REVIEW

SMOKING AND RISK OF VENOUS THROMBOEMBOLISM: A SYSTEMATIC REVIEW

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Abstract. The relationship between smoking and venous thromboembolism (VTE) is unclear, as a result we conducted a meta-analysis to assess the association between smoking and VTE. A comprehensive search was conducted to identify studies evaluating the relationship between smoking and VTE. Two reviewers independently selected studies and extracted data. The data were analyzed using Comprehensive Meta-Analysis software, version 2. Twenty-one studies were included. Our findings show current smoking (RR 1.24; 95%CI: 1.14-1.35) and former smoking (RR 1.05; 95%CI: 1.01-1.10) were associated with increased VTE risk. There was a dose-response relationship between cigarettes smoked per day and VTE: 1-14 cigarettes/day: RR 1.20; 95%CI: 1.08-1.34, I^2=0%; 15-24 cigarettes/day: RR 1.33; 95%CI: 1.15-1.54, I^2=0%; >25 cigarettes/day: RR 1.63; 95%CI: 1.37-1.95, I^2=6%. Our findings show smoking is a risk factor for VTE with a dose-response relationship.

Keywords: smoking, venous thromboembolism, meta-analysis

INTRODUCTION

Venous thromboembolism (VTE) results in substantial healthcare costs, morbidity and mortality (Abboushi *et al*, 2012; Enga *et al*, 2012a,b). VTE, which includes deep venous thromboembolism (DVT) and pulmonary embolism (PE), is potentially preventable and the commonest cause of cardiovascular death and disability after coronary heart disease and stroke (Lowe, 2012; Parkin *et al*, 2012). Annually an estimated 2 million Americans develop VTE and 200,000 patients die from VTE. VTE contributes to more annual deaths than breast cancer, AIDS and traffic accidents combined (Parkin *et al*, 2012). The annual incidence of VTE is approximately 1-3 per 1,000 adults, and VTE is the third most common cardiovascular disease (Braekkan *et al*, 2010; Enga *et al*, 2012a,b). The cost per case of VTE is substantial (USD10,000 for DVT and USD20,000 for PE) (Abboushi *et al*, 2012). It is important to determine risk factors for VTE (Lowe, 2012).

Although many clinicians assume a connection between smoking and VTE, the association is unclear (Holst *et al*, 2010). Some studies have shown smoking as an independent risk factor for VTE (Goldhaber *et al*, 1997; Hansson *et al*, 1999), while others have failed to find any associations

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(Tsai *et al*, 2002; Glynn and Rosner, 2005; Pomp *et al*, 2008). A recent meta-analysis of 7 case-control studies and 3 cohort studies, evaluating the association between smoking and VTE, found that smoking was not a risk factor for VTE (Ageno *et al*, 2008). The meta-analysis did not stratify amount smoked or distinguish between current smoking and former smoking. This was also confirmed by a recent cohort study (Gronich *et al*, 2011), but two other cohort studies (Holst *et al*, 2010; Lutsey *et al*, 2010) did find smoking was a risk factor for VTE. We decided to conduct a meta-analysis to assess the association between smoking and VTE by stratifying amount smoked and distinguish between current smokers and former smokers.

MATERIALS AND METHODS

We conducted this systematic review of available literature in accordance with the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) (Stroup *et al*, 2000).

Search strategy

We searched PubMed, EMBASE, and ISI Web of Knowledge using (venous thrombosis OR venous thromboembolism OR vein thrombosis OR venous thromboses) AND (smoking OR tobacco OR cigarette). The study type was also considered by searching search for Cohort OR Case Control OR retrospective OR prospective. If possible, subject heading terms were added. Reference lists of meta-analyses, review articles and identified studies were hand-searched to find further relevant studies. All searches were conducted independently by two reviewers (Ge Zhang and Xin Xu) in February 2013 without language, date or publication status; differences were discussed between the two researchers.

Inclusion criteria and study selection

We identified all published case-control studies and cohort studies that evaluated the relationship between smoking (current smoking and former smoking) and VTE. When multiple articles for a single study were published, we used the most recent publication. Studies which did not specify smoking status (current smoking or former smoking) were excluded. Letters, comments, editorials, practice guidelines and studies published without the outcome measures of interest were excluded. Two reviewers (Ge Zhang and Wei Su) independently assessed potentially relevant citations for inclusion and disagreements were resolved by a third reviewer (Qiuping Xu).

Data abstraction

Using a standardized data extraction form, we collected the following baseline characteristics: lead author, publication year, age, sex, and sample size. Any disagreements in abstracting data were resolved by a third reviewer. Adjusted risk ratios were extracted in preference to non-adjusted ratios; however, when ratios were not provided, unadjusted odds ratios and confidence intervals were calculated. When more than one adjusted ratio was reported, the ratio with the highest number of adjusted variables was selected.

Data analysis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) software, version 2. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic. Associations were considered significant when $p<0.05$ or $I^2 > 50\%$. Data were pooled using the random-effects model. A dose-response analysis for 1-14 cigarettes/day, 15-24 cigarettes/day, and >25 cigarettes/day was

conducted to find the influence of amount smoked on VTE risk.

Publication bias was assessed by visually inspecting a funnel plot. The small-study effect of publication bias was estimated using the Egger's linear regression test.

RESULTS

Search results

After a comprehensive search, we found 1,168 studies. We excluded 251 duplicates and 714 studies based on their titles and abstracts. After screening the full texts, we excluded those not about smoking (*n*=41), VTE (*n*=58), cohort or case-control studies (*n*=83). Finally, 21 studies were included (Thorogood *et al*, 1992; Goldhaber *et al*, 1997; Hansson *et al*, 1999; Klatsky *et al*, 2000; Lidegaard *et al*, 2002; Tsai *et al*, 2002; Sidney *et al*, 2004; Glynn and Rosner, 2005; Worralurt and Taneepanichskul, 2005; Pomp *et al*, 2008; Lindqvist *et al*, 2009; Severinsen *et al*, 2009; Bhoopat *et al*, 2010; Holst *et al*, 2010; Quist-Paulsen *et al*, 2010; Yamada *et al*, 2010; Gronich *et al*, 2011; Bergendal *et al*, 2012; Enga *et al*, 2012b; Blondon *et al*, 2013; Sweetland *et al*, 2013) (Fig 1). Of these, 10 were case-control and 11 were cohort studies.

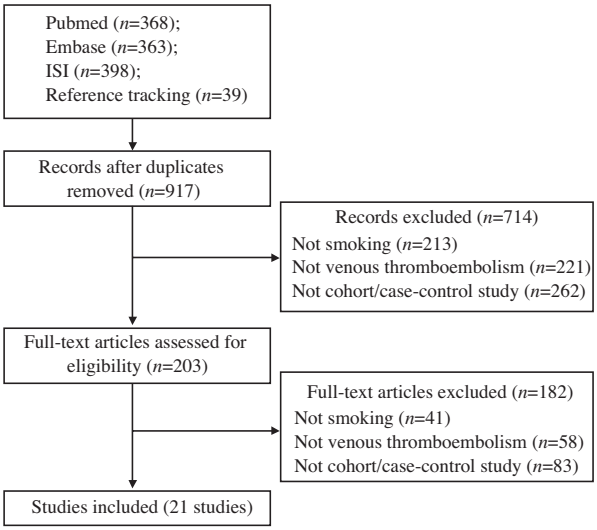

Fig 1–The flow chart.

Characteristics of included studies

Included studies were from the USA (*n*=6), Denmark (*n*=3), Sweden (*n*=3), Thailand (*n*=2), UK (*n*=2), Norway (*n*=2), Japan (*n*=1), the Netherlands (*n*=1) and Israel (*n*=1). The length of follow-up for cohort studies varied from 7 to 30 years. The total sample size of the case-control studies was 30,732 (cases: 10,351; controls: 20,381) and the total sample size of the cohort studies was 2,007,339 (the event size was 9,197) (Tables 1 and 2).

Results of meta-analysis

The pooled results showed being a current smoking (RR 1.24; 95%CI: 1.14-1.35; I^2=27%) (Fig 2) and a previous smoking (RR 1.05; 95%CI: 1.01-1.10; I^2=0%) (Fig 3) were associated with increased VTE risk.

Currently smoking 1-14 cigarettes/day (RR 1.25; 95%CI: 1.16-1.34; I^2=0%), 15-24 cigarettes/day (RR 1.33; 95%CI: 1.15-1.54; I^2=0%), and >25 cigarettes/day (RR 1.49; 95%CI: 1.27-1.74; I^2=39%) were associated with increased VTE risk (Fig 4). Meta-regression showed the coefficient (slope of the regression line) for different amounts smoked was statistically significant (slope 0.08; 95%CI: 0.00-0.17; *p*=0.04).

Publication bias

The funnel plot (Fig 5) was symmetrical meaning no significant publication bias. The Egger's test showed no evidence of publication bias (intercept -0.60; 95%CI: -1.61, 0.43, *p*=0.25).

DISCUSSION

The reviewed case-control studies had much weaker methodologies than the reviewed cohort studies, but they both

Table 1
Characteristic of included case-control studies.

Study	Study location	Definition of controls	Control selection	No. of patients (cases: controls)	Age (years)	Gender (males/females) Cases: Controls	VTE ascertainment	Confounders adjusted for
Bergendal *et al*, 2012	Sweden	No	Unclear	1,630:2,305	46.0/46.9	Female	Objectively confirmed	Age, BMI, smoking, use of hormones, exercise, surgery, cast, bedrest and carriership of the prothrombin gene mutation and/or factor V lei-den.
Bhoopat *et al*, 2010	Thailand	Yes	Healthy volunteers	97:195	17-93	29/68:59/136	Objectively confirmed	No.
Blondon *et al*, 2013	USA	Yes	Unclear	2,278/5,927	65.8:65.3	Female	Objectively confirmed	Age, hypertension, index year, race, diabetes, pregnancy, BMI, OC use or hormone therapy, education and occupation.
Lidegaard *et al*, 2002	Denmark	Unclear	Unclear	989:4,046	15-44	Female	Objectively confirmed	OC use, BMI, years of schooling.
Pomp *et al*, 2008	The Netherlands	Yes	Healthy volunteers	4,423:5,235	-	2,023/2,400:2,419/2,816	Medical records	Age, sex, BMI, and pregnancy.
Sidney *et al*, 2004	USA	Unclear	Unclear	196:746	-	Female	Objectively confirmed	OC use, age.
Thorogood *et al*, 1992	UK	Yes	Unclear	53:112	16-39	Female	Medical records	Unclear.
Worralurt *et al*, 2005	Thailand	Unclear	Healthy volunteers	70:140	-	Female	Objectively confirmed	Unclear.
Yamada *et al*, 2010	Japan	Unclear	Unclear	100:199	-	38/62:118/81	Objectively confirmed	Age and gender.
Quist-Paulsen *et al*, 2010	Norway	Unclear	Unclear	515:1,476	65.9:66.3	287/228:800/676	Objectively confirmed	Age and gender.

BMI, body mass index; OC, oral contraceptives.

Table 2
Characteristic of included cohort studies.

Study	Study location	Follow-up	No. of patients (Total number: event number)	Age (years)	Gender (male/female) cases: controls	VTE ascertainment	Confounders adjusted for
Enga *et al*, 2012b	Norway	12.5 years	25,788:389	45 ± 14	14,344/11,444	Objectively confirmed	Age, sex, BMI and higher education.
Goldhaber *et al*, 1997	USA	16 years	112,822:280	30-55	Female	Objectively confirmed	Age, oral contraceptive use, postmenopausal hormone use, BMI, diabetes, high blood pressure, high serum cholesterol, parity, and time period.
Glynn and Rosner, 2005	USA	20.1 years	22,071:358	40–84	Male	Objectively confirmed	Age.
Gronich *et al*, 2011	Israel	7 years	431,223:1,017	12–50	Female	Medical records	Unclear.
Hansson *et al*, 1999	Sweden	30 years	973:56:00	50	Male	Medical records	Waist circumference.
Holst *et al*, 2010	Denmark	19.5 years	17,985:969	51	8,356/9,629	Objectively confirmed	Gender, calendar time, and BMI.
Lindqvist *et al*, 2009	Sweden	7 years	29,518:312	25–64	Female	Medical records	Age.
Klatsky *et al*, 2000	USA	14.1 years	128,934:354	-	-	Objectively confirmed	Age, sex, race, BMI, marital status, education, smoking, alcohol, and coronary artery disease risk/symptoms composite.
Severinsen *et al*, 2009	Denmark	10.2 years	5,6014:617	51–64	26,674/29,340	Medical records	BMI, alcohol intake, recreational physical activity, and women's use of HRT.
Tsai *et al*, 2002	USA	7.8 years	19,293:215	59	8,660/10,633	Medical records	Age, race, and sex.
Sweetland *et al*, 2013	UK	6 years	1,162,718:4630	56	Female	Medical records	Region of recruitment, socioeconomic group, age, frequency of strenuous exercise, use of HRT, BMI, alcohol consumption, history of hypertension , and history of diabetes.

BMI, body mass index; HRT, hormone replacement therapy.

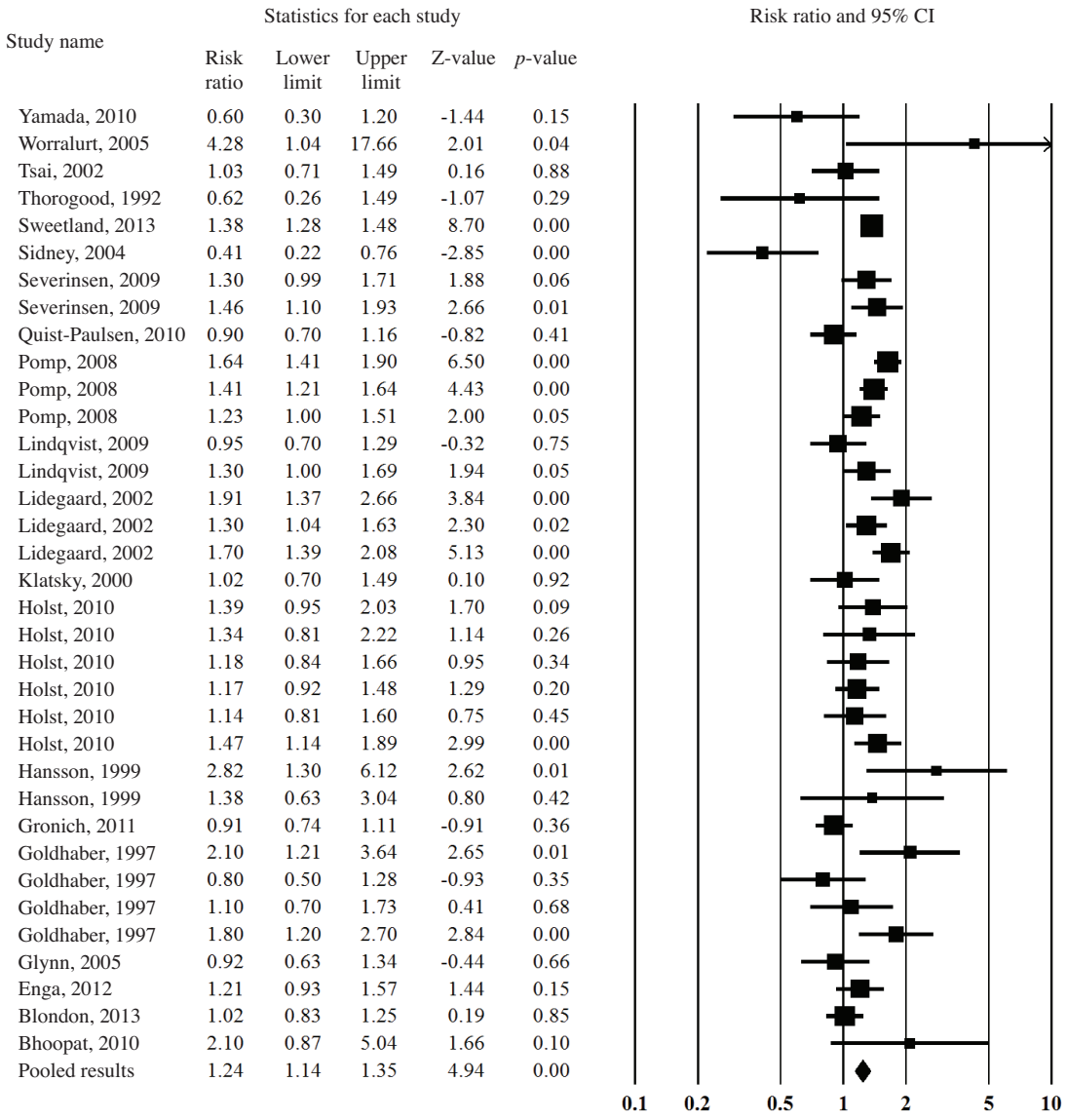

Fig 2–Subgroup analyses of the relationship between current smoking and VTE.

pointed to the same conclusion: smoking is a significant risk factor for VTE.

It has been reported that smoking increases the level of blood coagulation factors, such as plasma fibrinogen, which leads to the activation of the intrinsic coagulation pathway, such as impaired fibrinolysis and endothelial wall damage, and promotes activation of the inflammatory system (Miller *et al*, 1998; MacCallum and Meade, 1999; Lee and Lip, 2003; Fox and Kahn, 2005). Effective fibrinolysis requires rapid release of tissue plasminogen activator (tPA) from the vascular endothelium (Tapson, 2005). Studies have demonstrated the endothelium of cigarette smokers has an impaired capacity to release tPA acutely (Newby *et al*, 1999). Smoking causes en-

Study name	Risk ratio	Lower limit	Upper limit	Z-value	*p*-value
Tsai, 2002	1.02	0.75	1.39	0.12	0.90
Sweetland, 2013	1.08	1.01	1.16	2.18	0.03
Sidney, 2004	1.08	0.73	1.59	0.39	0.70
Severinsen, 2009	1.09	0.82	1.44	0.60	0.55
Severinsen, 2009	0.96	0.69	1.33	-0.24	0.81
Pomp, 2008	1.08	0.92	1.27	0.91	0.36
Pomp, 2008	1.22	1.03	1.45	2.28	0.02
Pomp, 2008	1.20	1.00	1.44	1.92	0.05
Lindqvist, 2009	1.12	0.90	1.40	1.01	0.31
Lidegaard, 2002	0.90	0.72	1.12	-0.95	0.34
Holst, 2010	0.94	0.67	1.32	-0.36	0.72
Holst, 2010	0.96	0.75	1.23	-0.32	0.75
Hansson, 1999	1.39	0.60	3.22	0.77	0.44
Goldhaber, 1997	0.90	0.70	1.16	-0.82	0.41
Glynn, 2005	0.92	0.73	1.15	-0.73	0.47
Enga, 2012	1.13	0.88	1.45	0.96	0.34
Blondon, 2013	0.95	0.83	1.08	-0.76	0.45
Pooled results	1.05	1.01	1.10	2.35	0.02

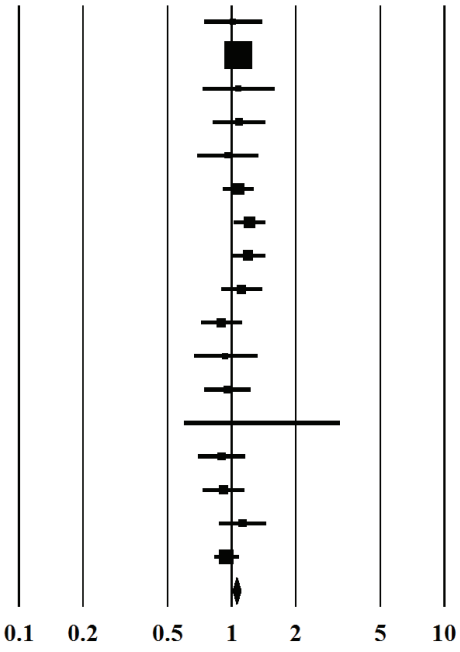

Fig 3–Subgroup analyses of the relationship between former smoking and VTE.

Group by dose	Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	Z-value	*p*-value
<15 cigarettes/d	Blondon, 2013	<10 cigarettes/d	1.18	0.78	1.79	0.78	0.44
<15 cigarettes/d	Lidegaard, 2002	1-10 cigarettes/day	1.30	1.04	1.63	2.30	0.02
<15 cigarettes/d	Goldhaber, 1997	1-14 cigarettes/d	0.80	0.50	1.28	-0.93	0.35
<15 cigarettes/d	Hansson, 1999	1-14 cigarettes/d	1.38	0.63	3.04	0.80	0.42
<15 cigarettes/d	Holst, 2010	1-14 cigarettes/day	1.17	0.92	1.48	1.29	0.20
<15 cigarettes/d	Holst, 2010	1-14 cigarettes/day	1.18	0.84	1.66	0.95	0.34
<15 cigarettes/d	Severinsen, 2009	<15 cigarettes/d	1.37	0.97	1.94	1.78	0.08
<15 cigarettes/d	Pomp, 2008	1-9 cigarettes/day	1.23	1.00	1.51	2.00	0.05
<15 cigarettes/d	Severinsen, 2009	<15 cigarettes/d	1.04	0.70	1.55	0.19	0.85
<15 cigarettes/d	Sweetland, 2013	<15 cigarettes/d	1.29	1.17	1.42	5.15	0.00
<15 cigarettes/d			1.25	1.16	1.34	6.18	0.00
>25 cigarettes/d	Severinsen, 2009	>35 cigarettes/d	1.85	1.10	3.11	2.33	0.02
>25 cigarettes/d	Goldhaber, 1997	25-34 cigarettes/d	1.80	1.20	2.70	2.84	0.00
>25 cigarettes/d	Severinsen, 2009	25-35 cigarettes/d	1.27	0.83	1.94	1.10	0.27
>25 cigarettes/d	Tsai, 2002	>25 cigarettes.d	1.05	0.74	1.48	0.28	0.78
>25 cigarettes/d	Holst, 2010	>25 cigarettes/day	1.34	0.81	2.22	1.14	0.26
>25 cigarettes/d	Holst, 2010	>25 cigarettes/day	1.39	0.95	2.03	1.70	0.09
>25 cigarettes/d	Goldhaber, 1997	>35 cigarettes/d	2.10	1.21	3.64	2.65	0.01
>25 cigarettes/d	Severinsen, 2009	>35 cigarettes/d	2.63	1.46	4.74	3.22	0.00
>25 cigarettes/d			1.49	1.27	1.74	4.99	0.00
15-25 cigarettes/d	Goldhaber, 1997	15-24 cigarettes/d	1.10	0.70	1.73	0.41	0.68
15-25 cigarettes/d	Holst, 2010	15-24 cigarettes/day	1.47	1.14	1.89	2.99	0.00
15-25 cigarettes/d	Holst, 2010	15-24 cigarettes/day	1.14	0.81	1.60	0.75	0.45
15-25 cigarettes/d	Severinsen, 2009	15-25 cigarettes/d	1.39	1.00	1.93	1.98	0.05
15-25 cigarettes/d	Severinsen, 2009	15-25 cigarettes/d	1.38	0.96	1.98	1.76	0.08
15-25 cigarettes/d			1.33	1.15	1.54	3.81	0.00

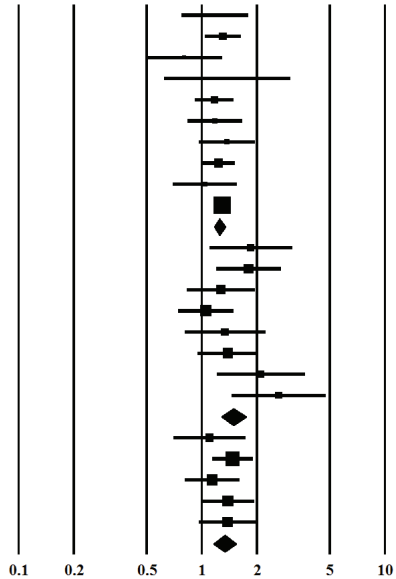

Fig 4–Dose-response analysis of current smoking.

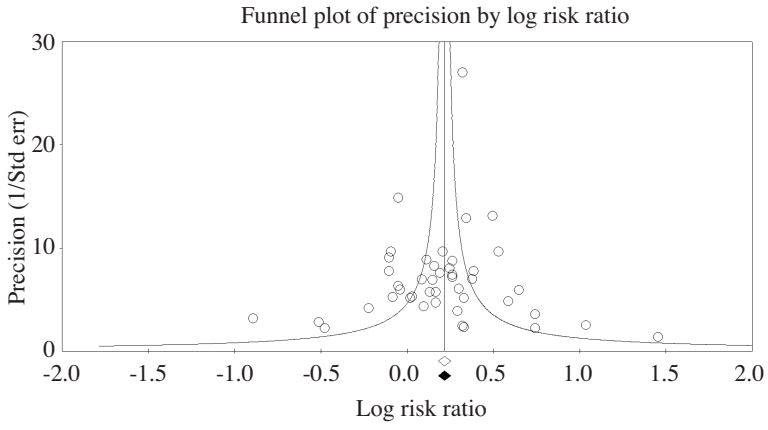

Fig 5–Publication bias.

dothelial dysfunction, which appears to impair local acute endogenous fibrinolytic activity and leads to ill effects on the venous side (Chia *et al*, 2002; Tapson, 2005; Ozaki *et al*, 2010).

Among the studies included in our meta-analysis, there were several classifications of cigarettes smoked. There were two units for measurement: pack-years and cigarettes/day. Four studies used pack-years (Tsai *et al*, 2002; Lindqvist *et al*, 2009; Bhoopat *et al*, 2010; Enga *et al*, 2012b) and the rest used cigarettes/day. Of the studies that used cigarettes/day, different cutoff levels of cigarettes smoked existed. Due to different cutoff levels of cigarettes smoked, there were difficulties in comparing the dose effect among the different studies and pooling the estimates using meta-analysis. However, we did find a dose-response relationship between current smoking and VTE risk based on pooled results, although some information may have been missed because of the complicated classification. An internationally accepted classification of current smoking would have been useful for analysis.

Our meta-analysis evaluated different smoking statuses (current and former smoking) and the different amounts smoked. Our meta-analysis had limitations. First, the methods of determining VTE varied among studies. Some studies (Thorogood *et al*, 1992; Hansson *et al*, 1999; Tsai *et al*, 2002; Pomp *et al*, 2008; Lindqvist *et al*, 2009; Severinsen *et al*, 2009; Lutsey *et al*, 2010; Tzankova *et al*, 2010; Gronich *et al*, 2011) used medical records to classify patients with VTE. Failure to define the incidence of VTE can lead to bias. In the future, when determining VTE incidence, the cases need to be confirmed. Second, the quality of case-control studies was not very good, especially for the selection and definition of controls. Only four studies (Thorogood *et al*, 1992; Pomp *et al*, 2008; Bhoopat *et al*, 2010; Blondon *et al*, 2013) mentioned the definitions of the controls, and only three studies (Worralurt and Taneepanichskul, 2005; Pomp *et al*, 2008; Bhoopat *et al*, 2010) described the nature of the controls (healthy volunteers). One of the most difficult parts of a case-control study is control selection. Hospital controls generally have worse health than community controls and may have a higher prevalence of smoking.

The etiologies of venous thromboembolism are important, but the best type of study to evaluate this is unclear (Lowe, 2012; Rosendaal, 2012). Case-control and cohort studies inevitably suffer from bias and unknown confounders. The conclusions of our meta-analysis should be confirmed with a randomized controlled trial (RCT) that evaluates the effects of smoking cessation interventions on the prevention of VTE.

In conclusion, smoking is a risk factor for VTE with a dose-response relationship. Smoking cessation should be encouraged to try to reduce the risk for VTE.

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