

Factor V Leiden and the Risk for Venous Thromboembolism in the Adult Danish Population

Klaus Juul, MD; Anne Tybjærg-Hansen, MD, DMSc; Peter Schnohr, MD; and Børge G. Nordestgaard, MD, DMSc

Background: Odds ratios for venous thromboembolism (deep venous thrombosis and pulmonary embolism) derived from case-control studies range from 3 to 16 for heterozygotes compared with noncarriers and up to 79 for homozygotes compared with noncarriers.

Objective: To estimate risks for venous thromboembolism in the adult Danish population according to factor V Leiden genotype.

Design: Cohort study with 23 years of follow-up.

Setting: Adult Danish population.

Participants: 9253 randomly selected individuals.

Measurements: Hospitalization and death from venous thromboembolism, factor V Leiden genotype, and additional thromboembolic risk factors.

Results: Adjusted hazard ratios in heterozygotes and homozygotes compared with noncarriers were 2.7 (95% CI, 1.8 to 3.8) and 18 (CI, 4.1 to 41) for venous thromboembolism overall, 2.4

(CI, 1.3 to 3.8) and 22 (CI, 0 to 60) for deep venous thrombosis, and 3.0 (CI, 1.7 to 4.9) and 11 (CI, 0 to 33) for pulmonary embolism. The lowest absolute 10-year risks for venous thromboembolism in factor V Leiden heterozygotes and homozygotes—0.7% (CI, 0.5% to 1.0%) and 3% (CI, 1% to 8%)—were found in nonsmokers younger than 40 years of age with a body mass index below 25 kg/m²; the corresponding highest risks—10% (CI, 7% to 14%) and 51% (CI, 13% to 100%)—were found in smokers older than 60 years of age with a body mass index above 30 kg/m².

Conclusions: Hazard ratios for venous thromboembolism in factor V Leiden heterozygotes and homozygotes compared with noncarriers in the adult Danish population were approximately 3 and 18, respectively. The simultaneous presence of smoking, obesity, and old age resulted in absolute 10-year thromboembolic risks of 10% in heterozygotes and 51% in homozygotes.

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For author affiliations, see end of text.

Venous thromboembolism is associated with more than 300 000 hospitalizations and 50 000 deaths every year in the United States alone (1). Factor V Leiden is the most frequent hereditary risk factor for venous thromboembolism; it is present in 1% to 7% of white persons and almost never affects black and Asian persons (1, 2).

The reported excess risk for venous thromboembolism associated with factor V Leiden (or its phenotype, resistance to activated protein C) varies considerably among studies: Compared with noncarriers, odds ratios between 3 and 16 have been reported for heterozygotes (3–10), while a single study reported an odds ratio of 79 for homozygotes (4). Most of these studies are case-control studies (3, 4, 6–10), and no population-based prospective study has been published. Because odds ratios from case-control studies may overestimate risk in healthy factor V Leiden heterozygotes and homozygotes, a study to estimate such risks in the adult population at large is warranted.

Our main purpose was to estimate hazard ratios for venous thromboembolism in factor V Leiden heterozygotes and homozygotes in the adult Danish population. We also investigated whether factor V Leiden increased hazard ratios for primary and secondary thromboembolic events equally and whether hazard ratios for deep venous thrombosis and pulmonary embolism differed. Finally, we estimated absolute risks for venous thromboembolism according to factor V Leiden genotype that depended on the presence or absence of other thromboembolic risk factors. For these purposes, we performed genotyping on 9253 in-

dividuals from the adult Danish population who were participants in the Copenhagen City Heart Study (11).

METHODS

Study Design

The Copenhagen City Heart Study is a prospective cardiovascular study of individuals randomly selected according to the Central-Population-Register code to reflect the adult Danish population at large. Those invited were stratified into 5-year age groups ranging from 20 to 95 years; 35- to 70-year-old persons were emphasized. In 1976–1978, 19 329 individuals were invited, of whom 74% (14 223) participated. In 1981–1983, the original cohort supplemented with 500 20- to 25-year-olds was invited to participate; 70% (12 698) participated. Finally, in 1991–1994 the cohort was further supplemented with 3000 20- to 49-year-old persons, and of those invited 61% (10 135) participated. More than 99% of participants were white persons of Danish descent. Of the 10 135 participants who attended the 1991–1994 examination, 9259 gave blood for DNA analyses. Of these, 9253 underwent genotyping for factor V Leiden as previously described (11, 12). We did not exclude participants with a thromboembolic event before entry into the Copenhagen City Heart Study.

Of the 9253 participants who were analyzed for factor V Leiden, all attended 1 examination, 80% attended 2 examinations, and 77% attended 3 examinations. Examinations included a self-administered questionnaire, a phys-

ical examination, and blood samples. Clinical and demographic data as well as data on nonresponders have been published previously (13–15). At some time during follow-up, 555 women used oral contraceptives and 1125 used postmenopausal hormone replacement therapy. No women experienced a thromboembolic event while using oral contraceptives, but 11 women had an event while using postmenopausal hormone replacement therapy.

We followed all individuals from baseline until the occurrence of a venous thromboembolic event or until censoring. Baseline was defined as the date at which the participant was first selected for inclusion into the Copenhagen City Heart Study. For 7166 participants, baseline was the 1976–1978 examination, for 277 it was the 1981–1983 examination, and for 1810 it was the 1991–1994 examination. We terminated any further follow-up on 31 December 1999 because this was the last date on which complete diagnostic information on end points was obtained.

Seventy-six participants emigrated during follow-up and were therefore censored at the emigration date. Four participants who could not be traced were censored at the date on which they were lost. Consequently, follow-up is more than 99% complete. Median follow-up time was 23 years (range, 0.04 to 23 years).

We gathered information on incident cases of deep venous thrombosis (International Classification of Diseases, 8th revision [ICD-8], codes 451.00, 451.08, 451.09, 451.90, 451.92, 671.01–671.09 and ICD, 10th revision [ICD-10], codes I80.1, I80.2, I80.3, O22.3, O87.1) and pulmonary embolism (ICD-8 codes 450.99, 673.99 and ICD-10 codes I26.0, I26.9, O88.2) until 31 December 1999 from the Danish National Hospital Discharge Register and from the Danish National Register of Causes of Death. We classified venous thromboembolic events as secondary if they occurred 1) in a participant with a history of cancer ($n = 27$) or with incident cancer within 5 years of the thromboembolic event ($n = 12$), 2) during a hospitalization for a cause other than venous thromboembolism ($n = 72$), 3) within 12 months of hospitalization for fracture of the lower extremities or for a cerebrovascular event ($n = 6$), 4) during pregnancy or puerperium ($n = 0$), 5) during use of oral contraceptives ($n = 0$), or 6) during postmenopausal hormone replacement therapy ($n = 11$). We classified all other events as primary thromboembolic events. In analyses on isolated deep venous thrombosis, we excluded participants with pulmonary embolism.

Venous thromboembolic events obtained by requesting hospital records on individuals registered with a venous thromboembolic event from 1980 through 2000 from the Danish National Hospital Discharge Register were validated by others: Among the 176 medical records from North Jutland County with a discharge ICD code for venous thromboembolism, 72% of cases met objective diagnostic criteria (Bjerregaard Larsen T. Personal communication). The diagnostic criteria used were ultrasonography or

Context

Estimates of risk for venous thromboembolism associated with factor V Leiden vary.

Contribution

This population-based cohort study found that heterozygotes and homozygotes for factor V Leiden had about 3 and 18 times higher risks for venous thromboembolism than noncarriers. Absolute 10-year risks for thromboembolism were 0.7% and 3% among heterozygotes and homozygotes younger than 40 years of age who did not smoke and were not overweight. The 10-year risks in heterozygotes and homozygotes older than age 60 years who smoked and were overweight were 10% and 51%.

Implications

Risks for thromboembolism associated with factor V Leiden are important but probably lower than previously reported.

—The Editors

venography in the case of deep venous thrombosis and ventilation–perfusion scintigraphy or pulmonary angiography in the case of pulmonary embolism. All hospitals in Denmark report to the Danish Hospital Discharge Register. Likewise, all death certificates in Denmark are registered in the Danish Register of Causes of Death. The physicians attending patients from the Copenhagen City Heart Study did not use a diagnostic protocol defined specifically by the Copenhagen City Heart Study but rather used Danish standard diagnostic practices, which included venography for the diagnosis of deep venous thrombosis and ventilation–perfusion scintigraphy for the diagnosis of pulmonary embolism in the period 1976–1999.

The Danish ethics committee for the City of Copenhagen and Frederiksberg approved the study (#100.2039/91). All participants gave written informed consent.

Statistical Analysis

We analyzed data using the Stata statistical software package, version 8.0 (Stata Corp., College Station, Texas). We made 2-group comparisons using the Pearson chi-square test, Student *t*-test, or Mann–Whitney U-test. A 2-sided *P* value less than 0.05 was considered statistically significant.

We present plots of cumulative incidence (Nelson–Aalen estimate) as a function of age, and we tested differences between factor V Leiden genotypes for significance by using the log-rank test. When left truncation (that is, delayed entry) was used with age as the time scale, Cox proportional hazards models estimated hazard ratios for venous thromboembolism. This means that differences in age are automatically adjusted for. The final Cox regression model included the following covariates, which were forced

Table 1. Baseline Characteristics of Participants according to Factor V Leiden Genotype

Characteristic	Noncarriers	Heterozygotes	Homozygotes
Sex, n			
Women	4713	397	10
Men	3821	302	10
Mean age \pm SD, y	45 \pm 12	46 \pm 12	47 \pm 8
Body mass index \pm SD, kg/m ²	25 \pm 3.8	25 \pm 3.9	24 \pm 3.0
Women using oral contraceptives, %	10	10	0
Women using postmenopausal hormone replacement therapy, %	11	9	20
Postmenopausal women, %	43	44	60
Smoking, %	58	58	60
Leisure time physical activity, %			
<2 h/wk	14	12	16
2–4 h light exercise/wk	52	57	58
2–4 h demanding exercise/wk	30	28	26
>4 h demanding exercise/wk	4	3	0

into all models: factor V Leiden genotype, sex, body mass index (<25, 25 to 30, and >30 kg/m²), smoking status (smoker or nonsmoker), previous myocardial infarction, leisure time physical activity (<2 hours per week, 2 to 4 hours of light exercise per week, 2 to 4 hours of demanding exercise per week, or >4 hours of exercise per week), use of oral contraceptives, use of postmenopausal hormone replacement therapy, menopausal status, and year of entry. We constructed 95% CIs using bootstrap estimation (10 000 replications) with the 2.5th and 97.5th percentiles of the generated hazard ratio distribution as the lower and upper limits. The baseline value for each covariate, as well as values from subsequent examinations, was used. Interaction between factor V Leiden genotype and other covariates in the models was tested for statistical significance by using the likelihood ratio test to compare the model with and without the 2-factor interaction term. Proportionality of hazards over time for the individual covariate was assessed by plotting $-\ln(-\ln(\text{survival}))$ versus $\ln(\text{analysis time})$. Suspicion of nonparallel lines was further tested by

using Schoenfeld residuals. We detected no violations of the proportional hazards assumption. To investigate whether factor V Leiden increases the risk for deep venous thrombosis rather than for pulmonary embolism and also increases the risk for primary thromboembolism rather than for secondary events, we performed Cox regression on participants with venous thromboembolism. The end points in these models were deep venous thrombosis or primary events, and the same covariates as mentioned above were forced into the models. A Wald test *P* value greater than 0.05 indicates no significant difference between the effect on primary and secondary events or between deep venous thrombosis and pulmonary embolism.

Estimated absolute risks for venous thromboembolism (deep venous thrombosis and pulmonary embolism combined) were calculated by using the regression coefficients from a Poisson regression model with the same covariates as previously described and, in addition, age at entry in 3 groups (<40 years, 40 to 60 years, and >60 years). We constructed 95% CIs using bootstrap estimation as previ-

Table 2. Hazard Ratios for Venous Thromboembolism by Factor V Leiden Genotype

Venous Thromboembolic Event*	Participants, n	Person-Years of Follow-up	Events, n	Incidence Rate: Events/1000 Person-Years	Hazard Ratio (95% CI)	
					Crude	Adjusted†
All						
Noncarriers	8534	161 874	173	1.1 (0.9–1.2)	1.0	1.0
Heterozygotes	699	12 970	38	2.9 (2.1–4.0)	2.7 (1.8–3.7)	2.7 (1.8–3.8)
Homozygotes	20	343	5	15 (4.7–34)	16 (3.5–33)	18 (4.1–41)
Primary event						
Noncarriers	8426	161 425	65	0.4 (0.3–0.5)	1.0	1.0
Heterozygotes	680	12 891	19	1.5 (0.9–2.4)	3.6 (2.0–5.8)	3.7 (2.0–6.1)
Homozygotes	19	337	4	12 (3.2–30)	31 (6.2–70)	36 (6.3–96)
Secondary events						
Noncarriers	8469	161 646	108	0.6 (0.5–0.8)	1.0	1.0
Heterozygotes	680	12 907	19	1.5 (0.9–2.3)	2.1 (1.2–3.3)	2.1 (1.1–3.3)
Homozygotes	16	328	1	3.2 (0.1–18)	5.6 (0–20)	6.9 (0–25)

* Venous thromboembolic events were classified as secondary if they occurred 1) in a participant with a history of cancer or with incident cancer within 5 years of the thromboembolic event, 2) during a hospitalization for a cause other than venous thromboembolism, 3) within 12 months of hospitalization for fracture of the lower extremities or cerebrovascular event, 4) during pregnancy or puerperium, 5) during use of oral contraceptives, or 6) during postmenopausal hormone replacement therapy. All other events were classified as primary thromboembolic events.

† Adjusted for sex, body mass index (<25, 25–30, and >30 kg/m²), smoking status (smoker or nonsmoker), previous myocardial infarction, leisure time physical activity (<2 h/wk, 2–4 h light exercise/wk, 2–4 h demanding exercise/wk, or >4 h exercise/wk), use of oral contraceptives, use of postmenopausal hormone replacement therapy, menopausal status, and year of entry.

ously described. Absolute risks are presented as estimated incidence rates (events/10 years) in percentages.

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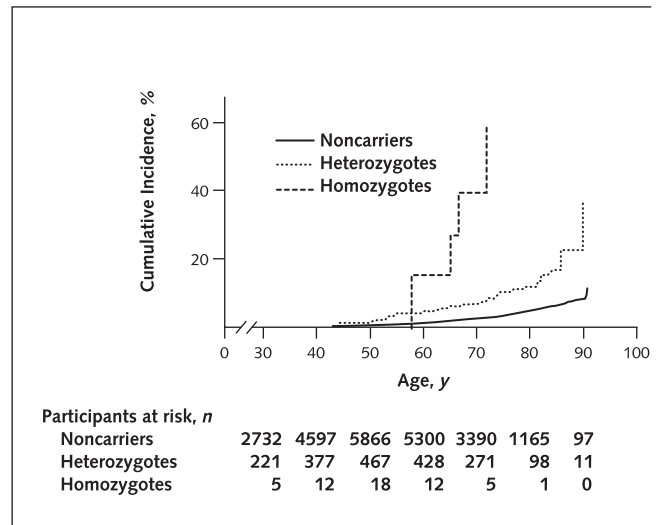
RESULTS

In this adult Danish population cohort, 8534 persons were noncarriers of factor V Leiden, 699 were heterozygotes, and 20 were homozygotes. This genotype distribution did not differ from that predicted by the Hardy-Weinberg equilibrium ($P = 0.16$). Baseline characteristics did not differ with respect to factor V Leiden genotype (Table 1).

Risk for Venous Thromboembolism

The cohort was followed for a total of 175 187 person-years, during which 216 thromboembolic events occurred, producing the following incidence rates: 1.1 events/1000 person-years (95% CI, 0.9 to 1.2) in factor V Leiden noncarriers, 2.9 events/1000 person-years (CI, 2.1 to 4.0) in heterozygotes, and 15 events/1000 person-years (CI, 4.7 to 34) in homozygotes (Table 2). The cumulative incidence of venous thromboembolism as a function of age differed among factor V Leiden noncarriers, heterozygotes, and homozygotes (Figure 1). Hazard ratios for venous thromboembolism adjusted for age, sex, smoking, body mass index, leisure time physical activity, previous myocardial infarction, oral contraceptives, hormone replacement therapy, menopause, and year of entry into the study were 2.7 (CI, 1.8 to 3.8) and 18 (CI, 4.1 to 41) in heterozygotes and homozygotes, respectively, compared with noncarriers (Table 2). Formal testing of bivariate multiplicative interaction between factor V Leiden genotype and age, sex, smoking, body mass index, leisure time physical activity, previous myocardial infarction, menopause, and year of entry did not reveal any significant interactions ($P > 0.2$; $P > 0.2$; $P = 0.13$; $P = 0.09$; $P > 0.2$; $P > 0.2$; $P > 0.2$; and $P = 0.06$, respectively). We could not test interaction

Figure 1. Cumulative incidence of venous thromboembolism (deep venous thrombosis and pulmonary embolism combined) according to factor V Leiden genotype.



For heterozygotes compared with noncarriers, homozygotes compared with noncarriers, and homozygotes compared with heterozygotes, log-rank $P < 0.001$.

between factor V Leiden and use of oral contraceptives and hormone replacement therapy because of an insufficient number of events in some strata.

Risk for Primary and Secondary Thromboembolic Events

Adjusted hazard ratios for primary venous thromboembolism in heterozygotes and homozygotes compared with noncarriers were 3.7 (CI, 2.0 to 6.1) and 36 (CI, 6.3 to 96) (Table 2). Corresponding hazard ratios for secondary events were 2.1 (CI, 1.1 to 3.3) and 6.9 (CI, 0 to 25). Hazard ratios for primary and secondary events did not differ in heterozygotes or homozygotes compared with noncarriers ($P = 0.16$ and $P = 0.11$, respectively).

Risk for Deep Venous Thrombosis and Pulmonary Embolism

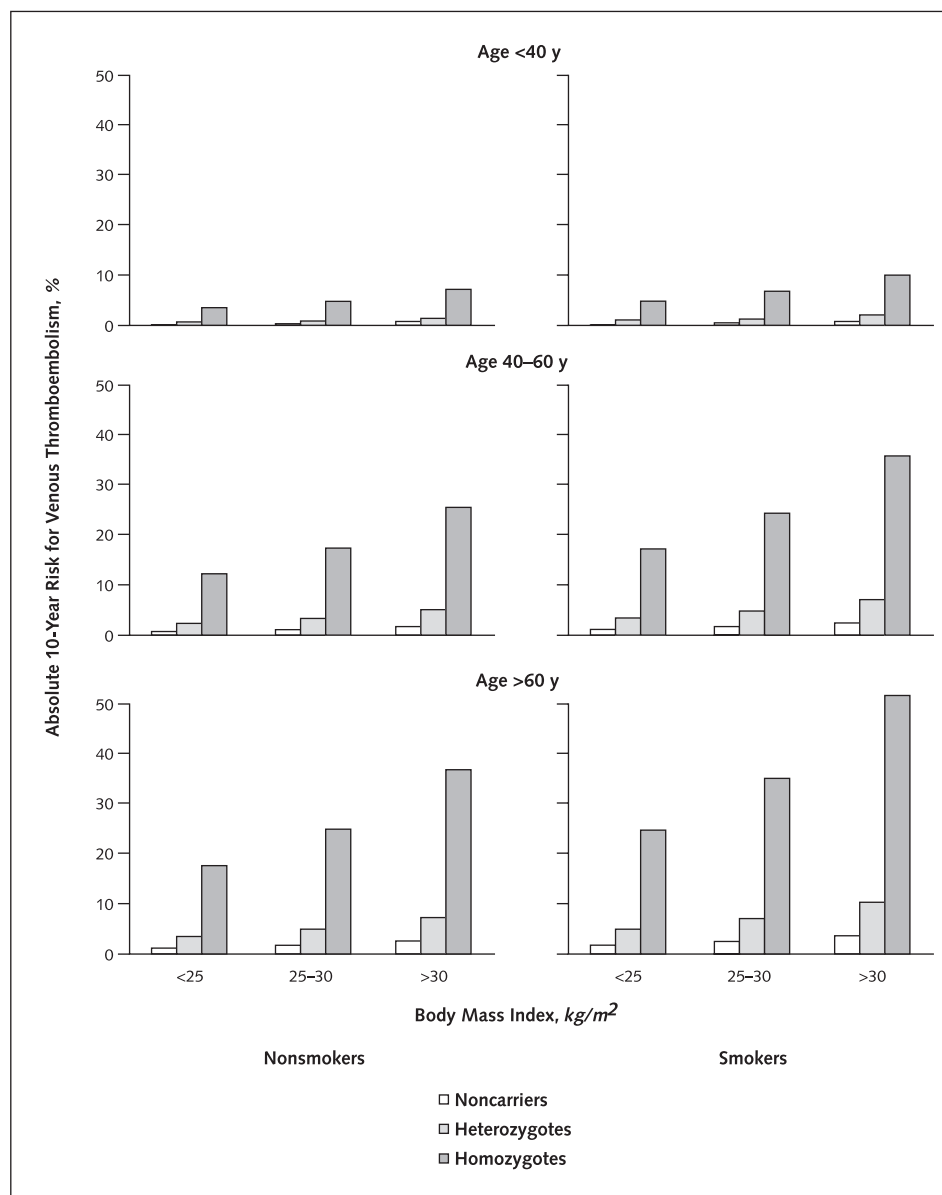
Adjusted hazard ratios for deep venous thrombosis in factor V Leiden heterozygotes and homozygotes compared

Table 3. Hazard Ratios for Deep Venous Thrombosis and Pulmonary Embolism by Factor V Leiden Genotype

Venous Thromboembolic Event	Participants, n	Person-Years of Follow-up	Events, n	Incidence Rate: Events/1000 Person-Years	Hazard Ratio (95% CI)	
					Crude	Adjusted*
Deep venous thrombosis						
Noncarriers	8456	160 695	95	0.6 (0.5–0.7)	1.0	1.0
Heterozygotes	680	12 742	19	1.5 (0.9–2.3)	2.5 (1.4–3.9)	2.4 (1.3–3.8)
Homozygotes	18	323	3	9.3 (1.9–27)	17 (0–43)	22 (0–60)
Pulmonary embolism						
Noncarriers	8534	162 648	78	0.5 (0.4–0.6)	1.0	1.0
Heterozygotes	699	13 129	19	1.4 (0.9–2.3)	2.9 (1.6–4.6)	3.0 (1.7–4.9)
Homozygotes	20	384	2	5.2 (0.6–19)	12 (0–32)	11 (0–33)

* Adjusted for sex, body mass index (<25, 25–30, and >30 kg/m²), smoking (smoker or nonsmoker), previous myocardial infarction, leisure time physical activity (<2 h/wk, 2–4 h light exercise/wk, 2–4 h demanding exercise/wk, or >4 h exercise/wk), use of oral contraceptives, use of postmenopausal hormone replacement therapy, menopausal status, and year of entry.

Figure 2. Absolute 10-year risk for venous thromboembolism (deep venous thrombosis and pulmonary embolism combined) according to age, smoking, body mass index, and factor V Leiden genotype.



with noncarriers were 2.4 (CI, 1.3 to 3.8) and 22 (CI, 0 to 60) (Table 3). Corresponding hazard ratios for pulmonary embolism were 3.0 (CI, 1.7 to 4.9) and 11 (CI, 0 to 33). Hazard ratios for deep venous thrombosis and pulmonary embolism did not differ in heterozygotes or homozygotes compared with noncarriers ($P > 0.2$ and $P > 0.2$).

Absolute Risk for Venous Thromboembolism

The lowest absolute 10-year risks for venous thromboembolism were 0.7% (CI, 0.5% to 1%) and 3% (CI, 1% to 8%) in factor V Leiden heterozygotes and homozygotes among nonsmokers younger than 40 years of age with a body mass index below 25 kg/m² (Figure 2). Absolute risk increased with increasing age, increasing body mass index,

smoking, and factor V Leiden genotype in a gene dose-dependent manner. The highest absolute 10-year risks for venous thromboembolism for factor V Leiden heterozygotes and homozygotes were 10% (CI, 7% to 14%) and 51% (CI, 13% to 100%) in smokers older than 60 years of age with a body mass index above 30 kg/m².

DISCUSSION

We conclude that the hazard ratios for venous thromboembolism (that is, deep venous thrombosis and pulmonary embolism) in factor V Leiden heterozygotes and homozygotes compared with noncarriers in the adult Danish

Table 4. Previous Studies of Factor V Leiden and Venous Thromboembolism*

Study, Year (Reference)	Study Design	Case-Patients/Controls, n/n	End Point	Odds Ratio (95% CI)
Heterozygotes only				
Rosendaal et al., 1995 (4)	Case-control	471/474	DVT	7.4 (4.1–13)
Ridker et al., 1995 (5)	Nested case-control	121/121	DVT/PE	2.7 (1.3–5.6)
Martinelli et al., 1997 (10)	Case-control	212/212	DVT/PE	7.3 (3.0–18)
Turkstra et al., 1997 (9)	Case-control	92/128	PE	4.2 (1.3–14)
Leroyer et al., 1997 (3)	Case-control	165/200	DVT/PE	4.1 (1.8–9.4)
Salomon et al., 1999 (8)	Case-control	162/336	DVT/PE	16 (8.5–31)
Cattaneo et al., 1999 (6)	Case-control	104/69	DVT	6.9 (3.2–15)
Gaustadnes et al., 1999 (7)	Case-referent	196/4188	DVT	5.1 (3.6–7.2)
Homozygotes only				
Rosendaal et al., 1995 (4)	Case-control	471/474	DVT	79 (22–289)
Heterozygotes and homozygotes combined				
Manten et al., 1996 (16)	Case-control	279/474	DVT/PE	6.2 (3.3–11)
Margaglione et al., 1998 (17)	Case-control	281/850	DVT/PE	4.2 (2.7–6.4)
Chamouard et al., 1999 (18)	Case-control	60/42	DVT	18 (3.9–79)
Catto et al., 1999 (19)	Case-control	226/254	DVT/PE	2.4 (1.2–4.9)
Aznar et al., 2000 (20)	Case-control	229/246	DVT	8.4 (2.9–24)

* Odds ratios are presented as reported in the original paper wherever possible; however, if odds ratios were not presented in the original paper, we calculated them on the basis of the original data presented. If possible, odds ratios for heterozygotes versus noncarriers were calculated from the presented data. DVT = deep venous thrombosis; PE = pulmonary embolism.

population are approximately 3 and 18. Our hazard ratio in heterozygotes is lower than odds ratios reported in most case-control studies (3, 4, 6–10) (Table 4). Likewise, our hazard ratio for homozygotes is lower than the odds ratio of 79 (CI, 22 to 289) reported in the Leiden Thrombophilia Study (4), even though both estimates are somewhat unstable.

Discrepancy between case-control studies and our study of the adult Danish population may reflect the fact that case-patients in case-control studies have other known and unknown risk factors, which may introduce so-called ascertainment bias. For example, 66% of female case-patients in the Leiden Thrombophilia Study were using oral contraceptives at the time of their thromboembolic event, while no patients in our study were using oral contraceptives at the time of their event. A consequence of ascertainment bias is an overestimation of the importance of a given risk factor. In other words, extrapolations from case-control studies to the population at large may not be appropriate. Ascertainment bias does not affect a study such as ours, in which participants are included irrespective of disease status.

Previous studies have reported that factor V Leiden heterozygosity increases the risk for deep venous thrombosis rather than pulmonary embolism (9, 16, 21–23). This could be because studies of pulmonary embolism enrolled unselected patients, whereas studies of deep venous thrombosis were from thrombosis clinics (24). In our study, we could not demonstrate that factor V Leiden heterozygosity or homozygosity increased the risk for deep venous thrombosis more than for pulmonary embolism. Furthermore, another previous report (5) suggested that factor V Leiden increases the risk for primary thromboembolic events rather than for secondary events. Again, we could not con-

firm this finding. However, lack of statistical power makes conclusions on homozygotes questionable.

We cannot exclude an effect of interaction between factor V Leiden and oral contraceptives or postmenopausal hormone replacement therapy on secondary venous thromboembolism because of lack of statistical power. This represents a limitation of our study; however, when we repeated the analysis after excluding events secondary to oral contraceptives ($n = 0$) or postmenopausal hormone replacement therapy ($n = 11$), adjusted hazard ratios for secondary thromboembolic events were similar: 2.3 (CI, 1.3 to 3.7) and 8.0 (CI, 0 to 30) (compare with Table 2).

Information on anticoagulant therapy is not available in the Copenhagen City Heart Study. Because we observed only 20 factor V Leiden homozygotes, hazard ratios for venous thromboembolism could be biased if some of the homozygotes received anticoagulant therapy for longer periods. To exclude such bias, we attempted telephone interviews with all homozygotes: Six had died, 2 could not be reached, and 12 were interviewed; of those 12, none had ever received anticoagulant therapy before or during follow-up. The 3 surviving homozygotes who sustained a thromboembolic event received anticoagulant therapy after the event for 6 months, 6 months, and 3 years, respectively; however, because these treatments occurred after events, they do not affect the reported hazard ratio. In contrast, we cannot exclude the possibility that some factor V Leiden heterozygotes or noncarriers received such treatment. However, if we assume that anticoagulant therapy totally prevents venous thromboembolism, that 2% of factor V Leiden noncarriers received anticoagulant therapy, and that 10% of heterozygotes received such treatment, the incidence rates would be affected only marginally. Incidence rates for venous thromboembolism would change

from 1.1 (CI, 0.9 to 1.2) to 1.1 (CI, 0.9 to 1.3) in non-carriers and from 2.9 (CI, 2.1 to 4.0) to 3.3 (CI, 2.3 to 4.5) in heterozygotes. Consequently, the incidence rate ratio would change from 2.7 (CI, 1.9 to 3.9) to 3.0 (CI, 2.0 to 4.3). Therefore, bias due to preferential use of oral anticoagulants in heterozygotes or homozygotes cannot explain our findings.

Confounding by unmeasured thromboembolic risk factors is another possible limitation of our study. Possible confounders include high homocysteine levels; protein C and protein S deficiency; antiphospholipid syndrome; elevated levels of coagulation factors II, VIII, IX, and XI; aspirin use; and the prothrombin G20210A polymorphism. However, for these factors to confound the results of this study they must be associated with venous thromboembolism as well as with factor V Leiden genotype. To our knowledge, none of these factors have been definitively associated with factor V Leiden, suggesting that it is unlikely that confounding by such factors explains our results.

Lack of identification of all thromboembolic events in this study could introduce misclassification bias. However, because all patients are treated in public hospitals in Denmark and all hospitals report to the Danish Hospital Discharge Register and the Danish National Register of Causes of Death, underestimation of disease incidence is unlikely to seriously affect our conclusions. In addition, the incidence rates for both deep venous thrombosis and pulmonary embolism reported in our study are similar to those reported elsewhere (25). Finally, misclassification of end points probably cannot explain our findings because such misclassification is probably independent of factor V Leiden genotype.

Finally, the fact that DNA samples were not obtained before the 1991–1994 examination is another source of potential bias. If the thromboembolic mortality rate is higher among factor V Leiden heterozygotes and homozygotes than among noncarriers, our study would underestimate the association between factor V Leiden and risk for venous thromboembolism. There are, however, at least 2 arguments against such bias: 1) The allelic frequency of factor V Leiden in this study did not differ from that observed among 4188 Danish newborns (26), and 2) a study on mortality did not find any evidence for decreased life expectancy in carriers of factor V Leiden (27).

In conclusion, hazard ratios for venous thromboembolism in factor V Leiden heterozygotes and homozygotes in the adult Danish population are approximately 3 and 18, somewhat lower than odds ratios reported in previous case-control studies. The lowest and highest absolute 10-year risks for venous thromboembolism were 1% and 10% in heterozygotes, depending on age, smoking status, and obesity. Likewise, homozygosity alone is associated with a moderate 10-year absolute risk of 3%, while the simultaneous presence of old age, smoking, and obesity results in a 10-year absolute risk of 51%.

From Herlev University Hospital, Herlev, Denmark; Rigshospitalet, Copenhagen University Hospital, University of Copenhagen, and The Copenhagen City Heart Study, Bispebjerg University Hospital, Copenhagen, Denmark.

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Requests for Single Reprints: Børge G. Nordestgaard, MD, DMSc, Department of Clinical Biochemistry, Herlev University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark; e-mail, brno@herlevhosp.kbh.amt.dk.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Juul and Nordestgaard: Department of Clinical Biochemistry, Herlev University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

Dr. Tybjærg-Hansen: Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 3, DK-2100 Copenhagen, Denmark.

Dr. Schnohr: The Copenhagen City Heart Study, Bispebjerg University Hospital, Bispebjerg Bakke 23, DK-2400 Copenhagen, Denmark.

Author Contributions: Conception and design: K. Juul, A. Tybjærg-Hansen, P. Schnohr, B.G. Nordestgaard.

Analysis and interpretation of the data: K. Juul, A. Tybjærg-Hansen, B.G. Nordestgaard.

Drafting of the article: K. Juul.

Critical revision of the article for important intellectual content: K. Juul, A. Tybjærg-Hansen, B.G. Nordestgaard.

Final approval of the article: K. Juul, A. Tybjærg-Hansen, B.G. Nordestgaard.

Statistical expertise: K. Juul, A. Tybjærg-Hansen, B.G. Nordestgaard.

Obtaining of funding: K. Juul, A. Tybjærg-Hansen, B.G. Nordestgaard.

Collection and assembly of data: K. Juul, A. Tybjærg-Hansen, P. Schnohr, B.G. Nordestgaard.