

# Activation of coagulation system during air travel: a crossover study

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## Summary

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\*This study was done in the framework of the WRIGHT initiative (WHO Research Into Global Hazards of Travel). Investigators listed at end of article

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**Background** There is an increased risk of venous thrombosis after air travel, but the underlying mechanism is unclear. Our aim was to ascertain whether flying leads to a hypercoagulable state.

**Methods** We did a crossover study in 71 healthy volunteers (15 men, 56 women), in whom we measured markers of activation of coagulation and fibrinolysis before, during, and after an 8-h flight. The same individuals participated in two control exposure situations (8-h movie marathon and daily life) to separate the effect of air travel on the coagulation system from those of immobilisation and circadian rhythm. To study the effect of risk factors for thrombosis, we included participants with the factor V Leiden mutation (n=11), those who took oral contraceptives (n=15), or both (n=15), as well as 30 individuals with no specific risk factors.

**Findings** After the flight, median concentrations of thrombin-antithrombin (TAT) complex increased by 30·1% (95% CI 11·2–63·2), but decreased by 2·1% (–11·2 to 14) after the cinema and by 7·9% (–16·2 to –1·2) after the daily life situation. We recorded a high response in TAT levels in 17% (11 of 66) of individuals after air travel (3% [2 of 68] for movie marathon; 1% [1 of 70] in daily life). These findings were most evident in the group with the factor V Leiden mutation who used oral contraceptives. We noted a high response in all variables (prothrombin fragment 1 and 2, TAT, and D-dimer) in four of 63 (6·3%) volunteers after the flight, but in no-one after either of the control situations.

**Interpretation** Activation of coagulation occurs in some individuals after an 8-h flight, indicating an additional mechanism to immobilisation underlying air travel related thrombosis.

## Introduction

Venous thrombosis was first linked to air travel in 1954,<sup>1</sup> but remains topical. The results from studies suggest a 2–4-fold increased risk of thrombosis after air travel;<sup>2–4</sup> with a greater risk after longer flights than after shorter ones.<sup>5,6</sup> The mechanism of thrombus formation during air travel, however, is unclear. Immobilisation for long periods could play a part,<sup>7,8</sup> as could flight specific factors—eg, hypobaric hypoxia, which might activate the clotting system. Bendz and colleagues<sup>9</sup> exposed volunteers to a hypoxic and hypobaric environment similar to that in an airplane. Markers of activated coagulation—ie, prothrombin fragment 1 and 2 (F1+2) and thrombin-antithrombin complex (TAT)—were transiently increased, but these findings could have been the result of artificial activation.<sup>10</sup> In another similar study,<sup>11</sup> no differences were noted compared with a control situation. Some studies done during air travel have shown an increase in activity of clotting factor VII and clotting factor VIII<sup>12</sup> and of D-dimer concentrations,<sup>13</sup> though one of young healthy men<sup>14</sup> indicated no effects. Furthermore, few studies have taken into account circadian variation and its possible effect on clotting factors, or distinguished between effects of immobilisation and hypoxic hypobaria. Finally, studies have mostly included participants without risk factors for thrombosis, whereas the risk of travel-related thrombosis is mainly increased in the presence of the factor V Leiden mutation and hormone use.<sup>3</sup>

Our aim, therefore, was to ascertain whether exposure to

an 8-h flight leads to a hypercoagulable state, with immobilisation and circadian rhythm accounted for.

## Methods

### Participants

Between May 24 and July 10, 2004, we did a crossover study in healthy volunteers, some of whom had risk factors for thrombosis. Volunteers with the factor V Leiden mutation were recruited by contacting participants of a previous study<sup>15</sup> for which 60 asymptomatic carriers had been identified after screening of 1083 students and employees aged 18–40 years at the University of Utrecht, Netherlands. We also screened healthy laboratory personnel of a participating clinic. We recruited volunteers without the factor V Leiden mutation by advertisement. Exclusion criteria were previous venous thrombosis, recent (12 weeks) surgery or immobilisation (including travel lasting >4 h or any air travel), active cancer, any drug use except of oral contraceptives, pregnancy or puerperium, and diseases affecting coagulation.

The medical ethics committee of the Academic Medical Center, Amsterdam, approved the study, and all participants gave written informed consent.

### Procedures

We exposed all participants to an 8-h flight, 8 h of immobilisation (movie marathon), and 8 h of regular daily activities, separating each exposure situation by 2 weeks or more (based on the half lives of the clotting factors). This design enabled us to investigate air travel with hypobaric

hypoxia controlled for effects of immobilisation at ground level and for circadian rhythm. We drew blood before, during, and after each exposure, at the same time of day.

For the first exposure situation, we chartered a Boeing 757 for a non-stop day flight of 8 h from and to Schiphol airport, Amsterdam. We instructed volunteers not to smoke, use drugs, drink alcohol, or take any prophylactic measures to prevent thrombosis—eg, heparin or aspirin use, or wearing of elastic stockings during the flight—to remain seated as much as possible, and to keep a structured record of fluid intake. 2–3 weeks after the flight, all participants sat for 8 h (for practical reasons two sessions with half the participants in each) in a cinema. We imposed the same restrictions during this second exposure situation as in the first with respect to moving, drugs, smoking, and drinking, and again asked participants to keep a record of their fluid intake. For the final exposure situation, 2 weeks after the movie marathon, we asked participants to live their lives as they normally would for a day, recording fluid intake. We asked participants not to drink alcohol, take drugs, or smoke, but did not restrict movement. We asked participants to keep their food and fluid intake constant during the three exposures.

Experienced technicians did the blood sampling (each time by fresh venepuncture) and recorded when blood was obtained and any problems that arose during sampling. Baseline blood sampling took place after an overnight fast before each exposure situation. Blood sampling took place between 0800 and 0830 h, around noon, and between 1630 h and 1730 h on the day of each exposure.

We centrifuged citrated (3.2%) blood twice within 15 min of venepuncture at 2500 g for 15 minutes at 15°C, and froze and immediately stored the plasma at –80°C. We extracted DNA from EDTA-anticoagulated blood and stored it at 4°C. We did the assays (all in duplicate except for the DNA tests) after all participants had completed the study. We assayed the TAT complexes and F1+2 by sandwich-type ELISA (Dade-Behring, Marburg, Germany). We measured D-dimer concentrations with the VIDAS D-dimer new (DD2) immunoassay and the miniVIDAS analyser (BioMerieux, Marcy-l’Etoile, France). We ascertained factor V Leiden and prothrombin G20210A status by PCR.

### Statistical analyses

We report the general characteristics of the volunteers as means and ranges. We calculated the median (95% CI) of the concentrations of the markers of activation of the coagulation and fibrinolytic system overall and for subgroups for each of the three exposures. We compared the levels of each marker after exposure to the flight, to the movie marathon, and to the daily life situation with the Friedman test. This test is a non-parametric equivalent of a one-sample repeated measures design or a two-way analysis of variance, with one observation per cell. We calculated relative changes in the variables for each

individual by subtracting the pre-exposure value from the post-exposure value, dividing it by the pre-exposure value, and multiplying the result by 100%. We calculated the medians (95% CI) of these individual changes.

We identified high responders for each assay by using as cutoff points the mean plus three times the SD for the relative change in that assay during the daily life situation. We also did this analysis with two times and four times the SD, which changed the numbers but not the overall pattern (data not reported). We compared the frequency of high-responders in each of the three exposure groups with Fisher’s exact test. For all individuals identified as high responders, we checked whether there had been any difficulties during blood sampling, whether vasovagal collapse had occurred, and whether patterns of response were related to seating location or the designated technician.

### Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

The flight took place on May 24, 2004, between 0830 h and 1619 h (flight time 7 h 49 min). There were no delays and no turbulence. The cabin pressure corresponded to an altitude of 1800–2100 m, and the cruising altitude was 11 000–12 000 m. The movie marathon took place on June 5 and June 12, 2004, between 08.30 h and 1630/1700 h. Movies shown were similar to those shown in-flight—ie, adventure and comedy. We drew blood for assessment of the daily life exposure situation in the last week of June or the first week of July. Fluid intake was similar during the 3 exposure days.

71 healthy volunteers aged 20–39 years participated in the study, of whom 56 (79%) were women (table 1). Of the 60 asymptomatic female carriers of the factor V Leiden mutation who were enrolled to the study by Kemmeren and colleagues (all heterozygous),<sup>15</sup> we traced 53. Of these, 25 were eligible, willing, and available to participate. We also included one other carrier of the factor V Leiden mutation, whom we identified through screening of healthy employees at a participating clinic. 15 of these 26 women with the factor V Leiden mutation used oral contraceptives. Of 60 people who responded to our advertisement, 49 were eligible and 45 were included (table 1). All volunteers returned for each stage in the study as planned. There were no episodes of venous thrombosis during the study.

We took 639 blood samples from the 71 volunteers during nine timepoints. 14 samples (2%) were unavailable for analysis: ten were visibly haemolytic, three were missing because of unsuccessful blood collection, and in one results were technically unreliable. Missing samples

	All (n=71)	Men (n=15)	Women (n=56)			
			FVL-/OC- (n=15)	FVL+/OC- (n=11)	FVL-/OC+ (n=15)	FVL+/OC+ (n=15)
Age (years)	28 (20-39)	28 (22-37)	28 (20-37)	32 (26-39)	24 (20-34)	28 (25-33)
Body-mass index (kg/m <sup>2</sup> )	23.0 (18-33)	24.9 (20.0-33.0)	21.6 (18.0-27.1)	22.8 (18.5-27.0)	22.5 (19.6-27.4)	23.2 (19.0-28.3)
Height (m)	1.75 (1.57-1.97)	1.84 (1.70-1.97)	1.73 (1.62-1.90)	1.73 (1.61-1.88)	1.73 (1.60-1.83)	1.72 (1.57-1.86)

Data are mean (range). FVL+/-=factor V Leiden mutation present/absent. OC+/-=oral contraceptive use or not.

**Table 1: Characteristics of volunteers**

were evenly distributed across the three exposure groups. For the measurement of D-dimer concentrations, three further samples could not be used.

During analyses, we did not identify any additional carriers of the factor V Leiden mutation, but we did identify one individual with a heterozygous prothrombin G20210A mutation. We left her in her group (no factor V Leiden mutation and no oral contraceptive use) for analysis; she did not respond differently from the other volunteers in her group to any of the three situations.

Median TAT baseline values were similar for the three exposures (figure 1), but were higher after the flight (2.8 µg/L, 95% CI 2.4-3.2) than after the movie marathon (2.2 µg/L, 1.9-2.5) or the daily life situation (1.7 µg/L, 1.6-2.0). The Friedman test showed a clear difference between the three after-values (p<0.0001), indicating a strong effect on an individual level. The TAT values of 33 of 71 individuals were highest after the flight, whereas in 15 they were highest after the movie marathon, and in only ten were they highest after the daily life situation. This individual effect was confirmed when, compared with baseline values, the median of the individual relative changes in TAT increased by 30.1% (11.2-63.2) after the flight, but decreased by 2.1% (-11.2 to 14.0) after the cinema and by 7.9% (-16.2 to -1.2) after the daily life situation. The median TAT values after the flight, compared with those after the cinema and the daily life situation, were higher in most

subgroups, but most clearly so in the group of women with the factor V Leiden mutation who also took oral contraceptives (figure 2). The median values in this group were 5.2 µg/L (3.2-7.5) after the flight, 2.6 µg/L (1.9-3.5) after the cinema, and 1.9 µg/L (1.4-2.4) after the daily life situation. With respect to TAT, 11 of 66 individuals (16.7%, 95% CI 8.6-27.9) were identified as high responders after the flight (table 2, table 3, figure 3). In the cinema exposure, two other individuals (2 of 68, 2.9%, 0.4-10.2) were identified as high responders. The daily life situation led to one high-responder (1 of 70, 1.4%, 0.0-7.7). She was also a high-responder during the flight (table 2, table 3, and figure 3).

Median baseline values of F1+2 were higher before the cinema exposure than before the other two exposure situations (figure 1). After the flight and the cinema exposures, the median F1+2 levels were the same (0.59 nmol/L, 95% CI 0.56-0.63) and lower than after the daily life exposure situation (0.62 nmol/L, 0.58-0.66, Friedman test for difference between the three after-values: p=0.050, again with most individual levels highest after the flight). The median of the individual relative changes in F1+2 was -9.9% (-12.8 to -4.3) after the flight, -14.1% (-20.7 to -12.0) after the cinema, and -8.2% (-11.6 to -5.2) after the daily life situation. Within each subgroup separately, we did not find a clear difference between the F1+2 levels after the three exposure situations (figure 2). We identified six

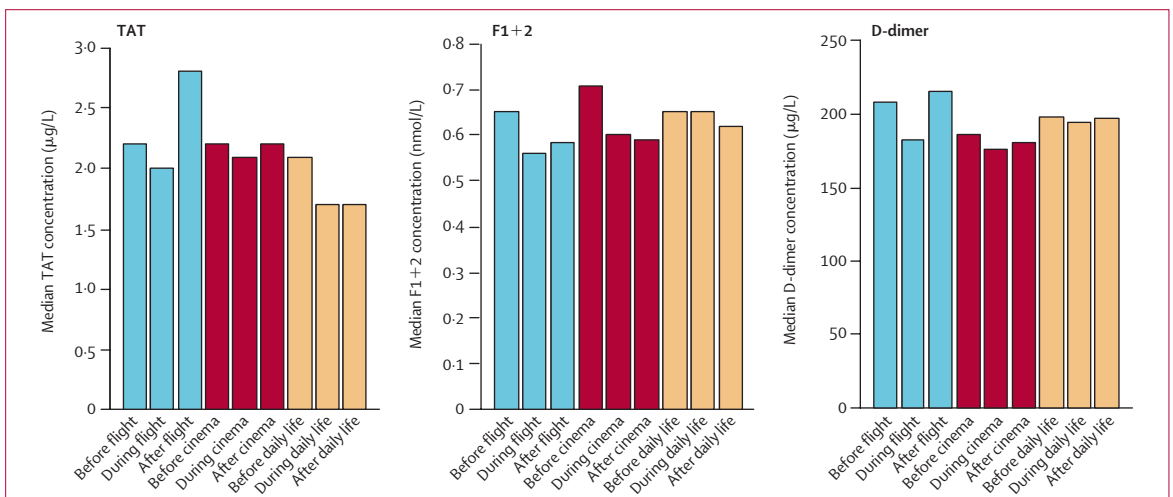
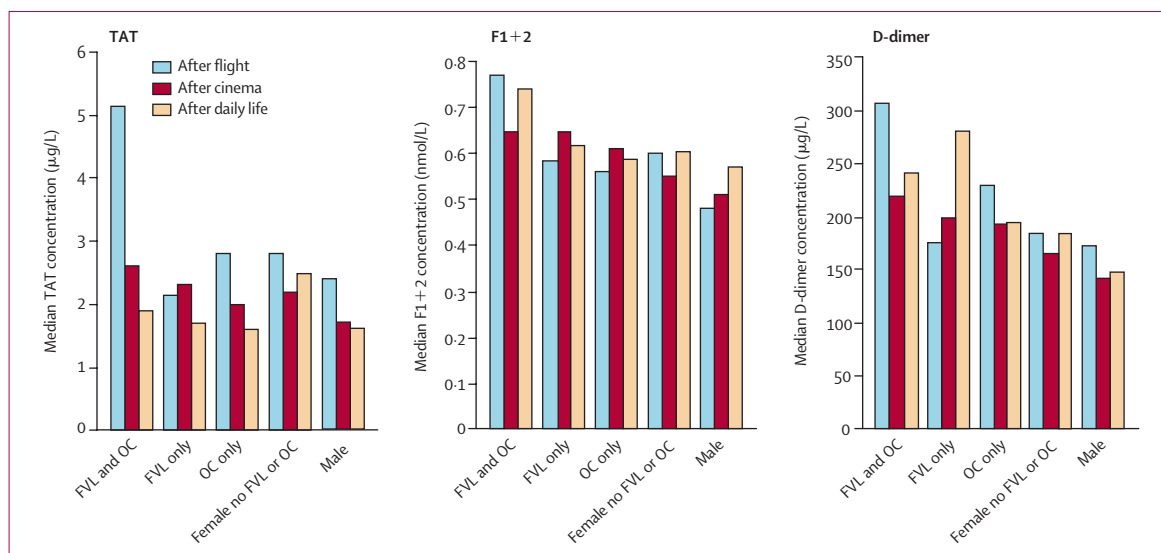


Figure 1: Absolute median values of coagulation variables before, during, and after exposure situations (n=71)



**Figure 2: Absolute median values of coagulation variables after exposure situations, by subgroup**  
FVL=factor V Leiden mutation. OC=oral contraceptive use.

individuals (6 of 66, 9.1%, 3.4–18.7) as high responders for F1+2 during the flight (table 2, figure 3), compared with only one after the cinema (1 of 68, 1.5%, 0.0–7.9%) and the daily life situation (1 of 70, 1.4%, 0.0–7.7). The woman with a high response in the daily life situation was also a high responder during the flight experiment (table 2, figure 3).

Finally, median D-dimer level after the flight rose to 216 µg/L (95% CI 182–240), but fell to 180 µg/L (155–211)

after the cinema and was unaltered by normal daily activity (198 µg/L, 176–231 (figure 1), Friedman test for difference between the three after values:  $p=0.012$ , again with most individual levels highest after the flight). The median of the individual relative changes in D-dimer values, compared with the baseline values, was  $-3.3\%$  after the flight ( $-8.5$  to  $2.2$ ),  $-5.8\%$  after the cinema ( $-12.8$  to  $-2.2$ ), and  $-5.5\%$  after the daily life situation ( $-9.5$  to  $-1.9$ ). Within the subgroups, D-dimer levels

Group		TAT			F1+2			D-dimer		
		Before (µg/L)	After (µg/L)	Change (%)	Before (nmol/L)	After (nmol/L)	Change (%)	Before (µg/L)	After (µg/L)	Change (%)
<b>High responders after flight*</b>										
3126	Female no FVL or OC	2.2	68.0	2991	0.60	2.59	332	208	1571	656
3158	Female no FVL or OC	1.6	37.5	2244	0.39	1.43	267	126	354	180
3147	Female OC only	1.9	30.7	1516	0.79	1.47	86	343	1353	294
3136	Female FVL and OC	3.0	38.4	1180	0.83	1.47	77	493	822	67
3148	Female OC only	1.7	15.4	806	0.63	0.87	38	142	209	48†
3108	Female FVL and OC	3.7	20.8	462	0.77	1.35	75	Missing	444	Unknown
3138	Female FVL and OC	2.2	10.7	386	0.75	0.87	16†	228	323	42†
3110	Female FVL and OC	1.6	6.4	300	0.78	0.84	8†	232	216	-7†
3143	Female FVL and OC	1.9	6.9	263	0.68	0.78	15†	202	311	54
3169	Male	2.2	7.7	250	0.64	0.72	12†	352	403	14†
3163	Female FVL and OC	1.1	3.5	218	0.57	0.58	2†	130	128	-2†
<b>High responders after cinema*</b>										
3153	Female FVL and OC	2.5	33.7	1248	0.86	1.44	67	694	538	-23†
3157	Female OC only	2.7	9.7	259	0.87	0.90	3†	189	193	2†
3120	Female no FVL or OC	5.5	10.3	87†	0.78	0.87	12†	139	211	52
<b>High responders after daily life situation*</b>										
3143	Female FVL and OC	2.2	10.5	377	0.75	0.99	32†	206	248	21†
3158	Female no FVL or OC	3.1	8.9	187†	0.44	0.65	48	133	143	7†
3120	Female no FVL or OC	1.7	1.9	12†	0.77	0.71	-8†	287	455	58
3125	Female OC only	1.4	2.0	43†	0.66	0.59	-11†	98	162	65

FVL=factor V Leiden mutation. OC=oral contraceptive use. Data are absolute values before and after exposure and relative change. \*Number in group after flight: TAT=66, F1+2=66, D-dimer=63; after cinema: TAT=68, F1+2=68, D-dimer=68; after daily life situation: TAT=70, F1+2=70, D-dimer=70. †Not a high responder for this measurement. Cut off point for high responders (mean plus three times SD in daily life situation): TAT 202.9%, F1+2 37.3%, D-dimer 51.7%.

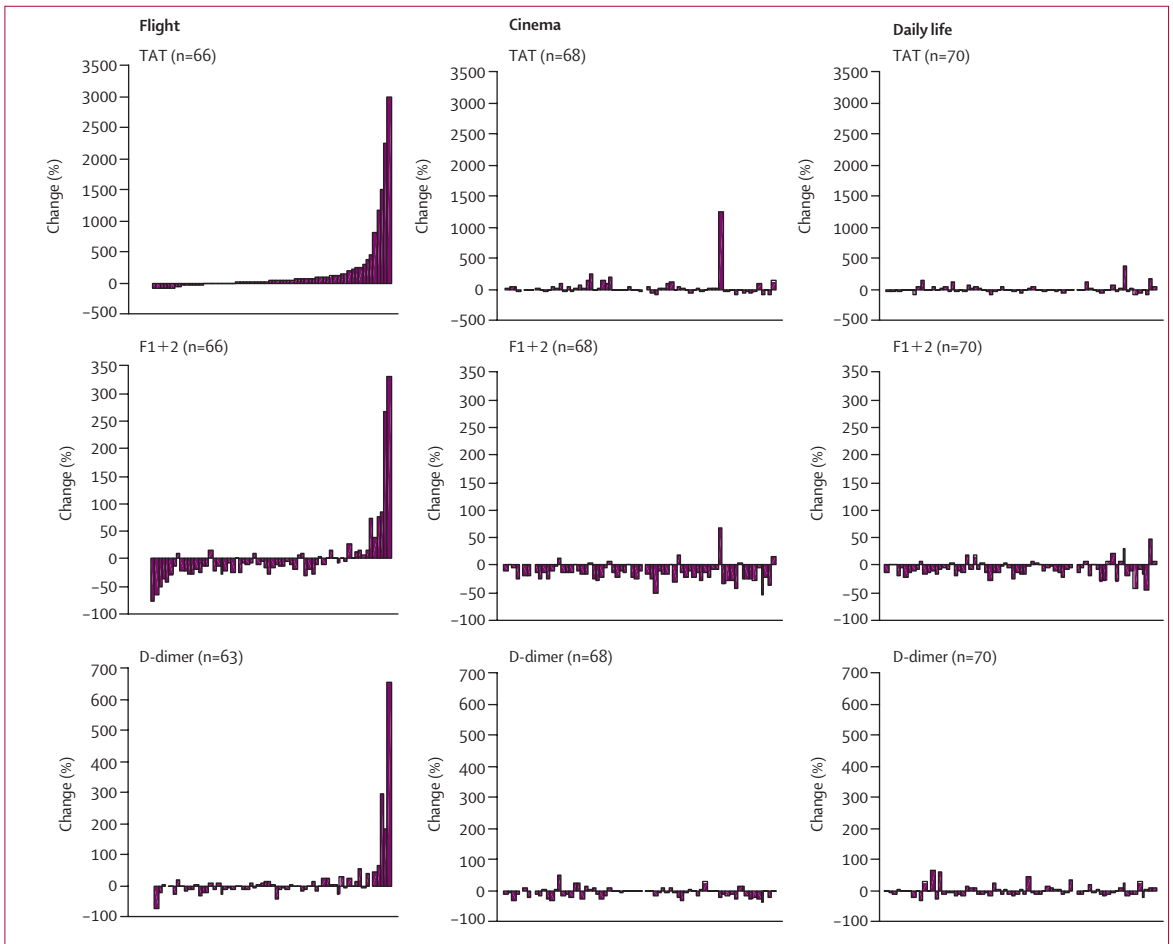
**Table 2: Individual data of high responders**

	High responders (total number [% , 95% CI])	0 risk factors (number, %)	1 risk factor (number, %)	2 risk factors (number, %)
<b>TAT</b>				
Flight	11/66 (17%, 8.6–27.9)	3/29 (10%)	2/23 (9%)	6/14 (43%)
Cinema	2/68 (3%, 0.4–10.2)	0/28	1/25 (4%)	1/15 (7%)
Daily life	1/70 (1%, 0.0–7.7)	0/29	0/26	1/15 (7%)
<b>TAT and F1+2</b>				
Flight	6/66 (9%, 3.4–18.7)	2/29 (7%)	2/23 (9%)	2/14 (14%)
Cinema	1/68 (2%, 0.0–7.9)	0/28	0/25	1/15 (7%)
Daily life	0/70 (0%, 0.0–5.1)	0/29	0/26	0/15
<b>TAT, F1+2, and D-dimer</b>				
Flight	4/63 (6%, 1.8–15.5)	2/29 (7%)	1/23 (4%)	1/14 (7%)
Cinema	0/68 (0%, 0.0–5.3)	0/28	0/25	0/15
Daily life	0/70 (0%, 0.0–5.1)	0/29	0/26	0/15

Proportions of high responders tested by  $\chi^2$  without continuity correction or Fisher's exact test when there were cells with five or less counts. Proportion of high responders after flight compared with daily life: TAT ( $p=0.002$ ), TAT and F1+2 ( $p=0.01$ ), TAT and F1+2 and D-dimer ( $p=0.048$ ). Within response to flight, proportion of high responders with 2 vs 0 risk factors: TAT ( $p=0.04$ ), TAT and F1+2 ( $p=0.58$ ), TAT and F1+2 and D-Dimer ( $p=1.0$ ).

**Table 3: Proportion of high-responders per exposure, for whole group and by number of risk factors (oral contraceptive use, factor V Leiden mutation, or both)**

were generally higher after the flight than after the cinema and daily life situation. This difference in levels was again most obvious in the group with the factor V Leiden mutation who were also taking oral contraceptives (figure 2). The median values in this group were 306  $\mu\text{g/L}$  (202–457) after the flight compared with 219  $\mu\text{g/L}$  (151–495) after the cinema and 240  $\mu\text{g/L}$  (197–355) after the daily life situation (figure 2). The flight caused a high



**Figure 3: Relative change in coagulation variables after exposure situations, by individual and ordered by change in TAT after flight**  
Order of bars (individuals) consistent across panels.

response in D-dimer concentrations in five individuals (5 of 63, 7.9%, 2.6–17.6; table 2, figure 3). The cinema experiment triggered a high-response in D-dimer in one other woman (1 of 68, 1.5%, 0.0–7.9) and the daily life situation did so in two women (2 of 70, 2.9%, –0.4 to 9.9; table 2, figure 3).

Table 3 shows the number of high responders after each exposure and for each combination of assays. We noted a high response in both variables of thrombin generation (F1+2 and TAT) in six volunteers after air travel, one individual after the movie marathon, and in no-one after the daily life situation (table 3). We also noted a high response in both TAT and D-dimer in five volunteers after the flight, but not in the two control situations. A high-response in all three variables (F1+2, TAT, and D-dimer) was seen in four volunteers after the flight, but not in anyone after the two control situations (table 3). Table 3 also shows the proportions of high responders with no, one, or two risk factors: the proportion of high responders was consistently highest for the volunteers with two risk factors.

## Discussion

Our findings indicate that flight-associated factors—eg, hypobaric hypoxia—lead to increased thrombin generation after air travel, especially in individuals with the factor V Leiden mutation who also took oral contraceptives.

Results of other studies<sup>9–14</sup> into the effects of hypobaric hypoxia are conflicting, possibly because of the small numbers involved or because of lack of control for the effects of immobilisation and circadian rhythm. When blood samples taken before and after a flight are simply compared, the differences noted can be the result of various indistinguishable factors—eg, circadian rhythm, immobilisation, or conditions present during the flight, like hypoxic hypoxia. To disentangle these factors, we compared findings from blood samples taken at the same time of day and from the same volunteers and looked at three situations—immobilisation and hypoxic hypoxia (flight), normobaric immobilisation (cinema), and normobaric non-immobilisation (daily life). We noted a higher response in TAT values and in the combination of an increase in TAT, F1+2, and D-dimer values after a flight than after a movie marathon or a period of normal daily activity.

Another explanation for the discrepancies between studies might be that only some individuals are susceptible to coagulation activation. Most studies do not enrol individuals with risk factors for thrombosis, and, when they do, results are presented at a group level, diluting individual effects. Our findings concur with those of previous studies<sup>3</sup> (MEGA-study, unpublished data) which show a synergistic effect for the combination of air travel with either the factor V Leiden mutation or oral contraceptive use. We are unaware of any study that has looked at the risk of thrombosis in those flying who have

both the factor V Leiden mutation and use oral contraceptives. Yet about 5% of users of oral contraceptives have the factor V Leiden mutation. As with most risk factors for venous thrombosis a combination of a genetic predisposition (factor V Leiden) and an environmental factor (oral contraceptives, hypobaric hypoxia) is probably the basis for venous thrombosis associated with air travel. There must also be other factors associated with clotting activation and thrombosis risk after air travel, however, since individuals without these characteristics can also develop travel-related venous thrombosis. Indeed, we noted that the two women with the highest TAT values neither took oral contraceptives nor had the factor V Leiden mutation.

Our study had various limitations. First, because of practical constraints, we could not randomise the order of the three exposure situations, nor could we blind the volunteers to the exposures. Second, although experienced laboratory technicians collected blood, conditions during the study were more difficult than those faced during a routine blood draw in our clinic. However, conditions for blood sampling during the flight were similar to those during the cinema exposure. The technicians had to report any difficulties during blood sampling, which occurred five times and only once during the flight. Four volunteers experienced a vasovagal collapse, but only before and during the flight, and not after; none of them were high responders. We excluded all visibly haemolytic samples. We investigated patterns of response related to seating position or the designated technician, and noted none. The seats in the cinema and in the airplane were slightly different, but leg space was similar. So, although there were practical difficulties, which we anticipated and recorded, these are not likely to have affected our results. Finally, some of the TAT values we noted in the high responders were very high. We cannot exclude that some of these values were artifacts due to preanalytic activation of coagulation, though we did all we could to prevent such confounding. Furthermore, that artifacts would arise only after the flight exposure, is unlikely. Nevertheless, we repeated the analysis without the highest TAT values; we noted no change to our overall conclusion. Although all three variables showed some degree of clotting activation, change was most apparent for TAT, both for the group as a whole and in high responders. One explanation for this finding could be a difference in sensitivity and specificity of the assays, or a difference in clearance. The shorter half-life of TAT (10 min vs 90 min for F1+2), could explain why it is more sensitive to changes, since F1+2 will be more diluted by what was already present.

When air travel leads to coagulation activation, are there alternative explanations to an effect of hypobaric hypoxia? All factors present during flights, but absent at other times could theoretically explain the observed effects. Such factors include anxiety and dehydration, neither of which seems likely to have affected our participants: the flight was calm and uneventful, and the mood on the plane

relaxed (individuals with a fear of flying are unlikely to have volunteered for our study), and dehydration, though known to occur during flying,<sup>16</sup> has no known effect on clotting. In any case, the volunteers were asked to keep their fluid intake constant during the three situations. Temperature changes, poor air quality, vibration, noise, acceleration, and electromagnetic radiation are also factors noted in-flight. However, to assume that any of these conditions has an effect on the coagulation system would be purely speculative.

Our participants, although some had common risk factors for thrombosis, were young and healthy individuals with no history of thrombosis. The effect of flying on the coagulation system of older individuals, or of those with other risk factors for venous thrombosis or a personal history of venous thrombosis, should also be investigated. We conclude that the coagulation and fibrinolytic system are activated in some susceptible individuals after an 8-h flight, indicating an additional mechanism to immobilisation for air travel related thrombosis.

#### Contributors

A J M Schreijer helped to coordinate the study, obtain data, do statistical analysis, and write the report. S C Cannegieter helped to coordinate the study, do statistical analysis, and write the report. J C M Meijers participated in obtaining of data and writing of the report. S Middeldorp and H R Büller helped to design the study and write the report. F R Rosendaal participated in study design, statistical analysis, and writing of the report.

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#### Conflict of interest statement

We declare that we have no conflict of interest.

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