

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



LSHTM Research Online

Clayton, TC; Gaskin, M; Meade, TW; (2011) Recent respiratory infection and risk of venous thromboembolism: case-control study through a general practice database. *International journal of epidemiology*, 40 (3). pp. 819-27. ISSN 0300-5771 DOI: <https://doi.org/10.1093/ije/dyr012>

Downloaded from: <http://researchonline.lshtm.ac.uk/1348/>

DOI: <https://doi.org/10.1093/ije/dyr012>

**Usage Guidelines:**

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact [researchonline@lshtm.ac.uk](mailto:researchonline@lshtm.ac.uk).

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

# Recent respiratory infection and risk of venous thromboembolism: case–control study through a general practice database

Tim C Clayton,<sup>1\*</sup> Marion Gaskin<sup>2</sup> and Tom W Meade<sup>1</sup>

<sup>1</sup>Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK and <sup>2</sup>IMS Health, LifeLink Centre of Excellence, 7 Harewood Avenue, London, NW1 6JB, UK

\*Corresponding author. Faculty of Epidemiology and Population Health, Department of Medical Statistics, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK. E-mail: [tim.clayton@lshtm.ac.uk](mailto:tim.clayton@lshtm.ac.uk)

---

**Accepted** 14 December 2010

**Background** The association between respiratory infection and risk of heart attacks and strokes is well established. However, less evidence exists for an association between respiratory infection and venous thromboembolism (VTE). In this article, we describe the associations between respiratory infection and VTE.

**Methods** All cases aged  $\geq 18$  years of first-time diagnosis of deep-vein thrombosis (DVT) or pulmonary embolism (PE) were identified together with single-matched controls from a primary care general practice database. In addition to the matching characteristics, information was collected on other potentially important confounding factors.

**Results** There were 457/11 557 (4.0%) DVT cases with respiratory infection in the year before the index date (73 in the preceding month) compared with 262/11 557 (2.3%) controls (24 in the preceding month). There was an increased risk of DVT in the month following infection [adjusted odds ratio (OR) = 2.64, 95% confidence interval (95% CI) 1.62–4.29] which persisted up to a year. There were 180/5162 (3.5%) PE cases with respiratory infection in the year before the index date compared with 94/5162 (1.8%) controls excluding those in the preceding month to avoid the possible misdiagnosis of early PE. There was an increased risk of PE in the 3 months following infection (adjusted OR = 2.50, 95% CI 1.33–4.72) which may have persisted up to a year.

**Conclusions** There are strong associations between recent respiratory infection and VTE. There should be less distinction between venous and arterial events in decisions about preventing or aborting infections, especially in high-risk patients.

**Keywords** Deep-vein thrombosis, pulmonary embolism, respiratory tract infection, case–control studies, venous thromboembolism

---

## Introduction

Several large-scale epidemiological studies have consistently demonstrated associations between respiratory infection and the risk of myocardial infarction (MI) or stroke within the next month or so, the highest risk occurring within the first few days and then gradually declining until there is little or no risk at a month.<sup>1–5</sup> Since infection influences processes likely to lead to thrombosis, the association between respiratory infection and vascular events may be causal.<sup>6,7</sup>

However, there has until recently been little epidemiological work from large-scale, population-based studies on the association of infection with venous thromboembolism (VTE). In 2006, Smeeth *et al.*<sup>8</sup> reported on the risk of deep-vein thrombosis (DVT) and pulmonary embolism (PE) after acute infection, using the self-controlled case-series method, carried out through the UK's Health Improvement Network database. They pointed out that pleuritic symptoms early on could have been due to either respiratory infection or PE. However, the risk of DVT was increased up to 6 months following respiratory infection with an incidence ratio of 1.91 [95% confidence interval (95% CI) 1.49–2.44] in the first 2 weeks. The risks of both DVT and PE were also raised following urinary tract infection.

It is important to confirm or refute these findings in a different population and by a different method. Accordingly, we now report results on infection and VTE in the IMS Disease Analyser-Mediplus (IMS) database using a different design and analytical method and on hitherto less well-known risk factors for VTE.

## Methods

The IMS database is a primary care database used widely in epidemiological research, recording contacts of some 3.5 million patients with ~670 general practitioners (GPs). In order to be included in the database, GPs need to meet a minimum quality score based on a number of pre-specified criteria e.g. the percentage of registered patients with completed demographic information.

### Cases and controls

Using the READ coding system, cases of DVT or PE were selected from those in whom one or other was a first-time diagnosis.<sup>9,10</sup> In order to avoid the risk of retrospective recording of events in patients joining the practice only recently and to allow a sufficient period for exposures and other risk factors to have been recorded, patients had to be registered on the IMS database for at least 2 years prior to the date of diagnosis. If the patient was admitted to hospital as an emergency, a summary is sent to the GP shortly after the patient's discharge or death, which includes date of onset. In addition to the date of diagnosis,

there was a requirement for cases to have information on their year of birth, gender and practice, which were the matching criteria for selecting controls. The only restriction on the age of cases was that they needed to be aged  $\geq 18$  years at the date of the index event.

In order to match on calendar time (to allow for seasonal variation), all potential controls have been registered on the IMS database for at least 2 years on the day of the index DVT or PE of the case, and to have no previous recorded diagnosis of the corresponding outcome by that date. A single control for each case was selected at random from among all potential controls before the exposure status or history of other risk factors was known.

## Measurement of risk factors

The definition for respiratory infection was established based on the READ codes using terms which included reference to diagnoses and symptoms such as 'acute laryngitis', 'acute bronchitis', 'pneumonia' and 'productive cough'. In order to exclude mild respiratory infections, we did not include terms for minor symptoms. Based on this definition, data for the most recent GP visit for respiratory infection over the year preceding the index date were extracted. To ensure the correct order of the timing of infection and outcome, any episode of respiratory infection recorded on the same day as the index date was excluded. In addition, information on GP visits for urinary tract infection over the preceding year was extracted.

In order to adjust for possible confounding and to identify the most important contributors to the underlying risk of participants, details of other possible risk factors recorded prior to the index date were also collected. Pre-defined criteria also based on the READ coding system were used to identify any history of hypertension, hyperlipidaemia, diabetes, coronary heart disease among first-degree relatives, peripheral vascular disease, angina, MI, stroke and chronic obstructive pulmonary disease. Data on Factor V Leiden and prothrombin gene mutations were also collected but these were identified only in two individuals (both with Factor V Leiden) and so were not considered in the analysis. Pregnancy within the last 7 months, giving birth within the last 3 months, and cancer, major surgery and vaccinations against influenza and pneumococcal disease, each within the last year, were also recorded. In addition, smoking status, weight, height and body mass index (BMI) were taken from the most recent recorded entry on the database. Categorical risk factors that were not recorded for an individual while registered on the IMS database were assumed to be absent. Continuous measures, such as weight, which were not recorded were taken as missing.

## Statistical methods

All individuals meeting the eligibility criteria on the IMS database in the 15 years up to November 2006 were included in the analysis. It was anticipated that in excess of 10 000 newly recorded cases of DVT would be included. Smeeth demonstrated an impact of respiratory infection on DVT up to 26 weeks following infection, and our study was anticipated to provide excellent power to detect small associations even at low levels of respiratory infection during this period. Thus a study of 10 000 DVTs would have well in excess of 95% power (at 5% significance) to detect an odds ratio (OR) of 1.5 based on a prevalence of respiratory infection of 2% within the preceding 26 weeks among controls.

In all analyses, cases of DVT and their controls were analysed separately from cases of PE and their controls. In order to exclude the possible misdiagnosis of early PE as a respiratory infection, cases and controls with infections recorded within the month preceding the index date were excluded.

Conditional logistic regression was used to account for the matched design of the study. Therefore all ORs are adjusted for year of birth, gender, calendar time (and therefore seasonal variation) and practice, the last of which may to some extent allow for socio-economic status and other confounding factors. In addition, other recorded risk factors were included in the two multivariable models if they were strong independent predictors ( $P < 0.01$ ) of at least one of the outcomes.

The timing of any respiratory infection was considered in the following categories: 1–4, 5–12, 13–26 and 27–52 weeks prior to the index date. A further analysis looking 1–2 weeks prior to the index date was conducted to compare results with the previous Health Improvement Network study.<sup>8</sup> The unexposed group are those with no infection in the previous year. In order to consider the impact of the severity of infection on the outcome, additional analyses categorized respiratory infections as (i) pneumonia or (ii) other infections.

A limited number of pre-specified subgroup analyses were undertaken to explore whether any associations between respiratory infection and DVT or PE were consistent across all levels of prior underlying risk of these events or whether those at an already higher risk had no additional risk from infection. Recent infection was considered as 1–4 and 5–52 weeks before the index date for DVTs, and 5–52 weeks for PEs, in order to give reasonable numbers for testing interactions. Patients were categorized into three groups according to their underlying risk of DVT or PE. A patient's risk was determined from the coefficients of the logistic model of risk factors related to each outcome, but excluding respiratory infection. Patients were then divided into approximate thirds of risk so that each group contained a similar number of patients. For both DVT and PE, the lowest risk

group comprised those patients with no recorded risk factors, since this applied to 36% of individuals in the DVT study and 34% in the PE study. Separate ORs for the impact of respiratory infection on the outcome were calculated for each risk group. The presence of effect modification between respiratory infection and the three risk groups was assessed by a test of interaction. Since cases and controls were matched on age and gender, it was not possible to assess the independent associations of these factors on outcome and so these were not included in categorization above. However, the impacts of age and gender on the association between respiratory infection and outcome were assessed using interaction tests.

The study was approved by the Independent Scientific and Ethical Advisory Committee of the IMS Disease Analyzer Mediplus Database and the Ethics Committee of the London School of Hygiene & Tropical Medicine.

## Results

There were 11 557 cases on the IMS database with a first-time diagnosis of DVT who met the inclusion criteria, of whom 42% were men (mean age 62 years) and 58% women (mean age 63 years) (Table 1). There were 5162 cases with a first-time diagnosis of PE, of whom 42% were men (mean age 64 years) and 58% women (mean age 63 years). The recorded risk factors, both familiar and those less well established, were more prevalent among the cases for both DVTs and PEs compared with the controls (Table 1).

In total, there were 457 (4.0%) DVT cases with respiratory infection in the year before the index date [73 (0.6%) in the preceding month] compared with 262 (2.3%) controls [24 (0.2%) in the preceding month]. There was very strong evidence of an increased risk of a DVT in the weeks following infection, which reduced over time but was still apparent up to a year later (trend test across the different time periods considered,  $P < 0.0001$ ) (Table 2). After adjustment for other risk factors, the OR of DVT within 4 weeks of an infection was 2.64 (95% CI 1.62–4.29) with an OR between 26 weeks to 1 year of 1.53 (95% CI 1.17–1.99).

Of the 719 respiratory infections in the year before the index date, the majority could be categorized under productive cough ( $n = 398$ ), acute laryngitis/tracheitis ( $n = 174$ ), pneumonia/influenza ( $n = 102$ ) or acute bronchitis ( $n = 19$ ). For the DVT study, of the 97 infections in the first month, 28 were reported as pneumonia and 69 as other infections. There was evidence that more severe infection with pneumonia was associated with increased risk of subsequent DVT (adjusted OR = 10.55, 95% CI 2.46–45.34) although associations were also seen with less severe infection (OR = 1.86, 95% CI 1.08–3.20). Further, of the 622 infections at between 1 month and 1 year, 74 were reported as pneumonia and 548 as other infections. The ORs for both

**Table 1** Baseline characteristics of cases and controls

	DVT		PE	
	Cases ( <i>n</i> = 11 557)	Controls ( <i>n</i> = 11 557)	Cases ( <i>n</i> = 5162)	Controls ( <i>n</i> = 5162)
<b>Matching variables</b>				
<b>Gender, <i>n</i> (%)</b>				
Male	4867 (42.1)	4867 (42.1)	2146 (41.6)	2146 (41.6)
Female	6690 (57.9)	6690 (57.9)	3016 (58.4)	3016 (58.4)
<b>Age (years)</b>				
Mean (SD)	63 (17)	63 (17)	64 (17)	64 (17)
<40, <i>n</i> (%)	1441 (12.5)	1441 (12.5)	602 (11.7)	602 (11.7)
40–49, <i>n</i> (%)	1237 (10.7)	1237 (10.7)	503 (9.7)	503 (9.7)
50–59, <i>n</i> (%)	1745 (15.1)	1745 (15.1)	743 (14.4)	743 (14.4)
60–69, <i>n</i> (%)	2356 (20.4)	2356 (20.4)	1041 (20.2)	1041 (20.2)
70–79, <i>n</i> (%)	2733 (23.6)	2733 (23.6)	1314 (25.5)	1314 (25.5)
≥80, <i>n</i> (%)	2045 (17.7)	2045 (17.7)	959 (18.6)	959 (18.6)
<b>Index month, <i>n</i> (%)</b>				
December–February	3054 (26.4)	3054 (26.4)	1470 (28.5)	1470 (28.5)
March–May	2943 (25.5)	2943 (25.5)	1248 (24.2)	1248 (24.2)
June–August	2839 (24.6)	2839 (24.6)	1206 (23.4)	1206 (23.4)
September–November	2721 (23.5)	2721 (23.5)	1238 (24.0)	1238 (24.0)
<b>Other risk factors, <i>n</i> (%)</b>				
Hyperlipidaemia	668 (5.8)	590 (5.1)	304 (5.9)	227 (4.4)
Hypertension	2960 (25.6)	2545 (22.0)	1407 (27.3)	1189 (23.0)
Diabetes	906 (7.8)	591 (5.1)	350 (6.8)	274 (5.3)
Chronic obstructive pulmonary disease	467 (4.0)	267 (2.3)	256 (5.0)	121 (2.3)
Family history of coronary heart disease	1108 (9.6)	960 (8.3)	499 (9.7)	422 (8.2)
Angina	985 (8.5)	706 (6.1)	667 (12.9)	309 (6.0)
Peripheral vascular disease	292 (2.5)	162 (1.4)	107 (2.1)	70 (1.4)
<b>Smoking status</b>				
Never <sup>a</sup>	8228 (71.2)	8815 (76.3)	3588 (69.5)	3963 (76.8)
Ex-smoker	1677 (14.5)	1433 (12.4)	860 (16.7)	635 (12.3)
Current	1652 (14.3)	1309 (11.3)	714 (13.8)	564 (10.9)
Previous MI	331 (2.9)	234 (2.0)	294 (5.7)	107 (2.1)
Previous stroke	304 (2.6)	163 (1.4)	129 (2.5)	67 (1.3)
Pregnancy within past 7 months	246 (2.1)	69 (0.6)	103 (2.0)	18 (0.3)
Birth within past 3 months	133 (1.2)	20 (0.2)	104 (2.0)	8 (0.2)
Cancer within past year	1062 (9.2)	317 (2.7)	585 (11.3)	139 (2.7)
Major surgery within past year	2922 (25.3)	1355 (11.7)	1528 (29.6)	600 (11.6)
Influenza vaccination <sup>b</sup>	3469 (30.0)	2771 (24.0)	1645 (31.9)	1385 (26.8)
Pneumococcal vaccination	450 (3.9)	390 (3.4)	231 (4.5)	199 (3.9)
<b>Weight (kg)</b>				
Total	<i>n</i> = 7694	<i>n</i> = 6835	<i>n</i> = 3403	<i>n</i> = 3064
Mean (SD)	79.2 (19.6)	73.3 (16.5)	78.5 (18.9)	72.9 (16.2)

(continued)



Table 1 Continued

	DVT		PE	
	Cases ( <i>n</i> = 11 557)	Controls ( <i>n</i> = 11 557)	Cases ( <i>n</i> = 5162)	Controls ( <i>n</i> = 5162)
<b>Respiratory tract infection (weeks), <i>n</i> (%)</b>				
1–4 <sup>c</sup>	73 (0.6)	24 (0.2)	–	–
5–12	86 (0.7)	54 (0.5)	47 (0.9)	16 (0.3)
13–26	115 (1.0)	78 (0.7)	46 (0.9)	29 (0.6)
27–52	183 (1.6)	106 (0.9)	87 (1.7)	49 (0.9)
None in previous year	11 100	11 295	4982	5068
<b>Urinary tract infection (weeks), <i>n</i> (%)</b>				
1–4	13 (0.1)	11 (0.1)	6 (0.1)	5 (0.1)
5–12	29 (0.3)	14 (0.1)	9 (0.2)	15 (0.3)
13–26	35 (0.3)	27 (0.2)	19 (0.4)	14 (0.3)
27–52	69 (0.6)	49 (0.4)	28 (0.5)	20 (0.4)
None in previous year	11 411	11 456	5100	5108

<sup>a</sup>These numbers include 11 192 patients in the DVT dataset, and 4904 in the PE dataset with no definite smoking status recorded.

<sup>b</sup>There were 49.6% of DVT cases and 42.4% of controls aged  $\geq 70$  years with a recorded influenza vaccination. There were 49.6% of PE cases and 44.3% of controls aged  $\geq 70$  years with a recorded influenza vaccination.

<sup>c</sup>For DVT: 39 cases and 14 controls in Weeks 1 and 2, and 34 cases and 10 controls in Weeks 3 and 4.

pneumonia and other infections remained raised (adjusted OR = 1.95, 95% CI 1.13–3.36 and adjusted OR = 1.44, 95% CI 1.19–1.75, respectively).

Further adjustment was made using the most recent weight measurement. This was available for both cases and controls in 43% of the matched sets, whereas both height and BMI were available for cases and controls in <10% of the matched sets. As expected, weight was a risk factor for DVT (OR 1.26 per 10 kg increase, 95% CI 1.22–1.29) although this had little impact on the relationship between respiratory infection and DVT.

There was a suggestion that the association between recent infection and DVT might depend on underlying prior risk (interaction  $P = 0.010$ ) (Table 3). Whereas there was a short-term (i.e. up to 4 weeks) increased risk of DVT in all three risk strata, the longer-term risk of DVT (i.e. >4 weeks) seemed to decrease in those with a higher underlying prior risk but the OR remained >1. There was little evidence that the risk of DVT from respiratory infection depended upon age or gender (interaction  $P$ -values 0.12 and 0.84, respectively). As expected, cases and controls had clearly different underlying risks. Hence more controls than cases were in the low-risk group, whereas there were more cases than controls in the higher-risk group.

There were 180 (3.5%) PE cases with respiratory infection in the year before the index date (excluding the previous month) compared with 94 (1.8%) controls. There was a similar association of respiratory infection with PE as for DVT, with an increased risk of a PE following infection which decreased over time, but still with a suggestion that the risk was raised a year after infection (trend test across the

different time periods considered,  $P = 0.001$ ) (Table 2). After adjustment for other risk factors, the OR of PE between 5 and 12 weeks after an infection was 2.50 (95% CI 1.33–4.72), with an OR between 26 weeks to 1 year of 1.38 (95% CI 0.93–2.04).

For the PE study, of the 274 infections in the year preceding the index date, 46 were reported as pneumonia and 228 as other infections. Infection with pneumonia was associated with a higher OR of PE although associations were also seen with less severe infection (adjusted OR = 2.38, 95% CI 1.13–4.99 and OR = 1.44, 95% CI 1.06–1.97, respectively).

Risk of PE from respiratory infection did not depend upon underlying prior risk, age or gender (interaction  $P$ -values 0.50, 0.16 and 0.84, respectively).

As for DVT, there was a strong association between weight and risk of PE (OR = 1.23 per 10 kg increase, 95% CI 1.18–1.29) although adjustment for weight had no impact on the relationship between respiratory infection and PE.

Urinary tract infection was less common than respiratory infection and numbers were small. There was weak evidence of an association with subsequent DVT (trend test,  $P = 0.065$ ) and no evidence of increased risk of PE following urinary tract infection (trend test,  $P = 0.32$ ).

## Discussion

We omitted PE events occurring within the first month after the onset of a respiratory infection and therefore avoided most, if not all, the period during which the pleuritic symptoms of infection and PE

**Table 2** Multivariable predictors of DVT and PE<sup>a</sup>

Risk factor	DVT		PE	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Respiratory infection (weeks)				
1–4 <sup>b</sup>	2.64 (1.62–4.29)	<0.0001 <sup>c</sup>	–	0.001 <sup>c</sup>
5–12	1.56 (1.08–2.25)		2.50 (1.33–4.72)	
13–26	1.39 (1.02–1.90)		1.36 (0.80–2.31)	
26–52	1.53 (1.18–2.00)		1.38 (0.93–2.04)	
None in previous year	1		1	
Major surgery within past year	2.41 (2.23–2.61)	<0.0001	3.03 (2.69–3.42)	<0.0001
Cancer within past year	3.16 (2.75–3.63)	<0.0001	4.25 (3.42–5.28)	<0.0001
Influenza vaccination	1.35 (1.25–1.45)	<0.0001	1.15 (1.03–1.29)	0.016
Pregnancy within past 7 months	3.6 (2.50–4.78)	<0.0001	4.92 (2.66–9.10)	<0.0001
Smoking status				
Never	1	<0.0001	1	<0.0001
Ex-smoker	1.17 (1.08–1.28)		1.43 (1.24–1.64)	
Current smoker	1.32 (1.20–1.44)		1.46 (1.26–1.69)	
Birth within past 3 months	4.67 (2.74–7.96)	<0.0001	16.74 (6.92–40.51)	<0.0001
Previous stroke	1.83 (1.48–2.25)	<0.0001	1.82 (1.30–2.57)	0.001
Diabetes	1.40 (1.24–1.57)	<0.0001	1.06 (0.88–1.28)	0.55
Chronic obstructive pulmonary disease	1.53 (1.29–1.82)	<0.0001	1.99 (1.55–2.55)	<0.0001
Angina	1.21 (1.08–1.36)	0.001	1.97 (1.66–2.33)	<0.0001
Peripheral vascular disease	1.45 (1.17–1.79)	0.001	1.24 (0.88–1.76)	0.22
Hypertension	1.13 (1.05–1.21)	0.001	1.17 (1.04–1.31)	0.007
MI	1.12 (0.92–1.36)	0.26	2.16 (1.66–2.80)	<0.0001
Urinary tract infection (weeks)				
1–4	1.10 (0.47–2.58)	0.065 <sup>c</sup>	0.99 (0.27–3.59)	0.32 <sup>c</sup>
5–12	2.28 (1.14–4.59)		0.49 (0.20–1.22)	
13–26	1.09 (0.63–1.88)		0.93 (0.41–2.10)	
26–52	1.15 (0.78–1.70)		1.08 (0.56–2.08)	
None in previous year	1		1	

<sup>a</sup>ORs for binary variables are for presence vs absence of risk factor. Note model also adjusted for the matching factors of age, sex, GP practice and index date (seasonality).

ORs adjusted for matching factors only: DVT 3.08, 1.61, 1.52 and 1.80 in the four time periods; PE 3.00, 1.66 and 1.82 in the three time periods.

<sup>b</sup>For DVT: Weeks 1 and 2 OR=2.26 (95% CI 1.19–4.31), Weeks 3 and 4 OR=3.19 (95% CI 1.51–6.73).

<sup>c</sup>Trend test across groups.

might be confused with each other. Thus we conclude that there probably is an increased risk following infection for PE as well as for DVT and that this may be related to the severity of the infection. Our results for VTE following urinary infections are inconclusive, mainly because of the relatively small number of urinary infections occurring.

One previous study based on 494 medical outpatients, compared with the same number of controls who had already had an infection selected from other patient groups, showed only a strong association between 'infectious disease' and DVT ( $P=0.001$ )

although the results are difficult to interpret.<sup>11</sup> Another study was a secondary analysis among 866 acutely ill and immobilized hospitalized patients taken from a randomized controlled trial of low molecular weight heparin for the prevention of VTE.<sup>12</sup> However, there has only been one other sufficiently large community-based epidemiological study, which used the Health Improvement Network general practice database, drawing patients and controls from the same defined population.<sup>8</sup> Ours has used a different general practice database and a different analytical method with the advantage that we have been able

**Table 3** Effect of respiratory infection within the preceding month on DVT and PE according to approximate third of risk<sup>a</sup>

Third of risk	Infections in period prior to index date	DVT			PE <sup>b</sup>		
		Cases (%)	Controls (%)	OR <sup>c</sup> (95% CI)	Cases (%)	Controls (%)	OR <sup>c</sup> (95% CI)
First (no risk factors)	1–4 weeks	11 (0.4)	9 (0.2)	2.06 (0.83–5.17)	–	–	–
	5–52 weeks	81 (2.7)	63 (1.2)	2.28 (1.60–3.25)	23 (2.0)	27 (1.2)	1.54 (0.85–2.78)
	Total patients	3053	5230		1179	2289	
Second	1–4 weeks	20 (0.6)	7 (0.2)	2.62 (1.07–6.40)	–	–	–
	5–52 weeks	104 (3.0)	81 (2.2)	1.45 (1.07–1.98)	47 (3.0)	40 (2.1)	1.40 (0.89–2.21)
	Total patients	3483	3657		1554	1876	
Third	1–4 weeks	42 (0.8)	8 (0.3)	2.76 (1.28–5.98)	–	–	–
	5–52 weeks	199 (4.0)	94 (3.5)	1.13 (0.87–1.47)	110 (4.5)	27 (2.7)	1.80 (1.13–2.86)
	Total patients	5021	2670		2429	997	

<sup>a</sup>Based on the models in Table 2 but excluding respiratory infection and factors unrelated to outcome: note the lowest third contains all patients with no risk factor present. A patient will be in the middle or highest third depending on which risk factors are present and also how many. For example, in the DVT study, patients with chronic obstructive pulmonary disease alone or diabetes alone would both be in the middle third of risk because of the strength of the coefficients whereas any individual with major surgery within the past year would be in the top third of risk because the coefficient for surgery was high.

<sup>b</sup>Respiratory infections within the month preceding the PE excluded.

<sup>c</sup>Interaction between infection and risk group: (i) DVT,  $P=0.010$ , (ii) PE,  $P=0.50$ .

to consider the effects of possibly less familiar risk factors for VTE as well as those that are well recognized.

One concern with case–control studies is that of residual confounding where confounders have not been accounted for adequately. However, our results are largely consistent with the Smeeth study which used the case–series method, thus virtually eliminating the possibility of residual confounding.<sup>8</sup> Further, our study matched on age, gender, seasonality and GP practice, all potentially important confounders of the association between respiratory infection and VTE. Other important predictors of VTE were also adjusted for in the analyses. Thus, residual confounding may not be an important factor in interpreting our results. There was a gradient of decreasing risk of VTE with increasing time after infection, and we consider it unlikely that further adjustment would explain this relationship. Smeeth summarized plausible mechanisms whereby infection might increase risk of arterial or venous clinical events, including increased thrombotic tendency, strengthening the case for at least considering causality, although some caution should be exercised as causality is only one possible explanation of the associations.

Consideration also needs to be given to the possible role of intermediate factors in the association between infection and VTE although these are unlikely to explain the strong associations seen. In particular, although we were not able to collect reliable information on physical activity following infection, we think the majority of individuals would not reduce their physical activity to the extent detailed in the NICE guidelines.<sup>13</sup> The exception might be following

pneumonia and influenza but these only account for ~15% of the infections and it is unlikely that reduced activity would account for the associations seen up to a year. In addition, our analyses show strong associations up to a year of infections other than pneumonia and influenza with VTE.

A further concern relates to the definition of respiratory infection used. We recognize mild infection is unlikely to be associated with VTE and have been careful to include terms which exclude minor symptoms of infection. Indeed our analyses indicate that the associations are associated with severity of symptoms. The number of infections reported is lower than expected and supports our view that we have captured the more severe infections. However, if less severe infections have been included this is likely to dilute any effect and underestimate the associations.

A link of infection with DVT for up to a year was observed in our study, substantially longer than for the association between respiratory infection and arterial events. This continued association (up to 26 weeks) was also observed in the Smeeth study.<sup>8</sup> One explanation for this time period might be that some respiratory infections trigger minor but entirely subclinical VTE, which build up and result in a major episode much later on. This pattern of high early risk of VTE following exposure to a risk factor which remains raised up to a year has also been seen in women after surgery from a very large, prospective cohort study.<sup>14</sup>

Not all cases and controls had information available on all risk factors, but the expected associations between these and DVT or PE support the general quality of the risk factor data. We were also able to assess



whether any increased risk operated at all levels of prior underlying risk. For DVT, the data suggest raised ORs associated with respiratory infection at all levels of risk particularly in the month following the infection. The results also suggest an increased risk of PE following infection irrespective of the underlying risk, although numbers are lower.

Our results, based on large numbers, contribute to clarifying risk factors for VTE, findings on some of which have hitherto been inconsistent. The associations for weight, recent surgery or cancer, pregnancy and parturition were all as expected, suggesting that the data on risk factors are reliable even if they are not recorded for all those concerned. We found potentially important associations with both DVT and PE of two other risk factors over which there have previously been uncertainties, i.e. for current smoking and hypertension. Most of the manifestations of arterial disease recorded in our study on heart attacks were also associated with VTE, especially previous stroke and also angina and peripheral vascular disease.<sup>4</sup> MI was not associated with DVT, but there was a strong association with PE.

Pomp *et al.*<sup>15</sup> have reported strong associations between current and former smoking with VTE: for example OR 1.43 (95% CI 1.28–1.60) for current smoking. There was also a graded risk according to daily cigarette consumption, OR 1.23 (95% CI 1.00–1.50) for 1–9 cigarettes a day and OR 1.64 (1.41–1.90) for  $\geq 20$  cigarettes a day. The number of pack-years was also strongly associated with risk of VTE. Thus, it seems possible that smoking is related to VTE. However, Ageno *et al.*<sup>16</sup> found no association for smoking, nor did Rosengren *et al.*<sup>17</sup> in a study primarily concerned with psychosocial factors, although they reported a strong association with treated hypertension (OR 1.95, 95% CI 1.37–2.80). Ageno also reported an increased risk associated with hypertension. Sorensen *et al.*<sup>18</sup> have recently reported that for patients with DVT, the relative risks for MI and stroke in the first year subsequently were 1.60 (95% CI 1.35–1.91) and 2.19 (95% CI 1.85–2.60), respectively. Uncertainty exists as to the benefits of

influenza immunization for reducing cardiovascular events.<sup>5</sup>

In summary, there are more similarities in the epidemiology of VTE and arterial disease than have previously been recognized. Thus, it may be inappropriate to distinguish rigidly between venous and arterial events when considering the possible risks of an exposure such as respiratory infection and monitoring patients for these events. It is by no means standard practice in the UK that patients with an acute respiratory infection should receive anti-thrombotic prophylaxis, but the possibility that they might benefit is one of the important questions raised by our study, which can only be settled by a randomized controlled trial. Planning any prophylactic measures should probably be considered in terms of thrombotic events as a whole rather than for arterial and venous events separately.

## Funding

British Heart Foundation (grant number PG/04/089/17456).

## Acknowledgements

The authors are very grateful for support by the British Heart Foundation who had no role in the study design, in the collection, analysis and interpretation of the data, in the writing of the report or in the decision to submit the paper for publication. The authors are also very grateful to Nicholas Counsell for extracting the relevant data from the IMS database ready for the statistical analysis.

**Conflict of interest:** Prof. Tom Meade has been a member of the IMS Health Independent Scientific and Ethical Advisory Committee (ISEAC) for several years for which he is paid on a sessional basis. Marion Gaskin is the UK Team Leader of the LifeLink Centre of Excellence at IMS Health.

### KEY MESSAGES

- There is little previous epidemiological evidence on the association of respiratory infection with VTE.
- This study shows clear associations of respiratory infection with both DVT and PE for up to a year following respiratory infection.
- Respiratory infection increases the risk of DVT within the next month and PE up to a year at all levels of prior underlying risk.
- As well as more familiar risk factors such as obesity, the study also suggests that cigarette smoking and hypertension are associated with VTE.
- Following respiratory infection, the risk of venous and arterial events should be considered jointly rather than in separate categories, and prophylactic measures should be planned accordingly.

## References

- <sup>1</sup> Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *Lancet* 1998;**351**:1467–71.
- <sup>2</sup> Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;**351**:2611–18.
- <sup>3</sup> Clayton TC, Capps NE, Stephens NG, Wedzicha JA, Meade TW. Recent respiratory infection and the risk of myocardial infarction. *Heart* 2005;**91**:1601–2.
- <sup>4</sup> Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. *Eur Heart J* 2008;**29**:96–103.
- <sup>5</sup> Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis* 2009;**9**:601–10.
- <sup>6</sup> Subauste MC, Jacoby DB, Richards SM, Proud D. Infection of a human respiratory epithelial cell line with rhinovirus. Induction of cytokine release and modulation of susceptibility to infection by cytokine exposure. *J Clin Invest* 1995;**96**:549–57.
- <sup>7</sup> Wedzicha JA, Seemungal TA, MacCallum PK *et al*. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000;**84**:210–15.
- <sup>8</sup> Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet* 2006;**367**:1075–79.
- <sup>9</sup> Chisholm J. The Read clinical classification. *BMJ* 1990;**300**:1092.
- <sup>10</sup> NHS Connecting for Health. <http://www.connectingforhealth.nhs.uk/systemsandservices/data/uktc/readcodes> (27 January 2011, date last accessed).
- <sup>11</sup> Samama MM. An epidemiological study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch Intern Med* 2000;**160**:3415–20.
- <sup>12</sup> Alikan R, Cohen AT, Combe S *et al*. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. *Arch Intern Med* 2004;**164**:963–68.
- <sup>13</sup> NICE. *Venous Thromboembolism – Reducing the Risk: Quick Reference Guide*. <http://guidance.nice.org.uk/CG92/QuickRefGuide/pdf/English> (27 January 2011, date last accessed).
- <sup>14</sup> Sweetland S, Green J, Liu B *et al*. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *BMJ* 2009;**339**:4583–90.
- <sup>15</sup> Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. *Am J Hematol* 2008;**83**:97–102.
- <sup>16</sup> Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation* 2008;**117**:93–102.
- <sup>17</sup> Rosengren A, Freden M, Hansson PO, Wilhelmsen L, Wedel H, Eriksson H. Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. *J Thromb Haemost* 2008;**6**:558–64.
- <sup>18</sup> Sorensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet* 2007;**370**:1773–79.