Systematic Review and Meta-Analysis

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Venous thromboembolism has the same risk factors as atherosclerosis

A PRISMA-compliant systemic review and meta-analysis

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Abstract

Background: Previous studies have shown that idiopathic pulmonary embolism is positively associated with other cardiovascular events, such as myocardial infarction and stroke, suggesting a potentially important association between atherosclerosis risk factors and venous thromboembolism (VTE). We performed a meta-analysis to evaluate the correlation between risk factors for atherosclerosis and VTE.

Methods: In December 2014, we searched MEDLINE and EMBASE for studies evaluating the associations between VTE and risk factors for atherosclerosis and pooled outcome data using random-effects meta-analysis. In addition, we analyzed publication bias.

Results: Thirty-three case-control and cohort studies with a total of 185,124 patients met the inclusion criteria. We found that participants with body mass index (BMI) $\geq$30 kg/m^2 had a significantly higher prevalence of VTE than those with BMI $<$30 kg/m^2 in both case-control studies (odds ratio [OR] = 2.45, 95% confidence interval [CI]: 1.78–3.35) and cohort studies (relative risk [RR] = 2.39, 95% CI: 1.79–3.17). VTE was more prevalent in patients with hypertension than without hypertension (OR = 1.40, 95% CI: 1.06–1.84; RR = 1.36, 95% CI: 1.11–1.67). The findings were similar for VTE prevalence between patients with and without diabetes (OR = 1.78, 95% CI: 1.17–2.69; RR = 1.41, 95% CI: 1.20–1.66). Current smoking was significantly associated with VTE prevalence in case-control studies (OR = 1.34, 95% CI: 1.01–1.77), but not in cohort studies (RR = 1.29, 95% CI: 0.96–1.72). In addition, we found that total cholesterol and triglyceride concentrations were significantly higher in patients with VTE than without VTE (weighted mean differences [WMD] = 8.94 mg/dL, 95% CI: 3.52–14.35 mg/dL, and WMD = 14.00 mg/dL, 95% CI: 8.85–19.16 mg/dL, respectively). High-density lipoprotein cholesterol concentrations were significantly lower in patients with VTE than without VTE (WMD = −2.03 mg/dL, 95% CI: −3.42 to −0.63 mg/dL). Higher quality studies were more homogeneous, but confirmed the same significant associations.

Conclusions: Based on our systematic review and meta-analysis, we observed a significant association between VTE and the risk factors for atherosclerosis. These results may make an important contribution to clinical practice regarding VTE treatment.

Abbreviations: BMI = body mass index, CI = confidence interval, DVT = deep venous thrombosis, HDL-C = high-density lipoprotein cholesterol, OR = odds ratio, PE = pulmonary embolism, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = relative risk, TC = total cholesterol, TG = triglyceride, VTE = venous thromboembolism, WMD = weighted mean differences.

Keywords: atherosclerosis, risk factors, venous thromboembolism

1. Introduction

Venous thromboembolism (VTE), which comprises pulmonary embolism (PE) and deep venous thrombosis (DVT), is common, and requires early diagnosis and treatment because of its association with high mortality and morbidity.[1,2] Even though Virchow's triad of factors contributing to thrombosis—vascular endothelial damage, hypercoagulation, and venous stasis—has been widely known for many years,[3] the role of PE as one of the leading causes of death is complex, multifactorial, and interactive. Venous and arterial thrombotic disorders have long been considered separate pathophysiological states, arterial thrombosis originating from platelet activation, and VTE from coagulation factors. However, the concept that VTE and atherosclerosis are 2 entirely distinct entities has recently been challenged.[4] Studies have shown that idiopathic PE (20%) is associated with other cardiovascular events such as myocardial infarction and stroke.[5] Furthermore, some studies have demonstrated a potential association between VTE and atherosclerosis.[6,7] Some studies have also shown that these 2 vascular complications share multiple risk factors such as age, obesity, smoking, diabetes mellitus, blood hypertension, dyslipidemia, and metabolic syndrome.[8] A 20-year cohort study has shown that patients with DVT and PE have a substantially increased risk of

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myocardial infarction and stroke during the first year after the thrombotic event,[9] whereas some studies have reported negative results for some risk factors.[10–13] Because there is still controversy about the relationship between VTE and risk factors for atherosclerosis, the most recent meta-analysis on this topic was published in 2008,[14] and several large case-control and prospective cohort studies have been reported since then, we performed a systematic review of published reports and a meta-analysis to update and reassess the strength of the evidence concerning risk factors for atherosclerosis and VTE. Clear evidence for an association between VTE and traditionally recognized risk factors for atherosclerosis would likely improve prevention of VTE by validating treatment of those risk factors.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in our study.[15] Ethical approval was not necessary for our meta-analysis because the results for publication only involved de-identified pooled data from individual studies which ethics approval has been received.

2.1. Data sources and search strategy

A systematic search was performed on December 29, 2014 by searching PubMed from 1974 to December 2014 and EMBASE (OvidSP) from 1980 to December 2014. The detail of search strategy was shown in Table 1. For the first search, titles alone were reviewed based on text key words. Then, the abstracts of suitable titles and full-text conforms to the abstracts were obtained and reviewed. We extracted the data from the suitable full-text reports as described in the following section. Parts of additional suitable reports in our study were supplemented when discovered by citation tracking.

2.2. Study selection

All published studies that evaluated the prevalence or severity of atherosclerosis risk factors in patients with VTE and met the following criteria were identified: English language articles; age from childhood to adulthood; prospective studies that recruited patients who had been diagnosed with VTE and included definitions of hypertension, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia; concentrations of high-density lipoprotein cholesterol (HDL-C); body mass index (BMI); and the presence or absence of diabetes mellitus. In the selected studies, VTE (deep vein thrombosis and/or PE) had been diagnosed by at least one of the following standard means: Doppler echocardiography, deep lower limb compression ultrasonography, Doppler venous ultrasound or venography, computed tomography pulmonary angiography, and radioisotope studies such as pulmonary ventilation-perfusion scans.[16] For atherosclerosis, outcomes that were reported for coronary arteriosclerotic cardiopathy, myocardial infarction, angina, acute coronary syndrome, or coronary disease were included.

All studies in which the entire cohort of patients with VTE had a concomitant, known, major risk factor (e.g., studies of patients undergoing major surgery or trauma, involving pregnant women only, patients with antiphospholipid antibody syndrome) were excluded.

2.3. Data extraction and quality assessment

References were screened and data extracted independently by 2 authors using a predetermined data collection template. In the case of disagreement about inclusion of studies and interpretation of data, a third investigator was consulted and consensus reached by discussion. The following data were recorded: publication characteristics, location of study, inclusion and exclusion criteria, sample size, and patients' characteristics. The following risk factors for atherosclerosis were collected from each included study: number and proportion of patients, BMI, blood pressure, cholesterol or triglyceride (TG) concentrations, HDL-C concentrations, diabetes mellitus, and smoking. If information on the proportion of patients with and without a particular risk factor was not available, mean levels and standard deviations were extracted for both cases and controls.

The quality of all included studies was assessed using a scoring system that resulted in total scores for each study from 0 to 5 points (the highest quality was defined as 5 for cohort studies or 4 for case-control studies). In the system we created, one point is allocated for each of the following items: appropriate inclusion and exclusion criteria; adequately reported methodology for measuring risk factors; sample size >500; follow-up duration >3 years; and adjustments made for risk factors such as age, sex, BMI, diabetes mellitus, hypertension, and smoking (Table 2).

2.4. Data synthesis and analysis

Pooled odds ratio (OR), relative risk (RR) or weighted mean difference (WMD), and 95% confidence interval (CI) were calculated using the DerSimonian-Laird random-effects model, which takes study heterogeneity into account to generate the

Table 1

Search Strategy: Searching MEDLINE and EMBASE (OvidSP) on December 25, 2014.

1. EMBASE (OvidSP) from 1980 to December 2014

("thromboembolism" OR "venous thrombosis" OR "venous thromboembolism" OR "pulmonary embolism" OR "pulmonary thromboembolism" OR "pulmonary emboli" OR "deep-vein thrombosis") AND ("atherosclerosis" OR "coronary arteriosclerotic cardiopathy" OR "angina" OR "coronary disease" OR "myocardial infarction" OR "acute coronary syndrome") AND ("hypertension" OR "dyslipidemia" OR "hyperlipoidemia" OR "hyperlipemia" OR "hypercholesterolemia" OR "cholesterol" OR "hypertriglyceridemia" OR "triglyceride" OR "high density lipoprotein" OR "high density lipoproteincholesterol" OR "obesity" OR "overweight" OR "metabolic syndrome" OR "blood pressure" OR "diabetes" OR "diabetes mellitus" OR "hyperglycemia" OR "impaired glucose tolerance" OR "cigarette smoking" OR "smoking") NOT ("Infant" OR "newborn" OR "fetus")

2. PubMed from 1974 to December 2014

("thromboembolism" OR "venous thrombosis" OR "venous thromboembolism" OR "pulmonary embolism" OR "pulmonary thromboembolism" OR "pulmonary emboli" OR "deep-vein thrombosis") AND ("atherosclerosis" OR "coronary arteriosclerotic cardiopathy" OR "coronary disease" OR "myocardial infarction" OR "acute coronary syndrome") AND ("hypertension" OR "dyslipidemia" OR "hyperlipoidemia" OR "hyperlipemia" OR "hypercholesterolemia" OR "cholesterol" OR "hypertriglyceridemia" OR "triglyceride" OR "high density lipoprotein" OR "high density lipoproteincholesterol" OR "obesity" OR "overweight" OR "metabolic syndrome" OR "blood pressure" OR "diabetes" OR "diabetes mellitus" OR "hyperglycemia" OR "impaired glucose tolerance" OR "cigarette smoking" OR "smoking") NOT ("Infant" OR "newborn" OR "fetus")

Table 2

Scoring System of Quality Assessment.

Author	Appropriate Inclusion and Exclusion Criteria	Adequately Reported Methodology of Measurement of Risk Factors	Sample Size* (>500)	Median Follow-Up Year	Adjustment for the Risk Factors†	Quality Score‡
Poulter et al[17]	√	√	√	—	√	4
Kawasaki et al[18]	√	√	X	—	X	2
Hoibraaten et al[19]	√	√	√	—	X	3
Hansson et al[20]	√	√	√	26 y	√	5
McColl et al[21]	√	√	X	—	√	3
Nightingale et al[22]	√	√	√	—	√	4
Seguí et al[23]	√	√	X	—	√	3
Vayá et al[24]	√	√	X	—	√	3
Tsai et al[11]	√	√	√	7.8 y	√	5
Lidegaard et al[25]	√	√	√	—	√	4
Abdollahi et al[26]	√	√	√	—	√	4
González-Ordóñez et al[27]	√	√	X	—	√	3
Paganin et al[28]	√	√	X	—	√	3
Prandoni et al[6]	√	√	X	—	√	3
Zamani et al[29]	√	√	X	—	X	2
Cushman et al[30]	√	√	√	5.6 y	√	5
Doggen et al[31]	√	√	√	—	√	4
Frederiksen et al[32]	√	√	√	23 y	√	5
Sydney et al[33]	√	√	√	—	√	4
Deguchi et al[34]	√	√	X	—	√	3
Vayá et al[35]	√	√	X	—	√	3
Pomp et al[36]	√	√	√	—	√	4
Hermanides et al[37]	√	√	√	—	√	4
Holst et al[38]	√	√	√	20 y	√	5
Delluc et al[39]	√	√	√	—	√	4
Wattanakit et al[12]	√	√	√	15.5 y	√	5
van Schouwenburg et al[10]	√	√	√	10.5 y	√	5
Enga et al[40]	√	√	√	12.5 y	√	5
Brækkan et al (Tromsø Study)[41]	√	√	√	10.8 y	√	5
Delluc et al[42]	√	√	√	—	√	4
Bell et al[43]	√	√	√	—	√	4
Lerstad et al (Tromsø study)[44]	√	√	√	7.1 y	√	5
Tala et al[45]	√	√	√	—	√	4

* One point was for follow-up duration >3 years.

† Adjustment for the risk factors: age, sex, body mass index, smoking, diabetes mellitus, and hypertension.

‡ Each study from 0 to 5 points (the highest quality was defined as 5 for cohort studies or 4 for case-control studies).

estimates. The extent of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic.[46] Meta-analyses were stratified by study design. Potential publication bias was assessed with the Egger test and is presented graphically by funnel plots of the natural log of the OR, RR, or WMD versus its standard error.[47] STATA 11 (Stata, College Station, TX) was used for statistical computations. A 2-sided $P < 0.05$ was considered significant. Sensitivity analyses were based on the quality of the studies to assess the robustness of our primary results.

3. Results

Figure 1 shows the process for selecting reports. Of 3490 reports selected in the initial search by scanning titles and abstracts, 48 seemed to meet the inclusion criteria. These were selected for detailed assessment, which resulted in exclusion of a further 15 studies for the following reasons: 3, no comparable data[2,48,49]; 4, no control group[50–53]; 2, only autopsies[54,55]; 2, no objective criteria for diagnoses[56–58]; and 3, duplicate data.[24,30,59] Finally, 33 studies with a total of 185,124 patients[6,10–12,17–45] were included in this meta-analysis. Relevant characteristics of these 33 studies are shown in Table 3. The number of subjects per study ranged between 86 and 26,185.[29,41] The mean age of participants varied widely from study to study because of the varied inclusion criteria, which ranged widely from children with diabetes mellitus only[45] to adults with various risk factors depending on the studies' inclusion criteria. Seven studies investigated only women[17,19,21,22,30,31,33] and 2 studies investigated only men.[20,34] Five studies involved oral contraceptives[17,19,22,25,26] and 3 studies inherited risk factors.[6,23,34] There were 10 prospective cohort studies [10–12,20,30,32,38,40,41,44] with durations of follow-up ranging from 5.6[30] to 26 years.[20] Twenty-three case-control studies included healthy subjects.[6,17–19,21–29,31,33–37,39,42,43,45] Two studies included only patients with DVT.[18,26] Three of the 33 studies identified no associations between VTE and risk factors for atherosclerosis; these were all cohort studies.[10,32,44] It was not possible to compare the prevalence of cardiovascular risk factors between patients with unprovoked and provoked VTE because there were too few studies for which this information was available.

3.1. Association between BMI and VTE

In this meta-analysis, 10 case-control studies and 4 cohort studies with 19,608 subjects with thrombosis and 68,521 controls

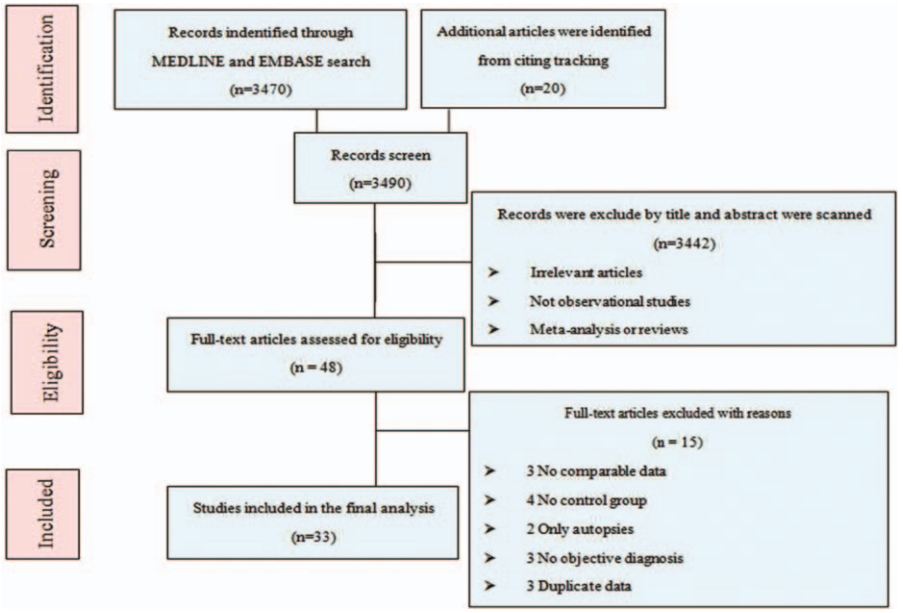

Figure 1. Study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Table 3

Characteristics of Included Trials in This Meta-Analysis.

Study	Sample Size, n	Year	Age, y	Sex (Women%)	Study Design	Risk Factors in Each Study
Poulter et al[17]	4141	1995	20–44	100	Case-control	Diabetes, smoking, hypertension
Kawasaki et al[18]	218	1997	49	51	Case-control	TC, TG
Hoibraaten et al[19]	528	1999	59	100	Case-control	Diabetes, smoking, hypertension
Hansson et al[20]	851	1999	>50	0	Prospective cohort	Smoking, hypertension
McColl et al[21]	160	2000	<51	100	Case-control	TC, TG, HDL-C
Nightingale et al[22]	1728	2000	15–49	100	Case-control	BMI, smoking, hypertension
Seguí et al[23]	283	2000	42	40	Case-control	TC, TG
Vayá et al[24]	337	2002	42	62	Case-control	BMI, TC, TG
Tsai et al[11]	21,680	2002	>45	55	Prospective cohort	BMI, diabetes, hypertension, TC, TG
Lidegaard et al[25]	5041	2002	15–44	100	Case-control	BMI, diabetes, smoking, hypertension
Abdollahi et al[26]	908	2003	45	58	Case-control	BMI
González-Ordóñez et al[27]	251	2003	62	51	Case-control	BMI, TC, TG, HDL-C
Paganin et al[28]	138	2003	51	51	Case-control	BMI
Prandoni et al[6]	203	2003	66	54	Case-control	BMI, diabetes, smoking, hypertension (thrombophilia)
Zamani et al[29]	86	2003	46	56	Case-control	TC, TG
Cushman et al[30]	16,608	2004	50–79	100	Prospective cohort	Diabetes, smoking
Doggen et al[31]	2413	2004	70	100	Case-control	TC, TG, HDL-C
Frederiksen et al[32]	7864	2004	48	57	Prospective cohort	Diabetes, smoking, hypertension, TC, TG, HDL-C
Sydney et al[33]	942	2004	15–44	100	Case-control	BMI, smoking
Deguchi et al[34]	198	2005	<55	0	Case-control	Diabetes, smoking, hypertension, TC, TG, HDL-C
Vayá et al[35]	334	2007	42 ± 12	47	Case-control	BMI, hypertension, TC, TG
Pomp et al[36]	8889	2008	25–66	54	Case-control	Smoking
Hermanides et al[37]	558	2009	57	56	Case-control	Diabetes
Holst et al[38]	18,954	2010	>20	54	Prospective cohort	BMI, diabetes, smoking, hypertension, T C, TG, HDL-C
Delluc et al[39]	934	2012	>18 (58–80)	59	Case-control	Diabetes, TC, TG, HDL-C
Wattanakit et al[12]	15,340	2012	54	55	Prospective cohort	BMI, diabetes, smoking, hypertension, TC
van Schouwenburg et al[10]	7627	2012	28–75	51	Prospective cohort	TC, TG, HDL-C
Enga et al[40]	11,302	2012	25–96	55	Prospective cohort	Smoking
Brækkan et al (Tromsø Study)[41]	26,185	2012	≥25	53	Prospective cohort	BMI, hypertension, TC, TG, HDL-C
Delluc et al[42]	1171	2013	73	57	Case-control	BMI
Bell et al[43]	12,298	2013	45–64	50	Case-control	Diabetes
Lerstad et al (Tromsø study)[44]	16,165	2014	≥25 (25–87)	47	Prospective cohort	Diabetes
Tala et al[45]	789	2014	≤18	58	Case-control	Diabetes

BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

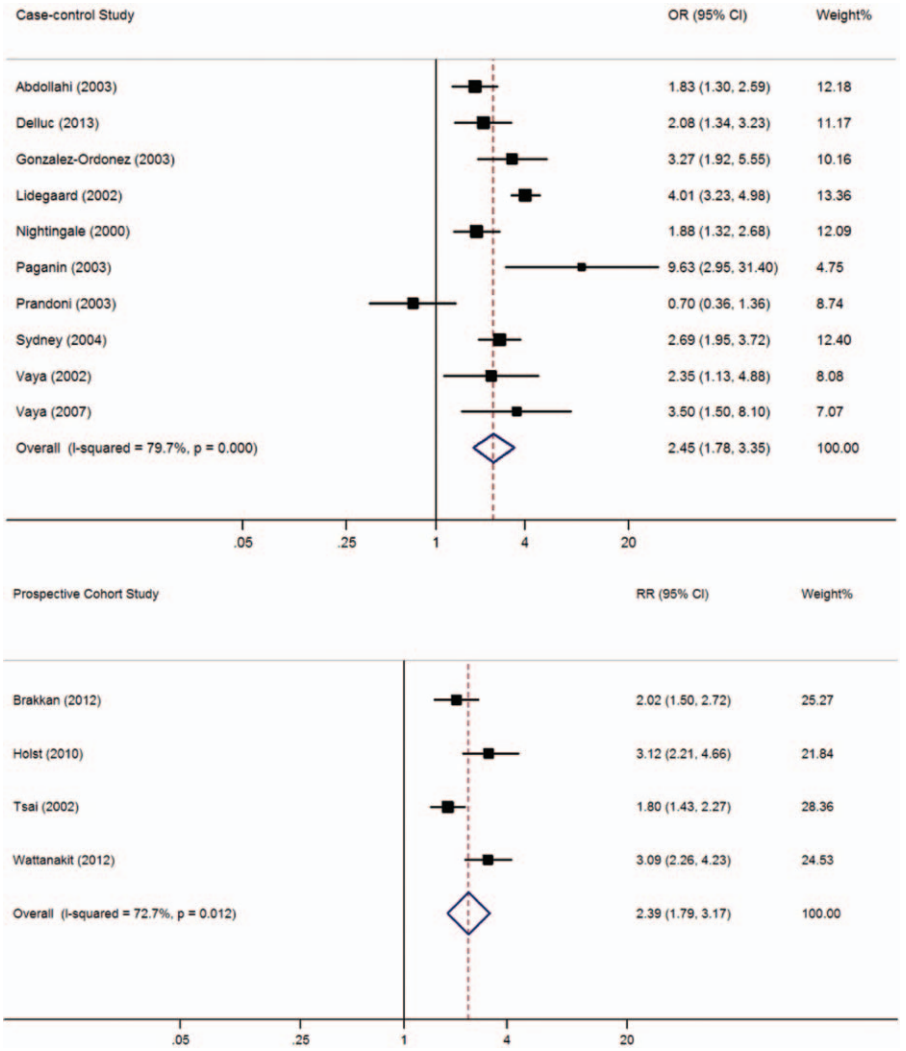

Figure 2. Meta-analysis of the effect of obesity (body mass index ≥30 kg/m^2) on venous thromboembolism (based on 10 case-control and 4 cohort studies). Squares represent point estimates for effect size expressed as an OR/RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, OR = odds ratio, RR = relative risk.

included data on BMI. As shown in Figure 2, participants with BMI ≥30 kg/m^2 had a significantly higher prevalence of VTE than those with BMI <30 kg/m^2 in both case-control (OR = 2.45, 95% CI: 1.78–3.35, I^2 = 79.7%) and cohort studies (RR = 2.39, 95% CI: 1.79–3.17, I^2 = 72.7%). When lower quality case-control studies were excluded, the 5 remaining high-quality case-control studies[22,25,26,33,42] still reported a significant difference between these 2 BMI categories (OR = 2.43, 95% CI: 1.72–3.44, I^2 = 82.6%).

3.2. Association between diabetes and VTE

In this meta-analysis, 9 case-control and 6 cohort studies with 44,809 subjects with thrombosis and 83,207 controls included data on subjects with diabetes mellitus. As shown in Figure 3, the prevalence of VTE was significantly higher among participants with diabetes than in those without diabetes (case-control studies: OR = 1.78, 95% CI: 1.17–2.69, I^2 = 66.4%; cohort studies: RR = 1.41, 95% CI: 1.20–1.66, I^2 = 0.0%). When lower quality case-control studies were excluded, the 6 remaining high-quality case-control studies[17,25,37,39,43,45] still showed a significant difference between participants with and without diabetes (OR = 1.99, 95% CI: 1.28–3.11, I^2 = 63.9%).

3.3. Association between hypertension and VTE

In this meta-analysis, 7 case-control and 6 cohort studies with 23,639 thrombosis patients and 74,249 controls included data on hypertension. Figure 4 shows that the prevalence of VTE was significantly higher among participants with hypertension than in those without hypertension (case-control studies: OR = 1.40, 95% CI: 1.06–1.84, I^2 = 49.9%; cohort studies: RR = 1.36, 95% CI: 1.11–1.67, I^2 = 71.7%). When lower quality case-control studies were excluded, the 3 remaining high-quality case-control studies[17,22,25] still reported a significant difference between subjects with and without hypertension (OR = 1.70, 95% CI: 1.36–2.13, I^2 = 0.0%).

3.4. Association between current smoking and VTE

In this meta-analysis, 8 case-control and 6 cohort studies with 16,555 patients with thrombosis and 71,946 controls included

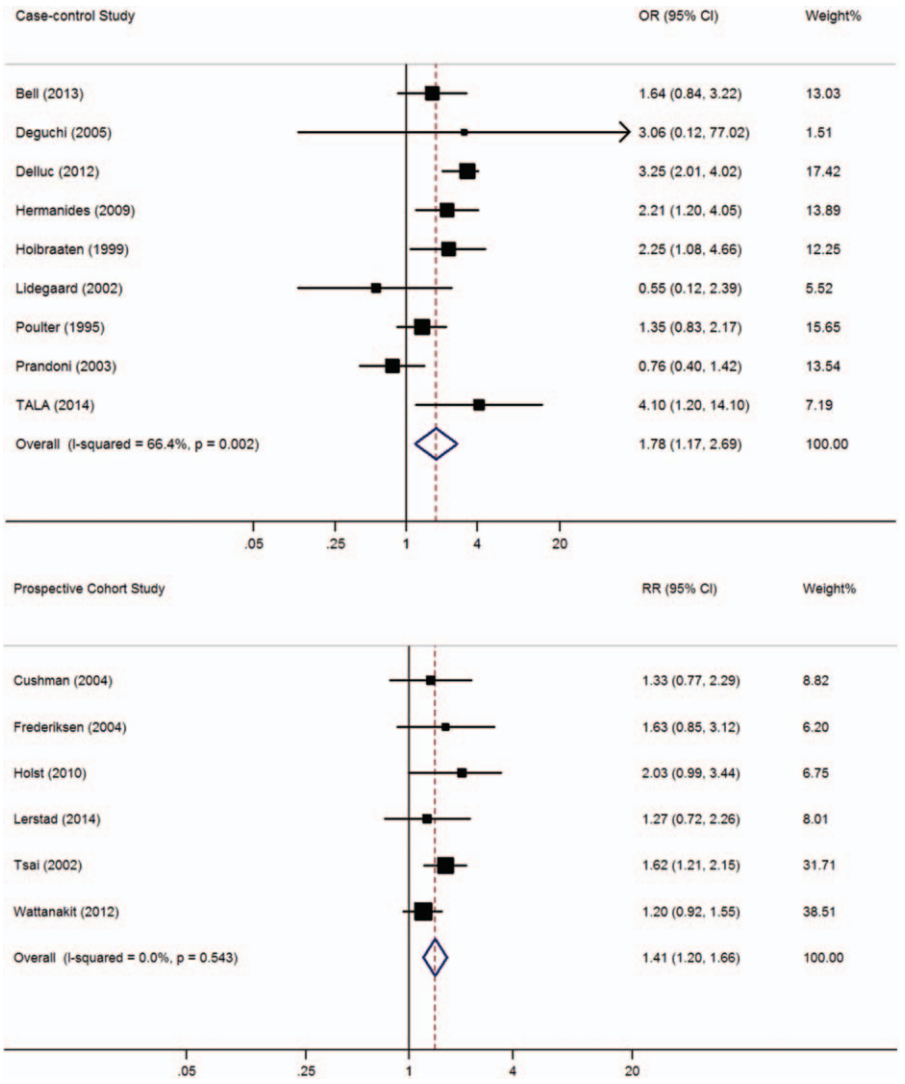

Figure 3. Meta-analysis of the effect of diabetes mellitus on venous thromboembolism (based on 9 case-control and 6 cohort studies). Squares represent point estimates for effect size expressed as an OR/RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, OR = odds ratio, RR = relative risk.

data on smoking. As shown in Figure 5, a significant association between current smoking and VTE prevalence was found in case-control studies (OR = 1.34, 95% CI: 1.01–1.77, $I^2 = 87.1\%$), but not in cohort studies (RR = 1.29, 95% CI: 0.96–1.72, $I^2 = 75.2\%$). When lower quality case-control studies were excluded, the 5 remaining high-quality case-control studies[17,22,25,33,36] still showed a significant difference between current smokers and nonsmokers (OR = 1.48, 95% CI: 1.04–2.11, $I^2 = 92.0\%$).

3.5. Association between total cholesterol and VTE

In this meta-analysis, 10 case-control and 6 cohort studies with 11,044 subjects with thrombosis and 79,974 controls included data on total cholesterol (TC) (Fig. 6). Overall, higher mean TC concentrations were reported in subjects with VTE than in those without VTE (WMD = 8.94 mg/dL, 95% CI: 3.52–14.35 mg/dL, $I^2 = 95.2\%$). Subgroup analysis indicated that significantly higher TC concentrations among subjects with VTE were observed in cohort studies (WMD = 15.89 mg/dL, 95% CI: 10.33–21.44 mg/dL, $I^2 = 95.0\%$), but not in case-control studies (WMD = 3.34 mg/dL, 95% CI: −7.16 to 13.85 mg/dL, $I^2 = 92.5\%$). When lower quality case-control and cohort studies were excluded, the 2 remaining high-quality case-control[31,39] and 6 cohort studies[10–12,32,38,41] still showed a significant difference between subjects with and without high TC concentrations (WMD = 12.90, 95% CI: 7.13–18.66, $I^2 = 96.0\%$).

3.6. Association between HDL-C and VTE

In this meta-analysis, 5 case-control and 4 cohort studies with 6589 patients with thrombosis and 51,484 controls included data on HDL-C concentrations (Fig. 7). Mean HDL-C concentrations were significantly lower in subjects with VTE than in those without VTE (WMD = −2.03 mg/dL, 95% CI: −3.42 to −0.63 mg/dL, $I^2 = 73.5\%$). Subgroup analysis showed that significantly lower HDL-C concentrations among VTE patients were observed in case-control studies (WMD = −1.95 mg/dL, 95% CI: −3.36 to −0.54 mg/dL, $I^2 = 14.7\%$), but not in cohort studies (WMD = −1.91 mg/dL, 95% CI: −4.36 to 0.54 mg/dL, $I^2 = 87.5\%$). When lower quality case-control and cohort studies were excluded, the

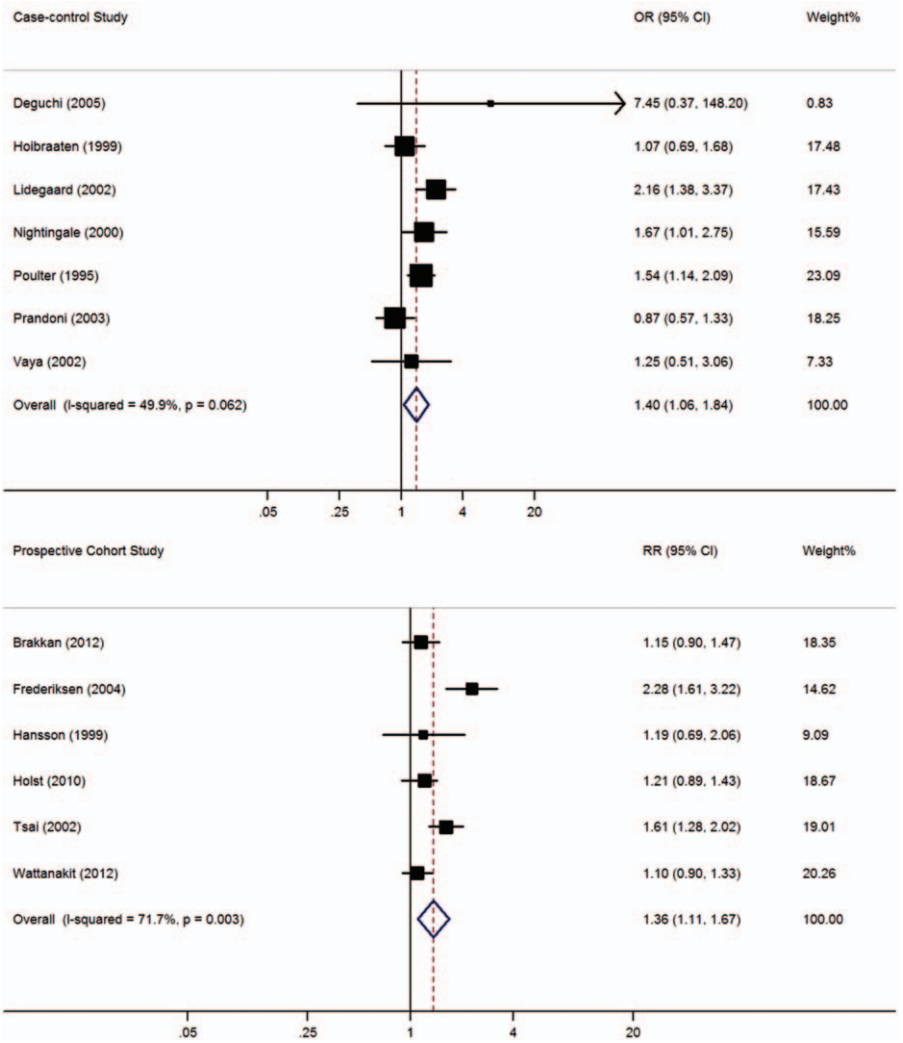

Figure 4. Meta-analysis of the effect of hypertension on venous thromboembolism (based on 7 case-control and 6 cohort studies). Squares represent point estimates for effect size expressed as an OR/RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, OR = odds ratio, RR = relative risk.

remaining 2 high-quality case-control[31,39] and 4 cohort studies[10,32,38,41] still showed a significant difference between subjects with and without high HDL-C concentrations (WMD = −1.75, 95% CI: −3.36 to −0.14, $I^2 = 81.5\%$).

3.7. Association between TG and VTE

In this meta-analysis, 10 case-control and 5 cohort studies with 7200 subjects with thrombosis and 72,206 controls included data on TG concentrations (Fig. 8). A significantly higher mean TG concentration was reported among patients with VTE than in those without VTE (WMD = 14.00 mg/dL, 95% CI: 8.85–19.16 mg/dL, $I^2 = 57.3\%$). Subgroup analysis indicated that the significantly higher TG concentrations among VTE patients were observed in both case-control (WMD = 19.32 mg/dL, 95% CI: 10.56–28.08 mg/dL, $I^2 = 52.9\%$) and cohort studies (WMD = 7.42 mg/dL, 95% CI: 5.16–9.68 mg/dL, $I^2 = 0.0\%$). When lower quality case-control and cohort studies were excluded, the 2 remaining high-quality case-control[31,39] and 5 cohort studies[10,11,32,38,41] still showed significantly higher mean TG concentrations in subjects with VTE than without VTE (WMD = 7.46, 95% CI: 5.26–9.65, $I^2 = 0.0\%$).

3.8. Publication bias

There was no evidence of publication bias on the basis of either visual inspection of funnel plots (Supplementary Figures S1–S6, http://links.lww.com/MD/B179) or Egger test for associations between VTE and BMI, diabetes, hypertension, current smoking, TC, or HDL-C (all $P > 0.05$) (Supplementary Figures E1–E6). However, a funnel plot (Supplementary Figure S7, http://links.lww.com/MD/B179) and Egger test (Supplementary Figure E7) suggested the presence of publication bias for the association between VTE and TG ($P = 0.020$).

4. Discussion

4.1. Our principle finding and its possible underlying mechanism(s)

Our present meta-analysis demonstrated that the major risk factors for atherothrombotic disease are also significantly associated with VTE, which explains why atherosclerosis is an independent risk factor for VTE.[7] Among the traditionally recognized risk factors for atherosclerosis we evaluated, obesity, diabetes mellitus, hypertension, and hypercholesteremia and

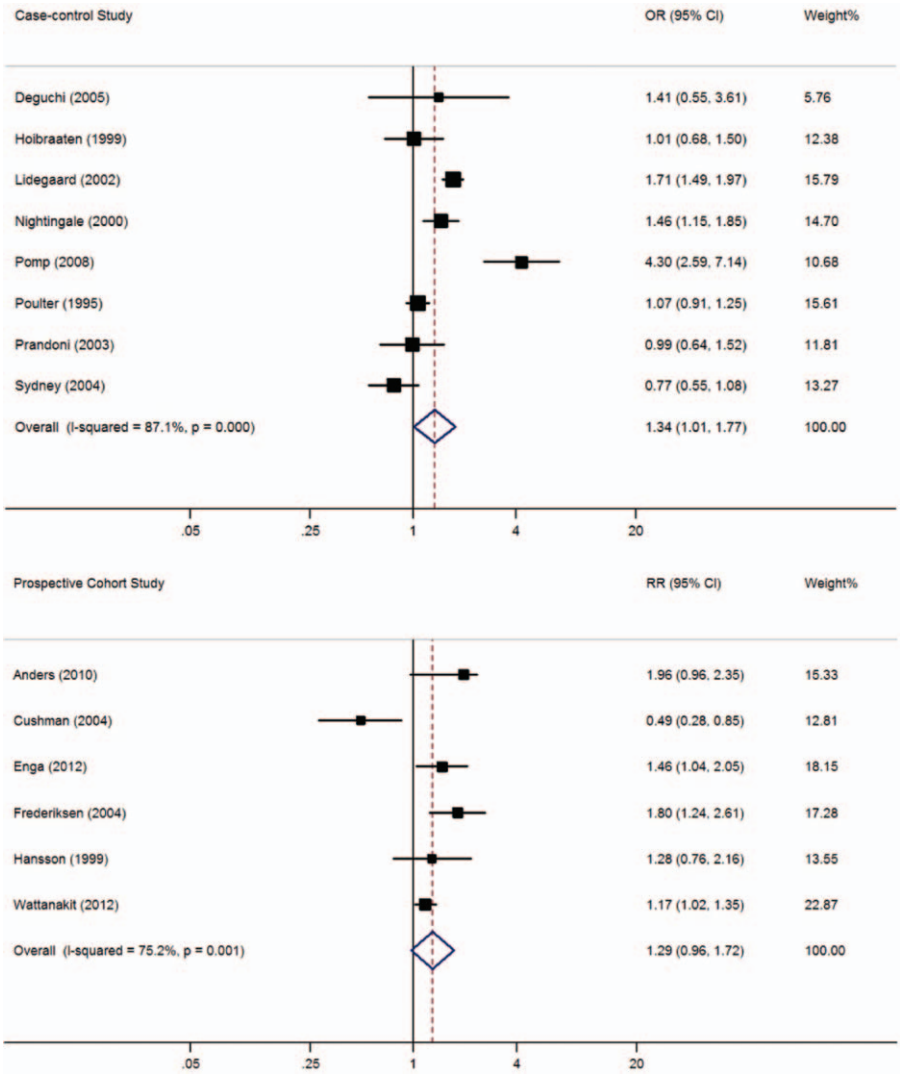

Figure 5. Meta-analysis of the effect of smoking on venous thromboembolism (based on 8 case-control and 6 cohort studies). Squares represent point estimates for effect size expressed as an OR/RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, OR = odds ratio, RR = relative risk.

hypertriglyceridemia in particular had clear positive correlations with VTE, whereas HDL-C concentrations had a clear negative correlation with VTE. We found a significant association between current smoking and VTE prevalence in case-control studies, but not in cohort studies; however, in the latter the pooled RR was close to reaching significance.

Obesity has consistently been identified as a common risk factor for both arterial and VTE. The risk of VTE in subjects with obesity was about 2.39 to 2.45 times higher than that in those with BMI $<30\,kg/m^2$ in our meta-analysis. All 14 studies that provided BMI data verified that BMI was closely associated with the prevalence of VTE; the same result was also reported for the high-quality studies. Previous reports on the association between atherosclerotic risk factors and VTE have thus far been inconsistent.[11,20,32,47,60] Studies conducted by Fronek et al[61] and Sugerman et al[62] have shown that abdominal obesity is associated with increased intraabdominal pressure and reduced venous blood flow velocity, which may increase susceptibility to thrombosis. Moreover, other studies[63,64] have shown that visceral adipose tissue is highly active metabolically, releasing proinflammatory, proatherogenic, and prothrombotic substances that may contribute to thrombosis risk. According to one study, the biological mechanisms may be involved high concentrations of fibrinogen and some clotting factors, low-grade systemic inflammation, increased intra-abdominal pressure, and reduced venous return from the lower limbs.[65] However, whether obesity itself definitely increases the risk of VTE is uncertain because several risk factors such as pregnancy,[66–68] oral contraceptive use,[69] and hormone replacement therapy[70] may coexist with obesity in subjects with current and recurrent VTE.

Eight of the 15 studies about diabetes mellitus reported a positive association[6,11,17,19,30,37,43,45] with VTE, whereas 7 did not.[12,25,32,34,38,39,44] Our pooled analysis resulted in a weak correlation; however, 4 cohort studies did not identify an association between diabetes mellitus and VTE.[12,32,38,44] A possible explanation for this discrepancy is that risk factors often coexist in patients with VTE, for example, diabetes mellitus may be result from metabolic syndrome.[71] The causal relationship between hyperglycemia and VTE has been confirmed by several

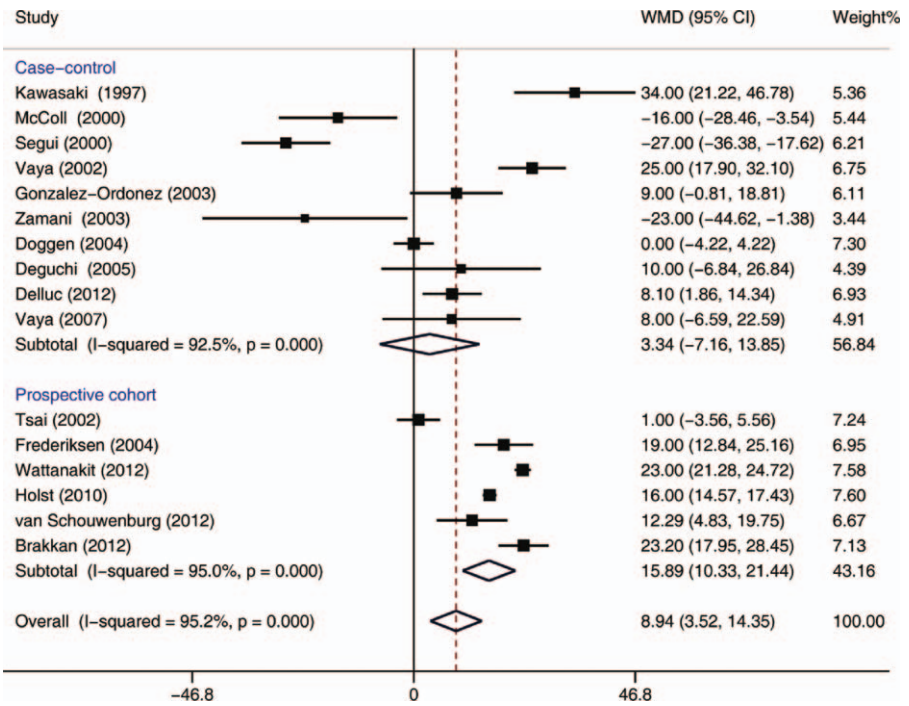

Figure 6. Meta-analysis of the effect of total cholesterol concentrations (mg/dL) on venous thromboembolism (based on 10 case-control and 6 cohort studies). Squares represent point estimates for effect size expressed as a WMD with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, WMD = weighted mean difference.

studies, the main mechanisms for the causality possibly involving activated factor VII activity, the increased thrombin-antithrombin complexes, and soluble tissue factor.[72,73] Whereas, study did not find the direct biological relationship between hyperglycemia and the coagulation system.[74]

Consistent with our study, several case-control studies have demonstrated an association between concentrations of serum lipids such as TG, TC, and lipoprotein (a) and VTE.[31,34,75,76] However, a number of large prospective studies have failed to confirm such associations, failing to support a role for serum lipids in the pathogenesis of VTE.[10,27,41,49] Our study showed that VTE was indeed associated with dyslipidemia; however, a funnel plot and Egger test suggested the presence of publication bias for the association between VTE and TG. This may be

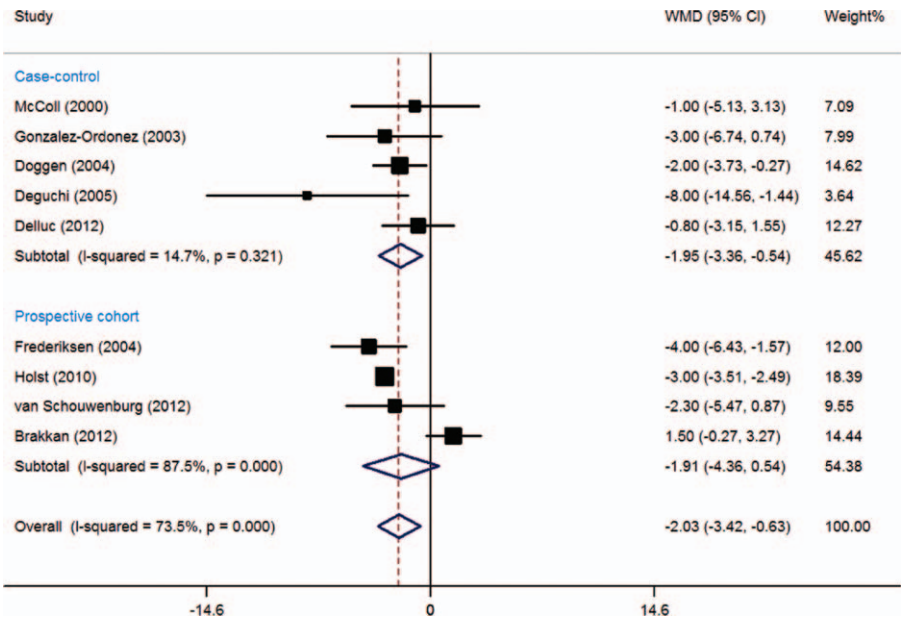

Figure 7. Meta-analysis of the effect of high-density lipoprotein cholesterol concentrations (mg/dL) on venous thromboembolism (based on 5 case-control and 4 cohort studies). Squares represent point estimates for effect size expressed as a WMD with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, WMD = weighted mean difference.

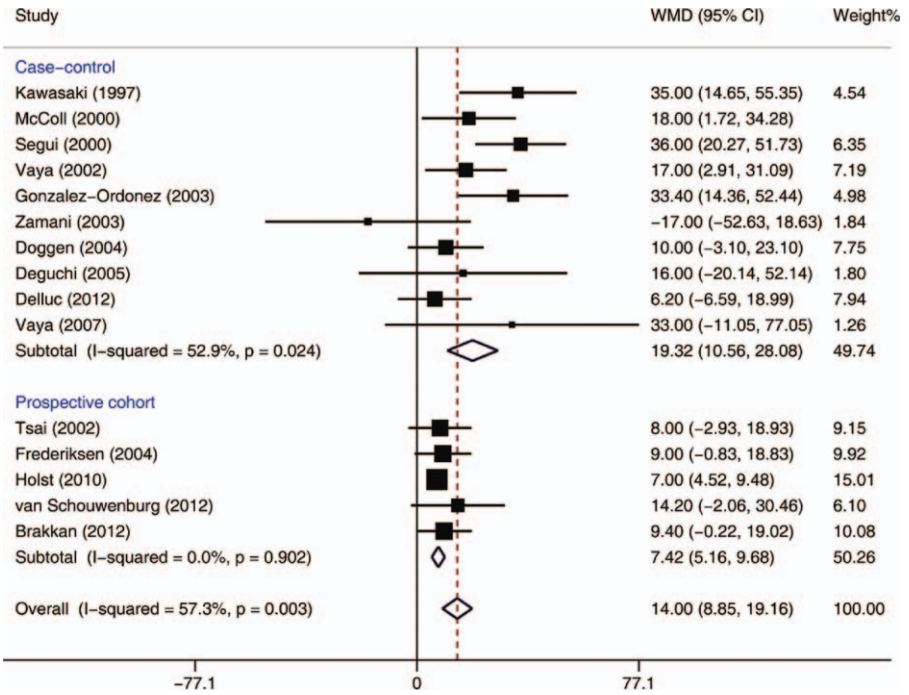

Figure 8. Meta-analysis of the effect of triglyceride concentrations (mg/dL) on venous thromboembolism (based on 10 case-control and 5 cohort studies). Squares represent point estimates for effect size expressed as a WMD with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, WMD = weighted mean difference.

attributable to failure to publish studies with negative result or to other variables such as race and geographical region. Funnel figures, which only determine whether a graph is symmetrical, cannot conclusively identify publication bias. The negative association between HDL-C and the prevalence of VTE in our study indicates that HDL-C may play a protective role in regulating thrombosis.

In the early days of research into this topic,[60] hypertension was identified as a risk factor for PE in the Nurses' Health Study; however, most more recent prospective studies have found no association between blood pressure and VTE.[11,20,38,49] In our study, 7 of the 13 articles providing data on hypertension reported a positive association between hypertension and VTE.[6,11,17,24,32,34,38] However, one reported a positive association in men,[34] only when combined with smoking and BMI ≥30 kg/m^2.[38] In addition, one of these studies involved subjects using oral contraception.[17] These findings suggest that patients with hypertension have a tendency to develop VTE when they also have other risk factors.

Daily smoking, regardless of duration and amount, was not found to be a risk factor in several studies,[11,41,49] However, other studies have identified heavy cigarette smoking as a risk factor for VTE.[20,36,39] In the current meta-analysis, smoking was positively correlated with VTE in 5 cohort[12,20,32,38,40] and 2 case-control studies[25,36] among the 14 studies in which smoking was assessed. Smoking is a well-established risk factor for atherosclerotic disease; however, its role as an independent risk factor or effect modifier for VTE remains controversial. Several prospective studies have reported that smoking is an independent risk factor.[38] One possible explanation for these discrepancies is that some studies have not provided sufficiently detailed information, such as current smoking versus previous smoking status and differences between heavier and lighter smokers. Current research suggests that the mechanisms by which smoking induces hypercoagulation may be associated with the reduced fibrinolysis, inflammation, and increased blood viscosity.[77–79] One study has shown a correlation between VTE and higher plasma fibrinogen and factor VIII concentrations among smokers,[80] and others have shown that fibrinogen concentration drops rapidly to a normal level after cessation of smoking.[81,82] Yarnell and other authors have detected a positive relationship between the amount of current tobacco consumption and plasminogen activator inhibitor-1 concentration, which may also be related to VTE.[70,83,84]

In contrast with a previous report,[14] we found in this meta-analysis that smoking and HDL-C were risk factors for VTE in case-control studies, whereas TC was a risk factor for VTE only in the cohort studies.

4.2. Clinical significance

Because VTE is associated with multiple interacting factors, to minimize their influences on each other we eliminated cases of VTE diagnosed on autopsy[55] and the subjects with definite provoking factors such as joint replacement.[85,86] Despite this, a mechanistic link between VTE and the risk factors for atherosclerosis remains uncertain. Based on the current findings, we speculate that both vascular disorders are simultaneously triggered by biological stimuli responsible for activating coagulation and inflammatory pathways in both the arterial and venous systems (VTE and atherothrombosis share common risk factors and the common pathophysiological characteristics of inflammation, hypercoagulability, and endothelial injury). Meanwhile, it is reasonable to assume that adequate management of the risk factors for atherosclerosis would reduce the risk of VTE. Studies have shown that statins may be protective against

VTE.[87,88] The obvious mechanism for such a protective effect is through improving lipid profiles; however, another possibility is that statins may directly affect endothelial function and coagulation.[89–91] Our findings are very important for informing further studies on the causes of VTE and new strategies for its primary prevention.

4.3. Study limitations

Our study has several potential limitations. First, we could not perform a sex-specific analysis because some variables were measured in only some of the studies and not in others for various reasons. Second, detailed information about VTE events was not always provided. Third, not all studies provided information on thrombophilia testing, making it difficult for us to distinguish the risk factors from hereditary thrombophilia. Fourth, several types of risk factors coexist in most cases, making it difficult to accurately analyze the influence of any one factor. Fifth, some of the summarized estimations for the association between the risk factor and VTE were highly heterogeneous ($I^2 > 70\%$) across the included studies, which may have affected the reliability of our results. Because it was not possible to adjust or stratify for potential confounders in the present meta-analysis, we could not resolve the heterogeneity by meta-regression. Lastly, the pooled ORs were calculated on study level and not individual level data, which means that ORs for meta-analyses were adjusted for different risk factors; we acknowledge that confounding may therefore have affected our findings.

5. Conclusions

This systematic review and meta-analysis showed significant associations between VTE and risk factors for atherosclerosis. Higher quality studies are needed in the future to clarify the nature of this association and whether VTE can be benefit from intensive treatment of established risk factors.

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