Chapter 1

Introduction
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In venous thrombosis, blood clot formation occurs at an inappropriate site in one of the veins, causing obstruction. This usually causes swelling, redness and pain at the affected site. Most often the deep veins of the legs are involved, but it may also occur in other sites, such as the upper extremity, cerebral sinus, liver or retina. Sometimes, parts of a blood clot dislodge and travel through the bloodstream. These so-called emboli usually end up in the lungs, where they reduce the blood flow, causing a potentially fatal condition called pulmonary embolism.

Venous thrombosis occurs at an incidence rate of approximately 1-2 per 1000 persons per year\textsuperscript{1,2,3}, with an estimated mortality of approximately 5% in patients with deep vein thrombosis of the leg and even 10% in those with pulmonary embolism\textsuperscript{2}. A serious complication is the disabling post-thrombotic syndrome, occurring in up to 50% of patients with deep vein thrombosis of the leg\textsuperscript{4}. Treatment consists of anticoagulant therapy, which is highly effective, but has the serious side-effect of bleeding. The annual risk of any bleeding in patients using oral anticoagulants is approximately 15% and that of a major hemorrhage (intracranial or life-threatening bleeding at other sites) approximately 3%\textsuperscript{5}.

Venous thrombosis is a multicausal disease, in which genes and environment interact\textsuperscript{6}. The strongest risk factor for venous thrombosis is older age, since the risk increases exponentially with age\textsuperscript{2}. The most prevalent genetic risk factors for venous thrombosis are factor V Leiden mutation\textsuperscript{7} and prothrombin G20210A mutation\textsuperscript{8}, each present in several percent of the population. Environmental factors that increase the risk of venous thrombosis include oral contraceptive use, hormone replacement therapy, pregnancy, recent delivery, recent surgery, major trauma, plaster cast, immobilization and malignant diseases\textsuperscript{6-9}. In the past decades, long distance travel, especially by air, has been identified as a risk factor for venous thrombosis as well.

The first cases of travel-related venous thrombosis were reported by Jacques Louvell in 1951\textsuperscript{10}. Since then, many case reports and case-series on venous thrombosis associated with long distance travel have been published. After a young woman died of pulmonary embolism at Heathrow airport, after a flight from Australia to the United Kingdom, the UK government and the European Union decided to fund a large international research program on the association between air travel and venous thrombosis. This research program was called
the WRIGHT project (World Health Organisation Research Into Global Hazards of Travel). This project was carried out, under auspices of the World Health Organisation, by researchers from the Netherlands (at the department of Clinical Epidemiology at the Leiden University Medical Center and the department of Vascular Medicine at the Academic Medical Center in Amsterdam) and the United Kingdom (at the department for Cardiovascular Sciences at the University of Leicester). Several studies were conducted at the same time, to study both epidemiologic and pathophysiological aspects of the association between venous thrombosis and air travel.

**Thesis outline**
This thesis focuses on epidemiological aspects of the association between long distance travel and venous thrombosis.
Chapter 2 summarizes all literature available on the association between venous thrombosis and travel so far. Both epidemiological studies and studies on the possible mechanisms responsible for the increased risk of venous thrombosis after travel are discussed.
In Chapter 3, a study on the use of prophylactic measures to prevent travel-related thrombosis amongst visitors of three international conferences is reported.
In Chapter 4, we present an estimate of the absolute risk of developing venous thrombosis shortly after air travel. Furthermore, the effect of exposure to several flights at the same time, duration of flights and time after a long haul flight was studied.
In Chapter 5, a study on the effect of elevated coagulation factors and combinations with other known risk factors for venous thrombosis (Factor V Leiden mutation, prothrombin 20210A mutation, increased body mass index and oral contraceptive use) on the risk of venous thrombosis within travellers is presented.
In Chapter 6, we present a study on the effect of transient risk factors for venous thrombosis (recent surgery, malignant diseases, plaster cast, oral contraceptive use, hormone replacement therapy, pregnancy or recent delivery) on the risk of travel-related venous thrombosis.
Finally, in Chapter 7, a study on the occurrence of symptomatic venous thrombosis in commercial airline pilots in the Netherlands is described.
Reference List


(10) Jacques-Louvel. [Four cases of phlebitis due to air travel.]. Arch Mal Coeur Vaiss 1951; 44:748-749.