Chapter 4

The absolute risk of venous thrombosis after air travel: a study of 8 755 employees of international organisations

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Abstract

Background: The risk of venous thrombosis is approximately 2-4 fold increased after air travel, but the absolute risk is unknown. The objective of this study was to assess the absolute risk of venous thrombosis after air travel.

Methodology and principle findings: We conducted a cohort study among employees of large international companies and organisations, who were followed between January 1st 2000 and December 31st 2005. The occurrence of symptomatic venous thrombosis was linked to exposure to air travel, as assessed by travel-records provided by the companies and organisations. A long-haul flight was defined as a flight of at least 4 hours and subjects were considered exposed for a post-flight period of 8 weeks. A total of 8 755 employees were followed during a total follow-up time of 38 910 person-years. The total time employees were exposed to a long-haul flight was 6 872 person-years. In the follow-up period, 53 thromboses occurred, 22 of which within 8 weeks of a long-haul flight, yielding an incidence rate of 3.2/1000 person-years, as compared to 1.0/1000 person-years in individuals not exposed to air travel (incidence rate ratio 3.2, CI95 1.8-5.6). This was equivalent to a risk of 1 event per 4 656 long-haul flights. The risk increased with exposure to more flights within a short time frame and with increasing duration of flights. The incidence was highest in the first two weeks after travel and gradually decreased to baseline after 8 weeks. The risk was particularly high in employees under 30, women who used oral contraceptives, individuals who were particularly short, tall or overweight.

Conclusions/significance: The risk of symptomatic venous thrombosis after air travel is moderately increased on average, and rises with increasing exposure and in high-risk groups.
Introduction

In 1951, Jacques Louvel reported four cases of venous thrombosis following air travel¹. More recently, several investigators have shown an association between air travel and venous thrombosis, with a 2-4 fold increased risk in most studies²-⁸. Two follow-up studies demonstrated a dose-response relationship between the occurrence of pulmonary embolism shortly after arrival at the airport and the distance travelled⁹,¹⁰. Still, the most relevant element, i.e. the absolute risk of symptomatic venous thrombosis after long distance air travel, remains unknown. One follow-up study demonstrated an absolute risk of severe pulmonary embolism occurring shortly after arrival of 1 per 200 000 passengers⁹, whereas another study showed a risk of fatal pulmonary embolism of 1.3 per million passengers¹¹. Asymptomatic clots have been found in 1 to 10% of air travellers¹²-¹⁴. Hence, the absolute risk of symptomatic venous thrombosis after long-haul travel must lie between these extremes.

Knowledge of the absolute risk of symptomatic thrombosis after air travel is needed to provide travellers with solid advice regarding their actual risk and to evaluate the utility of prophylactic measures. Since there are two billion passengers annually¹⁵, even a small increase in risk will have a major impact on the number of events. Overestimation of the risk may lead to inappropriate use of potentially dangerous antithrombotic drugs¹⁶,¹⁷.

In addition to estimating the absolute risk of symptomatic deep vein thrombosis or pulmonary embolism after long haul air travel, we assessed the effect of exposure to several flights within a short time frame, duration of travel and the occurrence of venous thrombosis in relation to the time passed after air travel. Finally, we determined the effect of air-travel within high-risk groups.

Methods

Study design
We performed a cohort study among employees of large international companies and organisations. During the follow-up period, thrombotic events were linked to exposure to air travel.

Participating companies and organisations
Participating companies and organisations were Nestlé (Vevey, Switzerland), General Mills (Minneapolis; Minnesota, USA), the Centers for Disease Control and Prevention (Atlanta; Georgia, USA), the World Bank and the International Monetary Fund (Washington; DC, USA), Shell Companies based in The Hague.
(The Netherlands) and London (UK), Shell Exploration and Production (SIEP) based in Rijswijk (The Netherlands) and Sakhalin Energy Investment Company Ltd (SEIC) based in Sakhalin (Russia) and TNT NV (Thomas Nationwide Transport, Hoofddorp; the Netherlands). All organisations and companies had a central database with records of employees’ business travel. Start of follow-up varied per company, between January 1st 1998 to January 1st 2001 or at start of the employment if later. Follow-up ended between December 1st 2002 and January 1st 2006, when venous thrombosis was diagnosed or at the end of employment, whichever occurred first, with approximately 5 years of follow-up per company.

Questionnaires and flight data
We developed web-based questionnaires, using Apian Survey Pro 3.0 (Seattle; Washington, USA). These contained questions about venous thrombosis occurrence (at any time point in the follow up period) and risk factors for venous thrombosis. Employees were invited to take part by a personal e-mail, containing a link to the questionnaire and a unique password, which ensured that each individual could enter only once. With intervals of a few weeks, non-responding employees received 2-3 reminders.

Date of travel and duration of travel (not including stop-over time) was taken from the organisations’ travel database.

Outcomes
Participants who reported venous thrombosis were asked to fill in a consent form for medical chart review. Only symptomatic first venous thrombotic events that were diagnosed with objective methods were considered. Deep vein thrombosis had to be diagnosed by compression ultrasonography or venography. Pulmonary embolism had to be diagnosed by spiral-CT scanning, high probability ventilation-perfusion scanning or angiography. Superficial thrombophlebitis was not included.

Statistical analysis
For the analysis of the overall effect of flying, exposure time was defined as a time-window of 8 weeks after a long haul flight (flights of at least 4 hours). For each individual, the total time exposed and not exposed was calculated. The incidence rate of venous thrombosis within 8 weeks of a long haul flight was calculated by dividing the number of cases that occurred in this exposure window by the number of exposed person-years. The incidence rate of venous thrombosis without exposure was calculated in the same way (events over
person-time outside exposure windows). The incidence rate ratio adjusted for age and sex was calculated using Poisson regression analysis. The overall effect of flying was assessed for the whole group of employees and separately for subgroups based on sex, age, oral contraceptive use, body mass index (BMI) and height. The number of person-years exposed and unexposed to oral contraceptive use was calculated for women younger than 50 years.

In addition, we calculated the absolute risk of venous thrombosis per flight, by dividing the number of cases that occurred within 8 weeks of a long haul flight by the total number of flights longer than 4 hours made by all responding employees.

Employees were often exposed to more than one flight in the eight weeks exposure windows, so time-windows were frequently overlapping. To assess the effect of number of flights, the total time employees were exposed to 1 to 5 flights or more was calculated. Thus, incidence rates and rate ratios for exposure to 1-2, 3-4 and 5 or more flights could be calculated (Figure 1a). Furthermore, we calculated the increase in risk for each extra flight using Poisson regression.

To assess the effect of duration of travel, we calculated incidence rates and rate ratios within 8 weeks of flights of varying duration, i.e. 0-4 hours, 4-8 hours, 8-12 hours, 12-16 and longer than 16 hours. If time windows were overlapping, only the duration of the longest flight was considered for this analysis (Figure 1b). The absolute risk per flight for each category of duration was calculated by dividing the number of cases that occurred within 8 weeks of a flight by the total number of flights in the corresponding category. Furthermore, we calculated the increase in risk for each extra hour of duration of a flight using Poisson regression.

The occurrence of venous thrombosis in relation to the period of time that had passed after travelling was assessed by calculating incidence rates and rate ratios for periods of 0-2, 2-4, 4-8 and 8-12 weeks after a flight of at least 4 hours. The period of 12 weeks after a flight was split into these 4 time windows, creating mutually exclusive exposure windows. If a person was exposed to several flights and hence to more than 1 time-window, the overlapping time was counted only in the time window closest to the flight (Figure 1c).
Figure 1: Example of the calculation of person-years of exposure in 3 different ways.

An employee makes one flight of 6 hours on day 1 and another flight of 11 hours on day 10.

a) Per number of flights: from day 1 to 10, this employee is exposed to only 1 flight. From day 10 to 56, he is exposed to 2 flights and from day 56 to 66 he is again exposed to 1 flight.

b) Per category of duration: from day 1-10 the employee is exposed to one flight of 6 hours (so 10 days in the category of 4-8 hours). From day 10 to 56, he is exposed to 2 of which the longest is 11 hours (so 46 days in the category of 8-12 hours). From day 56 to 66 he is exposed to one flight of 11 hours (so again 10 days in the category of 8-12 hours).

c) Per time window: from day 1 to 10, the employee is exposed to the time window of 0-2 weeks due to the first flight. At day 10, the time is ‘reset’, so from day 10 to 24, the employee is exposed to the time window of 0-2 weeks again. From day 24 to 38, he is exposed to the time window of 2-4 weeks, from day 38 to 66 he is exposed to the time window of 4-8 weeks and finally, from day 66 to 94 the time window is 8-12 weeks.

Results

A total of 27 496 employees were invited to participate. 8755 questionnaires were completed, yielding an overall response of 32% (range per organisation: 15-80%). General characteristics of the study population are shown in Table 1. More than half of the responders (n=4915, 56%) were men and the mean age was 40 years. The total follow-up time of participating employees was 38 910 person-years, with a mean follow-up per participant of 4.4 years.
Table 1: General characteristics of the study population and flight data

| Characteristic                        | Age, mean (range) | 39.9 (18-71) |
|--------------------------------------|-------------------|--------------|
|                                      | Sex, % male       | 56           |
| Oral contraceptive use (% in women <50) | No OC use entire FU period | 56.5 |
|                                      | OC use during part of the FU period | 26.1 |
|                                      | OC use during the complete FU period | 17.3 |
| Height: (n, %)                        | < 165 cm          | 2046 (23.5)  |
|                                      | 165-180 cm        | 5445 (62.6)  |
|                                      | > 180 cm          | 1202 (13.8)  |
| BMI: (n, %)                           | < 25              | 4741 (54.7)  |
|                                      | > 25              | 3934 (45.3)  |
| Flight data                           | Total number of flights | 315 762 |
|                                      | Flights 0-4 hours | 213 333 |
|                                      | Flights 4-8 hours | 46 272 |
|                                      | Flights 8-12 hours | 37 904 |
|                                      | Flights 12-16 hours | 13 208 |
|                                      | Flights >16 hours | 5 045 |
|                                      | Median number of flights per year (range) | 3.5 (0-143) |
|                                      | Median number of flights > 4 hours per year (range) | 0.8 (0-48) |
|                                      | Mean duration per flight | 3.9 hours (0-24 hours) |

*BMI = body mass index in kg/m²*

**Flight data**

Flight data are shown in Table 1. The 8 755 responders had made 315 762 flights during follow-up, and 6440 individuals had travelled by air at least once. Approximately one third of all flights were long haul flights (at least 4 hours, n=100 208). The mean number of long haul flights per person per year was 2.6 (range: 0-48, median: 3.5).

**Thrombotic events**

Seventy-six employees reported that they had suffered from venous thrombosis in the follow-up period. Of these 76 possible cases 23 were not validated: 4 employees did not give permission for medical chart review, 2 doctors could not be traced, 6 appeared to have suffered from an arterial event and 11 had been diagnosed with superficial thrombophlebitis. The remaining 53 employees all had an objectively confirmed venous thrombotic event. Deep vein thrombosis of the leg was diagnosed in 34, pulmonary embolism in nine, a combination in eight and deep vein thrombosis of the arm in two.

**Absolute risks and incidence rate ratios**

The overall incidence rate of venous thrombosis was 1.4 per 1000 person-years (95% confidence interval (CI95) 1.0-1.8/1000 person-years). The total time employees were exposed to a post-flight period of 8 weeks added up to 6872 person-years when only flights longer than 4 hours were considered. Twenty-two events occurred within eight weeks of a long haul flight, yielding an incidence
rate of 3.2 per 1000 person-years (CI95 2.0-4.7/1000 person-years). The time the employees were not exposed to any flight (long- or short haul) was 27 772 person-years, during which 29 cases occurred, yielding an incidence rate of 1.0 per 1000 person-years (CI95 0.7-1.5/1000 person-years). Thus, the incidence rate ratio (IRR) was 3.2 (CI95 1.8-5.6). The total number of long haul flights made by the employees was 102429, hence the absolute risk of venous thrombosis was 21.5/100 000 flights, or 1 per 4656 flights.

| Category | air travel | Cases | Py# | IR (CI95)** | IRR (CI95)## | Flights | Risk/flight *** | Case/number of flights ### |
|----------|------------|-------|-----|-------------|-------------|---------|----------------|------------------------|
| All (8 755) | No | 29 | 27 772 | 1.0 (0.7-1.5) | 1s | 102 429 | 21.5 | 1/4 656 |
| | Yes | 22 | 6 872 | 3.2 (2.0-4.7) | | | | |
| Men (4 915) | No | 12 | 14 728 | 0.8 (0.4-1.4) | 1s | 76 461 | 3.2 (1.8-5.6) | 1/4 656 |
| | Yes | 13 | 4 810 | 2.7 (1.4-4.4) | | | | |
| Women (3 819) | No | 17 | 12 968 | 1.3 (0.8-2.0) | 1s | 25 780 | 3.3 (1.5-7.5) | 1/2 864 |
| | Yes | 9 | 2050 | 4.4 (2.0-7.8) | | | | |
| <30 Yrs (1 392) | No | 3 | 4132 | 0.7 (0.1-1.8) | 1s | 8 014 | 7.7 (1.6-38.4) | 1/2671 |
| | Yes | 3 | 616 | 4.9 (0.9-12.1) | | | | |
| 30-50 Yrs (6017) | No | 17 | 19 576 | 0.9 (0.5-1.3) | 1s | 7 624 | 3.7 (1.8-7.5) | 1/4908 |
| | Yes | 15 | 4 879 | 3.1 (1.7-4.9) | | | | |
| >50 Yrs (1 345) | No | 9 | 4 063 | 2.2 (1.0-3.9) | 1s | 20 791 | 1.4 (0.4-4.6) | 1/5198 |
| | Yes | 4 | 1376 | 2.9 (0.7-6.5) | | | | |
| OC$$ No | No | 9 | 10 193 | 1.0 (0.5-1.8) | 1s | 18 085 | 2.2 (0.6-8.1) | 1/4938 |
| | Yes | 3 | 1 533 | 2.3 (0.4-5.6) | 1s | 7 695 | 3.6 (0.8-14.9) | 1/1808 |
| <165 cm | No | 5 | 2 367 | 1.9 (0.6-3.9) | 1s | 14 250 | 9.8 (3.1-30.9) | 1/2036 |
| | Yes | 3 | 436 | 6.6 (12.16-14) | 1s | 6 9095 | 1.9 (0.9-3.9) | 1/6281 |
| 165-185 cm | No | 7 | 1 108 | 0.7 (0.2-1.5) | 1s | 7 95 | 9.8 (3.1-30.9) | 1/2036 |
| | Yes | 21 | 16 759 | 6.3 (2.4-12.0) | 1s | 12 824 | 3.7 (0.8-16.9) | 1/4561 |
| >185 cm | No | 11 | 4 602 | 2.4 (1.2-4.0) | 1s | 6 9095 | 1.9 (0.9-3.9) | 1/6281 |
| | Yes | 3 | 3 493 | 0.9 (0.2-2.1) | 1s | 7 95 | 9.8 (3.1-30.9) | 1/2036 |
| BMI <25 | No | 16 | 1 4919 | 1.1 (0.6-1.7) | 1s | 51 958 | 1.9 (0.8-4.7) | 1/7 423 |
| | Yes | 7 | 3 617 | 1.9 (0.7-3.7) | 1s | 4 9509 | 4.9 (2.3-10.6) | 1/3 301 |
| BMI >25 | No | 13 | 12 546 | 1.0 (0.5-1.7) | 1s | 3 198 | 4.9 (2.3-10.6) | 1/3 301 |

Both the unexposed incidence rate and the incidence rate in the exposed were higher in women (1.3/1000 person-years and 4.4/1000 person-years) than in men (0.8/1000 person-years and 2.7/1000 person-years), so their rate ratios were approximately the same (Table 2). Although the unexposed incidence rate of venous thrombosis increased with age, the incidence rate in the subjects...
exposed to air travel was highest in the youngest age category (4.9/1000 person-years, CI95 0.9-12.1/1000 person-years) and lowest in the oldest (2.9/1000 person-years, CI95 0.7-6.5/1000 person-years), and hence the rate ratio decreased with age, with an IRR of 7.7 (CI95 1.6-38.4) for those under 30 (Table 2). Women using oral contraceptives had an increased risk of venous thrombosis, both at baseline (IR 1.9, CI95 0.6-3.9) and after long distance flights (IR 6.6, CI95 1.2-16.4). Thus, the incidence rate ratio of exposure to air travel was higher in women using oral contraceptives (3.6, CI95 0.8-14.9) than in women not using hormone therapy (2.2, CI95 0.6-8.1). The baseline incidence rate of venous thrombosis did not differ much between subgroups based on height.

The incidence rate after air travel was highest in individuals shorter than 165 cm (IR 6.3/1000 person years, CI95 2.4-12.0/1000 person years) and lowest in those between 165 and 185 cm (IR 2.4/1000 person years, CI95 1.2-4.0/1000 person years). In employees taller than 185 cm, the incidence rate after air travel was 3.6/1000 person years (CI95 0.9-8.1/1000 person years). Hence, the rate ratio was highest in the shortest employees (IRR 9.8, CI95 3.1-30.9). BMI did not affect the baseline thrombosis risk, but the incidence rate after air travel was higher in employees with a BMI over 25 kg/m² (IR 4.7/1000 person years, CI95 2.6-7.4/1000 person years) as compared to those with a BMI lower than 25 kg/m² (IR 1.9/1000 person years, CI95 0.7-3.7/1000 person years).

The risk of venous thrombosis increased with the number of flights per employee, as shown in Table 3. When someone was exposed to only one or two long haul flights, the incidence rate was 2.6 (CI95 1.4-3.2) per 1000 person-years, which tripled after exposure to 5 or more long haul flights. With each extra flight the employees were exposed to, the risk increased 1.4-fold (CI95 1.2-1.6).

Table 3: Incidence rates and incidence rate ratios for exposure to an increasing number of flights. Only flights longer than 4 hours were taken into account.

| Number of flights | Cases | PY* | IR (95%CI)** | IRR (95%CI)# |
|-------------------|-------|-----|-------------|-------------|
| 0                 | 29    | 27 772 | 1.0 (0.7-1.5) | 1$           |
| 1-2               | 13    | 5 052 | 2.6 (1.4-3.2) | 2.5 (1.2-4.9) |
| 3-4               | 6     | 1 494 | 4.4 (1.5-7.7) | 4.2 (1.4-10.3) |
| 5 or more         | 3     | 547  | 7.2 (1.3-18.0) | 6.9 (1.3-22.3) |

$ The reference category for calculation of incidence rate ratios was no flight longer than 4 hours in the preceding 8 weeks.

* PY= Person-years

** Incidence rate per 1000 person-years and 95% CIs

# Incidence rate ratio adjusted for age and sex and 95% CIs

The effect of duration of travel is shown in Table 4. The incidence rate increased from 0.5/1000 person-years (CI95 0-1.4/1000 person-years) when employees had travelled for less than 4 hours, to 5.9/1000 person-years (CI95 1.5-13.4/1000 person-years) when they had travelled for more than 16 hours. For each extra...
hour duration of the flight, the incidence rate ratio increased 1.1 fold (CI95 1.1-1.2). Expressed as risk per number of flights, the risk increased from 1/106 667 flights for flights shorter than 4 hours up to 1/1264 for flights longer than 16 hours.

Table 4: Incidence rates and incidence rate ratios after flights of increasing duration.

| Duration | Cases | PY* | IR(CI95)** | IRR(CI95)# | Flights | Risk/flight*** | Case/number of flights### |
|----------|-------|-----|------------|------------|---------|---------------|--------------------------|
| No flight| 29    | 2772| 1.0 (0.7-1.5) | 1$         | 213 333 | 0.9           | 1/106 667                |
| 0-4 hrs   | 2     | 4267| 0.5 (0-1.4)   | 0.4 (0.1-1.9) | 46 272 | 10.8          | 1/9 254                  |
| 4-8 hrs   | 5     | 2180| 2.3 (0.7-4.8) | 2.3 (0.9-5.9) | 37 905 | 15.8          | 1/6 317                  |
| 8-12 hrs  | 6     | 2576| 2.2 (0.8-4.4) | 2.2 (0.9-5.4) | 13 209 | 53.0          | 1/1 687                  |
| 12-16 hrs | 7     | 1344| 5.2 (2.0-9.9) | 5.3 (2.3-12.4) | 5 045  | 79.3          | 1/1 264                  |
| >16 hrs   | 4     | 672 | 5.9 (1.5-13.4) | 5.7 (2.0-16.5) | 672    |               |                          |

$ The reference category for calculation of incidence rate ratios was no flight in a time-window of 8 weeks
* PY: Person-years
** IR: Incidence rate per 1000 person-years with CI95s
# IRR: Incidence rate ratio adjusted for age and sex with CI95s
*** Risk per flight: risk per 100 000 flights
### Number of flights needed to cause one venous thrombosis

In Table 5, the incidence rates and rate ratios are shown in relation to the time that had passed after travelling. In the first two weeks after a long haul flight, the risk of venous thrombosis was highest, with an incidence rate of 4.7 per 1000 person-years (CI95 2.4-7.7/1000 person-years). The risk gradually decreased with time and returned to the baseline risk after 8 weeks.

Table 5: Incidence rates and incidence rate ratios in varying time windows after long haul flights. Only long haul flights (>4 hours) were taken into account

| Time window | Cases | PY* | IR (95%CI)** | IRR (95%CI)# |
|-------------|-------|-----|--------------|--------------|
| No flight <12 wks | 29    | 30 173 | 1.0 (0.6-1.4) | 1$          |
| 0-2 weeks   | 12    | 2 579 | 4.7 (2.4-7.7) | 4.9 (2.5-9.9) |
| 2-4 weeks   | 5     | 1 713 | 2.9 (0.9-6.1) | 3.1 (1.2-8.2) |
| 4-8 weeks   | 5     | 2 548 | 2.0 (0.6-4.1) | 2.2 (0.8-5.7) |
| 8-12 weeks  | 2     | 1 897 | 1.1 (0.1-3.1) | 1.2 (0.3-4.9) |

* Person-years
** Incidence rate per 1000 person-years and CI95s
# Incidence rate ratio adjusted for age and sex and CI95s
$ Reference category

Discussion
In this follow-up study, we found an overall absolute risk of symptomatic venous thrombosis of 1 per 4656 passengers within 8 weeks after flights longer than 4 hours. This is equivalent to an incidence rate of 3.2 per 1000 person-years. The risk was 3.2-fold increased compared to those who did not travel by air. The risk of venous thrombosis increased with exposure to several flights and longer duration of travel and it decreased with time after a flight. It was particularly high.
in younger travellers, women - especially those taking oral contraceptives - individuals who were particularly short or tall and those with a BMI over 25 kg/m², although due to the small number of cases, some confidence intervals were wide, indicating considerable uncertainty for the effect estimates.

The observed rate ratio of 3.2 for flights longer than 4 hours is similar to the odds ratios found in most case-control studies. Only two studies have previously described absolute risks of venous thrombosis after air travel, but only for severe pulmonary embolism occurring immediately after flying. In our study, the risk of venous thrombosis was highest in the first 2 weeks after air travel, which was also demonstrated by Kelman in a record-linkage study.

Previous studies showed a dose-response relationship between the distance travelled and the risk of venous thrombosis. In our study we observed three dose-response relationships. The risk of venous thrombosis increased with duration of air travel and number of flights and decreased with time after the flight. These dose-response relationships are in line with a causal association between air travel and deep vein thrombosis.

The effect of air travel was pronounced in women using oral contraceptives. This was also demonstrated in a previous case-control study. Travellers who were particularly short or tall also had a higher risk of venous thrombosis after air travel than those with a height between 165 and 185 cm. In the tall travellers, this may be explained by an extremely cramped position due to insufficient leg-space. In travellers who are shorter than 165 cm, the increased risk may be explained by pressure on the popliteal vein by the airplane seat, when their feet do not touch the floor. This higher risk in both tall and short travellers was previously found in a large population-based case-control study. This is an important finding that has now been demonstrated in two different populations, indicating a need for adjustable seating in the aircraft.

A remarkable finding in our study was that the incidence rate of venous thrombosis after exposure to flights shorter than 4 hours seemed lower (0.5/1000 person-years) than the unexposed incidence rate (1.0/1000 person-years). Although the confidence intervals overlap and a difference by chance cannot be ruled out, we think that it may be explained by a so-called healthy traveller effect, which has also been proposed by Kelman and colleagues. This implies that the incidence rate in the absence of travel is lower in a travelling population than in the general population, since the former is generally healthier. To assess whether this was the case in our study, we separately calculated the baseline (unexposed) incidence rates for employees who travelled at least once a year and for those who travelled less than once a year. We found that the baseline incidence rate was indeed lower in employees who travelled more frequently.
0.5/1000 person-years vs 1.2/1000 person-years for those who travelled hardly). One could therefore argue to use only employees who made at least one long haul flight per year as a reference group, which would have resulted in higher rate ratios (which can be inferred from the tables). However, the absolute risks would have remained the same.

Another remarkable finding in this study was the high risk in young travellers. This may be due to a phenomenon called attrition of susceptibles, meaning that susceptible individuals are likely to develop a disease shortly after start of exposure to a risk factor, such as haemorrhage shortly after start of anticoagulant therapy\(^{18}\). Most employees in our cohort had been frequent travellers long before our observation period started. Since the youngest employees are most likely to be ‘new frequent travellers’, this may explain the high absolute risk of thrombosis after air travel in the youngest age category. We assessed whether this was the case as follows: If attrition of susceptibles is present, the baseline incidence rate (i.e. the incidence rate of venous thrombosis without exposure to air travel) in employees who hardly travel (less than once a year) would increase with age. The baseline incidence in employees who do fly frequently (> once a year) would not increase as much with age, since in this group, susceptible individuals would already have suffered from VT at a younger age, soon after they became frequent traveller, and hence be excluded from our study population. We found that in our study, the baseline incidence in individuals with a low travel-frequency (less than once a year) indeed rose from 0.7/1000 person years in the youngest age category (<30 years), to 3.2/1000 person years in the oldest age category (>50 years). In contrast, in individuals with a higher travel frequency, the baseline incidence rate in both the youngest age category and those between 30 and 50 was 0.8 per 1000 person years, whereas no VT occurred in 1521 person-years in the oldest age category. Furthermore, in the individuals with a low travel-frequency (< once per year), the incidences in all age-groups were very high in case they did travel (24/1000 person years for those under 30, 7/1000 person years for those between 30-50 and 40/1000 person years for those over 50). So, in these subjects, who do not travel on a regular basis, the thrombosis risk is high when they occasionally do. These results all suggest that the risk of air-travel related VT is highest in susceptible subjects soon after they first start travelling by air, i.e. that attrition of susceptibles is present.

A possible limitation of this study is the response of 32%. Employees who suffered from venous thrombosis may be more likely to complete the questionnaire than employees who did not. This would only create bias if employees who suffered from VT directly after air travel responded more
frequently than those who suffered from thrombosis without air travel. The response varied considerably per organisation between 15% and 80%. To assess the effect of the response, we analyzed organisations with a low response (<60%) and those with a high response (>60%) separately. The outcomes did not differ substantially between these two groups of employees, indicating that the low response did not bias our findings. Furthermore, we may have missed employees who died or stopped working due to disability resulting from a venous thrombosis. Although this is unlikely to have occurred often, it may have led to an underestimation of the number of cases.

Another limitation is that these results cannot be generalized to an older, less healthy population. This study has been performed in a working population with a mean age of 40. We do not have any data on people older than 70, nor on individuals who are not fit enough to be employed. Considering this, the absolute risk of venous thrombosis in the general population is likely to be higher than the risk we found. Furthermore, the results cannot be generalized to individuals that have a history of venous thrombosis, as we only considered first events. From this cohort study among employees of international organisations and companies, we conclude that the absolute risk of symptomatic venous thrombosis within 8 weeks of a flight of at least 4 hours is approximately 1 per 4500 flights. Furthermore, we found 3 dose-response relationships: the risk of venous thrombosis increased with duration of travel and number of flights a person was exposed to and decreased with time after a long haul flight. The results of our study do not justify the use of potentially dangerous prophylaxis such as anticoagulant therapy for all long haul air travellers, since this may do more harm than good17. However, for some subgroups of people with a highly increased risk, the risk-benefit ratio may favour the use of prophylactic measures. Large randomized trials are required to assess who would benefit most from which prophylactic measure.
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