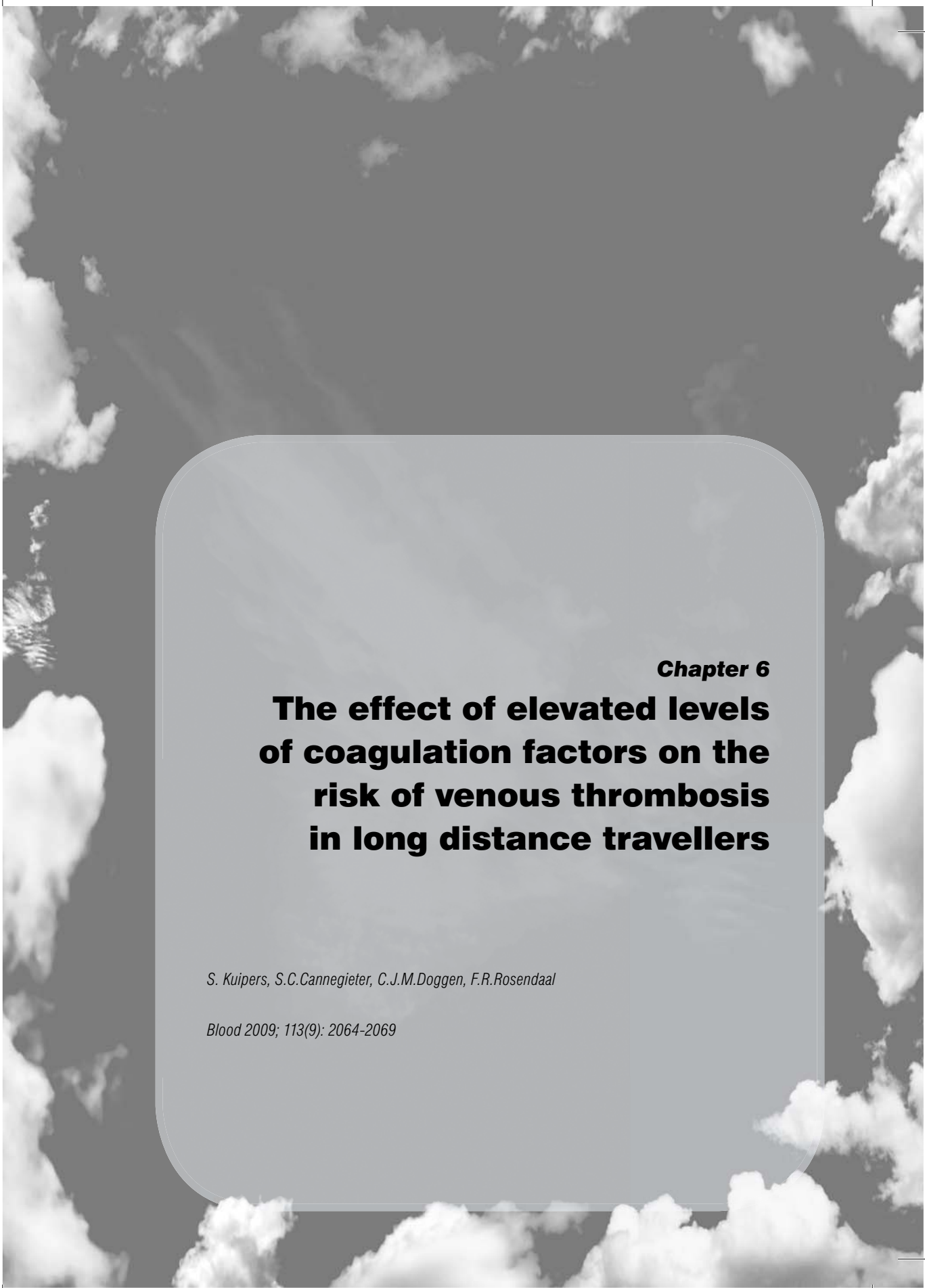
Air travel and venous thrombosis : results of the WRIGHT study : Part I: Epidemiology

Kuipers, S.



Chapter 6

The effect of elevated levels of coagulation factors on the risk of venous thrombosis in long distance travellers

S. Kuipers, S.C.Cannegieter, C.J.M.Doggen, F.R.Rosendaal

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Abstract

The risk of venous thrombosis is increased after long distance travel. Identifying high-risk groups may provide a basis for targeted prevention. We assessed the effect of increased levels of coagulation factors and combinations of risk factors on the risk of venous thrombosis in travellers in a large case-control study.

We calculated odds ratios for 334 travellers (200 cases and 134 controls) with coagulation factors II (prothrombin, FII), VII (FVII), VIII (FVIII) and IX (FIX), fibrinogen and vWF above the 80th percentile, for increasing numbers of risk factors and for specific combinations of risk factors. The risk was increased in travellers with a high FII (OR 2.2, CI95 1.3-3.7) and FVIII (OR 6.2, CI95 3.6-10.5) as compared to travellers with normal levels. High FIX and fibrinogen levels increased the risk in air travellers (OR FIX 3.2, CI95 0.9-11.0; OR fibrinogen 2.0, CI95 0.7-5.5), but not in other travellers. The odds ratios increased with the number of risk factors and the risk was increased the most in women with the combination of oral contraceptives and high FVIII levels (OR 51.7, CI95 5.4-498).

From this case-control study in travellers, we conclude that increased levels of factors II and VIII increase the risk of venous thrombosis. Furthermore, the risk is greatly increased if other risk factors are present as well.

Introduction

Several studies have shown an association between long distance travel and the risk of venous thrombosis. Most case-control[1-6] and follow up studies showed a 2-4 fold increased risk[7-9]. A dose-response relationship between the distance travelled and the incidence of venous thrombosis has been demonstrated in three studies[10-12] and the overall risk of venous thrombosis after air travel has been found to be 1 per 4500 flights in a frequently travelling population[12].

Even though the risk of venous thrombosis is increased after long distance travel, it is not sufficiently elevated to justify the use of prophylaxis in all long distance travellers, since most prophylactic measures, such as anticoagulant therapy, are potentially harmful[13]. Only in individuals at particularly increased risk the risk-benefit ratio may favour the use of such prophylactic measures. However, knowledge on who is most at risk among long distance travellers is limited. As a result, the use of prophylactic measures varies widel [14]. Previous reports showed excess risks for travellers carrying the factor V Leiden mutation (FVL) or the prothrombin mutation (PT20210A), women using oral contraceptives and travellers who are obese or particularly tall or short[5,6,12]. The joint effect of long distance travel, either by air or by other modes of transport, and elevated levels of pro-coagulant factors has not been previously investigated

The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study is a large population-based case-control study aimed at assessing the combined effect of genetic and environmental risk factors for venous thrombosis. The aim of the current analysis was to assess the effect of elevated levels of coagulation factors and combinations with other known risk factors (FVL mutation, prothrombin mutation, increased body mass index, oral contraceptive use and a positive family history of venous thrombosis) on the risk of venous thrombosis in long distance travellers, both by air and by other means of transport.

Materials and methods

Patients and control subjects

The MEGA study is a population-based case-control study on genetic and environmental risk factors for venous thrombosis. Cases were consecutive patients with a first episode of deep vein thrombosis or pulmonary embolism recruited at six anticoagulant clinics in the Netherlands. Patients who were unable to complete a questionnaire (due to language or severe psychiatric problems)

and patients who died soon after the diagnosis were not included, nor were patients without a partner. Partners of patients were invited as control subjects. Patients and their control subjects were recruited between March 1st 1999 and August 31st 2004. Details have been described previously [6]. From these patients and control subjects, we selected individuals who had travelled by air, bus, train or car in the 8 weeks prior to the index-date (date of the thrombotic event for each case-control pair). Each patient or control had made at least one journey of at least 4 hours. We used 4 hours and 8 weeks as cut off values for travel, because previous studies have found that the risk of venous thrombosis is increased in the first 8 weeks after journeys longer than 4 hours[12].

Questionnaire

All participants were asked to fill in a questionnaire, which contained questions regarding long distance travel by air, train, bus or car in the 8 weeks prior to the index date as well as questions on other (possible) risk factors for venous thrombosis, such as height, weight and oral contraceptive use. These questionnaires were sent to eligible patients and their partners shortly after the index date.

Laboratory assays

Approximately three months after discontinuation of oral anticoagulant therapy, patients and their partners were invited for collection of a blood sample. In patients who were still on anticoagulant therapy one year after their event, blood was drawn during anticoagulant therapy. All assays were performed in an automated machine by laboratory technicians who were unaware of the case-control status of the samples. Plasma samples were available for 200 out of 233 cases and 134 out of 181 control subjects. The remaining patients and control subjects either refused or were unable to visit the research centre for a blood draw.

Prothrombin activity (FII), Factor VII activity (FVII) and Factor VIII activity (FVIII) were measured with a mechanical clot detection method on a STA-R coagulation analyzer following the instructions of the manufacturer (Diagnostica Stago, Asnieres, France). Levels of factor IX antigen (FIX) were determined by enzyme-linked immunosorbent assay (ELISA). Fibrinogen activity was measured on the Sta-R analyzer according to methods of Clauss. In the presence of excess thrombin, the coagulation time of a diluted plasma sample was measured. Von Willebrand factor antigen (vWF) was measured with the immuno-turbidimetric method, using the STA liatest kit (rabbit anti-human vWF antibodies), following the instructions of the manufacturer.

Statistical analysis

The overall relative risk of travel in this study population has been previously described and was 2.1 (CI95 1.5-3.0)[6]. In the current analysis, we assessed the effect of elevated levels and activity of coagulation factors among travellers, as well as the effect of several combinations of risk factors. Hence, all relative risks are to be superimposed on the risk of travel itself when a comparison to non-travellers is made.

Odds ratios were adjusted for age and sex for elevated levels of all coagulation factors and their 95% confidence levels using logistic regression. Cut-off points were antigen or activity levels at the 80th and 90th percentile in the control population. Individuals who were using anticoagulant therapy at the time of blood collection were excluded from the analysis of the effect of vitamin K dependent coagulation factors (FII, FVII and FIX). Odds ratios were calculated separately for individuals who had travelled by air and those who had travelled by other means of transport.

In an effort to identify those at particularly high risk, we calculated risks for combinations of risk factors and determined the number of coagulation abnormalities present in each individual. Both high levels of coagulation factors that increased the risk of venous thrombosis in our population and well established prothrombotic risk factors[15-17] were taken into account, i.e. FII, FVIII, FVL mutation and the prothrombin mutation (PT20210A mutation). Odds ratios were calculated for the presence of 1 and 2 or more prothrombotic factors, with travellers in whom all of these factors were absent as the reference category. The same analysis was performed including also environmental risk factors. For this analysis, only risk factors that have previously been described in the literature and that were sufficiently prevalent in our population to allow such analyses were considered[6;18-20]. These were a high body mass index (BMI in the third tertile as compared to the first, i.e. higher than 26.9 kg/m^2 as compared to lower than 23.7 kg/m^2), oral contraceptive use and a positive family history for venous thrombosis (at least one thrombotic event in a parent, brother or sister).

For all analyses, one could discuss whether a conditional ('matched') analysis would be necessary, since partners of patients were used as a control population. As they were usually of the opposite sex, and generally in a similar age range, the controls were not a random sample of the population. Generally, whether or not this is relevant depends on the exposure in question. The exposure of interest here was the effect of coagulation abnormalities on travel-related thrombosis in addition to the actual travel itself. There is no reason to assume that high levels of clotting factors are more common among partners of patients than in the general population and an unconditional analysis suffices.

Therefore we performed unconditional analyses and adjusted for the potential confounders age and sex.

For all statistical analyses we used SPSS version 12.0 (SPSS, Chicago, Ill, United States).

Results

Patients and control subjects

Of the 1906 consecutive patients with venous thrombosis, 233 had travelled by air, bus, train or car in the 8 weeks prior to their thrombotic event. Of the 1906 control subjects, 182 had travelled before the index date. Plasma was available in 200 out of 233 patients (86%) and 134 of 182 control subjects (72%). Table 1 shows the general characteristics of cases and controls.

Table 1: General characteristics of patients with venous thrombosis and control subjects who travelled by air and those who travelled by other modes of transportation.

Characteristic		Air travellers		Other travellers	
		Cases (76)	Controls (52)	Cases (124)	Controls (82)
Age (yr)	Mean (range)	46.9 (22-65)	48.5 (23-68)	48.0 (21-69)	50.2 (21-68)
Sex	Men, n (%)	32 (42.1)	35 (67.3)	66 (53.2)	48 (58.5)
	Women, n(%)	44 (57.9)	17 (32.7)	58 (46.8)	34 (41.5)
BMI (kg/m^2)*	Mean (range)	26.5 (19-38)	25.7 (20-37)	27.2 (20-45)	25.6 (18-40)
OC use*	N (%**)	23 (88.5)	2 (40)	29 (82.9)	7 (43.8)
Malignancy	N (%)	0	1 (1.9)	2 (1.6)	2 (2.4)

* *BMI = body mass index, OC = oral contraceptives*

** *Percentage of pre-menopausal women.*

Coagulation factors

Mean FII, FVII, FVIII, FIX, fibrinogen and vWF levels are shown in table 2, as well as their cut-off levels for the 80th and 90th percentile in the control population. Odds ratios in travellers for elevated levels of these coagulation factors for both cut-off levels are shown in table 3. This table also shows the odds ratios separately for air travellers and other travellers, with the 80th percentile as cut-off level, all compared to travellers with normal levels.

Table 2: Levels and activity of coagulation factors in patients with venous thrombosis and control subjects and cut-off values for the 80th and 90th percentile in control subjects.

Coagulation factor	Mean (range) Cases	Mean (range) Controls	P80 Controls	P90 Controls
FII activity*, IU/ml	112 (65-150)	108 (75-150)	117	127
FVII activity, IU/ml	113 (58-250)	110 (47-170)	132	149
FVIII activity, IU/dl	140 (61-263)	106 (37-193)	130	144
FIX, IU/dl	106 (63-159)	105 (66-163)	118	128
Fibrinogen activity, g/l	3.3 (2.0-6.2)	3.2 (2.0-4.6)	3.6	3.9
vWF, g/l	147 (67-567)	109 (21-273)	134	154

* *Cases and controls that were using anticoagulant therapy at the time of the blood draw were excluded for calculation of means of vitamin-K dependent coagulation factors.*

High FII levels increased the risk of venous thrombosis among travellers. The odds ratio was similar for cut-off levels at the 80th (OR 2.2, CI95 1.3-3.7) and 90th percentile (OR 1.7, CI95 0.9-3.4). This association was somewhat stronger in air travellers (OR 3.0, CI95 1.2-7.7) than in other travellers (OR 1.9, CI95 1.0-3.7). Adjustment for presence of the PT20210A mutation did not affect our results. High FVII levels did not show an association with venous thrombosis in travellers, neither when we used the 80th percentile (OR 1.1, CI95 0.7-2.0) nor the 90th percentile (OR 0.6, CI95 0.3-1.3).

High levels of FVIII had the most pronounced effect on the risk of venous thrombosis among travellers. The odds ratio was 6.2 (CI95 3.6-10.5) when the 80th percentile was used and 7.5 (CI95 3.9-14.5) when the 90th percentile was used as cut-off level. After adjustment for vWF levels, the risk was attenuated but remained increased (OR 4.1, CI95 2.2-7.6 for FVIII above the 80th percentile). Neither FIX nor fibrinogen levels increased the risk of venous thrombosis when the 80th percentile was used. Using the 90th percentile, the odds ratio was 1.5 (CI95 0.7-3.2) for high levels of FIX and 1.5 (CI95 0.8-3.1) for high fibrinogen levels. FIX levels above the 80th percentile increased the risk of venous thrombosis in air travellers (OR 3.2, CI95 0.9-11.0), but not in other travellers (OR 0.9, CI95 0.5-1.7). For fibrinogen concentrations above the 80th percentile, we again found an effect in air travellers only (2.0 (CI95 0.7-5.5) vs 1.1 (CI95 0.6-2.0)).

Elevated levels of vWF increased the risk of venous thrombosis (OR 4.6, CI95 2.7-7.7) for all travellers, with no major differences between air travellers and other travellers. However, the effect disappeared after adjusting for FVIII.

Adjustment for oral contraceptive use did not affect any of the odds ratios mentioned above. We also calculated odds ratios separately for pulmonary embolism and deep vein thrombosis of the leg. There were no major differences between these 2 groups, although most odds ratios were slightly higher in the DVT group than in the PE group.

To assess whether duration of travel affected our results, we also calculated odds ratios including only individuals who had made at least 1 journey longer than 8 hours in the 8 weeks prior to the event or index-date. Again, this did not affect any of the results.

Table 3: Odds ratios for venous thrombosis for elevated coagulation factors in 334 travellers.

Coagulation Factor	P80[$] OR* (CI95)	P90[$$] OR* (CI95)	P80air** OR* (CI95)	P80other** OR* (CI95)
FII	2.2 (1.3-3.7)	1.7 (0.9-3.4)	3.0 (1.2-7.7)	1.9 (1.0-3.7)
FVII	1.1 (0.7-2.0)	0.6 (0.3-1.3)	1.3 (0.5-3.3)	1.2 (0.6-2.3)
FVIII	6.2 (3.6-10.5)	7.5 (3.9-14.5)	5.4 (2.3-13.0)	6.9 (3.4-13.8)
FIX	1.2 (0.7-2.1)	1.5 (0.7-3.2)	3.2 (0.9-11.0)	0.9 (0.5-1.7)
Fibrinogen	1.3 (0.8-2.2)	1.5 (0.8-3.1)	2.0 (0.7-5.5)	1.1 (0.6-2.0)
vWF	4.6 (2.7-7.7)	5.0 (2.6-9.3)	4.1 (1.7-9.9)	4.9 (2.5-9.5)

* *Odds ratios are adjusted for age and sex*

** *Air= Odds ratios for individuals who had travelled by air. Other= Odds ratios for individuals who had travelled by bus, train or car*

$: Odds ratios elevated levels of all coagulation factors with the P80 in the control population used as cut off levels (cut off levels are mentioned in Table 1)

$$: Odds ratio for elevated levels of all coagulation factors using the P90 in the control population as cut off levels (again, cut off levels are mentioned in Table 1)

Combinations of risk factors

Odds ratios for the number of coagulation abnormalities present per individual (FII, FVIII, FVL mutation and prothrombin mutation) are shown in Table 4. When one abnormality was present, the odds ratio was 4.3 (CI95 2.6-7.2) as compared to travellers in whom all factors were normal. This increased to an odds ratio of 10.0 (CI95 4.7-217) when 2 or more clotting abnormalities were present. The increase in odds ratios was more pronounced in air travellers than in other travellers.

Table 4: Odds ratios for venous thrombosis (adjusted for age and sex) for total number of risk factors present per individual.

	Cases n	Control n	All OR (CI95)	Air travellers OR (CI95)	Other travellers OR (CI95)
Number of laboratory risk factors*					
0	45	82	1#	1#	1#
1	99	42	4.3 (2.6-7.2)	3.1 (1.4-7.1)	5.4 (2.7-10.8)
≥ 2	56	10	10.0 (4.7-21.7)	36.4 (4.4-298)	7.3 (3.0-17.6)
Total number of risk factors**					
0	12	48	1#	1#	1#
1	54	48	4.4 (2.1-9.2)	2.9 (0.9-9.6)	5.8 (2.2-15.4)
2	54	28	7.4 (3.4-16.3)	7.5 (2.2-25.9)	8.0 (2.9-22.4)
3	60	7	32.1 (11.7-88.2)	-	22.9 (7.2-73.3)
4-7	20	3	23.9 (6.0-95.0)	-	16.8 (3.7-77.1)

* *High (>P80) FII, FVIII, FVL mutation and/or prothrombin mutation*

** *Any of the prothrombotic factors mentioned above, as well as oral contraceptives, positive family history (at least 1 thrombotic event in a parent, brother or sister) and BMI (3rd tertile as compared to 1st). The cut off values for tertiles of BMI were 23.7 and 26.9.*

\# *Reference category, travelling individuals in whom all coagulation factors are normal and in whom the clinical factors were absent*

The odds ratio also increased with the total number of risk factors (coagulation abnormalities and environmental risk factors combined) present per subject. When only one out of 7 possible risk factors (FII, FVIII, FVL mutation, prothrombin mutation, a high BMI, oral contraceptive use and a positive family history) was present, the odds ratio was 4.4 (CI95 2.1-9.2) as compared to travellers with none.

This increased to 23.9 (CI95 6.0-95.0) when a traveller had 4 or more risk factors. The risk again increased slightly more in air travellers than in other travellers.

Odds ratios for all combinations of risk factors are shown in Table 5. The risk was high for most combinations with FVL. Individuals with FVL combined with high FII had an odds ratio of 17.5 (CI95 2.3-135), combined with FVIII it was 24.7 (CI95 4.4-139) and combined with a high BMI it was 20.5 (CI95 2.5-170).

Women using oral contraceptives who also had FVL had an odds ratio of 18.3 (CI95 2.0-171). Having a positive family history did not add to the risk of FVL alone (OR 4.7, CI95 1.7-16.5). Women using oral contraceptives with a high FVIII had an odds ratio of 51.7 (CI95 5.4-498) and in those with a high body mass index the risk was 31.4 fold increased (CI95 3.0-334) as compared to women who did not use oral contraceptives with a low body mass index. In women using oral contraceptives, having a positive family history doubled the risk (OR of the combination 10.7, CI95 1.5-75.6). The number of cases and control subjects with specific combinations was too small to calculate odds ratios for air travellers and travellers by other means of transport separately.

Table 5 Odds ratios for venous thrombosis for combinations of risk factors.

	FII	FVIII	FVL*	OC*	BMI*	Fam**
FII	2.2 (1.3-3.7)					
FVIII	7.9 (3.4-18.3)	6.2 (3.6-10.5)				
FVL	17.5 (2.3-135)	24.7 (4.4-139)	4.5 (1.9-10.4)			
OC	4.6 (1.1-19.8)	51.7 (5.4-498)	18.3 (2.0-171)	5.0 (2.1-12.1)		
BMI	9.5 (3.6-25.1)	18.6 (7.0-49.9)	20.5 (2.5-170)	31.4 (3.0-334)	1.9 (1.4-2.7)	
Fam**	2.4 (0.9-6.1)	8.7 (3.5-21.7)	4.7 (1.7-16.5)	10.7 (1.5-75.6)	2.4 (1.0-5.8)	1.7 (1.0-2.9)

* *FVL = factor V Leiden mutation, OC= Oral Contraceptive use, BMI= body mass index > 26.9 kg/m^2 as compared to a BMI of <23.7 kg/m^2 . For each combination, the odds ratio for presence of both risk factors compared to absence of both factors is presented. In the boxes where the risk factor in the column is the same as in the row, the odds ratio for presence of only that risk factor is given. Fam: a positive family history, meaning at least one thrombotic event in a brother, sister or parent*

Discussion

In this case-control study amongst 334 long distance travellers, we demonstrated an increased risk of venous thrombosis in individuals with high levels of coagulation factors II and VIII. The relative risk increased with the number of coagulation abnormalities (factor II, VIII, prothrombin mutation and factor V Leiden mutation) and with the overall number of risk factors present per individual (coagulation factors, high body mass index, a positive family history and oral contraceptive use). The relative risk was highest in female travellers using oral contraceptives who also had high levels of FVIII (odds ratio 51.7, CI95 5.4-498). Combinations with the factor V Leiden mutation were associated with a particularly high relative risk as well. All these effects were superimposed on the relative risk of travel itself, which is about two in this population[6].

Previous studies have also demonstrated a synergistic effect between long distance travel and other risk factors for venous thrombosis. Individuals with obesity, thrombophilia (factor V Leiden or the prothrombin 20210A mutation) and women taking oral contraceptives were shown to have an additionally increased risk when they travelled long distances [5,6]. The effect of increased levels of coagulation factors and of combinations of other risk factors for venous thrombosis has not been studied in a travelling population before. In the general population, FVIII levels higher than 150% are associated with an approximately 5-fold increased risk of venous thrombosis [16,17] and high FII increases the risk approximately two-fold [18]. We observed similar odds ratios in our travelling population. However, levels of fibrinogen and FIX are also known to increase the risk of venous thrombosis [16,19] in the general population, while in our travelling population these factors were only associated with a mildly increased risk in individuals who travelled by air.

For most coagulation abnormalities and their joint effect with environmental risk factors we observed a more pronounced excess risk for travellers by air than for travellers by other modes of transport. This may be explained either by a difference in baseline thrombosis-risk or by a different underlying mechanism (air travel compared to other modes of transport). In general, individuals who travel by air may have a lower baseline risk, because they have less other risk factors for venous thrombosis, such as malignant disease or severe obesity. This would lead to higher relative risks in those who travel by air, when the absolute excess risk due to an increased coagulation factor is equal for both modes of travel. However, when the baseline risk is similar in all travellers, a higher odds ratio for high levels of coagulation factors after air travel than after travel by other means, would indicate a different underlying pathophysiology. In our population, there were no major differences in baseline characteristics between those who travelled by air and those who travelled by other modes of transportation (Table 1). This indicates that the mechanism of venous thrombosis related to air travel may be different from that related to other modes of travel. In a previous study, coagulation parameters were measured both after air travel and after immobilisation only. Only after air travel, hypercoagulability was observed in a small subgroup of the participants, indicating that not only immobilisation plays a role in the pathogenesis of air-travel related venous thrombosis[20]. However, the numbers in our study were too small to draw solid conclusions regarding the difference between thrombosis after air-travel and that after travel by other means.

A limitation of this study is that the blood sample was collected after the

thrombotic event. Therefore, we cannot exclude the possibility that differences in plasma levels of the coagulation factors between cases and control subjects were the result of the thrombotic event itself. However, the blood draw was performed at least 3 months after the thrombotic event and it is unlikely that the thrombotic event itself caused persistent abnormalities in coagulation factor levels. Furthermore, in a previous case-control study, no differences in coagulation factors were observed between patients in whom blood was drawn shortly after their thrombotic event as compared to those in whom the blood draw took place much later, sometimes even years after their diagnosis[16,19]. Anticoagulant therapy did not affect our results, since individuals who were still on anticoagulant therapy were excluded from analyses in which vitamin-K dependent coagulation factors were involved.

Another limitation is that we did not have plasma samples available of 14% of the cases and 26% of the control subjects. The reason for unavailability of a plasma sample may have been different in cases and control subjects. In cases, a reason for not visiting the research unit for a blood draw may have been severe illness, whereas in control subjects lack of motivation to visit the research centre for a blood draw may have been a reason for unavailability of a plasma sample. Cases who did not show up for a blood draw had more often suffered from pulmonary embolism than those in whom plasma was available, indicating that the former may have been more disabled after the thrombotic event. This would only have led to an underestimation of the effect of increased coagulation levels if pulmonary embolism is associated with higher levels of coagulation factors than other thrombotic events, which is unlikely. Only few studies have investigated this and the results are contradictory [21,22]. Furthermore, as we analyzed data in long distance travellers only, we do not expect that severe illness, such as advanced cancer, was a cause of unavailability of a plasma sample, as long distance travel requires some degree of healthiness.

One of the reasons for performing this study was to find out whether risk groups can be identified that could be specifically targeted for prevention. We therefore questioned whether the risk of venous thrombosis in individuals with any of the risk factors we studied would be high enough for cost-effective screening in all travellers. The absolute risk of venous thrombosis is estimated as 1 in 4500 flights of more than 4 hours [12]. This is the risk in the general travelling population, including individuals with and without the risk factors that could be screened for. The prevalence of increased FII, FVIII or FIX is 20% (as we used the 80th percentile in the control population as cut-off level), that of the FVL mutation is approximately 5% and of the prothrombin mutation 2% [23,24]. The

proportion of individuals with at least one of these risk factors in the general population is therefore 0.52 (1-0.8*0.8*0.8*0.95*0.98). In our study, the odds ratio for travellers with one or more of these risk factors, as compared to those with none, was 4.7. When 4500 travellers make a flight longer than 4 hours, one develops VT. Of these 4500 travellers, 2355 (52%) have at least one of the risk factors. Of the cases, 83.6% has at least one risk factor (cases are 4.7*52/48 times more likely to have at least one risk factor than to have none). If a 'positive test' would lead to treatment with for example low molecular weight heparin (LMWH), which can prevent approximately 70% of the cases [25], 57.5% of the cases (70% of 82%) would be prevented. So to prevent one case of venous thrombosis, 7826 travellers need to be screened (4500 travellers to prevent 0.575 thrombosis), of whom 4096 (52% of 7826) would have to be treated with LMWH. The risk of a major haemorrhage for the use of LMWH is approximately 0.4% over a 14-day period [26], which is 0.09% per 3 days (assuming that each traveller would take LMWH for 3 days per journey). These numbers are derived from studies including only acutely ill patients. The bleeding risk in healthy travellers is probably much lower. If we would assume that the bleeding risk in healthy travellers is approximately 1/4th of that in acutely ill patients, 3 days of anticoagulation therapy would lead to 1 serious bleeding complication per 4667 travellers, meaning that prevention of 1 thrombotic event would cause almost 1 serious bleeding complication. This strategy can therefore not be recommended, being costly and with an unfavourable risk-benefit ratio. However, if screening and subsequent treatment with LMWH would be restricted to for example women using oral contraceptives, prevention of one event would require screening of 534 travellers using oral contraceptives, of whom 255 would have to be treated. Targeted screening and prophylaxis may therefore be justifiable. Similarly, it may be considered to treat everyone with a substantially increased relative risk without screening, such as women with the combination of a high BMI and oral contraceptive use. These issues need to be further explored in a randomized controlled trial.

From this case-control study, we conclude that high levels of FII and FVIII increase the risk of venous thrombosis in travellers and that the risk is further increased with the number of risk factors present per individual, as well as in travellers with specific combinations of risk factors. The effect of the risk factors we studied is not strong enough to promote screening and subsequent potentially harmful prophylaxis in all long distance travellers. However, targeted screening and prophylaxis may be justifiable.

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