International Journal of General Medicine

Dovepress

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ORIGINAL RESEARCH

The Association of Waist Circumference and the Risk of Deep Vein Thrombosis

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Objective: In this study, we aimed to use a two sample Mendelian randomization (MR) method to identify a potentially causality between waist circumference and the risk of deep vein thrombosis (DVT).

Methods: With a two-sample MR approach, we analyzed the summary data. The main analysis was performed by using the summary genetic data from two large consortium cohorts. Three MR approaches were used to explore MR estimates of waist circumference for DVT (inverse-variance weighted [IVW] approach, weighted median method and MR-Egger method). A total of 224 single nucleotide polymorphisms (SNPs) were identified associated with the level of waist circumference at statistical significance ($P < 5*10^{-8}$; linkage disequilibrium $r^2 < 0.1$).

Results: The result of IVW indicated the positive association between waist circumference and the risk of DVT (OR 1.012, 95% CI 1.009–1.014, P 7.627E-17). The other two methods were observed with consistent result. MR-Egger regression analysis indicated that no evidence for the presence of directional horizontal pleiotropy. Additionally, DVT was not a causal factor for waist circumference.

Conclusion: In summary, we used the GWAS genetic data from two large consortium cohorts and indicated the positive association between waist circumference and DVT. Further researches are needed to investigate potential mechanism and clarify the role of waist circumference on DVT.

Keywords: waist circumference, deep vein thrombosis, coronary heart disease, Mendelian randomization, causality, MR, DVT

Introduction

As a subset of venous thromboembolism (VTE), deep vein thrombosis (DVT) is the medical condition when thrombus formation occurs in deep veins, occupying two-third of VTE cases.[1,2] Once the DVT falls off, it may block the pulmonary artery and form a fatal pulmonary embolism, which is an important cause of abnormal death in hospitalized patients.[3] Coronavirus disease 2019 (COVID-19) is an ongoing outbreak of respiratory illness worldwide.[4] Coagulation abnormalities and thromboembolism are becoming common complications in critically ill patients with COVID-19.[5,6] The high incidence of DVT in patients with COVID-19 has attracted the attention of researchers and clinicians. Exploring the risk factors of the DVT is even more important at present.

Obesity has been demonstrated with increased risk of DVT in several researches.[7–9] Recently, some studies have found that abdominal obesity might be a better predictor of DVT while waist circumference was the crucial indicator to evaluate abdominal obesity.[10,11] Relevant reports were mostly conventional

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Received: 21 October 2021
Accepted: 22 November 2021
Published: 2 December 2021

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retrospective observation studies, which are inevitably interfered by reverse causality and confounding factors.[12] Randomized controlled trials (RCTs) often require lots of time and money, and may involve ethical issues.[13] In recent years, Mendelian randomization (MR) have been widely used in causal inferences of exposure factors and outcomes.[14–16] Compared with RCTs, MR is more economical and cost-effective. However, there is no relevant reports of MR studies on abdominal obesity and DVT.

In this study, we aimed to determine the potential causal relationship between waist circumference and the risk of DVT by using MR analysis.

Materials and Methods

Genetic Variants Associated with Waist Circumference

The genetic variants associated with waist circumference was assessed from the Neale lab consortium, which consisted of 336,639 participants and 10,894,596 single nucleotide polymorphisms (SNPs). The detail of the consortium was shown in Table 1. As with most MR studies, the selection criteria for SNP was set as "P < 5×10-8, linkage disequilibrium r^2 < 0.1" to decrease the impact of linkage disequilibrium.[14,15] Finally, there were 229 SNPs met the above criteria.

Genetic Variants Associated with DVT

The summary data for DVT was extracted from Medical research council-Integrative Epidemiology Unit (MER-ICU) consortium. There were 9241 DVT patients and 453,692 controls in this consortium. Apart from 5 SNPs (rs11208779, rs11666480, rs12335914, rs13264909, rs1454687) not found in MER-ICU, the remaining 224 SNPs were included in the analysis.

Estimation of the Causal Relationship

Two-sample MR can be used to analysis the data without contacting with clinical individual patients.[17] We utilized a R (version 3.4.2) package "TwoSampleMR" (version 0.3.4) to implement operations. We estimated the causal effect of waist circumference on DVT and harnessed the statistical/6 power of pre-existing GWAS analyses with the SNP-exposure effects and the SNP-out-come effects which are obtained from different studies. Summary data were extracted from GWAS through MR-Base platform.[18] Three MR approaches were used to explore MR estimates of waist circumference for DVT (inverse-variance weighted [IVW] approach, weighted median method and MR-Egger method). At first, we carried out a random-effects IVW meta-analysis by regressing the SNP–waist circumference associations against the SNP–DVT associations. The inverse-variance weighted mean of ratio estimates was calculated from 224 instruments. Fixed effects IVW assumed none of the SNPs exhibit horizontal pleiotropy while random effects IVW allows each SNP having different mean effects.[18,19] Secondly, by using weighted median methods, we found the weighted empirical distribution function of ratio estimates of SNPs selected. Median-

Table 1 Details of the Traits Used in the Study

Trait	Waist Circumference	Deep Vein Thrombosis
ID	ukb-a-382	ukb-b-12040
Year	2017	2018
Author	Neale	Ben Elsworth
Consortium	Neale	MRC-IEU
Sex	Males and Females	Males and Females
Population	European	European
Unit	SD	SD
No. SNP	10,894,596	9,851,867
Sample size	336,639	462,933
Build	HG19/GRCh37	HG19/GRCh37
No. case	NA	9241
No. control	NA	453,692
Note	http://www.nealelab.is/uk-biobank	Output from GWAS pipeline using Phesant derived variables from UKBiobank

Abbreviations: DVT, self-reported deep vein thrombosis; ID, identity; MRC-IEU, Medical research council-Integrative Epidemiology Unit; SD, standard deviation; SNP, single nucleotide polymorphism; NA, not available.

based estimator had the advantage that only half of the SNPs needed to be valid instruments, which meant that the other SNPs might exhibit no horizontal pleiotropy, no association with confounders or robust associations with the exposure, to make sure the causal effect to be unbiased. Moreover, it allowed stronger SNPs to contribute more towards the estimate.[18,20] Third, MR-Egger analysis was implemented to assume that the horizontal pleiotropy had no association with the SNP-exposure effects.[20] When adapting the IVW analysis, MR-Egger allowed a non-zero intercept and unbalanced horizontal pleiotropy across all SNPs. MR-Egger regression could return an unbiased causal effect even all the SNPs were invalid instruments. It helped to figure out weighted linear regression of SNP–waist circumference risk against SNP–DVT effect estimates. The causal effect of DVT on waist circumference was also investigated by these three methods.

Sensitivity Analysis

Leave-one-out method that eliminated the included SNPs one by one and calculated the effect of the remaining instrumental variables to find the decisive SNPs, was applied in the sensitivity analysis. The intercept in MR-Egger was calculated to check the presence of directional horizontal pleiotropy.

Results

Detail Information of the Selected SNPs

Table 2 showed the detail information of these 224 SNPs, consisting of the name, effect allele (EA), chromosome location, effect allele frequency (EAF), the estimations of the associations both with waist circumference and DVT, and so on. There were 29 SNPs significantly associated with the risk of DVT, namely rs10100245 (β-0.0010; SE 0.0003; P 0.0005), rs10128597 (β −0.0010; SE 0.0003; P 0.0008), rs10172196 (β 0.0010; SE 0.0003; P 0.0011), rs1019240 (β 0.0013; SE 0.0004; P 0.0011), rs10236214 (β 0.0011; SE 0.0003; P 0.0012), rs10237306 (β 0.0011; SE 0.0003; P 0.0019), rs10269774 (β 0.0009; SE 0.0003; P 0.0046), rs10423928 (β −0.0008; SE 0.0003; P 0.0110), rs10459088 (β 0.0008; SE 0.0003; P 0.0120), rs1056441 (β 0.0007; SE 0.0003; P 0.0150), rs10787738 (β −0.0008; SE 0.0003; P 0.0180), rs10803762 (β −0.0007; SE 0.0003; P 0.0190), rs10938398 (β −0.0007; SE 0.0003; P 0.0190), rs10957088 (β −0.0008; SE 0.0004; P 0.0200), rs10992841 (β 0.0008; SE 0.0004; P 0.0220) rs11012732 (β 0.0009; SE 0.0004; P 0.0250), rs11039266 (β −0.0008; SE 0.0004; P 0.0260), rs11099020 (β −0.0007; SE 0.0003; P 0.0260), rs11150745 (β 0.0009; SE 0.0004; P 0.0290), rs111640872 (β 0.0007; SE 0.0003; P 0.0330), rs112566467 (β 0.0006; SE 0.0003; P 0.0360), rs11474838 (β −0.0006; SE 0.0003; P 0.0400), rs1154988 (β −0.0006; SE 0.0003; P 0.0410), rs1159974 (β 0.0011; SE 0.0005; P 0.0410), rs11636611 (β −0.0006; SE 0.0003; P 0.0430), rs11642015 (β −0.0007; SE 0.0004; P 0.0450), rs11653367 (β −0.0006; SE 0.0003; P 0.0460), rs11757278 (β −0.0006; SE 0.0003; P 0.0460) and rs11764337 (β 0.0009; SE 0.0005; P 0.0490). In this analysis, the F statistic was 878, which was larger than 10 and able to suppress the interference of weak instrumental variables.[21]

Causal Effect of Waist Circumference on DVT

The result of IVW indicated the positive association between waist circumference and the risk of DVT (OR 1.012, 95% CI 1.009–1.014, P 7.627E-17) while the consistent result was observed in weighted median (OR 1.012, 95% CI 1.007–1.016, P 1.048E-07) and MR-Egger (OR 1.014, 95% CI 1.005–1.022, P 0.002) in Table 3. Figures 1 and 2 also presented the same statistical result.

Sensitivity Analysis

For the MR-Egger regression, the presence of directional horizontal pleiotropy was not observed because the intercept was close to zero and P values was larger than 0.05 (intercept = −3.9E-05, P = 0.616) (Table 4). The method of leave-one-analysis indicated that there was no decisive SNP to reverse the result of causal inference (Figure 3).

Causal Effect of DVT on Waist Circumference

As presented in Table 5, DVT was not causally associated with the level of waist circumference (OR 1.198, 95% CI 0.719-1.996, P = 0.487). After weighted median and MR-Egger were applied, the consistent result was also observed (OR 1.273, 95% CI 0.750–2.160, P 0.906; OR 1.064, 95% CI 0.393–2.878, P 0.371).

Discussion

DVT is a common and frequently-occurring disease in clinical practice, and the incidence is increasing year by year. People with DVT might lead to disability and cause

Table 2 Associations of the Included SNPs with Waist Circumference and the Risk of DVT

SNP	EA	Chr	Waist Circumference				Deep Vein Thrombosis.			
			EAF	β	SE	P	EAF	β	SE	P
rs10100245	A	8	0.566	0.015	0.002	<0.001	0.564	3.22E-04	2.94E-04	0.270
rs10128597	A	11	0.274	−0.016	0.002	<0.001	0.276	−8.38E-05	3.27E-04	0.800
rs10172196	A	2	0.305	0.014	0.002	<0.001	0.305	3.24E-04	3.17E-04	0.310
rs1019240	T	9	0.644	0.013	0.002	<0.001	0.643	1.65E-04	3.05E-04	0.590
rs10236214	T	7	0.641	0.015	0.002	<0.001	0.642	4.57E-04	3.05E-04	0.130
rs10237306	T	7	0.380	0.013	0.002	<0.001	0.383	8.49E-05	2.99E-04	0.780
rs10269774	A	7	0.324	0.013	0.002	<0.001	0.326	2.52E-04	3.10E-04	0.420
rs10423928	A	19	0.193	−0.026	0.003	<0.001	0.194	−7.37E-04	3.67E-04	0.045
rs10459088	A	12	0.260	0.014	0.002	<0.001	0.263	4.82E-04	3.31E-04	0.150
rs1056441	C	20	0.673	0.013	0.002	<0.001	0.675	2.16E-04	3.11E-04	0.490
rs10787738	T	10	0.253	0.017	0.003	<0.001	0.255	1.11E-04	3.39E-04	0.740
rs10803762	A	2	0.679	0.014	0.002	<0.001	0.677	−4.52E-04	3.12E-04	0.150
rs10938398	A	4	0.433	0.021	0.002	<0.001	0.434	1.59E-04	2.94E-04	0.590
rs10957088	C	8	0.160	0.016	0.003	<0.001	0.160	5.12E-06	3.97E-04	0.990
rs10992841	T	9	0.685	−0.014	0.002	<0.001	0.682	−7.36E-04	3.14E-04	0.019
rs11012732	G	10	0.331	0.022	0.002	<0.001	0.332	1.01E-03	3.09E-04	0.001
rs11039266	G	11	0.278	−0.022	0.002	<0.001	0.279	−3.68E-04	3.24E-04	0.260
rs11099020	T	4	0.643	−0.013	0.002	<0.001	0.641	−6.15E-04	3.04E-04	0.043
rs11150745	G	17	0.319	−0.016	0.002	<0.001	0.318	−3.51E-04	3.13E-04	0.260
rs111640872	C	19	0.331	0.020	0.002	<0.001	0.331	7.80E-04	3.10E-04	0.012
rs112566467	T	1	0.213	0.018	0.003	<0.001	0.213	3.97E-04	3.58E-04	0.270
rs11474838	G	20	0.433	0.013	0.002	<0.001	0.423	3.27E-04	2.99E-04	0.280
rs1154988	A	3	0.774	0.018	0.003	<0.001	0.773	7.94E-04	3.47E-04	0.022
rs1159974	C	6	0.528	0.013	0.002	<0.001	0.524	−9.38E-05	2.91E-04	0.750
rs11636611	T	15	0.503	0.013	0.002	<0.001	0.503	3.00E-04	2.91E-04	0.300
rs11642015	T	16	0.402	0.056	0.002	<0.001	0.404	6.06E-04	2.96E-04	0.041
rs11653367	G	17	0.326	−0.018	0.002	<0.001	0.328	−5.11E-05	3.11E-04	0.870
rs11757278	C	6	0.306	−0.014	0.002	<0.001	0.304	−6.31E-04	3.16E-04	0.046
rs11764337	T	7	0.183	−0.015	0.003	<0.001	0.186	−1.89E-04	3.75E-04	0.610
rs1182199	A	7	0.305	−0.016	0.002	<0.001	0.304	−4.92E-04	3.16E-04	0.120
rs11824092	C	11	0.637	0.013	0.002	<0.001	0.636	7.37E-04	3.04E-04	0.015
rs1184570	T	6	0.525	−0.013	0.002	<0.001	0.526	−2.82E-04	2.91E-04	0.330
rs11878477	G	19	0.504	−0.014	0.002	<0.001	0.502	−6.86E-05	2.92E-04	0.810
rs12096864	C	1	0.118	0.022	0.003	<0.001	0.119	−2.17E-05	4.55E-04	0.960
rs12102086	A	15	0.218	−0.018	0.003	<0.001	0.216	−4.03E-04	3.55E-04	0.260
rs12103006	G	16	0.571	0.015	0.002	<0.001	0.569	1.79E-04	2.94E-04	0.540
rs12128526	A	1	0.460	0.012	0.002	<0.001	0.457	−9.34E-05	2.92E-04	0.750
rs12140153	T	1	0.097	−0.025	0.004	<0.001	0.094	−6.76E-04	5.11E-04	0.190
rs1218824	A	13	0.662	0.013	0.002	<0.001	0.662	4.72E-04	3.08E-04	0.120
rs12367809	T	12	0.368	0.022	0.002	<0.001	0.369	3.75E-04	3.02E-04	0.210
rs12375196	A	7	0.424	0.013	0.002	<0.001	0.424	−1.15E-04	2.96E-04	0.700
rs12619178	T	2	0.403	−0.015	0.002	<0.001	0.401	4.95E-04	2.97E-04	0.095
rs12679106	T	8	0.711	−0.022	0.002	<0.001	0.709	−1.40E-04	3.22E-04	0.660
rs12680342	G	8	0.229	−0.014	0.003	<0.001	0.229	1.98E-05	3.46E-04	0.950
rs12806052	T	11	0.165	−0.019	0.003	<0.001	0.164	−1.35E-04	3.94E-04	0.730
rs12877270	A	13	0.438	0.013	0.002	<0.001	0.442	2.83E-04	2.95E-04	0.340
rs12881629	G	14	0.082	0.022	0.004	<0.001	0.083	8.54E-04	5.27E-04	0.110
rs12926311	C	16	0.355	−0.014	0.002	<0.001	0.354	6.68E-06	3.05E-04	0.980
rs13022337	G	2	0.829	0.038	0.003	<0.001	0.828	1.26E-03	3.85E-04	0.001
rs13047416	G	21	0.375	−0.013	0.002	<0.001	0.377	3.69E-04	3.01E-04	0.220

(*Continued*)

Table 2 (Continued).

SNP	EA	Chr	Waist Circumference				Deep Vein Thrombosis.			
			EAF	β	SE	P	EAF	β	SE	P
rs13210406	G	6	0.291	−0.015	0.002	<0.001	0.292	−2.90E-04	3.21E-04	0.370
rs1321521	A	6	0.346	0.015	0.002	<0.001	0.345	8.04E-05	3.06E-04	0.790
rs13322435	G	3	0.402	−0.016	0.002	<0.001	0.404	−5.61E-04	2.98E-04	0.060
rs13333747	C	16	0.182	−0.023	0.003	<0.001	0.183	6.64E-04	3.78E-04	0.079
rs13420048	A	2	0.361	−0.014	0.002	<0.001	0.365	−3.15E-04	3.03E-04	0.300
rs13423444	A	2	0.139	0.018	0.003	<0.001	0.140	−4.29E-04	4.20E-04	0.310
rs13427822	G	2	0.272	−0.016	0.002	<0.001	0.271	−3.87E-04	3.31E-04	0.240
rs1379828	T	13	0.798	−0.017	0.003	<0.001	0.798	−4.46E-04	3.63E-04	0.220
rs1383723	T	4	0.782	−0.017	0.003	<0.001	0.783	3.26E-06	3.54E-04	0.990
rs1411432	C	9	0.184	0.016	0.003	<0.001	0.186	−6.10E-04	3.75E-04	0.100
rs1412239	G	9	0.325	0.020	0.002	<0.001	0.323	2.66E-04	3.11E-04	0.390
rs1441264	A	13	0.592	0.016	0.002	<0.001	0.594	−1.84E-04	3.02E-04	0.540
rs146311547	G	5	0.131	0.018	0.003	<0.001	0.129	3.48E-05	4.36E-04	0.940
rs1470749	T	7	0.511	−0.014	0.002	<0.001	0.510	−1.21E-04	2.91E-04	0.680
rs1472872	G	4	0.079	−0.022	0.004	<0.001	0.079	−8.59E-04	5.40E-04	0.110
rs147786161	G	12	0.436	0.012	0.002	<0.001	0.437	4.71E-04	2.95E-04	0.110
rs1559900	T	8	0.285	0.013	0.002	<0.001	0.286	9.53E-05	3.22E-04	0.770
rs1566085	T	8	0.545	−0.013	0.002	<0.001	0.546	−3.33E-04	2.94E-04	0.260
rs1582931	A	5	0.472	−0.015	0.002	<0.001	0.473	1.20E-04	2.94E-04	0.680
rs1609303	A	2	0.631	0.017	0.002	<0.001	0.631	3.91E-04	3.03E-04	0.200
rs1652376	T	18	0.464	−0.019	0.002	<0.001	0.462	−1.02E-03	2.92E-04	0.000
rs17060974	G	13	0.231	0.014	0.003	<0.001	0.233	−3.80E-04	3.46E-04	0.270
rs17149254	C	7	0.809	−0.017	0.003	<0.001	0.805	3.50E-04	3.76E-04	0.350
rs1724557	A	4	0.588	−0.014	0.002	<0.001	0.587	2.67E-04	2.97E-04	0.370
rs1752169	A	9	0.249	0.015	0.002	<0.001	0.251	−3.75E-04	3.36E-04	0.260
rs17639996	A	3	0.151	−0.017	0.003	<0.001	0.150	−5.49E-04	4.09E-04	0.180
rs17708311	C	6	0.067	−0.025	0.004	<0.001	0.067	4.21E-04	5.83E-04	0.470
rs17716502	T	8	0.207	−0.018	0.003	<0.001	0.204	−4.66E-04	3.64E-04	0.200
rs1776209	G	10	0.293	−0.014	0.002	<0.001	0.292	3.91E-04	3.21E-04	0.220
rs1782508	G	11	0.656	−0.015	0.002	<0.001	0.656	−4.16E-04	3.06E-04	0.170
rs1834144	A	18	0.374	−0.015	0.002	<0.001	0.373	−6.01E-04	3.01E-04	0.046
rs1914888	G	17	0.490	−0.012	0.002	<0.001	0.491	−5.58E-04	2.92E-04	0.056
rs1928496	T	13	0.742	0.014	0.002	<0.001	0.743	−6.55E-05	3.33E-04	0.840
rs1942826	A	18	0.124	0.021	0.003	<0.001	0.126	5.34E-05	4.38E-04	0.900
rs2016469	A	3	0.374	0.012	0.002	<0.001	0.372	−1.66E-04	3.03E-04	0.580
rs2032912	T	16	0.409	−0.017	0.002	<0.001	0.409	−4.37E-04	2.97E-04	0.140
rs208015	C	17	0.932	−0.032	0.004	<0.001	0.932	−1.05E-03	5.77E-04	0.069
rs2121058	C	13	0.229	−0.018	0.003	<0.001	0.228	4.31E-04	3.47E-04	0.210
rs2126165	G	5	0.511	−0.014	0.002	<0.001	0.512	2.89E-04	2.91E-04	0.320
rs2172131	C	10	0.581	−0.014	0.002	<0.001	0.579	−2.78E-04	2.95E-04	0.350
rs217671	G	14	0.272	0.014	0.002	<0.001	0.273	4.48E-04	3.27E-04	0.170
rs2183947	A	6	0.224	−0.024	0.003	<0.001	0.225	−1.51E-04	3.48E-04	0.660
rs2192527	G	4	0.465	0.015	0.002	<0.001	0.465	1.08E-04	2.92E-04	0.710
rs2242259	C	12	0.556	−0.014	0.002	<0.001	0.557	−3.10E-04	2.93E-04	0.290
rs2253310	G	6	0.628	0.019	0.002	<0.001	0.626	4.33E-04	3.01E-04	0.150
rs2306593	T	17	0.489	−0.017	0.002	<0.001	0.488	−4.22E-04	2.92E-04	0.150
rs2307111	C	5	0.393	−0.025	0.002	<0.001	0.395	−3.37E-04	2.98E-04	0.260
rs2370982	T	14	0.215	0.021	0.003	<0.001	0.214	2.60E-04	3.57E-04	0.470
rs2404324	G	7	0.155	−0.019	0.003	<0.001	0.155	−2.17E-04	4.02E-04	0.590

(*Continued*)

Table 2 (Continued).

SNP	EA	Chr	Waist Circumference				Deep Vein Thrombosis.			
			EAF	β	SE	P	EAF	β	SE	P
rs241461	A	1	0.681	−0.018	0.002	<0.001	0.682	−1.06E-04	3.12E-04	0.740
rs2417998	G	9	0.706	−0.016	0.002	<0.001	0.708	−3.54E-04	3.21E-04	0.270
rs2433733	A	2	0.681	−0.017	0.002	<0.001	0.678	6.65E-04	3.11E-04	0.033
rs2439823	G	10	0.548	0.016	0.002	<0.001	0.546	−1.47E-04	2.93E-04	0.620
rs2455821	A	3	0.271	0.015	0.002	<0.001	0.271	−8.57E-05	3.28E-04	0.790
rs245775	G	5	0.729	0.016	0.002	<0.001	0.729	−9.53E-05	3.28E-04	0.770
rs2470167	A	15	0.204	0.015	0.003	<0.001	0.204	−8.04E-04	3.62E-04	0.026
rs2482704	T	9	0.423	−0.013	0.002	<0.001	0.427	2.29E-04	2.94E-04	0.440
rs2492462	G	10	0.174	0.016	0.003	<0.001	0.175	2.19E-04	3.87E-04	0.570
rs254024	T	5	0.437	0.014	0.002	<0.001	0.438	4.14E-04	2.93E-04	0.160
rs2608703	A	12	0.461	0.014	0.002	<0.001	0.460	2.14E-04	2.92E-04	0.460
rs2660241	C	16	0.363	0.015	0.002	<0.001	0.365	3.09E-04	3.03E-04	0.310
rs2678204	G	1	0.342	0.019	0.002	<0.001	0.340	2.88E-04	3.07E-04	0.350
rs2725371	G	8	0.696	−0.018	0.002	<0.001	0.696	−7.42E-04	3.17E-04	0.019
rs2814943	A	6	0.140	0.034	0.003	<0.001	0.140	−5.92E-05	4.18E-04	0.890
rs28366156	C	6	0.131	−0.021	0.003	<0.001	0.131	5.45E-05	4.32E-04	0.900
rs2861692	C	2	0.276	−0.018	0.002	<0.001	0.275	1.05E-03	3.26E-04	0.001
rs286818	A	5	0.170	−0.018	0.003	<0.001	0.170	−3.05E-04	3.88E-04	0.430
rs2903738	T	19	0.220	−0.015	0.003	<0.001	0.221	−2.37E-04	3.50E-04	0.500
rs34045288	T	6	0.336	0.022	0.002	<0.001	0.334	2.87E-04	3.08E-04	0.350
rs34483452	A	5	0.135	0.025	0.003	<0.001	0.136	−6.45E-04	4.27E-04	0.130
rs34994596	C	15	0.298	−0.016	0.002	<0.001	0.297	−7.56E-04	3.18E-04	0.018
rs350832	A	19	0.771	0.016	0.003	<0.001	0.771	−1.37E-04	3.48E-04	0.690
rs35343344	A	19	0.267	−0.017	0.002	<0.001	0.267	−1.96E-04	3.35E-04	0.560
rs3764002	T	12	0.261	−0.015	0.002	<0.001	0.262	−9.90E-05	3.31E-04	0.760
rs3766823	A	1	0.172	0.016	0.003	<0.001	0.172	7.53E-05	3.86E-04	0.850
rs3784692	T	15	0.603	0.020	0.002	<0.001	0.602	−4.58E-04	2.97E-04	0.120
rs3802858	C	11	0.427	−0.012	0.002	<0.001	0.427	−5.61E-04	2.94E-04	0.057
rs3803286	G	14	0.666	−0.017	0.002	<0.001	0.667	−2.81E-04	3.08E-04	0.360
rs3814883	T	16	0.483	0.028	0.002	<0.001	0.482	−1.64E-04	2.92E-04	0.580
rs3826408	T	17	0.457	0.012	0.002	<0.001	0.457	2.28E-04	2.92E-04	0.430
rs3935032	T	1	0.378	−0.015	0.002	<0.001	0.377	2.83E-04	3.05E-04	0.350
rs429358	C	19	0.156	−0.024	0.003	<0.001	0.154	−5.01E-04	4.03E-04	0.210
rs4322261	A	1	0.836	−0.018	0.003	<0.001	0.837	5.08E-05	3.94E-04	0.900
rs4467770	A	6	0.731	0.014	0.002	<0.001	0.731	−1.44E-04	3.29E-04	0.660
rs4482463	A	2	0.924	−0.029	0.004	<0.001	0.923	−5.64E-04	5.47E-04	0.300
rs4549080	T	2	0.341	0.013	0.002	<0.001	0.343	1.75E-04	3.06E-04	0.570
rs4671328	G	2	0.553	−0.016	0.002	<0.001	0.551	7.88E-05	2.95E-04	0.790
rs4718964	T	7	0.412	0.015	0.002	<0.001	0.413	6.77E-06	2.96E-04	0.980
rs4722398	T	7	0.136	0.018	0.003	<0.001	0.136	9.22E-04	4.23E-04	0.029
rs4741546	T	9	0.397	−0.015	0.002	<0.001	0.396	−4.81E-05	2.99E-04	0.870
rs4790841	T	17	0.155	−0.025	0.003	<0.001	0.154	−2.48E-04	4.04E-04	0.540
rs4856407	T	3	0.364	0.015	0.002	<0.001	0.363	5.02E-05	3.02E-04	0.870
rs4856721	A	3	0.539	0.013	0.002	<0.001	0.539	2.71E-05	2.92E-04	0.930
rs4981693	A	14	0.773	0.018	0.003	<0.001	0.773	−6.45E-04	3.48E-04	0.063
rs525101	C	13	0.372	0.013	0.002	<0.001	0.370	8.55E-04	3.02E-04	0.005
rs539515	C	1	0.208	0.035	0.003	<0.001	0.205	2.64E-04	3.61E-04	0.460
rs541577	G	7	0.621	−0.012	0.002	<0.001	0.619	−1.91E-04	3.01E-04	0.530
rs55726687	A	12	0.211	0.018	0.003	<0.001	0.210	−7.15E-05	3.57E-04	0.840

(*Continued*)

Table 2 (Continued).

SNP	EA	Chr	Waist Circumference				Deep Vein Thrombosis.			
			EAF	β	SE	P	EAF	β	SE	P
rs56203712	G	4	0.238	−0.017	0.003	<0.001	0.234	−8.20E-04	3.51E-04	0.020
rs56362718	C	12	0.310	0.015	0.002	<0.001	0.307	7.28E-05	3.15E-04	0.820
rs56803094	G	15	0.227	−0.016	0.003	<0.001	0.227	1.10E-04	3.48E-04	0.750
rs57636386	C	18	0.083	−0.033	0.004	<0.001	0.084	−9.76E-04	5.26E-04	0.064
rs58568715	G	11	0.164	0.017	0.003	<0.001	0.165	8.87E-04	3.95E-04	0.025
rs58862095	T	7	0.420	−0.018	0.002	<0.001	0.419	−6.07E-04	2.95E-04	0.040
rs588660	A	1	0.586	0.014	0.002	<0.001	0.584	−1.09E-04	2.95E-04	0.710
rs59227842	G	11	0.312	0.019	0.002	<0.001	0.311	−8.01E-04	3.17E-04	0.011
rs6096886	G	20	0.190	−0.024	0.003	<0.001	0.190	−2.18E-04	3.71E-04	0.560
rs61813324	T	1	0.135	0.020	0.003	<0.001	0.136	6.55E-04	4.31E-04	0.130
rs61826867	G	1	0.110	0.019	0.003	<0.001	0.111	−3.34E-04	4.63E-04	0.470
rs61888762	G	11	0.322	0.027	0.002	<0.001	0.319	2.17E-04	3.12E-04	0.490
rs61992671	G	14	0.496	−0.013	0.002	<0.001	0.492	−4.37E-04	3.04E-04	0.150
rs62071997	C	17	0.219	0.016	0.003	<0.001	0.218	1.76E-05	3.54E-04	0.960
rs62106258	C	2	0.048	−0.068	0.005	<0.001	0.049	−8.92E-04	6.77E-04	0.190
rs62120394	A	19	0.291	0.021	0.002	<0.001	0.292	3.94E-04	3.21E-04	0.220
rs62246314	A	3	0.101	0.022	0.004	<0.001	0.103	9.43E-04	4.79E-04	0.049
rs62261725	G	3	0.327	−0.018	0.002	<0.001	0.326	−7.87E-05	3.11E-04	0.800
rs6433243	C	2	0.648	−0.014	0.002	<0.001	0.648	5.52E-05	3.05E-04	0.860
rs6575340	A	14	0.637	0.018	0.002	<0.001	0.636	3.00E-04	3.03E-04	0.320
rs6687953	G	1	0.391	0.013	0.002	<0.001	0.391	−3.79E-05	2.98E-04	0.900
rs6688826	C	1	0.300	0.013	0.002	<0.001	0.298	−2.61E-04	3.18E-04	0.410
rs66922415	G	18	0.234	0.043	0.003	<0.001	0.233	1.07E-03	3.44E-04	0.002
rs6699744	T	1	0.614	0.018	0.002	<0.001	0.616	7.53E-05	3.00E-04	0.800
rs6739755	G	2	0.603	−0.017	0.002	<0.001	0.603	−6.63E-04	2.98E-04	0.026
rs67632512	A	5	0.117	0.019	0.003	<0.001	0.117	8.24E-04	4.58E-04	0.072
rs704061	C	12	0.453	0.016	0.002	<0.001	0.455	6.13E-04	2.92E-04	0.036
rs7094644	A	10	0.674	0.014	0.002	<0.001	0.678	1.26E-05	3.17E-04	0.970
rs71495049	A	10	0.084	0.023	0.004	<0.001	0.084	−1.91E-04	5.26E-04	0.720
rs7154982	A	14	0.269	−0.015	0.002	<0.001	0.270	2.03E-05	3.28E-04	0.950
rs71658797	A	1	0.124	0.029	0.003	<0.001	0.121	4.86E-04	4.47E-04	0.280
rs7171864	A	15	0.661	0.014	0.002	<0.001	0.660	4.59E-04	3.08E-04	0.140
rs7206608	G	16	0.323	0.013	0.002	<0.001	0.322	2.00E-04	3.12E-04	0.520
rs7239114	A	18	0.543	0.013	0.002	<0.001	0.542	1.61E-04	2.94E-04	0.590
rs7259070	C	19	0.599	0.017	0.002	<0.001	0.596	−2.52E-04	2.99E-04	0.400
rs72793809	T	16	0.404	0.027	0.002	<0.001	0.401	5.07E-05	2.97E-04	0.860
rs72892910	T	6	0.170	0.032	0.003	<0.001	0.172	5.14E-04	3.86E-04	0.180
rs72917544	A	2	0.186	−0.017	0.003	<0.001	0.185	−4.31E-04	3.77E-04	0.250
rs73140125	G	3	0.130	−0.019	0.003	<0.001	0.129	−7.06E-04	4.38E-04	0.110
rs73213484	T	4	0.139	−0.019	0.003	<0.001	0.141	−7.93E-04	4.18E-04	0.058
rs7377083	A	4	0.431	0.014	0.002	<0.001	0.431	4.03E-04	2.96E-04	0.170
rs73985439	C	2	0.308	0.014	0.002	<0.001	0.307	3.35E-04	3.16E-04	0.290
rs7442885	G	5	0.210	−0.022	0.003	<0.001	0.214	−2.07E-04	3.55E-04	0.560
rs750090	C	4	0.356	−0.013	0.002	<0.001	0.357	−2.68E-04	3.07E-04	0.380
rs76040172	A	21	0.054	−0.034	0.005	<0.001	0.054	−2.76E-04	6.47E-04	0.670
rs76286777	C	2	0.219	0.026	0.003	<0.001	0.218	−1.99E-04	3.52E-04	0.570
rs7635592	T	3	0.205	0.021	0.003	<0.001	0.206	5.31E-04	3.61E-04	0.140
rs76929617	G	12	0.039	−0.043	0.006	<0.001	0.039	−1.07E-03	7.54E-04	0.150
rs7707394	A	5	0.354	−0.016	0.002	<0.001	0.357	−2.69E-04	3.03E-04	0.370

(*Continued*)

Table 2 (Continued).

SNP	EA	Chr	Waist Circumference				Deep Vein Thrombosis.			
			EAF	β	SE	P	EAF	β	SE	P
rs7728095	G	5	0.388	0.014	0.002	<0.001	0.389	1.87E-04	3.01E-04	0.540
rs7752202	T	6	0.143	0.021	0.003	<0.001	0.145	5.61E-04	4.12E-04	0.170
rs7925100	A	11	0.396	0.014	0.002	<0.001	0.396	−3.05E-04	2.98E-04	0.310
rs7930006	T	11	0.454	−0.013	0.002	<0.001	0.456	−4.43E-04	2.93E-04	0.130
rs7948120	T	11	0.259	−0.014	0.002	<0.001	0.261	5.83E-04	3.33E-04	0.080
rs7952436	T	11	0.083	−0.026	0.004	<0.001	0.082	−1.01E-04	5.30E-04	0.850
rs80135947	C	17	0.195	0.025	0.003	<0.001	0.195	6.17E-04	3.67E-04	0.093
rs80330591	A	2	0.147	−0.017	0.003	<0.001	0.146	−5.51E-04	4.11E-04	0.180
rs8097672	T	18	0.145	0.018	0.003	<0.001	0.145	2.34E-04	4.15E-04	0.570
rs809955	A	4	0.367	−0.012	0.002	<0.001	0.366	−1.02E-03	3.02E-04	0.001
rs815163	C	1	0.562	−0.014	0.002	<0.001	0.563	−3.28E-04	2.93E-04	0.260
rs8192675	C	3	0.287	0.015	0.002	<0.001	0.289	3.19E-04	3.21E-04	0.320
rs868784	A	11	0.380	−0.012	0.002	<0.001	0.381	−2.11E-04	3.00E-04	0.480
rs869400	G	3	0.816	0.020	0.003	<0.001	0.815	2.24E-04	3.75E-04	0.550
rs879620	T	16	0.615	0.021	0.002	<0.001	0.613	2.27E-04	3.00E-04	0.450
rs894736	G	12	0.362	0.018	0.002	<0.001	0.363	−7.76E-05	3.04E-04	0.800
rs9289630	C	3	0.391	0.016	0.002	<0.001	0.389	3.70E-05	2.99E-04	0.900
rs9370243	T	6	0.081	0.022	0.004	<0.001	0.082	1.08E-03	5.30E-04	0.041
rs9378684	T	6	0.201	0.017	0.003	<0.001	0.201	−2.57E-04	3.67E-04	0.480
rs9402104	A	6	0.584	0.012	0.002	<0.001	0.582	5.21E-04	2.97E-04	0.079
rs9522279	T	13	0.425	0.013	0.002	<0.001	0.423	3.83E-04	2.95E-04	0.190
rs9610311	C	22	0.307	0.014	0.002	<0.001	0.308	−3.86E-04	3.24E-04	0.230
rs9688977	C	6	0.146	0.019	0.003	<0.001	0.145	−5.10E-05	4.14E-04	0.900
rs9835772	T	3	0.243	0.015	0.003	<0.001	0.244	−8.77E-05	3.39E-04	0.800
rs9843653	C	3	0.515	0.021	0.002	<0.001	0.512	3.66E-04	2.91E-04	0.210
rs9867068	G	3	0.246	0.018	0.002	<0.001	0.246	−1.80E-04	3.38E-04	0.590
rs9968060	T	3	0.647	0.015	0.002	<0.001	0.643	−2.87E-04	3.09E-04	0.350

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome location; EA, effect allele; EAF, effect allele frequency; SE, standard error.

death for severe cases, which seriously affect the prognosis and quality of life of patients. In present study, we explored the causal association between waist circumference and DVT through the two-sample MR analysis. The result indicated that higher level of waist circumference was causally associated with a higher risk of DVT while DVT did not contribute to the level of waist circumference. The finding highlighted the great importance of prevention and screening in the patients with abdominal obesity, especially during the COVID-19 pandemic.

Against the background of a sharp increase in obesity incidence worldwide, obesity has been the independent risk factors of DVT for long.[22,23] The MR research from Denmark demonstrated the causal relationship between obesity and risk of DVT while similar result was observed in another MR study.[24,25] Recently, abdominal obesity was recommended as the more suitable predictor for DVT in several researches. Yuan and his colleagues adjusted the factor of waist circumference and found that the association between body mass index (BMI) and DVT was

Table 3 MR Estimates of the Associations Between Waist Circumference and Risk of DVT

Outcome	IVW Method		MR-Egger		Weight Median Method	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Deep vein thrombosis	1.012 (1.009–1.014)	<0.001*	1.014 (1.005–1.022)	0.002*	1.012 (1.007–1.016)	<0.001*

Note: **P* valve<0.05.
Abbreviations: IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval.

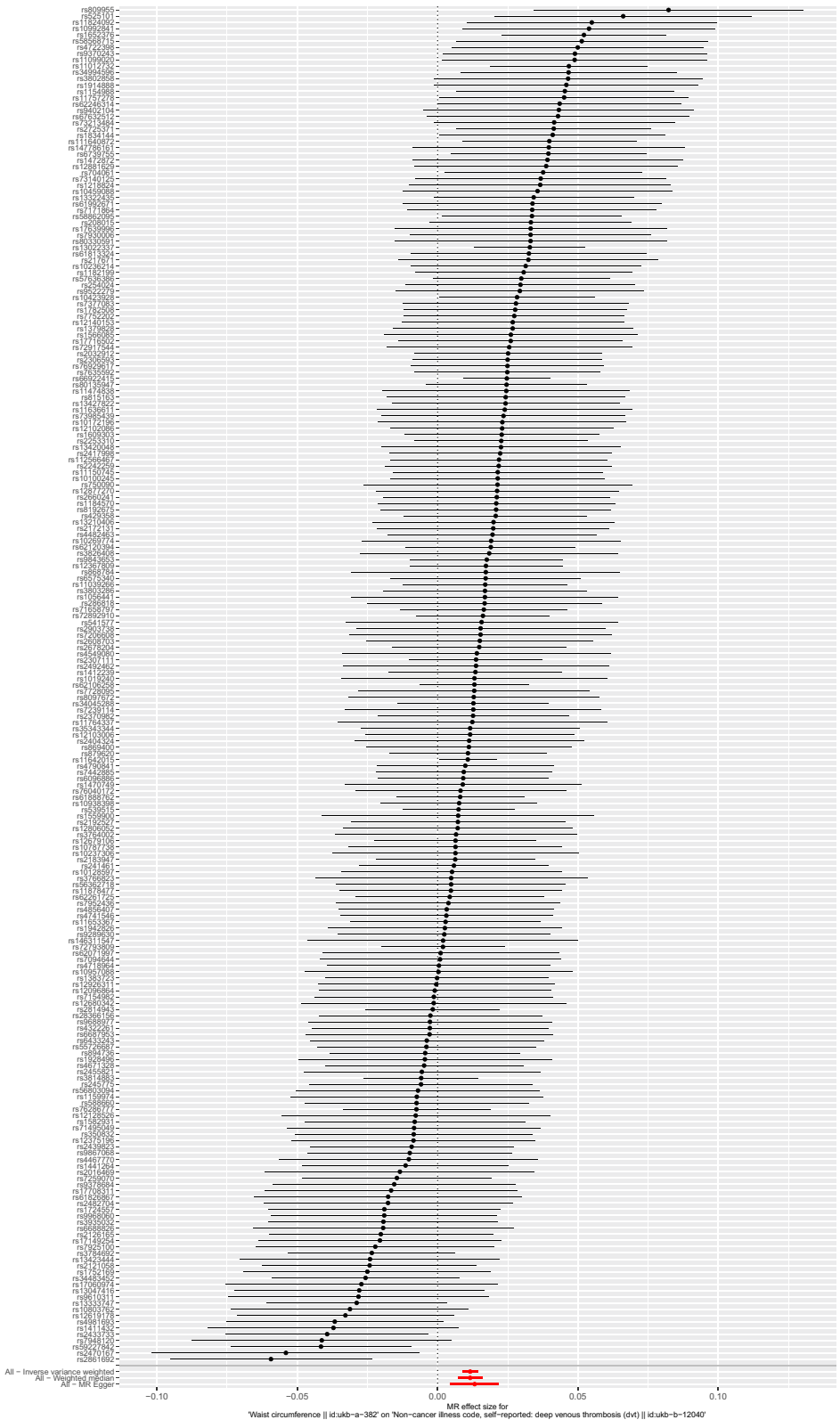

Figure 1 Forest plot of the causal effect of waist circumference on DVT. Black points represent the log odds ratio for osteoarthritis per standard deviation increase in waist circumference, which is produced by using each SNP selected as a separate instrument. Red points show the combined causal estimate using all SNPs together as a single instrument, using the three different MR methods. Horizontal line segments denote 95% confidence intervals of the estimate.

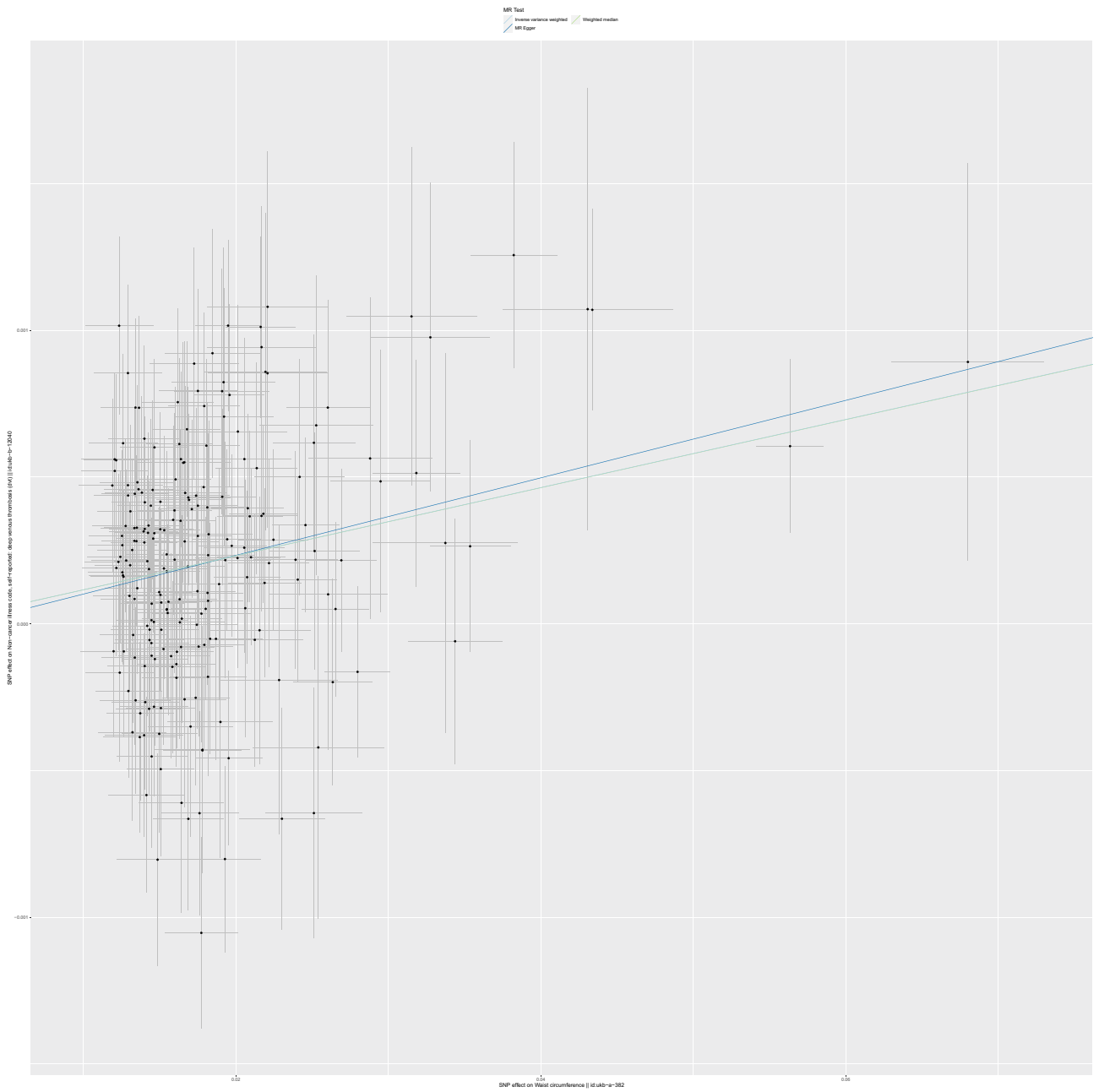

Figure 2 Scatter plot of the causal effect of waist circumference on DVT. The plot presents the effect sizes of the SNP–waist circumference association (x-axis, standard deviation units) and the SNP–DVT association (y-axis, log [odds ratio]) with 95% confidence intervals. The regression slopes of the lines correspond to causal estimates using the three MR methods.

relativity weakened, indicating that waist circumference might be the preferable indicator of DVT.[10] A Swedish study found that abdominal obesity was an independent risk factor for middle-aged men in community.[26] Borch et al[27] provided evidence for the abdominal obesity as the pivotal risk factor among the individual components of the metabolic syndrome for the risk of VTE. It is with regret that few researches mentioned above were not able to clearly demonstrate the causal relationship due to the evidence from conventional observational studies. There were limited researches to explore the causal relationship

Table 4 MR-Egger Pleiotropy Test of the Associations Between Waist Circumference and Risk of DVT

Outcome	MR-Egger Method	
	Intercept	*P* value
Deep vein thrombosis	−3.9e-05	0.616

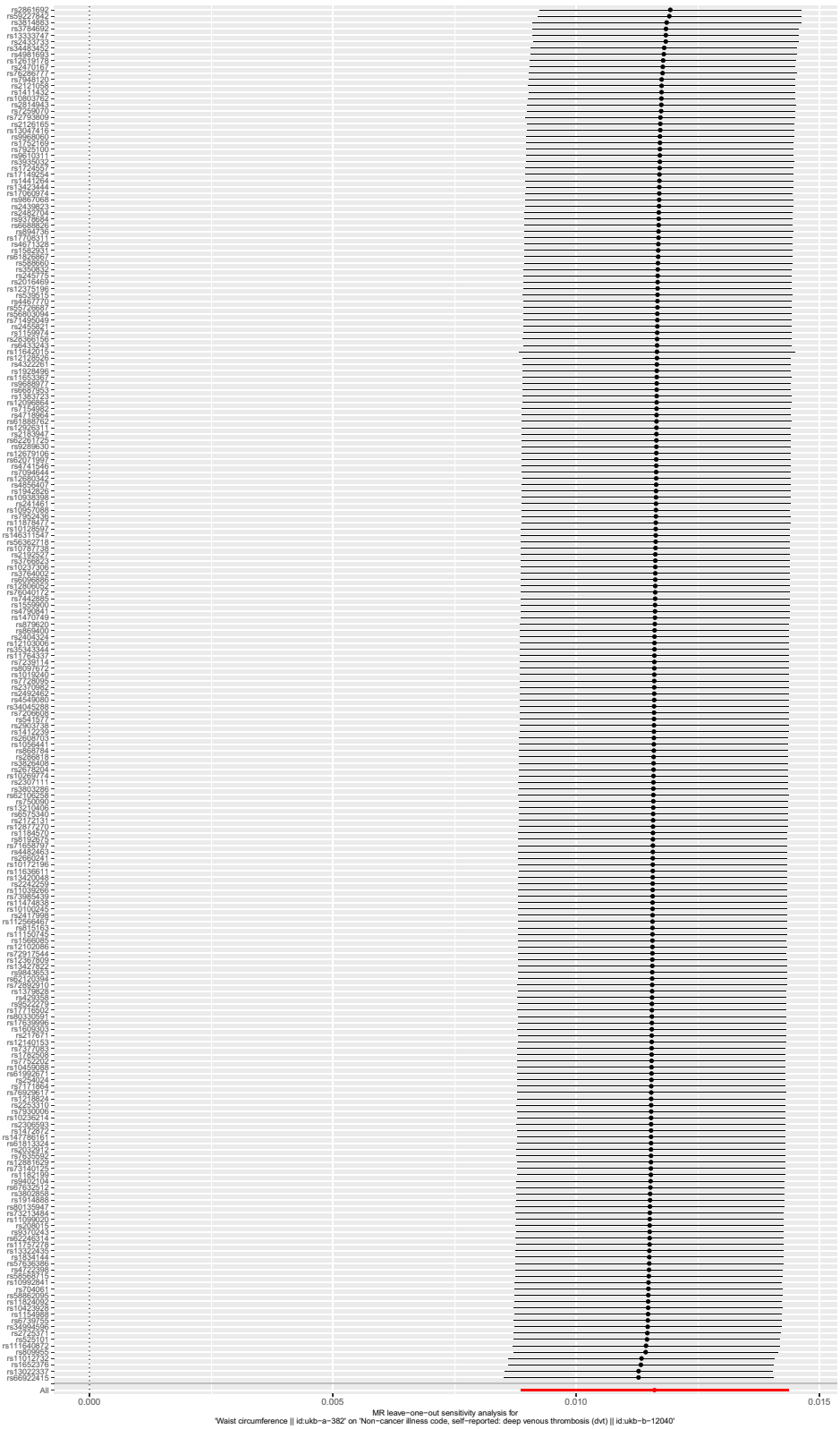

Figure 3 Forest plot of the causal effect of waist circumference onDVT. Black points represent the log odds ratio for waist circumference by DVT, which is produced by using each SNP selected as a separate instrument. Red points show the combined causal estimate using all SNPs together as a single instrument, using the three different MR methods. Horizontal line segments denote 95% confidence intervals of the estimate.

Table 5 MR Estimates of the Associations Between DVT and Waist Circumference

Methods	OR (95% CI)	*P* value
IVW	1.198 (0.719–1.996)	0.487
MR-Egger	1.064 (0.393–2.878)	0.371
Weighted median	1.273 (0.750–2.160)	0.906

Abbreviations: IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval.

between abdominal obesity and DVT. In present study, we performed a two-sample MR analysis to investigate the causal relationship between waist circumference and DVT. Odds ratio of 1.012 in IVW indicated that 1% higher waist circumference was associated with a 1.012-fold risk of DVT. In the other two methods, the similar results were also shown. Though the clinical relevance was relatively modest, the present research showed that abdominal obesity was a causal risk factor in the risk of DVT. Unlike the previous studies, reverse causality and confounding factors can be well avoided due to the application of a two sample MR method. Several recent studies have used the MR analysis to found that genetic variants for waist circumference were causally associated with other outcomes, such as coronary heart disease, type II diabetes mellitus, lower gray matter volume and so on.[14,27,28] Till now, we were the first to investigate the association between waist circumference and DVT through the method of two-sample MR analysis. Moreover, a large sample size (more than 400 thousand) reduced the bias from weak instrumental variables and provided enough power to robust causal detection.

Although the mechanism of abdominal obesity and DVT remains unclear, several possible mechanisms may explain the causal association. More than a century ago, Rudolf Virchow came up with three critical factors, venous stasis, activation of blood clotting, and venous damage.[29] As the key component in metabolic syndrome, abdominal obesity plays a role in the insulin resistance while body fat distribution is a determined factor in insulin resistance.[30] In comparison with subcutaneous adipose tissue, the abdominal fat had greater ability in insulin resistance, in which the balance of nitric oxide (NO) production and endothelin-1 secretion is broken, leading to the damage of endothelial cells.[31] Adipocytes secrete inflammatory factors, such as IL-6, MCP-1, MCP-1 and so on. Overexpression of MCP-1 leads to increased free fatty acids in plasma, increases the recruitment of macrophages and the expression of inflammatory cytokines, then the coagulation system is activated.[32] In addition, central obesity has been demonstrated with elevated intra-abdominal pressure and decreased flow velocity of venous blood, thus is more likely to form DVT.[33,34] The patients with abdominal obesity are more likely with less physical activity, which might lead to the formation of DVT. Fat mass and obesity-associated gene (FTO) rs11642015 polymorphism was found significantly associated with risk of DVT in present study. Elevated FTO expression can decrease the expression of AKT phosphorylation in endothelial cells,[35] which might lead to the dysfunction of endothelial and the development of DVT. It is a remarkable fact that the role of the other SNPs is still not clear. Therefore, further researches are needed to explore the potentially biological pathways in the progression of DVT.

Our analysis had several important strengths. First, compared with the traditional observational studies, MR analysis can avoid the reverse causality between exposure and outcome and not be affected by classical confounding factors. Larger sample size can bring more accurate estimation of causality. Second, three statistical approaches (IVW random-effect, weighted median and MR-Egger regression) were performed to test the causal relationship and make our finding more reliable. Horizontal pleiotropy might affect the validity of result. The consistency in the findings from these four different methods helps to adjust for pleiotropy. Third, our analysis is more economical and time-saving. There were also some limitations in this analysis. First, 224 SNPs were finally included in this analysis and invalid instrument variables might arise, which results in the biased estimates for causal effect and increases type I error rates.[36] However, the result of MR Egger was coincident with the other methods, indicating the robustness of the findings. Second, for the limitation of summary data, we were not able to perform further subgroup analysis or mechanism of action. Third, the data for both exposure and outcome were extracted from European consortiums. Therefore, variations in genetic background are various among different populations and ethnicities, further researches are needed to investigate whether the conclusion can be genialized to other races.[37]

Conclusion

In summary, we used the GWAS genetic data from two large consortium Cohorts and indicated the positive association between waist circumference and the risk of DVT. Further researches are needed to investigate potential

mechanism and clarify the role of waist circumference in DVT.

Ethics Approval and Informed Consent

There were no patients involved in the research design, recruitment or conduct, so the ethical approval was waived by ethic committee of Guangdong Provincial People's Hospital. No participants were requested to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Funding

This research was funded by the Technology Planning Project of Guangdong Province (2018KJY2017).

Disclosure

The authors declare that they have no competing interests.

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