# Effect of elevated levels of coagulation factors on the risk of venous thrombosis in long-distance travelers

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**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 in travelers in a large case-control study. We calculated odds ratios (ORs) for 334 travelers (200 cases and 134 controls) with coagulation factors II (prothrombin), VII, VIII, and IX; fibrinogen, and von Willebrand factor (VWF) above the 80th percentile; for increasing numbers of risk factors; and for specific combinations. The risk was increased in travelers with high FII (OR, 2.2: 95% CI, 1.3-3.7) and FVIII (OR, 6.2, (95% CI, 3.6-10.5) compared with travelers with normal levels. High FIX and fibrinogen levels increased the risk in air travelers (FIX: OR, 3.2; 95% CI, 0.9-11.0; fibrinogen: OR, 2.0; 95% CI, 0.7-5.5) but not in other travelers. The ORs increased with the number of risk factors, and the risk was increased most in women with the combination of oral contraceptives and high FVIII (OR, 51.7; 95% CI, 5.4-498). We conclude that increased levels of FII and FVIII increase the risk of venous thrombosis in travelers. Furthermore, the risk is greatly increased if other risk factors are present as well. (Blood. 2009;113: 2064-2069)**

## 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- to 4-fold increased risk.[7-9] A dose-response relation between the distance traveled and the incidence of venous thrombosis was shown in 3 studies,[10-12] and the overall risk of venous thrombosis after air travel was found to be 1 per 4500 flights in a frequently traveling 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 travelers, because most prophylactic measures, such as anticoagulant therapy, are potentially harmful.[13] The risk-benefit ratio may favor the use of such prophylactic measures only in persons at particularly increased risk. However, knowledge on who is most at risk among long-distance travelers is limited. As a result, the use of prophylactic measures varies widely.[14] Previous reports showed excess risks for travelers carrying the factor V Leiden (FVL) mutation or the prothrombin mutation (PT20210A), women using oral contraceptives, and travelers 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 coagulation factors and combinations with other known risk factors (FVL mutation, prothrombin mutation, increased body mass index [BMI; in kg/m$^2$], and oral contraceptive use) on the risk of venous thrombosis in long-distance travelers, both by air and by other means of transport.

## Methods

### Patients and control subjects

The MEGA study is a population-based case-control study on genetic and environmental risk factors for venous thrombosis. The study protocol was approved by the Ethics Committee of the Leiden University Medical Center. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Cases were consecutive patients with a first episode of deep vein thrombosis or pulmonary embolism recruited at 6 anticoagulant clinics in The Netherlands. Patients who were unable to complete a questionnaire (because of 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 1, 1999, and August 31, 2004. Details were described previously.[6] From these patients and control subjects, we selected persons who had traveled by air, bus, train, or car in the 8 weeks before the index date (date of the thrombotic event for each case-control pair). Each patient or control had made at least 1 journey of at least 4 hours. We used 4 hours and 8 weeks as cutoff 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 complete a questionnaire, which contained questions about long-distance travel by air, train, bus, or car in the 8 weeks

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

| | Air travelers | | Other travelers | |
|---|---|---|---|---|
| **Characteristic** | **Cases (76)** | **Controls (52)** | **Cases (124)** | **Controls (82)** |
| Mean age, y (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) |
| Mean BMI (kg/m$^2$; 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 indicates body mass index; and OC, oral contraceptives.
*Percentage of premenopausal women.

before 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 3 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 1 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 of 233 cases and 134 of 181 control subjects. The remaining patients and control subjects either refused or were unable to visit the research center for a blood draw.

Prothrombin activity (factor II [FII]), factor VII (FVII) activity, and factor VIII (FVIII) activity 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.[15] In the presence of excess thrombin, the coagulation time of a diluted plasma sample was measured. von Willebrand factor (VWF) antigen was measured with the immunoturbidimetric method, using the STA Liatest kit (rabbit anti–human VWF antibodies), following the instructions of the manufacturer (Diagnostica Stago).

### Statistical analysis

The overall relative risk of travel in this study population was previously described and was 2.1 (95% CI, 1.5-3.0).[6] In the current analysis, we assessed the effect of elevated levels and activity of coagulation factors among travelers, 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 nontravelers is made.

Odds ratios (ORs) were adjusted for age and sex for elevated levels of all coagulation factors and their 95% confidence levels (95% CIs) with the use of logistic regression. Cutoff points were antigen or activity levels at the 80th and 90th percentiles in the control population. Persons 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 persons who had traveled by air and persons who had traveled by other means of transport.

In an effort to identify persons at particularly high risk, we calculated risks for combinations of risk factors and determined the number of coagulation abnormalities present in each person. Both high levels of coagulation factors that increased the risk of venous thrombosis in our population and well-established prothrombotic risk factors[16-18] were taken into account, ie, FII, FVIII, FVL mutation, and the prothrombin mutation (PT20210A). Odds ratios were calculated for the presence of 1 and 2 or more prothrombotic factors, with travelers 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.[6,19-21] These were a high BMI in the third tertile compared with the first, ie, higher than 26.9 compared with lower than 23.7), oral contraceptive use, and a positive family history for venous thrombosis (at least 1 thrombotic event in a parent, brother, or sister). We did not use BMI cut off values that define obesity ($> 30$), because there were insufficient participants with a BMI higher than 30 (13 controls and 36 cases) to allow such analysis.

For all analyses, one could discuss whether a conditional ("matched") analysis would be necessary, because partners of patients were used as a control population. Because they were obviously of the opposite sex and generally in a similar age range, the controls were not a random sample of the population. Generally, whether 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 confounder's age and sex.

For all statistical analyses we used SPSS version 12.0 (SPSS, Chicago, IL).

## Results

### Patients and control subjects

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

### Coagulation factors

Mean FII, FVII, FVIII, FIX, fibrinogen, and VWF levels are shown in Table 2, as well as their cutoff levels for the 80th and 90th percentiles in the control population. Odds ratios in travelers for elevated levels of these coagulation factors for both cutoff levels are shown in Table 3. This table also shows the ORs separately for air travelers and other travelers, with the 80th percentile as cutoff level, all compared with travelers with normal levels.

High FII levels increased the risk of venous thrombosis among travelers. The odds ratio was similar for cutoff levels at the 80th (OR, 2.2; 95% CI, 1.3-3.7) and 90th (OR, 1.7; 95% CI, 0.9-3.4) percentiles. This association was somewhat stronger in air travelers (OR, 3.0; 95% CI, 1.2-7.7) than in other travelers (OR, 1.9; 95% CI, 1.0-3.7). Adjustment for the presence of the PT20210A mutation did not affect our results.

**Table 2. Levels and activity of coagulation factors in patients with venous thrombosis and control subjects and cutoff values for the 80th and 90th percentile in control subjects**

| Coagulation factor | Cases, mean (range) | Controls, mean (range) | 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 FVII levels did not show an association with venous thrombosis in travelers, neither when we used the 80th percentile (OR, 1.1; 95% CI, 0.7-2.0) or the 90th percentile (OR, 0.6; 95% CI, 0.3-1.3).

High levels of FVIII had the most pronounced effect on the risk of venous thrombosis among travelers. The odds ratio was 6.2 (95% CI, 3.6-10.5) when the 80th percentile was used and 7.5 (95% CI, 3.9-14.5) when the 90th percentile was used as the cutoff level. After adjustment for VWF levels, the risk was attenuated but remained increased (OR, 4.1;95% CI, 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. With the use of the 90th percentile, the odds ratio was 1.5 (95% CI, 0.7-3.2) for high levels of FIX and 1.5 (95% CI, 0.8-3.1) for high fibrinogen levels. FIX levels above the 80th percentile increased the risk of venous thrombosis in air travelers (OR, 3.2; 95% CI, 0.9-11.0) but not in other travelers (OR, 0.9; 95% CI, 0.5-1.7). For fibrinogen concentrations above the 80th percentile, we again found an effect in air travelers only (2.0; 95% CI, 0.7-5.5 compared with 1.1; 95% CI, 0.6-2.0).

Elevated levels of VWF increased the risk of venous thrombosis (OR, 4.6; 95% CI, 2.7-7.7) for all travelers, with no major differences between air travelers and other travelers. 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. No major differences were observed between these 2 groups, although most odds ratios were slightly higher in the group with deep vein thrombosis than in the group with pulmonary embolism.

To assess whether duration of travel affected our results, we also calculated odds ratios, including only persons who had made at least 1 journey longer than 8 hours in the 8 weeks before the event or index-date. Again, this did not affect any of the results. Furthermore, we assessed the effect of exclusion of women using oral contraceptives, and, again, this did not affect the results.

### Combinations of risk factors

Odds ratios for the number of coagulation abnormalities present per person (FII, FVIII, FVL mutation, and prothrombin mutation) are shown in Table 4. When 1 abnormality was present, the odds ratio was 4.3 (95% CI, 2.6-7.2) compared with travelers in whom all factors were normal. This increased to an odds ratio of 10.0 (95% CI, 4.7-217) when 2 or more clotting abnormalities were present. The increase in odds ratios was more pronounced in air travelers than in other travelers.

The odds ratio also increased with the total number of risk factors (coagulation abnormalities and environmental risk factors combined) present per subject. When only 1 of 6 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 (95% CI, 2.1-9.2) compared with travelers with none. This odds ratio increased to 23.9 (95% CI, 6.0-95.0) when a traveler had 4 or more risk factors. The risk again increased slightly more in air travelers than in other travelers.

Odds ratios for all combinations of risk factors are shown in Table 5. The risk was high for most combinations with FVL. FVL combined with high FII had an odds ratio of 17.5 (95% CI, 2.3-135), combined with FVIII it was 24.7 (95% CI, 4.4-139), and combined with a high BMI it was 20.5 (95% CI, 2.5-170). Women using oral contraceptives who also had FVL had an odds ratio of 18.3 (95% CI, 2.0-171). Having a positive family history did not add to the risk of FVL alone (OR, 4.7; 95% CI, 1.7-16.5). Women using oral contraceptives with a high FVIII had an odds ratio of 51.7 (95% CI, 5.4-498) and in those with a high BMI the risk was 31.4-fold increased (95% CI, 3.0-334) compared with women who did not use oral contraceptives with a low BMI. In women using

**Table 3. Odds ratios for venous thrombosis for elevated coagulation factors in 334 travelers**

| Coagulation factor | P80,* OR (CI95) | P90,† OR (CI95) | P80 air,‡ OR (CI95) | P80 other,‡ 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 for elevated levels of all coagulation factors with the P80 in the control population used as cut off levels (cutoff levels are mentioned in Table 1). Odds ratios are adjusted for age and sex.

†Odds ratios for elevated levels of all coagulation factors using the P90 in the control population as cutoff levels (again, cutoff levels are mentioned in Table 1). Odds ratios are adjusted for age and sex.

‡Air indicates odds ratios for individuals who had traveled by air; and other indicates odds ratios for individuals who had traveled by bus, train, or car. Odds ratios are adjusted for age and sex.

**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 travelers, OR (CI95) | Other travelers, 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.

†Reference category, traveling individuals in whom all coagulation factors are normal and in whom the clinical factors were absent.

‡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 (third tertile as compared to first). The cutoff values for tertiles of BMI were 23.7 and 26.9.

oral contraceptives, having a positive family history doubled the risk (OR of the combination, 10.7; 95% CI, 1.5-75.6). The number of cases and control subjects with specific combinations was too small to calculate odds ratios for air travelers and travelers by other means of transport separately.

## Discussion

In this case-control study among 334 long-distance travelers, we showed an increased risk of venous thrombosis in persons with high levels of coagulation factors II and VIII. The relative risk increased with the number of coagulation abnormalities (FII, FVIII, prothrombin mutation, and FVL mutation) and with the overall number of risk factors present per person (coagulation factors, high BMI, a positive family history, and oral contraceptive use). The relative risk was highest in female travelers using oral contraceptives who also had high levels of FVIII (OR, 51.7; 95% CI, 5.4-498). Combinations with the FVL 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 approximately 2 in this population.[6]

Previous studies have also shown a synergistic effect between long-distance travel and other risk factors for venous thrombosis. Persons with obesity, thrombophilia (FVL or the prothrombin 20210A mutation), and women taking oral contraceptives were shown to have an additionally increased risk when they traveled 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 traveling population before. In the general population, FVIII levels higher than 150% are associated with an approximately 5-fold increased risk of venous thrombosis[17,18] and high FII increases the risk approximately 2-fold.[19] We observed similar odds ratios in our traveling population. However, levels of fibrinogen and FIX are also known to increase the risk of venous thrombosis in the general population,[17,20] whereas in our traveling population these factors were only associated with a mildly increased risk in persons who traveled by air.

For most coagulation abnormalities and their joint effect with environmental risk factors, we observed a more pronounced excess risk for travelers by air than for travelers 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 with other modes of transport). In general, persons 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 because of an increased coagulation factor is equal for both modes of travel. However, when the baseline risk is similar in all travelers, 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, no major differences were observed in baseline characteristics between those who traveled by air and those who traveled 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 variables were measured both after air travel and after immobilization only. Only after air travel, hypercoagulability was observed in a small subgroup of the participants, indicating that not only immobilization plays a role in the pathogenesis of air-travel related venous thrombosis.[21] However, the numbers in our study were too small to draw solid conclusions about the difference between thrombosis after air travel and that after travel by other means.

**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 indicates 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 indicates a positive family history, meaning at least one thrombotic event in a brother, sister, or parent.

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 compared with those in whom the blood draw took place much later, sometimes even years after diagnosis.[17,20] Anticoagulant therapy did not affect our results, because persons 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 for 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 subject's lack of motivation to visit the research center 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 experienced pulmonary embolism than those in whom plasma was available, indicating that the former may have been more disabled after the thrombotic event. This would 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.[22,23] Furthermore, because we analyzed data in long-distance travelers only, we do not expect that severe illness, such as advanced cancer, was a cause of unavailability of a plasma sample, because long-distance travel requires some degree of healthiness.

Another possible limitation in our study is the use of self-reported data on body weight. This may have caused underestimation of the real BMI in our population. If BMI was underreported to the same extent in cases and controls (random misclassification), this would have led to an underestimation of the relative risk. If cases would have underreported their BMI to a greater extent than did controls, this underestimation would have been even more pronounced.

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 persons with any of the risk factors we studied would be high enough for cost-effective screening in all travelers. 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 traveling population, including persons with and without the risk factors that could be screened for. The prevalence of increased FII, FVIII, or FIX is 20% (because we used the 80th percentile in the control population as the cutoff level), that of the FVL mutation is approximately 5%, and that of the prothrombin mutation is 2%.[24,25] The proportion of persons with at least 1 of these risk factors in the general population is therefore 0.52 ($1 - 0.8 \times 0.8 \times 0.8 \times 0.95 \times 0.98$). In our study, the odds ratio for travelers with 1 or more of these risk factors, compared with travelers with none, was 4.7. When 4500 travelers make a flight longer than 4 hours, 1 develops venous thrombosis. Of these 4500 travelers, 2355 (52%) have at least 1 of the risk factors. Of the cases, 83.6% has at least 1 risk factor (cases are $4.7 \times 52/48$ times more likely to have at least 1 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,[26] 57.5% of the cases (70% of 82%) would be prevented. So to prevent 1 case of venous thrombosis, 7826 travelers need to be screened (4500 travelers to prevent 0.575 thrombosis), of whom 4096 (52% of 7826) would have to be treated with LMWH. The risk of a major hemorrhage for the use of LMWH is approximately 0.4% during a 14-day period,[27] which is 0.03% per day. This means that prevention of 1 thrombotic event would cause more than 1 serious bleeding complication. These numbers are derived from studies that include only acutely ill patients. Although we have no information or insight in bleeding risk at high altitude, it may be lower in healthy travelers than in severely ill patients. When we assume that the bleeding risk in healthy travelers is approximately one-fourth of that in acutely ill patients, 1 serious bleeding complication would occur in 14 000 travelers if they would take low molecular weight heparin for 1 day. This strategy can therefore not be recommended, being costly and with an unfavorable risk-benefit ratio. However, if screening and subsequent treatment with LMWH would be restricted to, for example, women using oral contraceptives, prevention of 1 event would require screening of 534 travelers 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 travelers and that the risk is further increased with the number of risk factors present per person, as well as in travelers 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 travelers. However, targeted screening and prophylaxis may be justifiable.

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## Authorship

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