MR, Mendelian randomization; SNP, single nucleotide polymorphism; HDL-C, high-density lipoprotein cholesterol.

it can obtain a robust result by integrating the Wald ratio of each SNP into an overall weighted effect [22]. The Bonferroni-corrected $p < 0.0013$ (0.05/36) is regarded as the statistical significance. All analyses are performed using R packages including "TwoSampleMR", "mr.raps", and "cause", in R software (version: 4.1.2, The R Foundation, Vienna, Austria).

Sensitivity analyses

We also chosen five methods to perform sensitivity analyses, including MR robust adjusted profile score (MR.RAPS), MR-PRESSO, weighted median, MR-Egger, and Maximum likelihood. When there were weak IVs that led to horizontal pleiotropy, the results of MR.RAPS could remain stable [23]. Significant outliers could be detected using MR-PRESSO and then removed for pleiotropy [21]. The weighted median approach could obtain consistent results even though 50% of SNPs were invalid [24]. The results of the comparison between the egger intercept term and zero were introduced in MR-Egger analysis, which represented the directional pleiotropy [25]. In the maximum likelihood analysis, a relatively low standard error existed, and it might be deviated by a small sample [26]. Furthermore, the egger intercept term in MR-Egger analysis and the p value in MR-PRESSO analysis were introduced into the regression model to test the directional pleiotropy. Cochran's Q test was performed to identify possible heterogeneity. In addition, leave-one-out analysis was utilized to explain the robustness of the results when removing SNPs in turn.

RESULTS

THE CASUAL EFFECTS OF GENETICALLY PREDICTED METS AND ITS COMPONENTS ON DEMENTIA

The results of this MR study are presented in Table 2. The demographic characteristics for dementia are displayed in Tables 3–5.

As to any dementia, it can be found that MetS, WC, hypertension, FBG, TG, and HDL-C are not causally associated with the risk of any dementia (all $p > 0.0016$, Table 2, Fig. 2). The results of Cochran's Q analysis show a visible heterogeneity between TG and any dementia (Table 2), while a symmetry of MR results in the funnel plot (Fig. 3) is observed. In the MR-Egger and MR-PRESSO analyses, no pleiotropy is identified (MR-Egger: all $p > 0.05$; MR-PRESSO: all $p > 0.05$, Table 2). Additionally, no influential SNPs are detected in the leave-one-out analysis when excluding any one of the SNP in turn (Fig. 4). Figure 5 presents the results of the causal estimate of every SNP on any dementia.

For AD, the results of IVW method show that no causal relationship of MetS and its subtypes is identified (all $p > 0.0016$, Table 2, Fig. 2). No evidence of heterogeneity is detected in Cochran's Q analysis (all

Table 1
The R^2 and F-statistics for the genetic instruments in the MR analyses

Exposure	Outcome	No. SNP	R^2	F-statistic
Mets	Any Dementia	122	3.04%	66.77
WC	Any Dementia	561	7.21%	53.67
Hypertension	Any Dementia	66	0.85%	46.78
FBG	Any Dementia	108	4.37%	101.31
TG	Any Dementia	749	17.90%	110.95
HDL-C	Any Dementia	900	29.50%	161.96
Mets	Alzheimer's disease	119	3.07%	68.89
WC	Alzheimer's disease	565	7.23%	53.89
Hypertension	Alzheimer's disease	66	0.84%	46.24
FBG	Alzheimer's disease	107	4.33%	102.01
TG	Alzheimer's disease	789	19.77%	118.26
HDL-C	Alzheimer's disease	951	30.53%	159.49
Mets	Vascular dementia	124	3.13%	67.69
WC	Vascular dementia	564	7.26%	53.76
Hypertension	Vascular dementia	66	0.85%	46.78
FBG	Vascular dementia	108	4.37%	101.31
TG	Vascular dementia	757	18.43%	113.44
HDL-C	Vascular dementia	906	29.70%	162.42
Mets	Frontotemporal dementia	46	1.27%	75.39
WC	Frontotemporal dementia	227	3.14%	57.51
Hypertension	Frontotemporal dementia	23	0.27%	50.25
FBG	Frontotemporal dementia	32	1.06%	79.91
TG	Frontotemporal dementia	199	5.25%	109.23
HDL-C	Frontotemporal dementia	237	8.63%	146.18
Mets	Dementia with Lewy bodies	114	2.96%	69.56
WC	Dementia with Lewy bodies	516	6.66%	53.54
Hypertension	Dementia with Lewy bodies	63	0.82%	47.14
FBG	Dementia with Lewy bodies	101	4.20%	102.97
TG	Dementia with Lewy bodies	698	18.16%	121.05
HDL-C	Dementia with Lewy bodies	831	27.99%	161.51
Mets	Dementia due to Parkinson's disease	125	3.19%	68.12
WC	Dementia due to Parkinson's disease	565	7.28%	53.88
Hypertension	Dementia due to Parkinson's disease	66	0.85%	46.78
FBG	Dementia due to Parkinson's disease	108	4.37%	101.31
TG	Dementia due to Parkinson's disease	758	18.74%	115.63
HDL-C	Dementia due to Parkinson's disease	907	29.90%	163.85

MetS, metabolic syndrome; WC, waist circumference; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

$p > 0.05$, Table 2) and the funnel plot (Fig. 3). Furthermore, no signs of pleiotropy is found in MR-Egger and MR-PRESSO analyses (Table 2). The leave-one-out analyses indicate the robustness of our MR results (Fig. 4). The causal estimate of each IV on AD is shown in Fig. 5.

In MR analysis for vascular dementia, we do not observe significant causal association between MetS, its subtypes, and vascular dementia (all $p > 0.0016$, Table 2, Fig. 2). In sensitivity analysis, Cochran's Q test does not find any heterogeneity (Fig. 3, Table 2). In addition, there is no evidence of pleiotropyin MR-Egger and MR-PRESSO analyses (Table 2). The causal estimates are not driven by single SNP in the leave-one-out analysis (Fig. 4, Table 2). The frost plot manifesting the casual estimate of every SNP on vascular dementia is shown in Fig. 5.

As to frontotemporal dementia, there is no causal association between MetS, WC, hypertension, FBG, TG, HDL-C, and frontotemporal dementia (all $p > 0.0016$, Table 2, Fig. 2). Although the results in Cochran's Q test demonstrate a visible heterogeneity between MetS and frontotemporal dementia (Table 2), the funnel plot reveals a symmetry of MR results (Fig. 3). We do not find pleiotropy in MR-Egger and MR-PRESSO analyses (Table 2), and the results of leave-one-out analysis remain robust (Fig. 4, Table 2). The causal estimate of each IV on frontotemporal dementia is displayed in frost plot (Fig. 5).

HDL-C decreases the risk of dementia with Lewy bodies (odd ratios (OR) = 0.81, 95% confidential index (CI) = 0.72–0.92, $p = 0.0010$), while no causal relationship is observed between MetS, WC, hyper-

Table 2
The causal effect of MetS and its components on different types of dementia

Exposure	Outcome	Methods	OR (95%)	*p*	Egger_intercept	*p*-Egger intercept	Cochran's	Cochran's *p*
MetS	Any Dementia	IVW	0.98 (0.92,1.06)	0.7564			128.71	0.2985
		MR-Egger	0.90 (0.77,1.07)	0.2574	0.0062	0.2678	127.40	0.3046
		Weighted median	0.95 (0.85,1.05)	0.3646				
		Maximum likelihood	0.98 (0.92,1.06)	0.7537				
		RAPS	0.97 (0.90,1.05)	0.5708				
WC	Any Dementia	IVW	1.07 (0.93,1.22)	0.3128			562.58	0.4613
		MR-Egger	1.48 (0.99,2.22)	0.0544	–0.0051	0.0923	559.73	0.4832
		Weighted median	1.11 (0.87,1.41)	0.3627				
		Maximum likelihood	1.07 (0.93,1.22)	0.3086				
		RAPS	1.04 (0.91,1.21)	0.5050				
Hypertension	Any Dementia	IVW	0.97 (0.31,3.02)	0.9590			69.91	0.3159
		MR-Egger	1.28 (0.02,5.46)	0.9048	–0.0015	0.8890	69.89	0.2862
		Weighted median	1.48 (0.28,7.79)	0.6416				
		Maximum likelihood	0.97 (0.32,2.93)	0.9574				
		RAPS	1.00 (0.31,3.16)	0.9975				
FBG	Any Dementia	IVW	1.26 (1.01,1.57)	0.0394			111.27	0.3444
		MR-Egger	1.08 (0.72,1.60)	0.7039	0.0045	0.3525	111.36	0.3417
		Weighted median	1.29 (0.91,1.84)	0.1474				
		Maximum likelihood	1.27 (1.02,1.58)	0.0321				
		RAPS	1.23 (0.97,1.57)	0.0780				
TG	Any Dementia	IVW	0.94 (0.86,1.02)	0.1481			829.31	0.0202
		MR-Egger	0.87 (0.76,0.99)	0.0470	0.0024	0.1628	827.15	0.0216
		Weighted median	0.93 (0.80,1.07)	0.3398				
		Maximum likelihood	0.94 (0.87,1.01)	0.1300				
		RAPS	0.94 (0.86,1.02)	0.1799				
HDL-C	Any Dementia	IVW	1.04 (0.97,1.12)	0.1751			931.91	0.2169
		MR-Egger	1.03 (0.93,1.15)	0.4753	0.0002	0.8435	931.87	0.2103
		Weighted median	0.96 (0.85,1.09)	0.6065				
		Maximum likelihood	1.04 (0.98,1.11)	0.1693				
		RAPS	1.03 (0.96,1.10)	0.3650				

(*Continued*)

Table 2
(*Continued*)

Exposure	Outcome	Methods	OR (95%)	*p*	Egger_intercept	*p*-Egger intercept	Cochran's	Cochran's *p*
MetS	Alzheimer's disease	IVW	1.00 (0.99,1.00)	0.9354			107.68	0.7415
		MR-Egger	0.99 (0.99,1.00)	0.8255	6.82e-06	0.7737	107.60	0.7215
		Weighted median	1.00 (0.99,1.00)	0.7967				
		Maximum likelihood	1.00 (0.99,1.00)	0.9354				
		RAPS	1.00 (0.99,1.00)	0.9205				
WC	Alzheimer's disease	IVW	1.00 (0.99,1.00)	0.0628			563.75	0.4949
		MR-Egger	1.00 (1.00,1.00)	0.0143	–2.61e-05	0.0534	560.01	0.5276
		Weighted median	1.00 (1.00,1.00)	0.0227				
		Maximum likelihood	1.00 (0.99,1.00)	0.0628				
		RAPS	1.00 (0.99,1.00)	0.0875				
Hypertension	Alzheimer's disease	IVW	1.00 (0.99,1.01)	0.1914			57.11	0.7461
		MR-Egger	1.01 (0.99,1.02)	0.2078	–4.51e-05	0.3491	56.22	0.7445
		Weighted median	1.00 (0.99,1.01)	0.4181				
		Maximum likelihood	1.00 (0.99,1.01)	0.1914				
		RAPS	1.00 (0.99,1.01)	0.2233				
FBG	Alzheimer's disease	IVW	1.00 (0.99,1.00)	0.5977			104.17	0.5318
		MR-Egger	1.00 (0.99,1.00)	0.4385	–1.24e-05	0.5615	103.84	0.5136
		Weighted median	1.00 (0.99,1.00)	0.4037				
		Maximum likelihood	1.00 (0.99,1.00)	0.5989				
		RAPS	1.00 (0.99,1.00)	0.6898				
TG	Alzheimer's disease	IVW	0.99 (0.99,1.00)	0.7071			824.29	0.1795
		MR-Egger	1.00 (0.99,1.00)	0.6987	–5.82e-06	0.4371	823.65	0.1770
		Weighted median	1.00 (0.99,1.00)	0.9353				
		Maximum likelihood	0.99 (0.99,1.00)	0.7023				
		RAPS	0.99 (0.99,1.00)	0.8574				
HDL-C	Alzheimer's disease	IVW	1.00 (0.99,1.00)	0.9896			974.46	0.2837
		MR-Egger	1.00 (0.99,1.00)	0.9293	–6.79e-07	0.9170	974.45	0.2761
		Weighted median	1.00 (0.99,1.00)	0.9875				
		Maximum likelihood	1.00 (0.99,1.00)	0.9895				
		RAPS	0.99 (0.99,1.00)	0.9850				
MetS	Vascular dementia	IVW	1.05 (0.89,1.24)	0.5115			121.13	0.5305
		MR-Egger	1.04 (0.73,1.50)	0.7929	0.0004	0.9726	121.13	0.5050
		Weighted median	1.18 (0.91,1.53)	0,1970				
		Maximum likelihood	1.05 (0.89,1.24)	0.5076				
		RAPS	1.06 (0.89,1.25)	0.4906				

WC	Vascular dementia	IVW	1.30 (0.94,1.79)	0.1028			539.81	0.7520
		MR-Egger	1.32 (0.50,3.43)	0.5652	–0.0002	0.9757	539.81	0.7424
		Weighted median	1.26 (0.70,2.24)	0.4304				
		Maximum likelihood	1.31 (0.95,1.81)	0.0955				
		RAPS	1.27 (0.91,1.78)	0.1516				
Hypertension	Vascular dementia	IVW	4.17 (0.23,75.75)	0.3336			80.22	0.0966
		MR-Egger	1.56 (4.71e-05,51732.67)	0.9332	0.0055	0.8476	80.18	0.0833
		Weighted median	12.82 (0.26,628.59)	0.1987				
		Maximum likelihood	4.37 (0.31,61.56)	0.2740				
		RAPS	6.69 (0.32,136.52)	0.2165				
FBG	Vascular dementia	IVW	1.09 (0.63,1.87)	0.7435			114.96	0.2819
		MR-Egger	0.67 (0.26,1.76)	0.4275	0.0137	0.2389	113.46	0.2922
		Weighted median	1.16 (0.51,2.63)	0.7138				
		Maximum likelihood	1.09 (0.64,1.84)	0.7362				
		RAPS	1.06 (0.60,1.87)	0.8399				
TG	Vascular dementia	IVW	0.97 (0.81,1.17)	0.8242			737.33	0.6796
		MR-Egger	0.92 (0.68,1.24)	0.6011	0.0019	0.6250	737.10	0.6726
		Weighted median	1.14 (0.82,1.59)	0.4237				
		Maximum likelihood	0.97 (0.81,1.17)	0.8251				
		RAPS	1.01 (0.83,1.22)	0.9121				
HDL-C	Vascular dementia	IVW	0.93 (0.79,1.09)	0.3940			838.12	0.9448
		MR-Egger	0.93 (0.72,1.19)	0.5739	8.37e-05	0.9807	838.12	0.9421
		Weighted median	0.81 (0.61,1.07)	0.1495				
		Maximum likelihood	0.93 (0.79,1.09)	0.3960				
		RAPS	0.93 (0.79,1.10)	0.4526				
MetS	Frontotemporal dementia	IVW	1.26 (0.81,1.95)	0.2926			67.29	0.0172
		MR-Egger	2.76 (0.85,8.94)	0.0965	–0.0535	0.1667	64.39	0.0240
		Weighted median	1.55 (0.89,2.71)	0.1155				
		Maximum likelihood	1.26 (0.88,1.81)	0.1929				
		RAPS	1.31 (0.82,2.06)	0.2470				
WC	Frontotemporal dementia	IVW	0.88 (0.45,1.73)	0.7227			235.42	0.3196
		MR-Egger	0.70 (0.10,4.65)	0.7140	0.0031	0.8267	235.37	0.3038
		Weighted median	1.00 (0.31,3.20)	0.9941				
		Maximum likelihood	0.88 (0.45,1.71)	0.7160				
		RAPS	0.84 (0.42,1.69)	0.6413				
Hypertension	Frontotemporal dementia	IVW	9.15 (0.01,7.77e+03)	0.5200			28.00	0.1756
		MR-Egger	1.95e+08 (0.001,2.35e+19)	0.1573	–0.0925	0.1937	25.78	0.2146
		Weighted median	9.66e+02 (0.13,6.86e+06)	0.1287				
		Maximum likelihood	1.01e+01 (0.02,4.33e+03)	0.4533				
		RAPS	3.37e+01 (0.02,4.03e+04)	0.3305				

(*Continued*)

Table 2
(*Continued*)

Exposure	Outcome	Methods	OR (95%)	*p*	Egger_intercept	*p*-Egger intercept	Cochran's	Cochran's *p*
FBG	Frontotemporal dementia	IVW	0.49 (0.08,2.98)	0.4446			39.37	0.1437
		MR-Egger	0.20 (0.01,32.55)	0.5440	0.0174	0.7153	39.19	0.1213
		Weighted median	1.49 (0.13,16.66)	0.7417				
		Maximum likelihood	0.50 (0.10,2.50)	0.4034				
		RAPS	0.58 (0.09,3.43)	0.5492				
TG	Frontotemporal dementia	IVW	1.40 (0.86,2.28)	0.1675			220.16	0.1338
		MR-Egger	2.45 (1.08,5.52)	0.0317	–0.0164	0.0975	217.11	0.1552
		Weighted median	1.61 (0.76,3.42)	0,2079				
		Maximum likelihood	1.40 (0.88,2.23)	0.1450				
		RAPS	1.47 (0.91,2.37)	0.1135				
HDL-C	Frontotemporal dementia	IVW	0.91 (0.61,1.35)	0.6463			244.24	0.3424
		MR-Egger	0.75 (0.40,1.42)	0.3888	0.0060	0.4596	243.67	0.3350
		Weighted median	0.65 (0.33,1.29)	0.2209				
		Maximum likelihood	0.90 (0.61,1.34)	0.6380				
		RAPS	0.87 (0.58,1.31)	0.5139				
MetS	Dementia with Lewy bodies	IVW	1.15 (1.01,1.30)	0.0252			114.09	0.4533
		MR-Egger	1.19 (0.90,1.59)	0.2149	0.0098	0.7750	114.01	0.4292
		Weighted median	1.21 (1.01,1.46)	0.0422				
		Maximum likelihood	1.15 (1.01,1.31)	0.0242				
		RAPS	1.14 (0.99,1.31)	0.0530				
WC	Dementia with Lewy bodies	IVW	0.94 (0.73,1.21)	0.6346			522.79	0.3965
		MR-Egger	0.85 (0.40,1.80)	0.6814	0.0014	0.7902	522.72	0.3854
		Weighted median	0.98 (0.64,1.51)	0.9278				
		Maximum likelihood	0.94 (0.73,1.21)	0.6445				
		RAPS	0.96 (0.73,1.25)	0.7733				
Hypertension	Dementia with Lewy bodies	IVW	1.02 (9.75e-02,10.83)	0.9817			86.68	0.0209
		MR-Egger	0.04 (7.97e-06,273.56)	0.4914	0.0170	0.4706	85.94	0.0193
		Weighted median	1.74 (8.96e-02,34.00)	0.7129				
		Maximum likelihood	1.02 (1.36e-01,7.76)	0.9781				
		RAPS	1.02 (8.49e-02,12.36)	0.9845				
FBG	Dementia with Lewy bodies	IVW	1.50 (1.01,2.24)	0.0423			94.59	0.6339
		MR-Egger	1.13 (0.56,2.30)	0.7173	0.0080	0.3467	93.69	0.6316
		Weighted median	1.19 (0.63,2.26)	0.5789				
		Maximum likelihood	1.51 (1.01,2.25)	0.0420				
		RAPS	1.49 (0.98,2.25)	0.0561				

TG	Dementia with Lewy bodies	IVW	1.07 (0.93,1.23)	0.3290			748.16	0.0875
		MR-Egger	1.04 (0.83,1.31)	0.7078	0.0009	0.7670	748.06	0.0838
		Weighted median	0.99 (0.78,1.25)	0.9756				
		Maximum likelihood	1.07 (0.93,1.23)	0.3144				
		RAPS	1.05 (0.91,1.22)	0.4502				
HDL-C	Dementia with Lewy bodies	IVW	0.81 (0.72,0.92)	0.0010			836.34	0.4318
		MR-Egger	0.71 (0.59,0.87)	0.0007	0.0045	0.0918	833.48	0.4497
		Weighted median	0.78 (0.63,0.97)	0.0257				
		Maximum likelihood	0.81 (0.72,0.92)	0.0010				
		RAPS	0.82 (0.72,0.93)	0.0026				
MetS	Dementia due to Parkinson's disease	IVW	0.84 (0.63,1.12)	0.2546			125.51	0.4451
		MR-Egger	0.60 (0.31,1.14)	0.1270	0.0254	0.2527	124.17	0.4532
		Weighted median	0.74 (0.48,1.12)	0.1600				
		Maximum likelihood	0.84 (0.63,1.12)	0.2517				
		RAPS	0.84 (0.62,1.13)	0.2661				
WC	Dementia due to Parkinson's disease	IVW	0.65 (0.36,1.17)	0.1542			592.46	0.1966
		MR-Egger	0.72 (0.12,4.04)	0.7112	–0.0015	0.9092	592.45	0.1886
		Weighted median	0.91 (0.36,2.29)	0.8494				
		Maximum likelihood	0.66 (0.37,1.17)	0.1628				
		RAPS	0.68 (0.37,1.24)	0.2105				
Hypertension	Dementia due to Parkinson's disease	IVW	0.05 (4.11e-04,6.36)	0.2270			70.94	0.2861
		MR-Egger	0.01 (2.04e-10,2.09e+05)	0.5704	0.0115	0.8087	70.88	0.2590
		Weighted median	0.02 (2.44e-05,28.70)	0.3137				
		Maximum likelihood	0.04 (4.51e-04,5.13e)	0.2029				
		RAPS	0.01 (1.09e-04,1.77e)	0.0841				

(*Continued*)

Table 2
(*Continued*)

Exposure	Outcome	Methods	OR (95%)	*p*	Egger_intercept	*p*-Egger intercept	Cochran's	Cochran's *p*
FBG	Dementia due to Parkinson's disease	IVW	1.79 (0.71,4.48)	0.2100			96.64	0.7536
		MR-Egger	1.14 (0.22,5.84)	0.8744	0.0130	0.5124	96.21	0.7414
		Weighted median	1.89 (0.43,8.33)	0.3962				
		Maximum likelihood	1.79 (0.71,4.50)	0.2113				
		RAPS	1.81 (0.70,4.68)	0.2165				
TG	Dementia due to Parkinson's disease	IVW	1.01 (0.73,1.39)	0.9441				
		MR-Egger	0.99 (0.59,1.68)	0.9900	0.0004	0.9442		
		Weighted median	1.25 (0.71,2.23)	0.4296				
		Maximum likelihood	1.01 (0.73,1.39)	0.9444				
		RAPS	1.01 (0.72,1.41)	0.9389				
HDL-C	Dementia due to Parkinson's disease	IVW	1.07 (0.80,1.42)	0.6446			982.43	0.0389
		MR-Egger	1.67 (1.07,2.63)	0.0239	–0.0162	0.0107	975.39	0.0516
		Weighted median	1.45 (0.86,2.45)	0.1621				
		Maximum likelihood	1.07 (0.81,1.41)	0.6326				
		RAPS	1.09 (0.81,1.47)	0.5292				

MetS, metabolic syndrome; WC, waist circumference; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; IVW, inverse-variance weighted; RAPS, robust adjusted profile score; OR, odds ratio.

Table 3
The demographic characteristics for any dementia, vascular dementia, dementia due to Parkinson's disease

Exposure	Female	Male	Mean age at first event (year-old)	Absolute risk (15 years)
Any dementia	4,281	5,441	77.53	0.02
Vascular dementia	567	1,035	78.53	0.01
Dementia due to Parkinson's disease	128	262	75.53	–

Table 4
The demographic characteristics for frontotemporal dementia

Exposure	Female	Male	Mean age of onset (year-old)	Mean age of death (year-old)	Motor neuron disease (present)	Family history
Frontotemporal dementia	227	286	59.8	67.6	104	169

Table 5
The demographic characteristics for dementia with Lewy bodies

Exposure	Female	Male	Clinically ascertained	Pathologically diagnosed	Mean age (year-old)
Dementia with Lewy bodies	948	1,643	802	1,789	75

tension, FBG, TG, and dementia with Lewy bodies (all $p > 0.0016$, Table 2, Fig. 2). The funnel plot is symmetrical despite a visible heterogeneity in Cochran's Q analysis (Table 2, Fig. 3). MR-Egger method and MR-PRESSO do not find potential pleiotropy (Table 2). The results of the leave-one-out analysis are stable (Fig. 4). The causal estimate of each SNP on dementia with Lewy bodies is depicted in Fig. 5.

As shown in Table 2 and Fig. 2, MetS and its five components are not causally related to dementia due to Parkinson's disease (all $p > 0.05$). In sensitivity analyses, although there has pleiotropy (MR-Egger: p-Egger intercept <0.05, Table 2), the relationship still does not exist after performing CAUSE analysis ($p = 0.94$). There is no evidence of heterogeneity according to the findings of Cochran's Q test and the funnel plot (Fig. 3, Table 2). Additionally, the robustness of the MR estimates is verified by the leave-one-out analysis (Fig. 4). Figure 5 demonstrates the casual estimate of each SNP on dementia due to Parkinson's disease.

DISCUSSION

In our MR analysis, we find that no significant causal association exists between MetS, its five components, and different dementia types, including any dementia, AD, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and dementia due to Parkinson's disease, except for the relationship between HDL-C and dementia with Lewy bodies. HDL-C may play a protective role in dementia with Lewy bodies.

The previous results of the association between MetS, its components, and dementia is summarized in Table 6. The role of MetS on any dementia is not yet concluded. Some studies support the association between MetS and any dementia. For example, a cohort study including 1,519 participants conducted in Singapore finds that the MetS is associated with an increased risk of dementia [6]. The findings in the Whitehall II study also reveal that persistent MetS decline cognitive performance in late midlife [7]. In contrast, other studies do not support the association. In a cross-sectional and prospective study consisting of 2,476 men and women aged 65 years, researchers find that MetS is not associated with the increasing risk of dementia after 4.4 years of follow-up [8]. A recent meta-analysis including 18,313 participants ranging from January 1, 2000 to August 31, 2018 shows that no statistical significance pooled association emerges between MetS and dementia [27]. Some studies even support the protective role of MetS on dementia [9]. In our MR study, we do not identify the causal association between MetS and any dementia.

For the relationship between five components of MetS and any dementia, the association remains inconsistent. As to waist circumference, Abbatecola and his colleagues think that WC can predict the risk of cognitive decline during the 12-year follow-up in older patients with diabetes [28]. However, a study including 2,565 men and women does not find the association [29]. In our MR study, we do not support

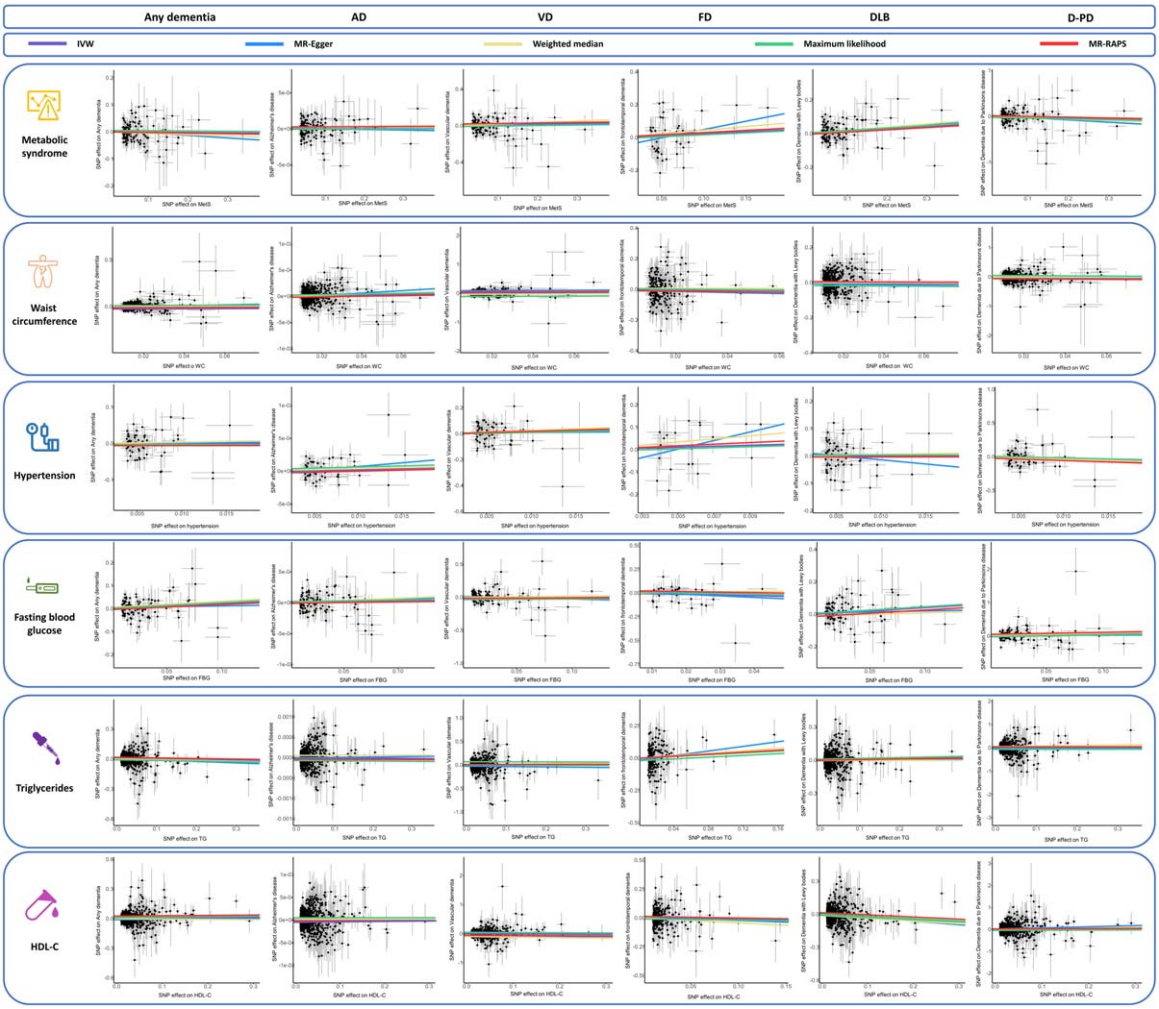

Fig. 2. The scatter plots of the association between genetically predicted MetS and its components on dementia in the MR analysis. MetS, metabolic syndrome; WC, waist circumference; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; AD, Alzheimer's disease; VD, vascular dementia; FD, frontotemporal dementia; DLB, dementia with Lewy bodies; D-PD, dementia due to Parkinson's disease.

the causal association. The effect of hypertension on dementia remains unclear. Considering the numerous factors affecting hypertension, such as age and hypertension chronicity, the role of hypertension in dementia is complex [30]. For example, large epidemiological studies have demonstrated a consistent association between high midlife blood pressure and cognitive decline, while a similar association between late-life blood pressure and cognition decline is not consistent [31]. From the perspective of neuroimage, a recent study finds that hypertension may alter brain structure and function, which may result in disruption in cognitive function [32]. However, the causal association between hypertension and dementia does not exist in this study. FBG represents the abnormality of glucose level and is recognized as a well-known risk factor for dementia [33, 34], while we do not identify the causal association. In the association of TG, HDL-C, and dementia, the results also remain inclusive [35–37]. Our MR analysis does not find a causal relationship.

Inconsistent conclusions are also obtained about the association between MetS, its components, and AD [27, 38]. A meta-analysis, including a total of 18,313 participants aged older than 40 years with mean MetS prevalence of 22.7% and followed on average for 9.41 years, found that no significant pooled association existed between MetS and AD [27]. However, contradictory results also been reported [39], and the inverse association also have

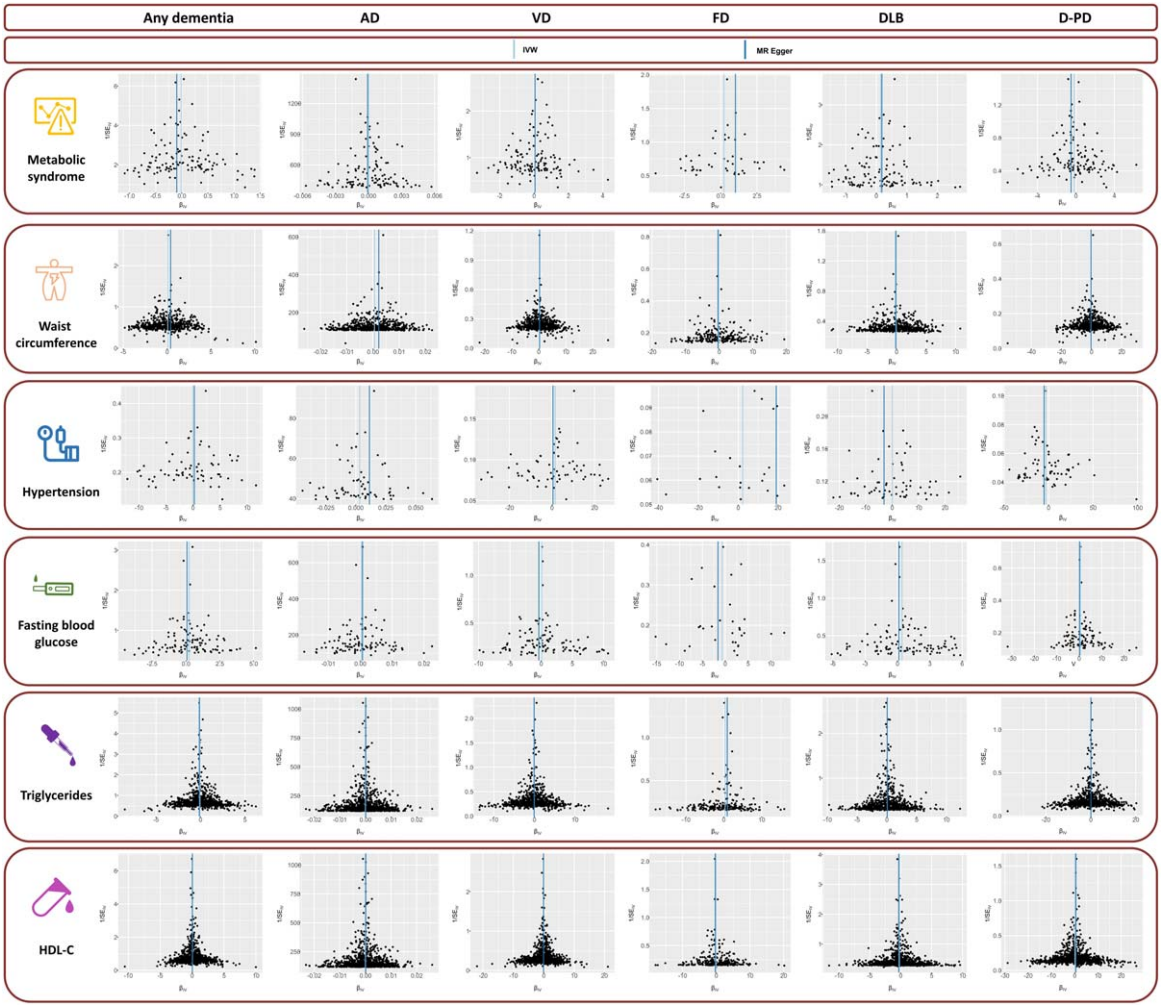

Fig. 3. The funnel plots of the association between genetically predicted MetS and its components on dementia in the MR analysis. AD, Alzheimer's disease; VD, vascular dementia; FD, frontotemporal dementia; DLB, dementia with Lewy bodies; HDL-C, high-density lipoprotein cholesterol; MR, Mendelian randomization; D-PD, dementia due to Parkinson's disease.

been observed [40]. As for MetS components, the effects on AD remain inconsistent. For example, a meta-analysis including 16 cohort studies and 41,781 participants and 4,511 dementia cases, no beneficial impacts of obesity in older age on incident dementia is found [41]. However, a study including a total of 10,308 adults found the detrimental effects on AD incidence [42]. In our MR study, no causal association between MetS, its components and the risk of AD were identified.

The studies related to the role of MetS on vascular dementia support the detrimental effect of MetS and may increase the risk of vascular dementia [43, 44], although these studies are scarce. In the Italian Longitudinal Study on Ageing including a total of 2,097 participants (MetS subjects [$n = 918$], subjects without MetS [$n = 1{,}179$]), studies found that MetS elevated the risk of vascular dementia [44]. So far, potential associations between frontotemporal dementia, and head trauma [45], diabetes [46], and autoimmune conditions may exist [47]. However, the study about the causal association between MetS and frontotemporal dementia is limited [48]. The study related to the association between MetS and dementia with Lewy bodies [49] and dementia due to Parkinson's disease is also scarce, and no association between MetS, its components and dementia due to Parkinson's disease was identified [50]. In our MR study, we find no significant casual association between MetS, its components and vascular dementia, frontotemporal dementia, and dementia due to Parkinson's disease. As for dementia with Lewy bod-

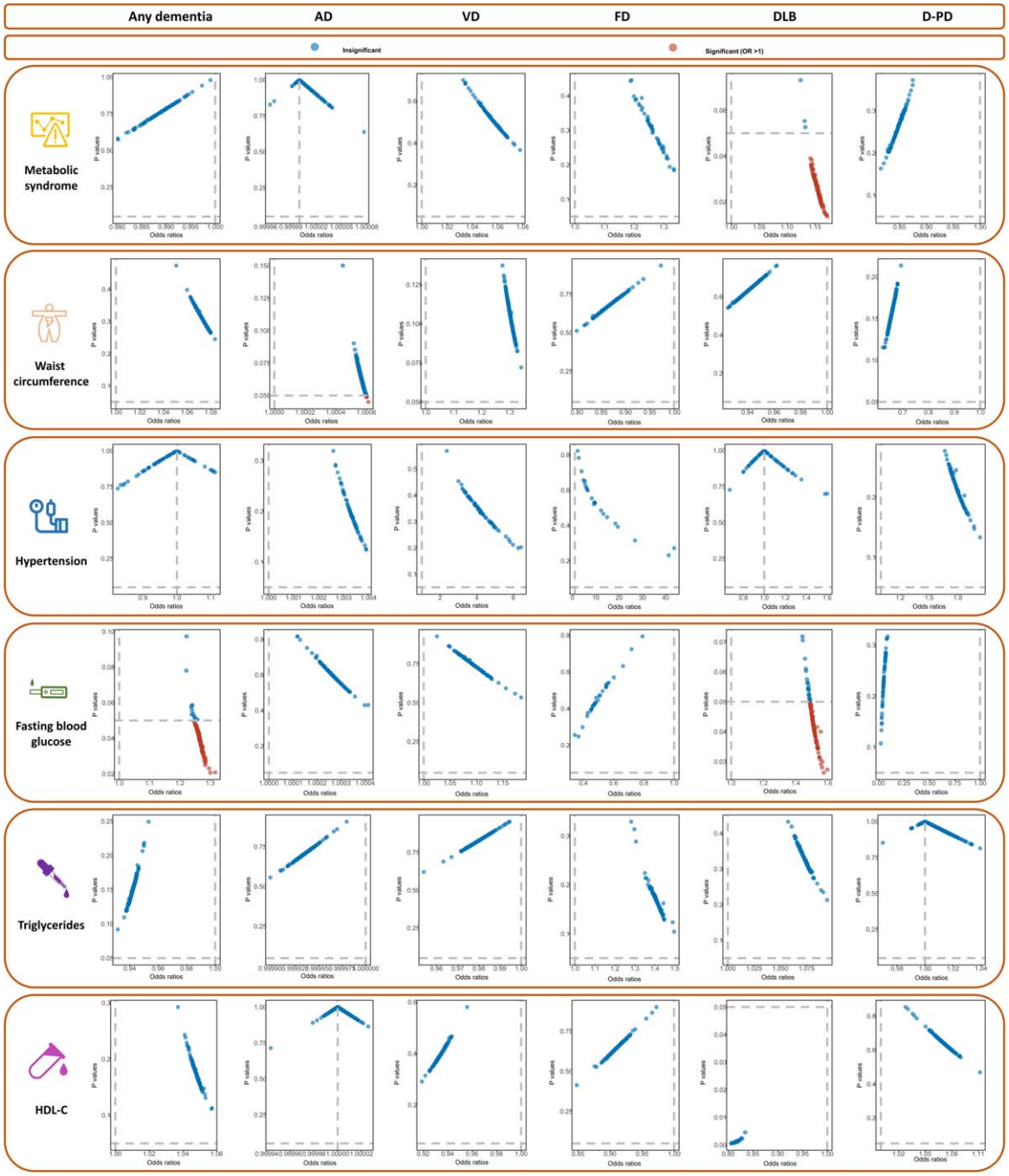

Fig. 4. The leave-one-out analysis of the association between genetically MetS and its components on dementia in the MR analysis. AD, Alzheimer's disease; VD, vascular dementia; FD, frontotemporal dementia; DLB, dementia with Lewy bodies; HDL-C, high-density lipoprotein cholesterol; MR, Mendelian randomization; D-PD, dementia due to Parkinson's disease.

ies, Dou and colleagues thought that reduced levels of HDL-C were associated with the development of dementia with Lewy bodies in a case-control study including 65 patients with Lewy body dementia and 110 older adult controls [51]. Several studies also supported the relationship [52, 53].

Many observational studies may be influenced by many confounding factors such as limited sample

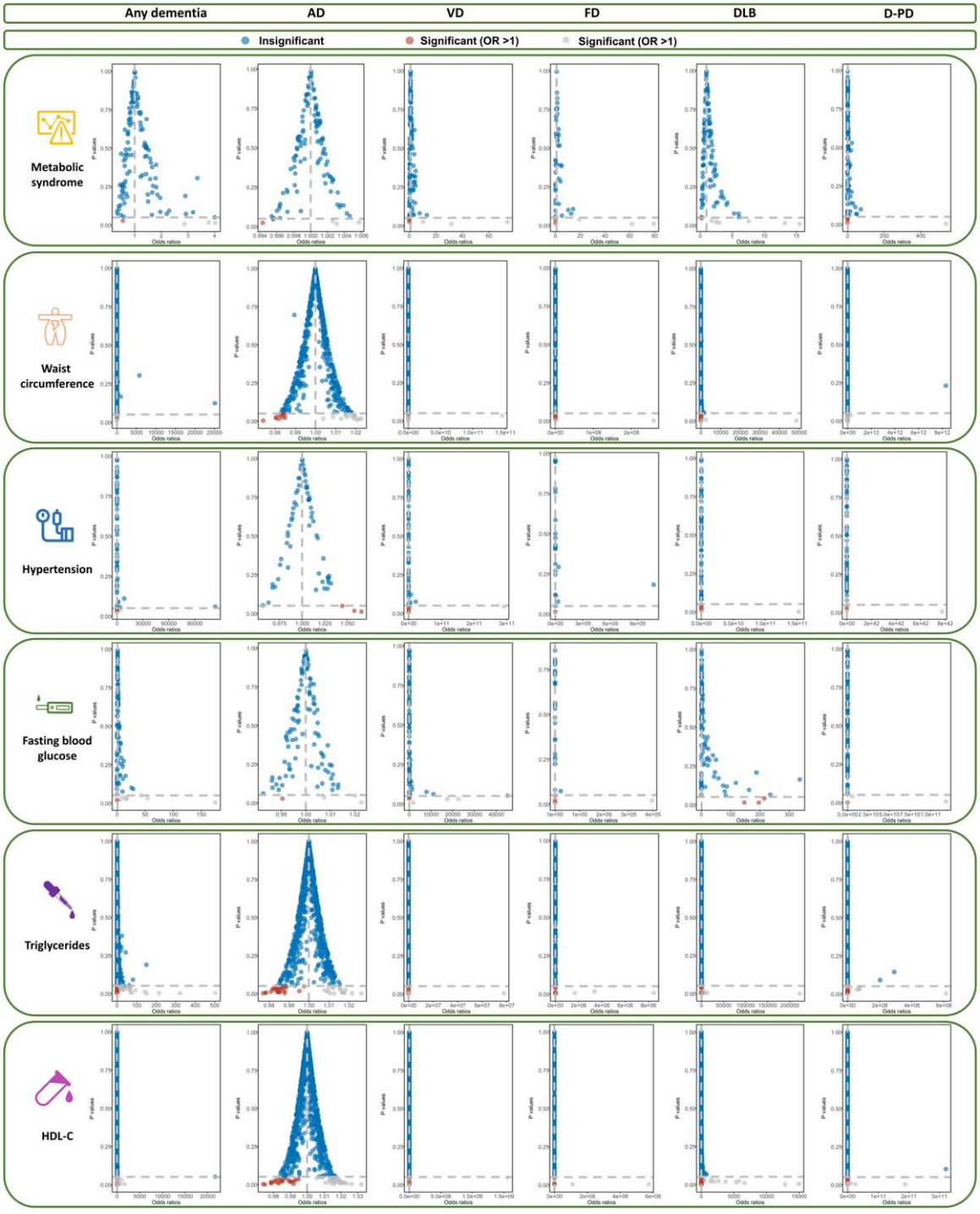

Fig. 5. The frost plots of the association between genetically MetS and its components on dementia in the MR analysis. AD, Alzheimer's disease; VD, vascular dementia; FD, frontotemporal dementia; DLB, dementia with Lewy bodies; HDL-C, high-density lipoprotein cholesterol; MR, mendelian randomization; D-PD, dementia due to Parkinson's disease.

size or (and) retrospective study. The strength of our MR study overcomes the possible confounders and clarifies the causal association between MetS and different dementia types. Additionally, it is the first study

Table 6
The opinion about the relationship between MetS, its components and dementia in references

Author	Study	Relationship	Opinion
Ng TP [6]	Singapore Longitudinal Ageing Study Cohort	MetS and any dementia	Harm
Akbaraly TN [7]	Whitehall II study	MetS and any dementia	Harm
Muller M [8]	Multiethnic elderly cohort	MetS and any dementia	None
Atti AR [27]	Meta-Analysis of Longitudinal Studies	MetS and any dementia	None
Watts AS [9]	–	MetS and any dementia	Protective
Abbatecola AM [28]	–	WC and any dementia	Harm
Ong HL [29]	Cross-sectional epidemiological study	WC and any dementia	None
Walker KA [31]	–	Hypertension and any dementia	Harm
Sierra C [30]	–	Hypertension and any dementia	Unknown
Jennings JR [32]	–	Hypertension and any dementia	Harm
Barbiellini Amidei C [33] and Mortimer JA [34]	–	FBG and any dementia	Harm
Reitz C, Li J, Han KT [35–37]	–	TG, HDL-C and any dementia	Inclusive
Atti AR [27]	Meta-analysis	MetS and AD	None
Lee JE [39]	–	MetS and AD	Harm
Forti P [40]	Prospective population-based cohort	MetS and AD	Protective
Danat IM [41]	Meta-analysis	WC and AD	None
Singh-Manoux A [42]	Whitehall II Study	WC and AD	Harm
Raffaitin C and Solfrizzi V [43, 44]	–	MetS and vascular dementia	Harm
Golimstok A [46]	Case-control study	FBG and frontotemporal dementia	Harm
Schelp AO [50]	Cross-sectional study	MetS, its components and dementia due to Parkinson's disease	None
Dou Y, Yasuno F, Svensson T [51–53]	–	HDL-C and dementia with Lewy bodies	Protective

AD, Alzheimer's disease; MetS, metabolic syndrome; WC, waist circumference; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

to illustrate their association. However, this study has several limitations. Firstly, the cases of different dementia are relatively small. Second, there is an ethnic bias because the datasets are all of European ancestry, which may limit the generalization of the conclusion. Third, we do not make stratification based on some factors such as age and gender due to the unavailability of stratification datasets. Future studies are required to verify these association in other ancestries, larger studies, and proper stratification people.

Conclusion

In our MR study, MetS and its components do not increase the risk of different dementia types., while

HDL-C may play a protective role in dementia with Lewy bodies.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

All data in our MR analyses are available from public databases (https://gwas.mrcieu.ac.uk/).

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