# Genetic Predisposition of Both Waist Circumference and Hip Circumference Increased the Risk of Venous Thromboembolism

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Thromb Haemost 2023;123:347–361.

## Abstract

**Background** Obesity, especially abdominal obesity, is an independent indicator of increased cardiovascular risk. Observational studies have shown an observational association between obesity and venous thromboembolism (VTE). As a type of VTE, pulmonary embolism (PE) is also associated with obesity. However, it is unclear whether the observed associations are causal or caused by confounding bias or reverse causality.

**Methods** We performed a two-sample test by obtaining the exposure dataset of waist circumference (WC) and hip circumference (HC) from the Neale Laboratory Consortium's genome-wide association study summary data and the summary-level outcome data of VTE and PE from FinnGen Biobank of European ancestry to determine the causal effect of WC and HC on VTE and PE.

**Results** All three Mendelian randomization methods displayed a positive association between WC/HC and VTE/PE. WC and HC were positively associated with VTE (odds ratio [OR] = 1.803 per 1 standard deviation [SD] increase in WC, 95% confidence interval [CI] = 1.393–2.333; $p < 0.001$; OR = 1.479 per 1 SD increase in HC, 95% CI = 1.219–1.796; $p < 0.001$, respectively). Furthermore, we found a causal association between genetically predicted WC/HC and a higher risk of PE (OR = 1.929 per 1 SD increase in WC, 95% CI = 1.339–2.778, $p < 0.001$; OR = 1.431 per 1 SD increase in HC, 95% CI =1.095–1.869; $p = 0.009$, respectively).

**Conclusion** There is a significant causal relationship between WC/HC and VTE/PE, which is consistent with observational studies. Taking measures to reduce WC/HC of obesity may help reduce the incidence of VTE/PE.

**Keywords**
- waist circumference
- hip circumference
- venous thromboembolism
- Mendelian randomization study
- obesity

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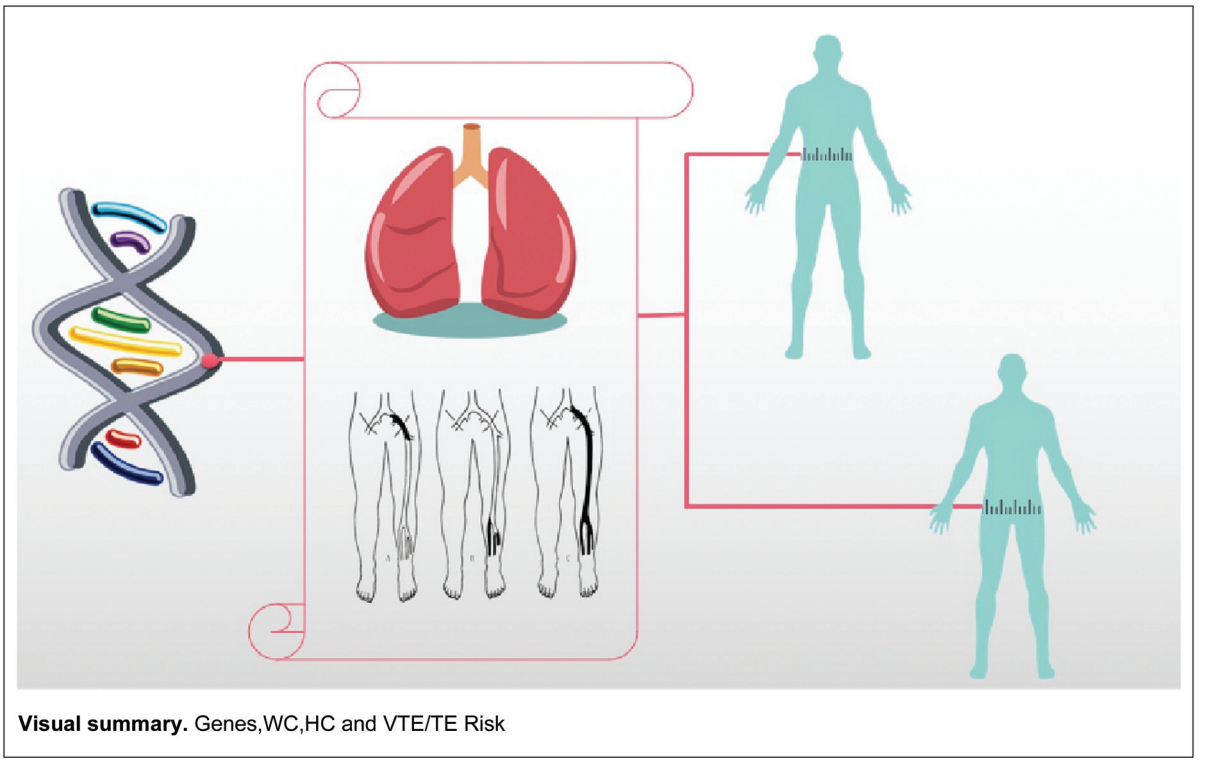
**received**
June 25, 2022
**accepted after revision**
November 11, 2022
**accepted manuscript online**
November 16, 2022
**article published online**
January 5, 2023

**DOI** https://doi.org/10.1055/a-1980-8852.
**ISSN** 0340-6245.



Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



**Visual summary.** Genes,WC,HC and VTE/TE Risk

## Introduction

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of vascular death after heart disease. The first incidence of VTE is 1 in 1,000 and increases with age.[1] In the United States, clinicians have diagnosed more than 200,000 patients with acute PE, and relevant statistics show that the 90-day mortality after acute PE may be as high as 17%.[2] Therefore, exploring the risk factors and etiological mechanism of VTE has important clinical value for the prevention and control of VTE, especially for life-threatening PE.

VTE is a complex multifactorial disease that integrates genetics and many well-recognized traditional risk factors, such as hormone replacement therapy, cancer, heart failure, chronic obstructive pulmonary disease, trauma, surgery, immobilization, and paraplegia, have been identified.[3–5] In a retrospective cohort study, Stewart and Kline found that four components of metabolic syndrome: hyperlipidemia, hypertension, hyperglycemia, and abdominal obesity, were statistically associated with VTE.[6] Recently, some observational studies have also confirmed the correlation between obesity and VTE. Higher visceral fat mass is an indicator independent of total fat mass, which can predict the increased risk of cardiovascular metabolic disease.[7] Elevated body mass index (BMI) has been identified as a risk factor for VTE in most observational population-based studies.[8] However, Borch et al displayed that waist circumference (WC) is a better anthropometric method for obesity and can predict the risk of VTE in high-risk groups through the data of adult BMI, WC, hip circumference (HC), and waist-hip-ratio (WHR) registered in the Tromsø study.[9]

Despite the above observational findings indicating that anthropometric indicators of obesity were associated with VTE, these observational studies cannot explain the inevitable causal relationship between them, so it is necessary to explore the causal relationship between anthropometric indicators and VTE using new research methods such as Mendelian randomization (MR) analysis. As an alternative to randomized controlled trials, MR research has been increasingly used to strengthen causal inference of association in observational studies.[10] Based on Mendelian independent distribution law (alleles are randomly assigned to offspring gametes during gamete formation), the associations between genes and diseases will not be perturbed by common confounding factors such as postnatal environment, socioeconomic status, and behavioral factors, and the causal timing is reasonable, which makes the effect estimation closer to the real situation.[10]

In recent years, through the method of MR analysis, some anthropometric measurements have been confirmed to have a causal relationship with VTE. Lindström et al determined that 95 single nucleotide polymorphisms (SNPs) were associated with BMI through an MR study, and genetically predicted the causality between high BMI and VTE in the population of European descent.[11] Yuan et al conducted a cohort study of adults in Sweden and confirmed a dose–response association between BMI or WC and VTE through MR analysis.[12] The association of BMI with VTE was greatly attenuated after adjustment for WC. Among individuals with normal BMI, participants with significantly increased WC had a 53% higher risk of VTE than those with normal WC (hazard ratio [HR]: 1.53; 95% confidence interval [CI]: 1.28–1.81). The causality between WC and VTE adjusted for BMI was confirmed in MR analysis. The estimated population-attributable risk due to

increased BMI and WC was 12.4% (8.4–16.5%) and 23.7% (18.1–29.4%), respectively. Thus, WC may be the preferred index to link obesity with VTE. Most cases of VTE can be prevented if the population maintains a healthy BMI and WC.[12]

Although Yuan et al preliminarily discussed the effect of WC on VTE through SNPs, the extent of the influence of WC and other anthropometric parameters such as HC on VTE, and active sites of gene polymorphism leading to VTE is an indefinite issue. To explore the causal impact of WC and HC on VTE, we applied two-sample MR to evaluate the causal associations between WC, HC, and VTE by using SNPs of a large-scale genome-wide association study (GWAS) in a VTE study comprising 2,872 patients with VTE and 93,627 controls from UK Biobank. Besides, we also explored the causal association between WC, HC, and the risk of PE in further analysis.

## Material and Methods

### Overall Study Design

All of the summary data were obtained from previously published studies.[13] Therefore, they have been approved respectively by the institutional review committee and no further sanction was required. In the present study, the two-sample MR[14,15] was used to assess the causal effect of WC and HC on the risk of VTE (►**Fig. 1**).

### Data Sources

#### Waist Circumference and Hip Circumference

In the present MR analysis, SNPs of the exposure dataset (WC and HC) were used as instrumental variables (IVs). However, three basic assumptions have to be met. First, the IVs must be associated with WC or HC (IV assumption 1). Second, the IVs affect the risk of VTE only via WC or HC (IV assumption 2). Third, no measured or unmeasured confounders are involved in the IVs (IV assumption 3).[16] For the exposure dataset of WC, the SNPs were obtained from the Neale Laboratory Consortium's GWAS summary data of 336,639 participants of European ancestry (►**Table 1**), which was built on HG19/GRCh37 and included 10,894,596 SNPs (►**Table 1**). This dataset was publicly available from the Neale Laboratory analysis of UK Biobank phenotypes, round 1,[17] and MR-Base[18] given as GWAS-ID of "ukb-a-382."

#### Venous Thromboembolism and Pulmonary Embolism

For the outcome dataset of VTE and PE, the SNPs were obtained from summary-level GWAS data of FinnGen Biobank analysis, with a total of 96,499 participants (2,872 patients with VTE and 93,627 controls) and 96,389 participants (95,023 controls and 1,366 patients with PE) of European ancestry (►**Table 1**), which included 16,152,119 SNPs (►**Table 1**) and was publicly available at https://gwas.mrcieu.ac.uk/datasets.

#### Gene Ontology and Pathway Enrichment Analysis

The gene ontology (GO) analysis can help us to annotate the gene products and to identify the functional characteristics of genes, which includes three main branches: Cellular Component (CC), Molecular Function (MF), and Biological Process (BP). The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a useful and effective tool for pathway enrichment analysis. In the present study, the GO and KEGG enrichment

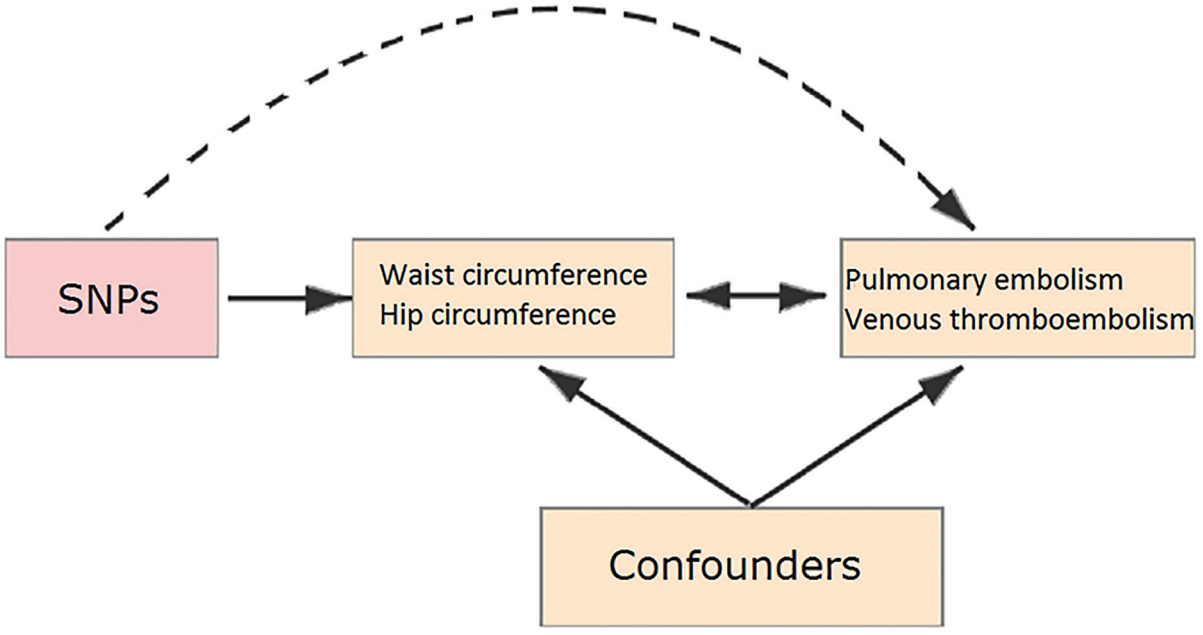



**Fig. 1** Schematic representation of an MR analysis. We selected SNPs associated with waist circumference and hip circumference. The corresponding effects for these SNPs were estimated based on the risk of venous thromboembolism. Because of the randomization and independence of alleles at meiosis, MR analysis is a powerful predictive tool to assess the causality of biases inherent to observational study designs. The bi-directional arrow means the observational associations. The dotted arrow means that these SNPs should not be associated with the outcomes significantly, which is one of the basic assumptions of MR. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

**Table 1** Characteristics of genome-wide association study in exposures and outcomes

| Exposure/outcomes | No. of controls | No. of cases | Sample size | Year of publication | Number of SNPs | Build | Study population |
|---|---|---|---|---|---|---|---|
| Waist circumference | – | – | 336,639 | 2017 | 10,894,596 | HG19/GRCh37 | European |
| Hip circumference | – | – | 462,117 | 2018 | 9,851,867 | HG19/GRCh37 | European |
| Pulmonary embolism | 95,023 | 1,366 | 96,389 | 2020 | 16,152,119 | HG19/GRCh37 | European |
| Venous thromboembolism | 93,627 | 2,872 | 96,499 | 2020 | 16,152,119 | HG19/GRCh37 | European |

Abbreviation: SNP, single nucleotide polymorphism.

of candidate overlapping genes was finished by the DAVID, which was available at https://david.ncifcrf.gov/. The statistics with a $p < 0.05$ were considered statistically significant.

### Drug–Gene Interactions

To find the potential drugs which may contribute to the disruptions in such processes of WC/HC to VTE, the Drug Gene Interaction database (DGIdb) was used (available at http://www.dgidb.org). Due to the large number of predicted drugs, we only chose the targeted drugs being approved by the Food and Drug Administration. These candidate drugs targeting the genes/pathways relevant to WC and HC may represent potential treatments.

### Statistical Analysis

To identify independent genome-wide significant SNPs, we used the following criteria: (1) the SNPs were significantly associated with WC/HC at a genome-wide significance threshold ($p < 5.0 \times 10^{-8}$); (2) excluding SNPs in linkage disequilibrium with the other SNPs ($r^2 < 0.001$ and distance $> 10{,}000$ kb)[13,16]; (3) to exclude weak associations between IVs and WC/HC, we used F statistic for SNPs (F statistic = (β/SE)2) in this MR. And for the SNPs with F statistic < 10, they would be excluded to avoid bias of IVs. There are no available individual-level GWAS data. Therefore, the recently developed method of two-sample MR analyses was used to assess the causal association between WC or HC and VTE, as described previously.[19]

In the principal analyses, inverse-variance weighted (IVW) meta-analysis with a random-effects model was used.[20] To reduce the bias due to horizontal pleiotropy, two sensitivity analyses were performed, including the weighted median approach[21] and the MR-Egger method.[22] All of the above-mentioned analytical methods are based on different models of horizontal pleiotropy. Therefore, comparing the consistency of three different methods can help us determine whether our results are reliable.[23,24] A two-tailed test was used in all statistical tests. Bonferroni-corrected analysis was used with a threshold of $p < 0.025$ ($a = 0.05/2$ outcomes).[25] Associations with $p$-values between 0.025 and 0.05 were considered suggestive evidence of associations, requiring further confirmation.[25] Besides, we used the "mRnd" tool to calculate the power of the current MR analysis.

All statistical analyses were performed using R version 4.0.3 (2020–10–10) (The R Foundation for Statistical Computing, Vienna, Austria) and the MR software packages.[26,27]

## Results

### Genetic Instrumental Variables for Waist Circumference and Hip Circumference

There were 179 and 330 independent variants for WC and HC (►**Supplementary Tables S1** and **S2**, available in the online version), respectively. Genetic instruments for VTE, WC, and HC by each instrumental SNP (GWAS significance with $p < 5 \times 10^{-8}$ and linkage disequilibrium threshold with $r^2 < 0.001$) are listed in ►**Supplementary Tables S1** and **S2** (available in the online version).

### GO and Pathway Enrichment Analysis

In analyzing the biological information regarding the genetic variants associated with WC and HC, the top 20 KEGG signal pathways and the top 6 significant enrichment terms for BP, CC, and MF were taken, shown in ►**Figs. 2** to **5**.

►**Figs. 2** and **3** show the GO and pathway enrichment analysis of WC. In BP terms, these genes were mainly enriched in the heterocycle biosynthetic compartment, positive regulation of the metabolic process, and positive regulation of the macromolecule metabolic process. In CC terms, these genes were significantly enriched in the neuron part, neuron projection, and somatodendritic density. In MF terms, these genes were mainly enriched in the transcription regulatory region sequence-specific DNA binding, regulatory region DNA binding, and transcription regulatory region DNA binding. As for signal pathway enrichment, these genes were mainly involved in the Akt signaling pathway, MAPK signaling pathway, and amyotrophic lateral sclerosis, respectively.

►**Figs. 4** and **5** show the GO and pathway enrichment analysis of HC. In BP terms, these genes were mainly enriched in the phosphorus metabolic process, nervous system development, and cell proliferation. In CC terms, these genes were significantly enriched in the neuron part, synapse, and synapse part. In MF terms, these genes were mainly enriched in ion binding, metal ion binding, and cation binding. As for signal pathway enrichment, these genes were mainly involved in cancer, PI3K-Akt signaling pathway, and MAPK signaling pathway, respectively.

### Drug–Gene Interaction Analysis for the Common Genes of WC and HC

In the drug–gene interaction analysis, 62 common genes were found in both WC and HC (►**Fig. 6**). There were 13 genes

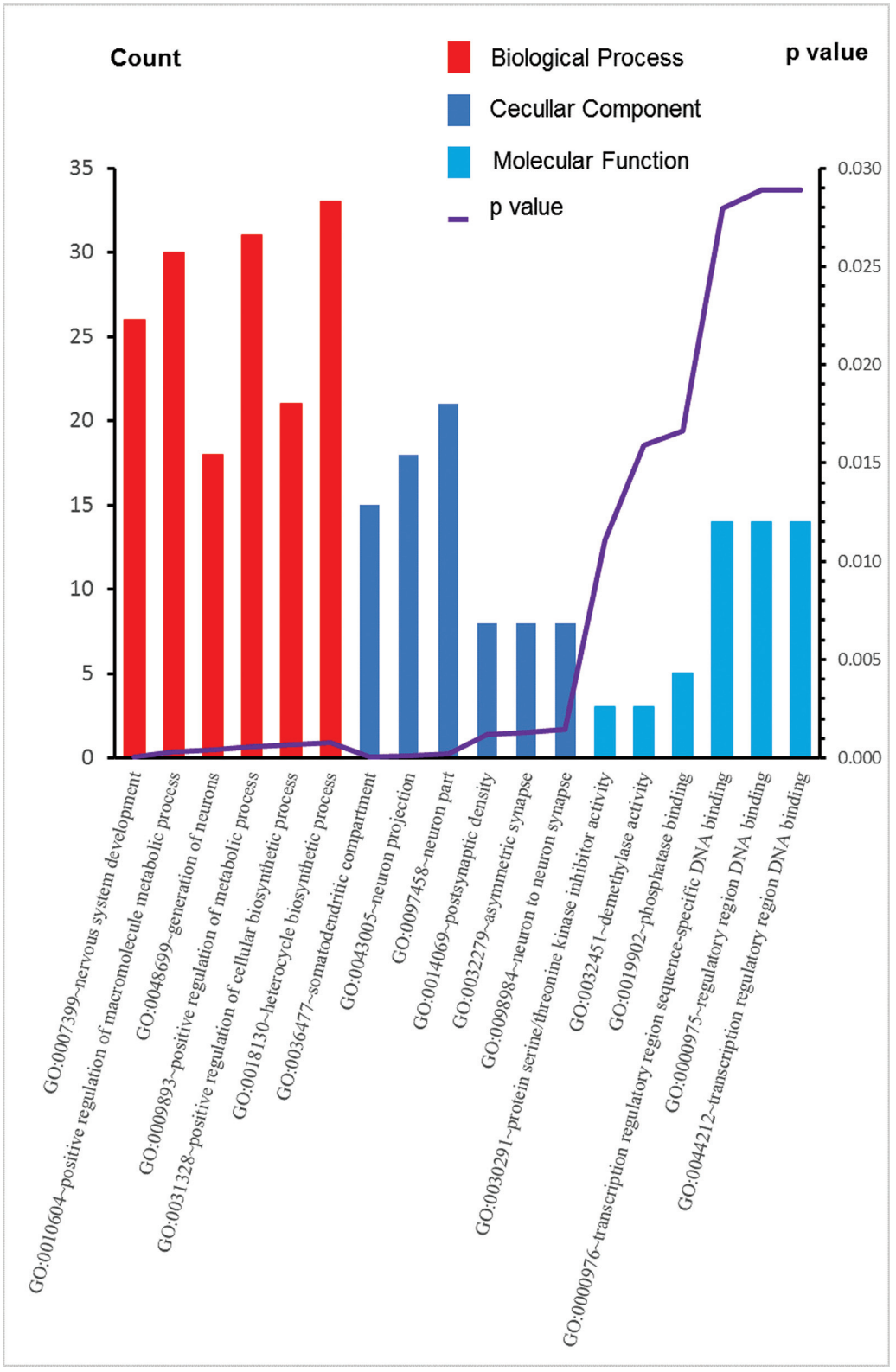



**Fig. 2** The results of GO enrichment analysis in waist circumference. The top six significant enrichment terms of biological process, cellular component, and molecular function of overlapping genes are shown. GO, gene ontology.

targeted to 50 potential existing drugs, which have been divided into three drug–gene interaction types (►**Table 2**). Potential gene targets of the drugs on this list are CDK6, RPTOR, PDE4B, FTO, MAD1L1, DDC, FBXL17, MAP2K5, WNK1, IGF1R, FOSL1, ETV5, and CADM2.

### Effects of Waist Circumference on VTE and PE

Genetically predicted WC was causally associated with higher risk of VTE (odds ratio [OR] = 1.803; 95% CI: 1.393–2.333; $p < 0.001$; ►**Figs. 7A** and **8A**). In further analysis, we found a causal association between genetically predicted WC and a

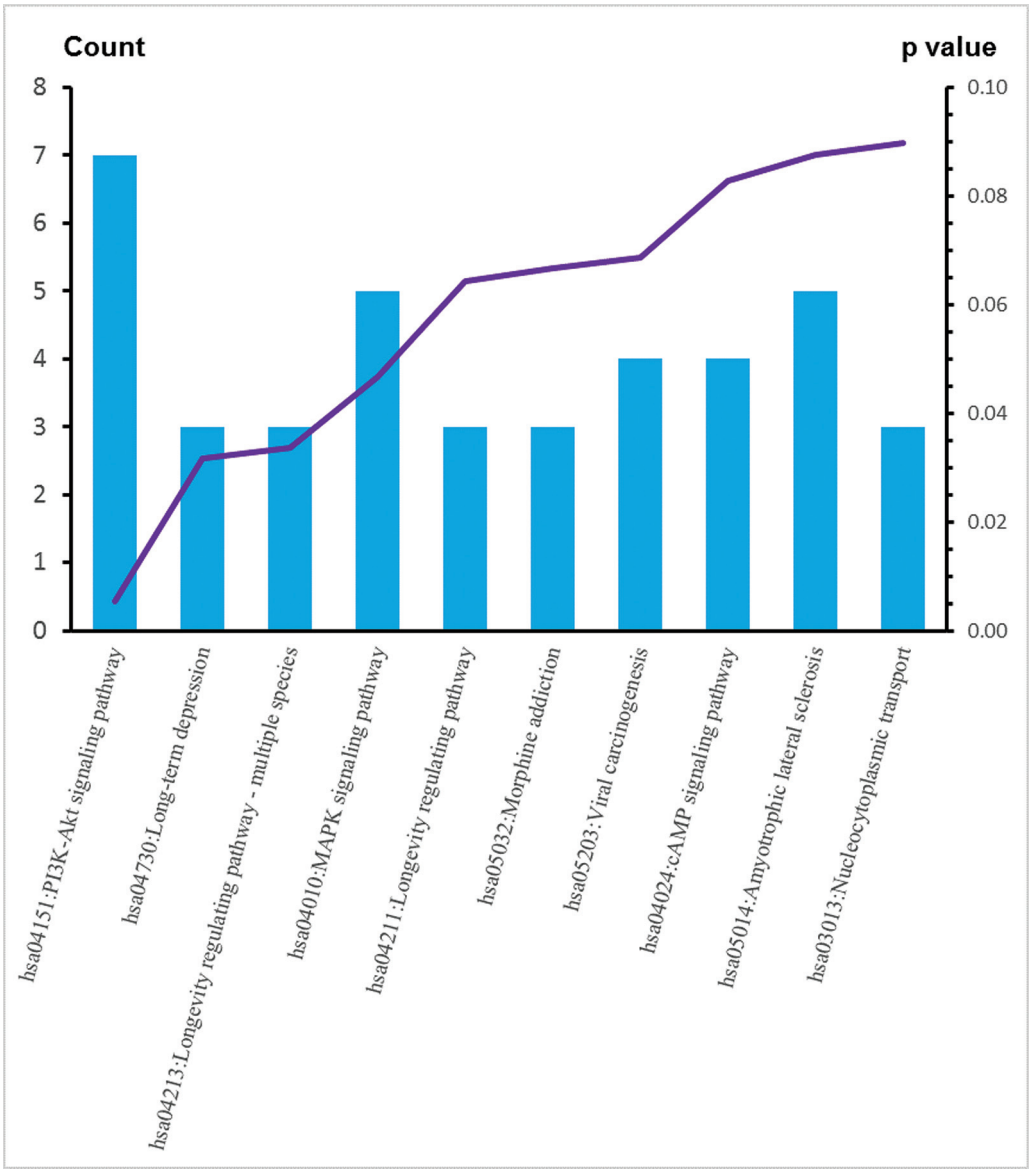



**Fig. 3** The results of KEGG enrichment analysis in waist circumference. A total of 20 KEGG signaling pathways of overlapping genes are shown. KEGG, Kyoto Encyclopedia of Genes and Genomes.

higher risk of PE, with an OR of 1.929 (95% CI 1.339–2.778; $P < 0.001$) (►**Fig. 8B**). The MR powers of WC on VTE and PE were both 100% based on calculations by using the "mRnd" tool.

### Effects of the Hip Circumference on VTE and PE

Genetically predicted HC was causally associated with higher risk of VTE (OR: 1.479, 95% CI: 1.219–1.796; $p < 0.001$) (►**Figs. 7B** and **8A**). In further analysis, a causal association between genetically predicted HC and higher risk of PE was observed, with an OR of 1.431 (95% CI: 1.095–1.869; $p = 0.009$) (►**Fig. 8B**). And the MR powers of HC on VTE and PE were both 100%.

### Sensitivity Analysis for our MR

The OR estimates of the weighted median analysis and MR-Egger analysis (►**Fig. 8**) revealed similar results with the standard MR analysis (IVW method) but of low precision.

### Heterogeneity Test of Instrumental Variables (SNPs)

The modified Cochran Q statistic revealed nonnotable heterogeneity across WC ($Q = 186.87$; $p = 0.291$) and HC SNP effects ($Q = 347.26$; $p = 0.271$).

### Analysis of Horizontal Pleiotropy

The result from the MR-Egger intercept test did not reveal any unbalanced horizontal pleiotropy in WC (intercept $p$-value = 0.948). However, the unbalanced horizontal pleiotropy was revealed in the MR-Egger intercept test of HC (intercept $p$-value = 0.005). Therefore, MR-Egger analysis (OR: 2.993, 95% CI: 1.757–5.100; $p < 0.001$) (►**Fig. 8**) may be more suitable for the causal estimate of HC on VTE, which was also consistent with that of IVW method. In the funnel plots, no signs of directional horizontal pleiotropy were revealed in both effects of WC and the effects of HC on VTE (►**Figs. 9** and **10**).

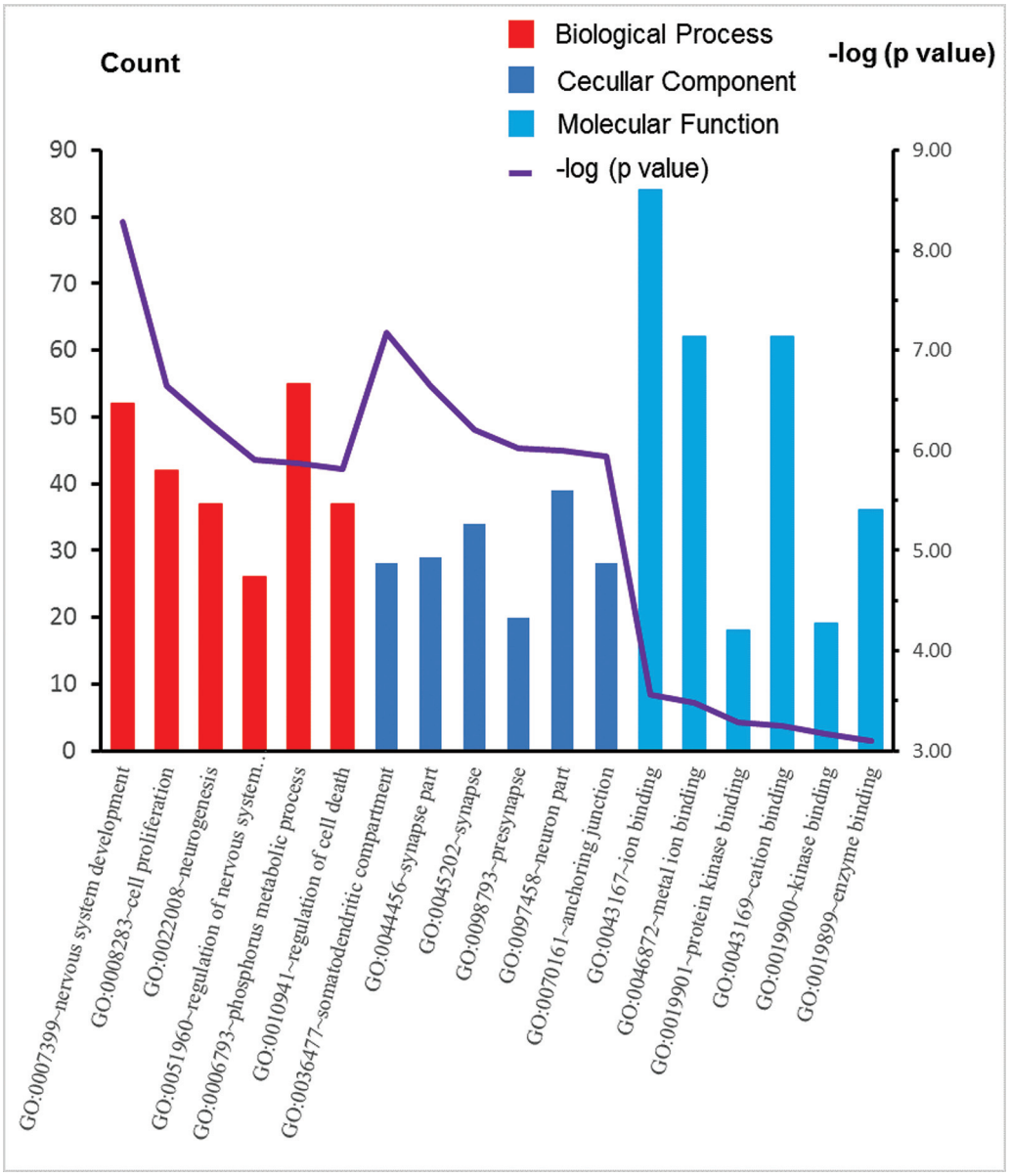



**Fig. 4** The results of GO enrichment analysis in hip circumference. The top six significant enrichment terms of biological process, cellular component, and molecular function of overlapping genes are shown. GO, gene ontology.

### Effects of Individual Genetic Instruments in Relation to VTE

To verify the influence of each SNP on the estimate of exposures on VTE, leave-one-out analyses were performed. There was no significant difference observed in the estimated causal effect of the WC or HC on VTE when systematically removing individual SNP (►**Supplementary Figs. S1** and **S2**, available in the online version). Therefore, no single genetic instrument would change our estimated effects.

## Discussion

The present two-sample MR investigation was used to assess the causal relationship between WC or HC and VTE in patients of European ancestry. Generally consistent with previous observational studies, our results showed that genetically determined WC/HC was causally associated with an increased risk of VTE, in which an increase of WC or HC at 1 standard deviation (SD) increased the risk of VTE by 80.3 and 47.9%, respectively. Our results indicate that controlling WC and HC may contribute to the prevention of VTE.

VTE is a multifactorial and polygenic disease and the synergistic effect of genetic and acquired conditions strongly regulates the occurrence and progress of VTE.[3] Genetic risk factors predispose to thrombosis and play the most important pathogenic role in VTE in people under 50 years of age. In 20 to 50% of idiopathic cases, PE without inducement can be explained by hereditary thrombophilia.[28] At least one genetic risk factor can be identified in about half of cases of first-episode idiopathic VTE.[29] The most prominent genetic risk factors for VTE are deficiencies of the natural

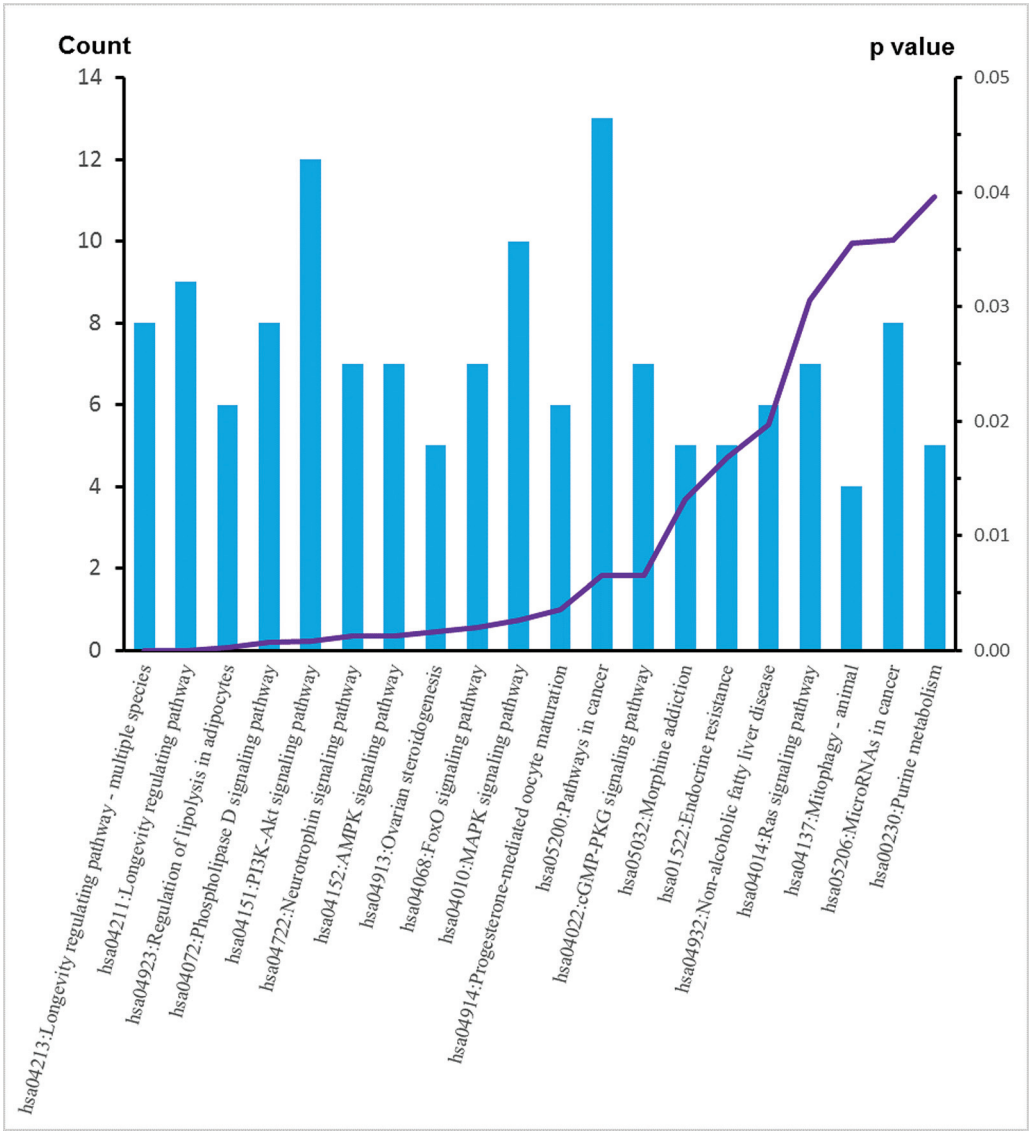



**Fig. 5** The results of KEGG enrichment analysis in hip circumference. A total of 20 KEGG signaling pathways of overlapping genes are shown. KEGG, Kyoto Encyclopedia of Genes and Genomes.

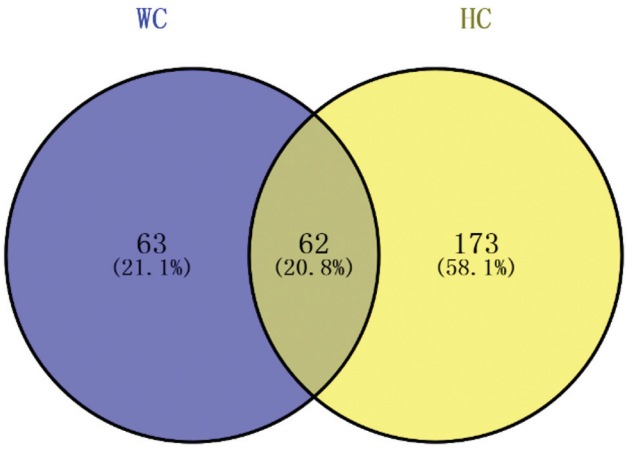



**Fig. 6** The common genes of waist circumference and hip circumference. A total of 125 genes were related to waist circumference, 235 genes were related to hip circumference, and 173 genes overlapped between waist circumference and hip circumference.

anticoagulants (antithrombin, protein C, and protein S) and genetic mutations associated with coagulation factors such as factor V Leiden (FVL), factor II, and factor XI (FXI) mutations.[3,30,31] However, the main hereditary thrombotic disorders such as antithrombin, protein C, and protein S deficiency accounted for only 5 to 10% of cases.[32] Some thrombogenic genes have been confirmed to have common loci and low-frequency susceptibility alleles.[30] The introduction of GWAS enabled the identification of genetic alterations associated with complex diseases.[30]

Ahmad et al held the honor that a single gene biomarker could not accurately predict the risk of VTE recurrence,[33] or develop a multiple SNP model to predict the risk of VTE recurrence.[33] In fact, no single genetic defect can predict the risk of VTE recurrence. Therefore, individual genetic risk analysis may be helpful.[3] In the Tromsø study and Nord Trøndelag Health Study, Evensen et al demonstrated that six SNPs were significantly correlated with VTE (PTM [prothrombin]

**Table 2** The available drugs that can target the common genes

| Gene | Drug | Interaction types | PMID |
|---|---|---|---|
| CDK6 | APREMILAST | | |
| CDK6 | PALBOCICLIB | Inhibitor | 28203301\|15542782 |
| CDK6 | RIBOCICLIB SUCCINATE | Inhibitor | |
| CDK6 | FULVESTRANT | | 27252418 |
| CDK6 | RIBOCICLIB | Antagonist/inhibitor | 24045179\|29408328 |
| CDK6 | DEXAMETHASONE | | 29408328 |
| CDK6 | ABEMACICLIB | Inhibitor | 24919854 |
| RPTOR | EVEROLIMUS | | |
| PDE4B | PAPAVERINE | Inhibitor | 19231363\|12646997\|17139284\|17016423 |
| PDE4B | AMLEXANOX | Inhibitor | |
| PDE4B | DIPYRIDAMOLE | Inhibitor | |
| PDE4B | INAMRINONE | Inhibitor | 17139284\|17016423 |
| PDE4B | PENTOXIFYLLINE | Inhibitor | 17139284\|17016423 |
| PDE4B | THEOPHYLLINE SODIUM GLYCINATE | Inhibitor | |
| PDE4B | DYPHYLLINE | Inhibitor | 7925603\|17139284\|17016423\|225216 |
| PDE4B | ALCOHOL | | 32451486 |
| PDE4B | CRISABOROLE | Inhibitor | 22841723 |
| PDE4B | CAFFEINE | Inhibitor | 17139284\|17016423\|17514358 |
| PDE4B | AMINOPHYLLINE | Inhibitor | |
| PDE4B | OXTRIPHYLLINE | Inhibitor | |
| PDE4B | THEOPHYLLINE | Inhibitor | 15639300 |
| PDE4B | ROFLUMILAST | Inhibitor | 17726343 |
| PDE4B | APREMILAST | Antagonist/inhibitor | 25864487\|17352685 |
| PDE4B | FLAVOXATE HYDROCHLORIDE | Inhibitor | |
| FTO | ALCOHOL | | 32451486 |
| FTO | ATENOLOL | | |
| FTO | RIBAVIRIN | | 25367448 |
| FTO | MERCAPTOPURINE | | 27558924 |
| FTO | AZATHIOPRINE | | 27558924 |
| MAD1L1 | PACLITAXEL | | 23407047 |
| MAD1L1 | CARBOPLATIN | | 23407047 |
| DDC | SIROLIMUS | | 16126007 |
| DDC | NICOTINE | | 16740595 |
| DDC | CARBIDOPA | Inhibitor | 12885750\|11106255\|17241115\|11752352\|11709201\|16184369\|10934669 |
| DDC | BENSERAZIDE | Inhibitor | |
| FBXL17 | HYDROCHLOROTHIAZIDE | | |
| MAP2K5 | COBIMETINIB | Inhibitor | |
| MAP2K5 | TRAMETINIB | Inhibitor | |
| MAP2K5 | BINIMETINIB | Inhibitor | |

(*Continued*)

**Table 2** (*Continued*)

| Gene | Drug | Interaction types | PMID |
|---|---|---|---|
| WNK1 | HYDROCHLOROTHIAZIDE | | 18591455 |
| IGF1R | RALOXIFENE | | 14533013 |
| IGF1R | MECASERMIN RINFABATE | Agonist | |
| IGF1R | PAZOPANIB | | |
| IGF1R | THROMBIN | | 7499260\|11375274 |
| IGF1R | MECASERMIN | Agonist | 19198769 |
| IGF1R | CERITINIB | Inhibitor | 23837797 |
| IGF1R | ACETYLCYSTEINE | | 12485928 |
| FOSL1 | ALTEPLASE | | 7761434 |
| ETV5 | TRAMETINIB | | 28178529 |
| CADM2 | ALCOHOL | | 32451486 |

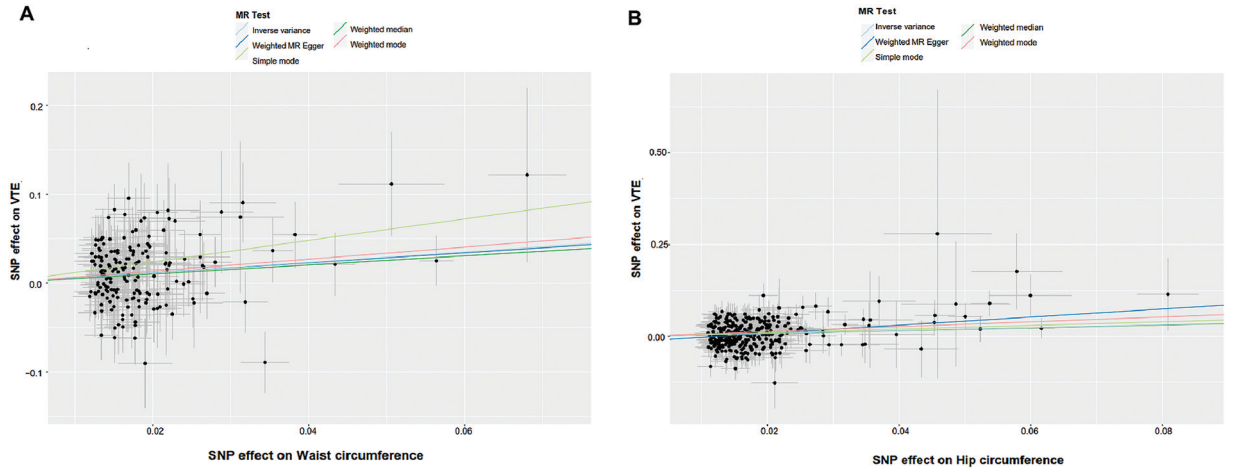



**Fig. 7** Scatter plot to visualize the causal effect of waist circumference (A) and hip circumference (B) on the risk of venous thromboembolism. The slope of the straight line indicates the magnitude of the causal association. IVW, inverse-variance weighted; MR, Mendelian randomization.

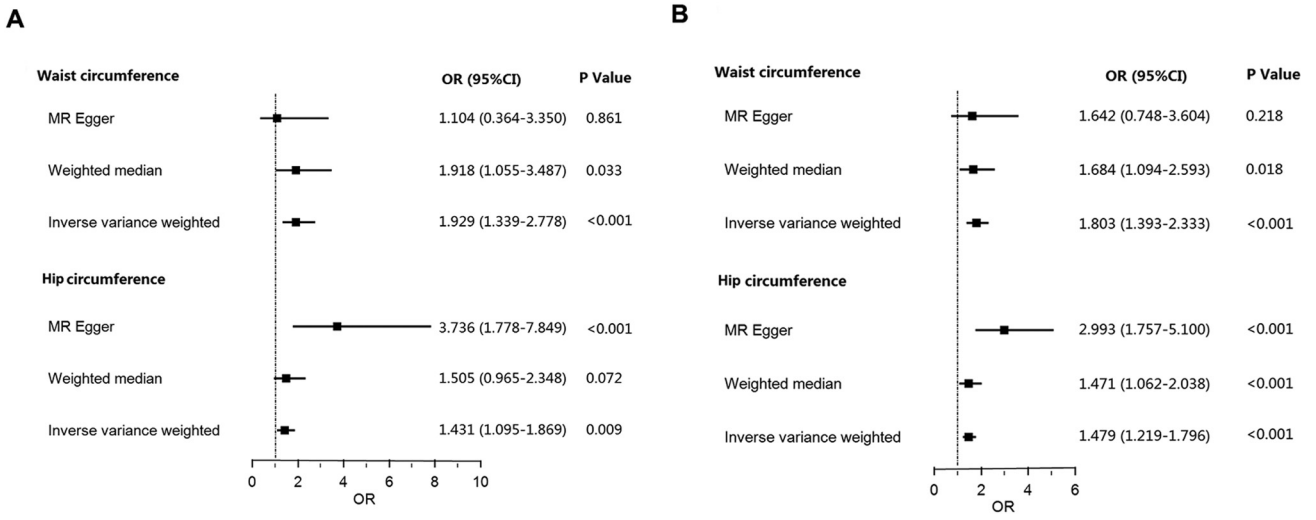



**Fig. 8** Forest plot to visualize the causal effect of waist circumference and hip circumference on the risk of venous thromboembolism (A) and pulmonary embolism (B). IVW, inverse-variance weighted; MR, Mendelian randomization.

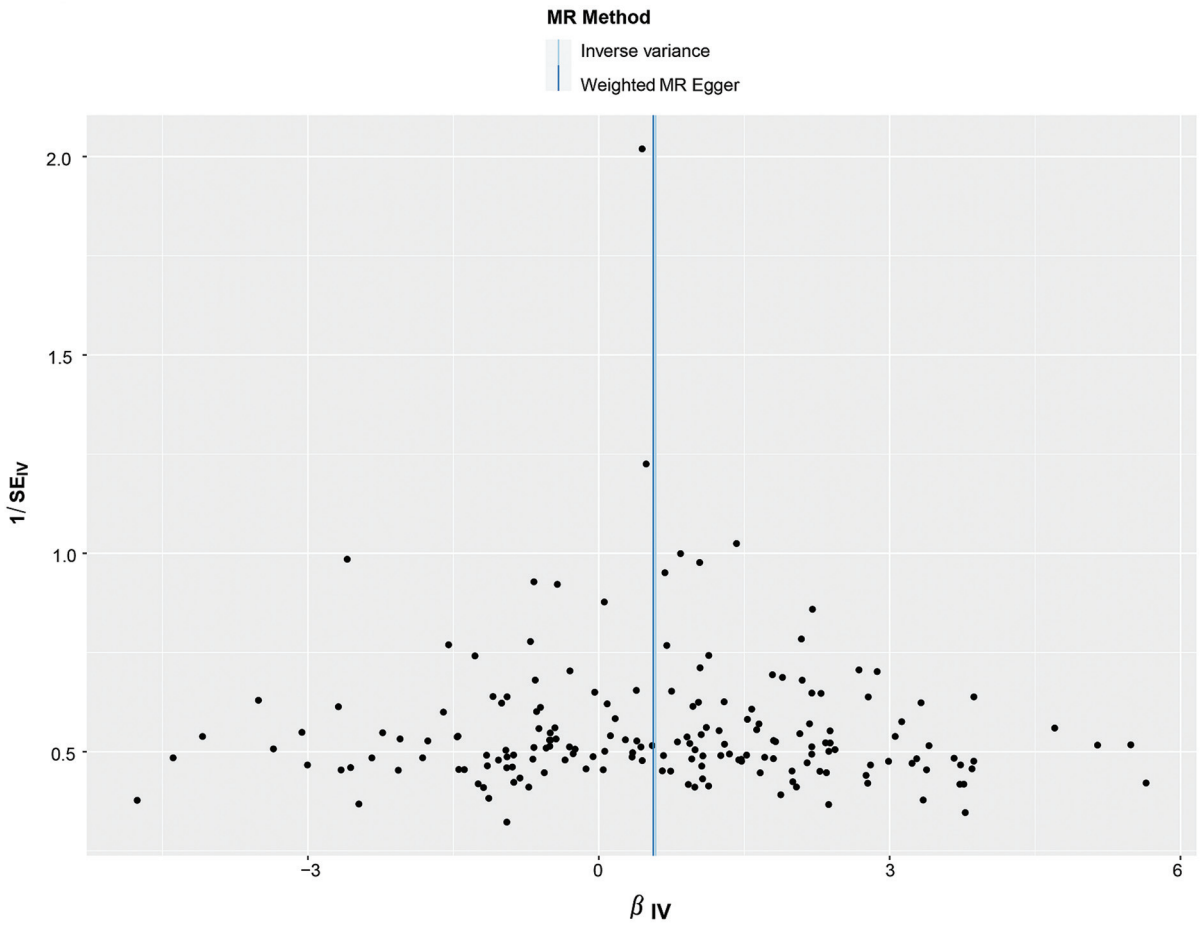



**Fig. 9** Funnel plots to visualize the overall heterogeneity of MR estimates for the effect of waist circumference on the risk of venous thromboembolism. IVW, inverse-variance weighted; MR, Mendelian randomization.

rs1799963, FVL rs6025, FGG rs2066865, FXI rs2036914,FXI rs2289252, and ABO rs8176719), and finally concluded that 45 to 62% of VTE events in the population could be attributed to known prethrombotic genotypes. Recently, Evensen et al also corroborated that the above-mentioned six SNPs were markedly interrelated to VTE.[34]

Obesity, especially excess visceral adiposity, is an independent risk factor for the development of cardiovascular disease and poor cardiovascular outcomes.[35] Although some somatotype parameters such as BMI and WC are susceptible to confounders, these ergonomic indicators have been well established by previous observational studies to strongly associate with VTE.[10,36,37] Recent data emphasize that abdominal obesity determined by WC or WHR is a cardiovascular risk marker independent of BMI.[35] However, the literature reports on the impact of WC and HC on VTE are controversial.[9,38,39] Cushman et al displayed that the higher the level of all body parameters (weight, height, WC, HC, calf circumference, BMI, WHR, fat mass, and fat-free mass), the higher the risk of VTE.[36] Stefan believes that the impact of fat in different parts was different on the risk of cardiovascular metabolic diseases.[39] The low proportion of fat in the hips and legs is the most powerful indicator to predict someone's normal weight but unhealthy metabolism, that is, hip fat is a favorable factor to protect cardiovascular diseases. Contrary to this view, this study found that the increase of HC was associated with a higher risk of VTE (►**Figs. 7–10** and ►**Supplementary Figs. S1** and **S2**, available in the online version), although it was less sensitive than WC.[39] Adipose tissue is the main component of obesity, especially visceral adipose tissue. It can secrete a variety of important biomarkers, which can not only affect insulin resistance, but also affect blood lipid, blood pressure, coagulation, fibrinolysis, and inflammation, resulting in endothelial dysfunction, atherosclerosis, and venous thrombosis.[12] Obesity-induced increases in triglycerides, low density lipoprotein-C, and lipoprotein(a) also increase the risk of VTE by inhibiting the fibrinolytic system.[40,41] It has been found that in comparison with normal-weight patients, overweight patients had a significantly delayed ECLT (euglobulin clot lysis time), lower tissue plasminogen activator (t-PA) activity, and higher t-PA antigen, PAI-1 activity and antigen.[42] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, on the other hand, reduces lipoprotein(a) and low-density lipoprotein cholesterol levels, thereby reducing the risk of VTE.[43] Besides, abdominal obesity presents a chronic low-grade inflammatory response as a result of adipose-derived hormones with proinflammatory effect.[44] Visceral obesity

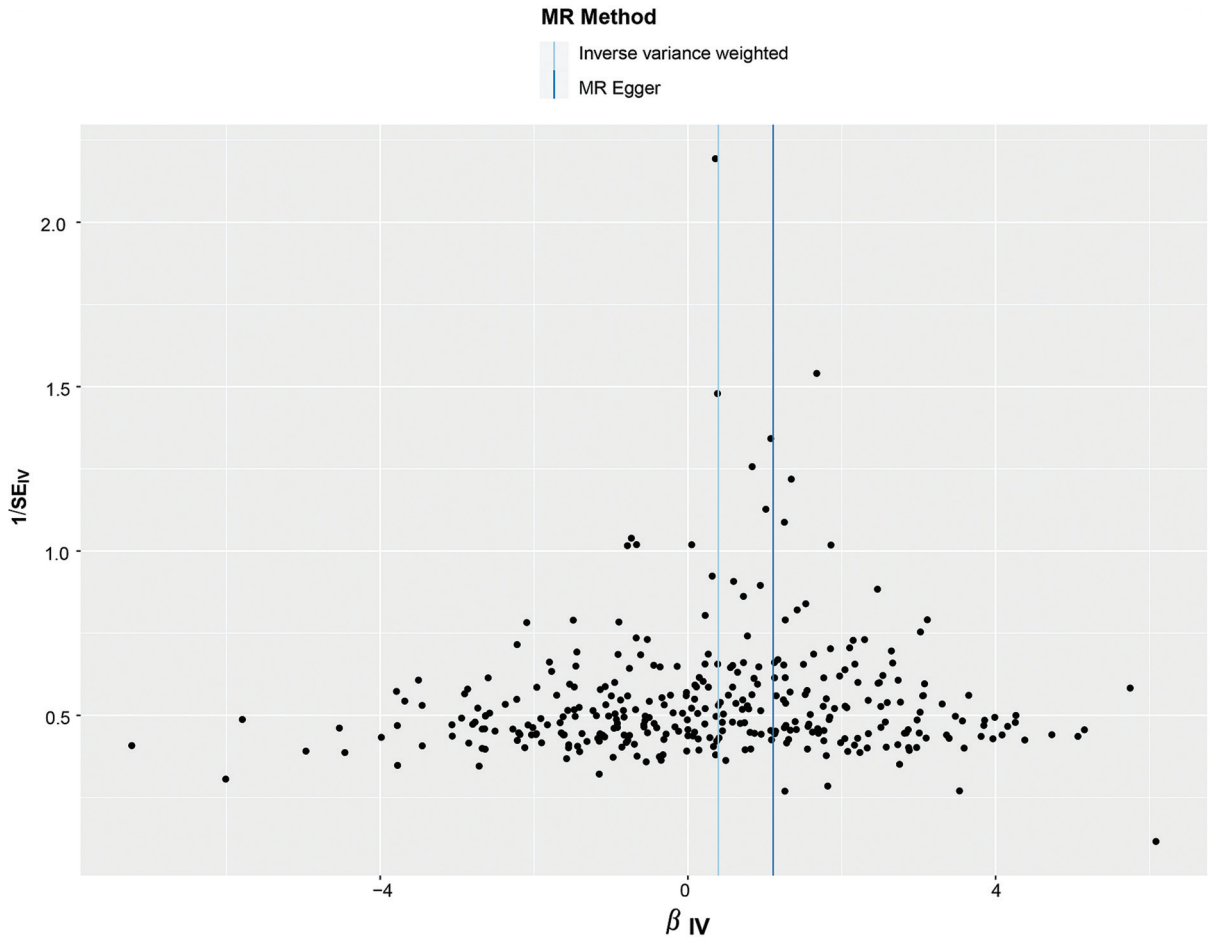



**Fig. 10** Funnel plots to visualize the overall heterogeneity of MR estimates for the effect of hip circumference on the risk of venous thromboembolism. IVW, inverse-variance weighted; MR, Mendelian randomization.

further increases intra-abdominal pressure and reduces venous blood flow velocity.[44] On the other hand, lifestyle interventions may have multiple effects on the body. Therefore, randomized controlled trials aimed at weight loss are difficult to explain the impact of obesity on VTE.[45]

At present, the problem in a clinical study is that the conclusion obtained in observational research is often association rather than causation. However, MR can be adopted to determine the cause and effect.[10] Currently, MR is rapidly becoming a popular method in epidemiological etiology and genetic variation is used as a natural experiment and IV to study causality due to no traditional bias of reverse causality and residual confusion in MR analysis.[46] Recently, an MR study by Lindström et al genetically identified the causality between high BMI and VTE based on the INVENT consortium, including 7,507 cases of VTE and 52,632 controls of European descent.[11] Larsson et al adopted an MR study to confirm that higher BMI, especially fat mass index, was genetically associated with an increased risk of most cardiovascular outcomes.[20] In this study, we found that both WC and HC had a causal relationship with VTE by the method of MR study. To the best of our knowledge, this is the first report to confirm the causal relationship between WC, HC, and VTE.

To reduce potential pleiotropy as small as possible in this MR study, three different methods (IVW, MR-Egger, and weighted median) were used to estimate the directional pleiotropy in the present sensitivity analysis. The consistency of the three methods makes our results more reliable. And the GO, KEGG analysis, and the DGIdb were also used to annotate the gene products, identify the functional characteristics of genes, and to find the potential drugs which may contribute to the disruptions in such processes of WC/HC to VTE. The MR analysis in this study confirms and extends the results of our previous MR study by Tan et al, showing that a genetically higher BMI is associated with an increased risk of VTE. In this study, Cochran Q statistic revealed no notable heterogeneity. The MR-Egger intercept test did not reveal any unbalanced horizontal pleiotropy in WC but not HC. The funnel plots demonstrated that directional horizontal pleiotropy was not disclosed in both effects of WC and HC on VTE (►**Figs. 9** and **10**). The leave-one-out analyses displayed that removing any individual SNP produced no significant difference in the causal effect of WC or HC on VTE (►**Supplementary Figs. S1** and **S2**, available in the online version). The GO and pathway enrichment analyses showed that the enrichment of genetic variants associated with WC

was different from those associated with HC. But they all enrich in the MAPK signaling pathway (►**Figs. 2–5**). The drug–gene interaction analysis found 62 common genes in both WC and HC (►**Fig. 6**) and showed the genes target and potential existing drugs.

To sum up, through MR analysis and its sensitivity analysis, we revealed that WC and HC significantly affected VTE through SNPs. Compared with HC, WC has a more important predictive value for VTE. And by the GO analysis and the DGIdb, we identified functional characteristics of genes and predicted potential existing drugs, which may guide future preventive medication.

In our previous study, all three MR methods (IVW, MR-Egger, and weighted median regression) showed a positive correlation between BMI and DVT, but failed to clarify the causal relationship between WC and HC on VTE.[13] Although BMI is a good indicator of the total amount of fat in adults, it does not take the distribution of adipose tissue in the body into account. The distribution of body fat may have different effects on the risk of cardiovascular disease.[47] A large number of studies have shown that abdominal obesity as measured by WHR or WC is a better predictor of arterial thromboembolic events, such as coronary heart disease and stroke, than general obesity as measured by BMI.[47] While several studies have reported associations between different body size measurements and the risk of VTE, the results are inconsistent in different genders and studies.[47] Severinsen et al investigated and verified the relationship between 641 VTE events and anthropometric values of all participants in a Danish prospective study. The results showed that the female HC was positively correlated with VTE, while there was no correlation in men. WC was positively correlated with male VTE, but not with female VTE. Borch et al in the Tromsø study disclosed that although BMI, HC, and WC were all closely related to VTE, WC is the preferable anthropometric indicator to identify high-risk groups and predict the risk of VTE.[9] The results of two studies involved above indicated that WC could better predict the occurrence of VTE than HC and BMI.

Our previous results confirmed that there was a causal relationship between genetically determined BMI and increased DVT risk. Every 1 SD increase in BMI will increase DVT risk by 67%.[13] Consistent with the trend of our previous study, our study showed that the risk of VTE heightened 80.3% for every 1 SD increase in WC, and raised by 47.9% for every 1 SD increase in HC (►**Fig. 8**). Therefore, different from the results of the study by Borch et al, we concluded that compared with HC and BMI, WC might have a higher predictive value for VTE (►**Fig. 8**). To verify the results obtained by the MR method, three sensitivity analysis methods, Cochran Q statistic test for heterogeneity, pleiotropy test, and leave-one-out test, to evaluate the reliability of MR study were used. Considering the possibility of SNP heterogeneity and pluripotency, we not only gave priority to the estimation results of IVW, but also used the Cochran Q statistic test for excluding heterogeneous confounders, MR-Egger algorithms for excluding pluripotency confounders, and leave-one-out test for investigating the effect of some IVs on the overall MR results (►**Fig. 7–10** and ►**Supplementary Figs. S1** and **S2**, available in the online version), to make the statistical results more objective.

In general, through MR analysis, we confirmed that both WC and HC had a causal relationship with VTE. Compared with HC, WC is a better anthropometric index to predict VTE in obese patients. Taking positive measures to reduce the proportion of abdominal obesity may help reduce the incidence of VTE.

### Limitations

First, a plausible limitation of this study is that we only used summary-level statistics in our study, not individual-level data. Therefore, we cannot further explore causal relationships between subgroups such as females and males, smokers and nonsmokers. Second, the potential drugs came from the DGIdb. Therefore, the specific effect of these drugs should be confirmed by basic research in the future. At last, some studies suggest that race and ethnicity play a role in the risk of VTE.[48–50] It is reported that the mutations in the genes encoding anticoagulants are the main genetic cause of PE in Asia.[49] However, these mutations can only account for 12.04% of VTE patients.[49] The data in this study came from European samples, so we need a further test to explore whether the conclusion can be applied to other regions and races.

## What is known about this topic?

- There is an observational association between obesity and venous thromboembolism.
- Waist circumstance can predict the risk of venous thromboembolism.

## What does this paper add?

- Provide evidence of causality between waist circumstance/hip circumstance and venous thromboembolism/pulmonary embolism.
- Draw conclusions after removing interference from common factors.

**Contribution to the Field Statement**

Obesity, especially abdominal obesity, is an independent indicator of increased cardiovascular risk. There have been observational studies that showed an observational association between obesity and venous thromboembolism. As a type of venous thromboembolism, pulmonary embolism is also associated with obesity. But it is unclear whether the observed association is causal or caused by confounding bias or reverse causality. To verify and compare the effects of waist circumstance and hip circumstance on venous thromboembolism and life-threatening pulmonary embolism, we used the method of Mendelian randomization study to analysis the exposure data from the Neale Laboratory Consortium's GWAS summary data

and the summary-level outcome data from FinnGen Biobank of European ancestry. Then we found a causal association between genetically predicted waist circumstance/hip circumstance and higher risk of pulmonary embolism, and compared with hip circumstance, waist circumstance is a better anthropometric index to predict venous thromboembolism in obese patients. This conclusion is consistent with observational studies. But compared with observational studies, our findings provide evidence of significant causality between waist circumstance/hip circumstance and venous thromboembolism/pulmonary embolism. Based on the above conclusions, we make the case that taking measures to reduce waist circumstance/hip circumstance of obesity may help reduce the incidence of venous thromboembolism.

### Author Contributions

Project design and interpretation: J.T. and P.L.; data curation: J.T. and J.W.; statistical analysis: J.T.; methodology: J. T. and P.L.; validation: P.L., Q.S., and X.H.; writing—original draft: J.T. and J.W.; review, revision, and editing: P.L., J.T., and L.H. All authors have read and agreed to the published version of the manuscript.

### Funding

This study and this research group were supported by grants from the Science and Technology Innovation Project of Jinan City (No. 201602153; No. 202019193), the Major Research and Development Project of Shandong Province (No. ZR2020MH041), the Natural Fund Project of Shandong Province (No. G201703080074), the project of the Central Government Guides Local Science and Technology Development (2021Szvup073), the National Natural Science Foundation of China (No. 81170274; No. 82170462), and the National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences (NCRC2020007).

### Conflict of Interest

None declared.

### Acknowledgments

Genetic instruments for estimated anthropometric measurements were obtained from the Neale Laboratory Consortium's GWAS summary data of European ancestry. Summary-level data for venous thromboembolism were obtained from the FinnGen consortium (https://www.finngen.fi/) and UK Biobank study (Neale Laboratory; http://www.nealelab.is/uk-biobank). The authors thank all investigators for sharing these data.

## References

1 Weitz JI, Chan NC. Novel antithrombotic strategies for treatment of venous thromboembolism. Blood 2020;135(05):351–359
2 Bledsoe JR, Woller SC, Stevens SM, et al. Management of low-risk pulmonary embolism patients without hospitalization: the low-risk pulmonary embolism prospective management study. Chest 2018;154(02):249–256
3 Hodeib H, Youssef A, Allam AA, et al. Genetic risk profiling associated with recurrent unprovoked venous thromboembolism. Genes (Basel) 2021;12(06):874
4 Keller K, Wöllner J, Schmitt VH, et al. Risk factors for pulmonary embolism in patients with paralysis and deep venous thrombosis. J Clin Med 2021;10(22):5412
5 Gervaso L, Dave H, Khorana AA. Venous and arterial thromboembolism in patients with cancer: *JACC*: *CardioOncology* state-of-the-art review. JACC CardioOncol 2021;3(02):173–190
6 Stewart LK, Kline JA. Metabolic syndrome increases risk of venous thromboembolism recurrence after acute deep vein thrombosis. Blood Adv 2020;4(01):127–135
7 Maners J, Gill D, Pankratz N, et al; CHARGE Inflammation Working Group. ; INVENT Consortium. ; MEGASTROKE consortium of the International Stroke Genetics Consortium (ISGC) A Mendelian randomization of γ′ and total fibrinogen levels in relation to venous thromboembolism and ischemic stroke. Blood 2020;136 (26):3062–3069
8 Cavallari I, Morrow DA, Creager MA, et al. Frequency, predictors, and impact of combined antiplatelet therapy on venous thromboembolism in patients with symptomatic atherosclerosis. Circulation 2018;137(07):684–692
9 Borch KH, Braekkan SK, Mathiesen EB, et al. Anthropometric measures of obesity and risk of venous thromboembolism: the Tromso study. Arterioscler Thromb Vasc Biol 2010;30(01):121–127
10 Kim MS, Kim WJ, Khera AV, et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. Eur Heart J 2021;42(34):3388–3403
11 Lindström S, Germain M, Crous-Bou M, et al; INVENT Consortium. Assessing the causal relationship between obesity and venous thromboembolism through a Mendelian Randomization study. Hum Genet 2017;136(07):897–902
12 Yuan S, Bruzelius M, Xiong Y, Håkansson N, Åkesson A, Larsson SC. Overall and abdominal obesity in relation to venous thromboembolism. J Thromb Haemost 2021;19(02):460–469
13 Tan JS, Liu NN, Guo TT, Hu S, Hua L. Genetically predicted obesity and risk of deep vein thrombosis. Thromb Res 2021;207:16–24
14 Richmond RC, Hemani G, Tilling K, Davey Smith G, Relton CL. Challenges and novel approaches for investigating molecular mediation. Hum Mol Genet 2016;25(R2):R149–R156
15 Lawlor DA. Commentary: Two-sample Mendelian randomization: opportunities and challenges. Int J Epidemiol 2016;45(03):908–915
16 Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. eLife 2018;7:e34408
17 Rapid GWAS of thousands of phenotypes for 337,000 samples in the UK Biobank—Nealelab. Accessed July 18, 2019 at: http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank
18 MR-Base Accessed February 12, 2022 at: http://app.mrbase.org/
19 Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013;37(07):658–665
20 Larsson SC, Bäck M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. Eur Heart J 2020;41(02):221–226
21 Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. Epidemiology 2017; 28(01):30–42
22 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(02):512–525
23 Burgess S, Dudbridge F, Thompson SG. Re: "Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects". Am J Epidemiol 2015;181(04):290–291

24 Xu L, Borges MC, Hemani G, Lawlor DA. The role of glycaemic and lipid risk factors in mediating the effect of BMI on coronary heart disease: a two-step, two-sample Mendelian randomisation study. Diabetologia 2017;60(11):2210–2220

25 Liu N, Tan J-S, Liu L, Wang Y, Hua L, Qian Q. Genetic predisposition between COVID-19 and four mental illnesses: a bidirectional, two-sample Mendelian randomization study. Front Psychiatry 2021;12:746276

26 Broadbent JR, Foley CN, Grant AJ, Mason AM, Staley JR, Burgess S. MendelianRandomization v0.5.0: updates to an R package for performing Mendelian randomization analyses using summarized data. Welcome Open Res 2020;5:252

27 Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50(05):693–698

28 Obaid M, El-Menyar A, Asim M, Al-Thani H. Prevalence and outcomes of thrombophilia in patients with acute pulmonary embolism. Vasc Health Risk Manag 2020;16:75–85

29 Hotoleanu C. Genetic risk factors in venous thromboembolism. Adv Exp Med Biol 2017;906:253–272

30 Romano AVC, Barnabé A, Gadelha TB, et al. Gene variants associated with venous thrombosis: a replication study in a Brazilian multicentre study. Clin Appl Thromb Hemost 2020;26; 1076029620962225

31 Middeldorp S. Inherited thrombophilia: a double-edged sword. Hematology (Am Soc Hematol Educ Program) 2016;2016(01):1–9

32 Morimont L, Haguet H, Dogné JM, Gaspard U, Douxfils J. Combined oral contraceptives and venous thromboembolism: review and perspective to mitigate the risk. Front Endocrinol (Lausanne) 2021;12:769187

33 Ahmad A, Sundquist K, Palmér K, Svensson PJ, Sundquist J, Memon AA. Risk prediction of recurrent venous thromboembolism: a multiple genetic risk model. J Thromb Thrombolysis 2019;47(02): 216–226

34 Evensen LH, Arnesen CAL, Rosendaal FR, et al. The Risk of Venous Thromboembolism Attributed to Established Prothrombotic Genotypes. Thromb Haemost 2022;122(07):1221–1230

35 Powell-Wiley TM, Poirier P, Burke LE, et al; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2021;143 (21):e984–e1010

36 Cushman M, O'Meara ES, Heckbert SR, Zakai NA, Rosamond W, Folsom AR. Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: the longitudinal investigation of thromboembolism etiology. Thromb Res 2016;144: 127–132

37 Hagan KA, Harrington LB, Kim J, et al. Adiposity throughout the life course and risk of venous thromboembolism. Thromb Res 2018;172:67–73

38 Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjønneland A, Overvad K. Anthropometry, body fat, and venous thromboembolism: a Danish follow-up study. Circulation 2009;120 (19):1850–1857

39 Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. Lancet Diabetes Endocrinol 2020;8 (07):616–627

40 Deguchi H, Banerjee Y, Elias DJ, Griffin JH. Elevated CETP lipid transfer activity is associated with the risk of venous thromboembolism. J Atheroscler Thromb 2016;23(10):1159–1167

41 Onida S, Tan MKH, Kafeza M, et al. Metabolic phenotyping in venous disease: the need for standardization. J Proteome Res 2019;18(11):3809–3820

42 Salobir B, Sabovic M. A metabolic syndrome independent association between overweight, fibrinolysis impairment and low-grade inflammation in young women with venous thromboembolism. Blood Coagul Fibrinolysis 2006;17(07):551–556

43 Schwartz GG, Steg PG, Szarek M, et al; ODYSSEY OUTCOMES Committees and Investigators* Peripheral artery disease and venous thromboembolic events after acute coronary syndrome: role of lipoprotein(a) and modification by alirocumab: prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial. Circulation 2020;141(20):1608–1617

44 Caiano LM, Costanzo S, Panzera T, et al; Moli-sani Study Investigators. Association between body mass index, waist circumference, and relative fat mass with the risk of first unprovoked venous thromboembolism. Nutr Metab Cardiovasc Dis 2021;31 (11):3122–3130

45 Giordano NJ, Jansson PS, Young MN, Hagan KA, Kabrhel C. Epidemiology, pathophysiology, stratification, and natural history of pulmonary embolism. Tech Vasc Interv Radiol 2017;20(03): 135–140

46 Cao W, Li X, Zhang X, et al. No causal effect of telomere length on ischemic stroke and its subtypes: a Mendelian randomization study. Cells 2019;8(02):159

47 Kaze AD, Bigna JJ, Nansseu JR, Noubiap JJ. Body size measures and risk of venous thromboembolism: protocol for a systematic review and meta-analysis. BMJ Open 2018;8(03):e018958

48 White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res 2009;123 (Suppl 4):S11–S17

49 Tan JS, Yan XX, Wu Y, et al. Rare variants in MTHFR predispose to occurrence and recurrence of pulmonary embolism. Int J Cardiol 2021;331:236–242

50 Tan JS, Ren JM, Fan L, et al. Genetic predisposition of anti-cytomegalovirus immunoglobulin G levels and the risk of 9 cardiovascular diseases. Front Cell Infect Microbiol 2022;12:884298