# Factor V Leiden and the 10-year incidence of depression: a retrospective cohort study conducted in Germany

**Running title:** Factor V Leiden and depression

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**Abstract**

There is limited literature on the long-term relationship between the diagnosis of factor V Leiden (FVL) and depression. Therefore, the aim of this retrospective cohort study was to investigate the association between FVL and the 10-year incidence of depression in Germany. Patients diagnosed with FVL for the first time in one of 1,274 general practices in Germany between 2000 and 2019 were included in this study (index date). Patients without FVL were matched (1:5) to those with FVL by sex, age, index year, and the average number of consultations per year. In individuals without FVL, index date corresponded to a randomly selected visit date between 2000 and 2019. The association between the diagnosis of FVL and the 10-year incidence of depression was analyzed using Kaplan-Meier curves and Cox regression models. This study included 1,070 patients with and 5,350 patients without FVL (64.9% women; 46.0 [16.5] years). Ten years after the index date, 21.4% and 14.1% of individuals with and without FVL were diagnosed with depression, respectively (log-rank p-value<0.001). After adjusting for thromboembolic events, the Cox regression analysis further showed that FVL was associated with a significant increase in the incidence of depression (HR = 1.61, 95% CI = 1.33-1.95). In this study conducted in Germany, FVL was identified as a long-term risk factor for depression. More research is needed to confirm or refute the present findings in other settings.

**Keywords:** Factor V Leiden; depression; retrospective cohort study; Germany; epidemiology

## Introduction

Factor V Leiden (FVL) is a common hereditary thrombophilia resulting in activated protein C (APC) resistance (Van Cott et al., 2016). FVL is caused by a missense mutation in the gene coding for the factor V protein (i.e., G1691A), and the diagnosis of this genetic disorder relies on DNA testing (Campello et al., 2016). The prevalence of FVL varies across regions of the world, and is between 3% and 15% in European countries (Kujovich, 2011). FVL is a risk factor for venous thromboembolism, with deep venous thrombosis and pulmonary embolism being two relatively frequent manifestations in people with FVL (Kujovich, 2011).

Given the heightened risk of venous thromboembolic disorders associated with FVL, and as these conditions may be life-threatening events (Elias et al., 2016), the diagnosis of FVL potentially has immediate deleterious effects on the mental well-being of patients newly diagnosed with this hereditary thrombophilia. Indeed, research suggests that being tested for thrombophilia may lead to short-term emotional disturbances (Eichinger, 2009) and increased worries (Elson et al., 2020; Hellmann et al., 2003). An Austrian study, including 379 women undergoing FVL testing before the potential introduction of an oral contraceptive therapy, revealed that the majority of these women (76%) reported emotional disturbances in relation to this investigation (Eichinger, 2009). In a US survey of 110 patients being tested positive for FVL mutation, it was further observed that the prevalence of increased worries was approximately 43% in the sample, while 68% of individuals had numerous unanswered questions following the diagnosis (Hellmann et al., 2003). Less is known about the long-term impact of FVL diagnosis on mental health and particularly depression.

However, it may be hypothesized that FVL could lead to depression via several mediating factors such as pulmonary embolism (Tzeng et al., 2019), obstetrical complications (e.g., miscarriage (Jacob et al., 2019; Meinardi et al., 1999) and stillbirth (Gold et al., 2016; Hiltunen et al., 2010)) and early menopause in women (Georgakis et al., 2016; van Asselt et al., 2003), and being denied health and disability insurance (Bank et al., 2004; Tian et al., 2012). For example, FVL is a risk factor for stillbirth in pregnant women (Hiltunen et al., 2010), while stillbirth is known to have an negative impact on mental health (Gold et al., 2016). In this context, and as depression may also be a risk factor for recurrent thromboembolic events (von Känel et al., 2015), more data of a longitudinal nature are needed on the potential long-term relationship between FVL and incident depression.

Therefore, the goal of this retrospective cohort study conducted in Germany was to investigate the association between the diagnosis of FVL and the 10-year incidence of depression.

## Material and methods

### *Database*

Data from the Disease Analyzer database (IQVIA) were used for this study. This database has been extensively described in the literature (Rathmann et al., 2018). Briefly, the Disease Analyzer database contains demographic, diagnosis and prescription data anonymously obtained from general and specialized practices in Germany. Diagnoses are coded using the German adaptation of the International Classification of Diseases, 10$^{th}$ revision (ICD-10), while prescriptions are coded using

the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Marketing Research Association (EphMRA). Quality assessment of the data relies on several criteria such as completeness of documentation and linkage between diagnoses and prescriptions. Several variables (e.g., age of physician, specialty, community size category, and German federal state) are used for the selection of the panel of practices, and around 3% of German general and specialized practices are included in the Disease Analyzer database. Finally, previous research has shown that this database is representative of primary care practices from Germany (Rathmann et al., 2018).

*Study population*

This study included patients aged ≥18 years who received a first diagnosis of FVL (ICD-10 D68 and additional text written by the physician) in one of 1,274 general practices in Germany between January 2000 and December 2019 (index date). To be included, patients had to be followed-up for at least six months after the index date, and not be diagnosed with bipolar disorder (ICD-10 F30), depression (ICD-10 F32 and F33) and anxiety disorder (ICD-10 F41) prior to or at the index date. After applying similar inclusion criteria, individuals without FVL were matched (1:5) with those with FVL by sex, age, index year, and average number of consultations per year. In patients without FVL, the index date corresponded to a randomly selected visit date between January 2000 and December 2019. Mean (standard deviation) follow-up was 6.0 (4.3) years in the FVL group and 5.6 (4.3) years in the no FVL group. Finally, the selection of study patients is displayed in **Figure 1**.

*Study outcome*

The outcome of the study was the 10-year incidence of depression (ICD-10 F32 and F33) in patients with and without FVL.

*Covariates*

Covariates included sex, age, average number of consultations per year, and thromboembolic disorders (i.e., pulmonary embolism [ICD-10 I26], phlebitis and thrombophlebitis [ICD-10 I80], varicose veins of lower extremities [ICD-10 I83], and other disorders of veins [ICD-10 I87]). Thromboembolic disorders may have been diagnosed prior to or after the index date. The average number of consultations per year corresponded to the number of consultations during the follow-up divided by the number of years of follow-up (rounded value).

*Statistical analyses*

Baseline characteristics were compared between patients with FVL and patients without FVL using McNemar tests for sex and thromboembolic disorders, the Stuart-Maxwell test for categorical age, and Wilcoxon signed-rank tests for continuous age and the average number of consultations per year. In addition, the 10-year cumulative incidence of depression in the FVL and the no FVL group was studied using Kaplan-Meier curves, and the two curves were compared using the log-rank test. Finally, Cox regression analyses were conducted to assess the association between FVL and depression in the overall population and sex (i.e., female and male) and age subgroups (i.e., 18-30, 31-40, 41-50, 51-60, and >60 years). These analyses were conducted without and with adjustment for thromboembolic disorders. Given that sex, age and the average number of consultations per year were used to match people without FVL with

their counterparts with FVL, these variables were not included in the regressions. P-values lower than 0.050 were considered statistically significant. Finally, analyses were conducted with SAS 9.4.

## Results

This study included 1,070 patients with and 5,350 patients without FVL. A total of 64.9% of the sample were female, and mean (standard deviation) age of the sample was 46.0 (16.5) years (**Table 1**). The mean (standard deviation) average number of consultations per year was 3.1 (4.0) in both groups. Pulmonary embolism (12.2% versus 0.7%), phlebitis and thrombophlebitis (28.5% versus 2.9%), varicose veins of lower extremities (17.1% versus 8.0%), and other disorders of veins (14.6% versus 3.4%) were significantly more frequent in people with than without FVL (p-values<0.001). After 10 years of follow-up, 21.4% of patients with FVL and 14.1% of those without FVL were diagnosed with depression (log-rank p-value<0.001; **Figure 2**). The results of the Cox regression analyses are displayed in **Table 2**. Overall, FVL was positively and significantly associated with the incidence of depression after adjusting for thromboembolic disorders (HR = 1.61, 95% CI = 1.33-1.95). The FVL-depression relationship was further found to be significant in females, males and those aged ≤40 years, with HRs ranging from 1.58 in women to 2.05 in those aged 18-30 years.

## Discussion

### *Main findings*

In this study of 6,420 patients followed in general practices in Germany, the 10-year cumulative incidence of depression was around 21% in those with FVL and 14% in those without FVL. In addition, Cox regression analyses revealed that there was a positive and significant association between FVL and the incidence of depression (HR = 1.61). To the best of the authors' knowledge, this is the first study investigating the longitudinal association between FVL and the long-term risk of depression.

### *Interpretation of findings*

Several factors may play a mediating role in the association between FVL and depression. First, FVL is a well-known risk factor for thromboembolic events. For example, it was observed in a study, including 753 participants from the Netherlands, that those diagnosed with pulmonary embolism were more likely to be subsequently tested positive for FVL compared with their counterparts without pulmonary embolism (Manten et al., 1996). Moreover, a nationwide cohort study of 21,916 adults living in Taiwan showed that, after adjusting for a wide range of covariates (e.g., gender, education and physical comorbidities), pulmonary embolism was positively and significantly associated with the incidence of depression (HR = 2.04) (Tzeng et al., 2019). The deleterious effects of pulmonary embolism on mental health may be, at least partially, explained by hypoxemia, brain hypoxia and inflammation (Tzeng et al., 2019).

Interestingly, given that Cox regression analyses conducted in the present study were adjusted for pulmonary embolism and other thromboembolic disorders, it is likely that additional mediators are involved in the relationship between FVL and the incidence of depression. Importantly, FVL has been identified as a risk factor for several obstetrical complications (e.g., miscarriage and still birth) as well as early menopause. One Dutch retrospective cohort study, including 349 women with an history of at least one pregnancy, found that fetal loss and miscarriage were more frequent in the FVL than in the no FVL group (Meinardi et al., 1999). Another case-control study of 57,770 women from Germany further showed a positive relationship between induced and spontaneous abortion and psychiatric disorders (i.e., depression, anxiety, adjustment disorder, and somatoform disorder) (Jacob et al., 2019). In terms of early menopause, previous research has indicated that the onset of menopause tends to occur earlier when the FVL mutation is present (van Asselt et al., 2003). In a systematic review and meta-analysis of 14 studies including a total of 67,714 women, there was an inverse relationship of age at menopause and duration of the reproductive period with depression (Georgakis et al., 2016).

Finally, it is important to note that testing positive for FVL may have a long-term economic impact on patients' lives. Although quantitative studies on this topic are lacking, previous research of a qualitative nature revealed that carriership of FVL may result in being denied a full disability insurance (Bank et al., 2004), and this potential stigmatization may subsequently trigger the occurrence of psychiatric disorders. Moreover, not having health insurance has been found to be significantly associated with depression in a cohort of 4,079 participants from China (Tian et al., 2012), and this relationship could be explained by a sense of insecurity and the financial stress

related to the treatment of the potential thromboembolic complications of FVL such as pulmonary embolism (Fanikos et al., 2013) and deep venous thrombosis (MacDougall et al., 2006).

*Clinical implications and directions for future research*

Based on the findings of this study, people with FVL are at a long-term increased risk of being diagnosed with depression compared with their counterparts without FVL. In this context, mental health should be assessed shortly after the initial diagnosis of FVL but also on a regular basis in the decade following this diagnosis. The occurrence of depression may be particularly high in individuals undergoing thromboembolic disorders and in women with obstetrical complications. In terms of future research, more prospective data are needed to corroborate or invalidate the relationship between FVL and depression, while more studies are warranted to better characterize factors playing a mediating role in this association.

*Strengths and limitations*

Two strengths of this study are the large sample size and the use of longitudinal data. However, the study findings should be interpreted in light of several limitations. First, more data on the context of the diagnosis of FVL (e.g., personal or family history of thromboembolic events) would have allowed more detailed analyses. Second, there was no data on the severity of depression, and it was not possible to conduct sensitivity analyses by depression severity. Third, as this study included general practices only, and as depression may have been diagnosed in psychiatric practices, the 10-year incidence of this psychiatric disorder may have been underestimated. Fourth, the initial FVL diagnosis is usually confirmed by hematologists, and no data from hematologist

practices and no hospital data are available in the database used. Fifth, the data does not contain any information about physical activity or smoking status of the study patients, and this information therefore could not be included in the analysis.

*Conclusions*

Overall, this retrospective cohort study, including more than 6,400 patients followed in general practices in Germany, showed that FVL was associated with a significant increase in the 10-year incidence of depression. Future studies should seek to investigate the relationship between FVL and depression in other settings, while more research should focus on the factors playing a mediating role in this association.

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## Tables and Figures

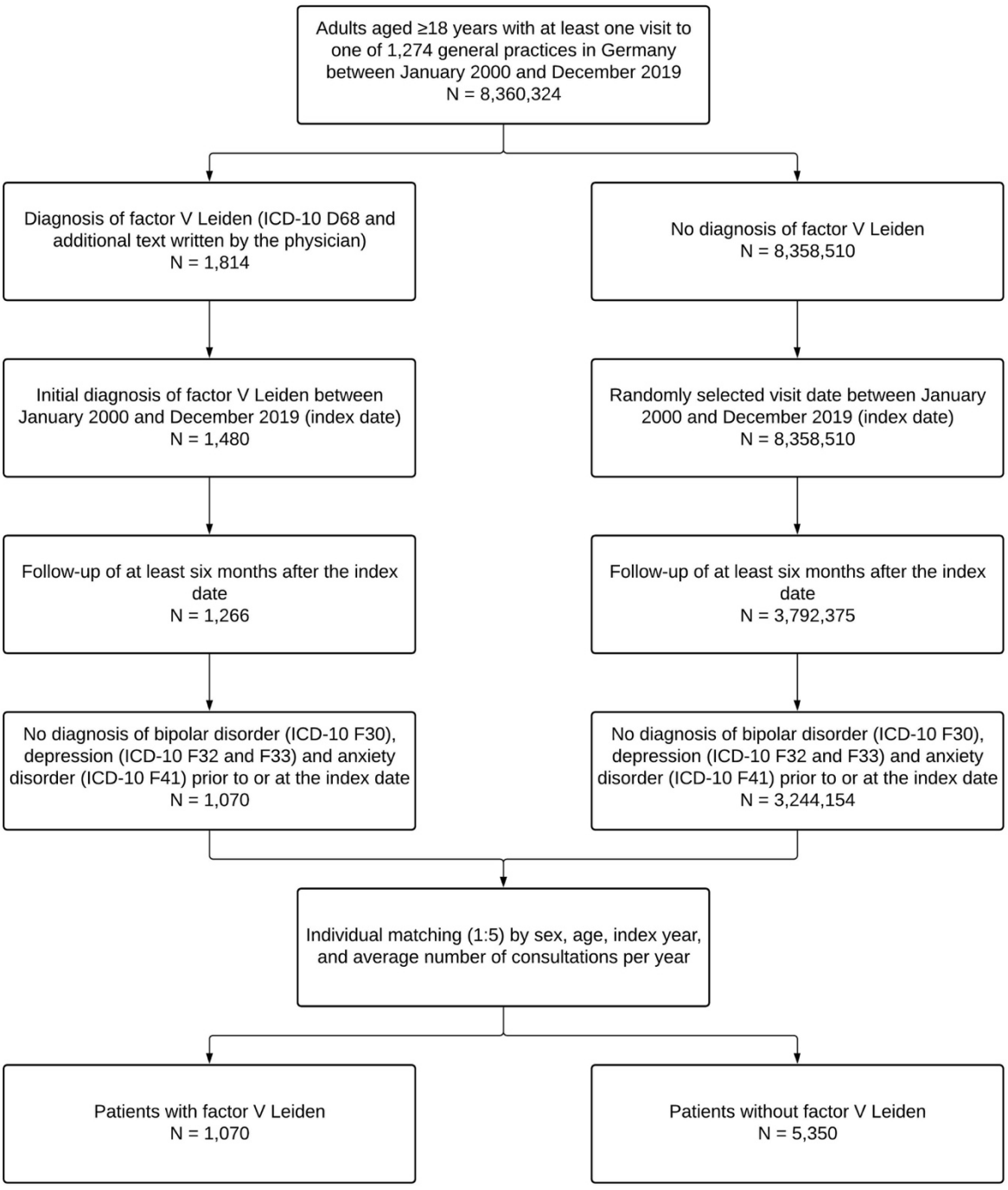


**Figure 1.** Selection of study patients

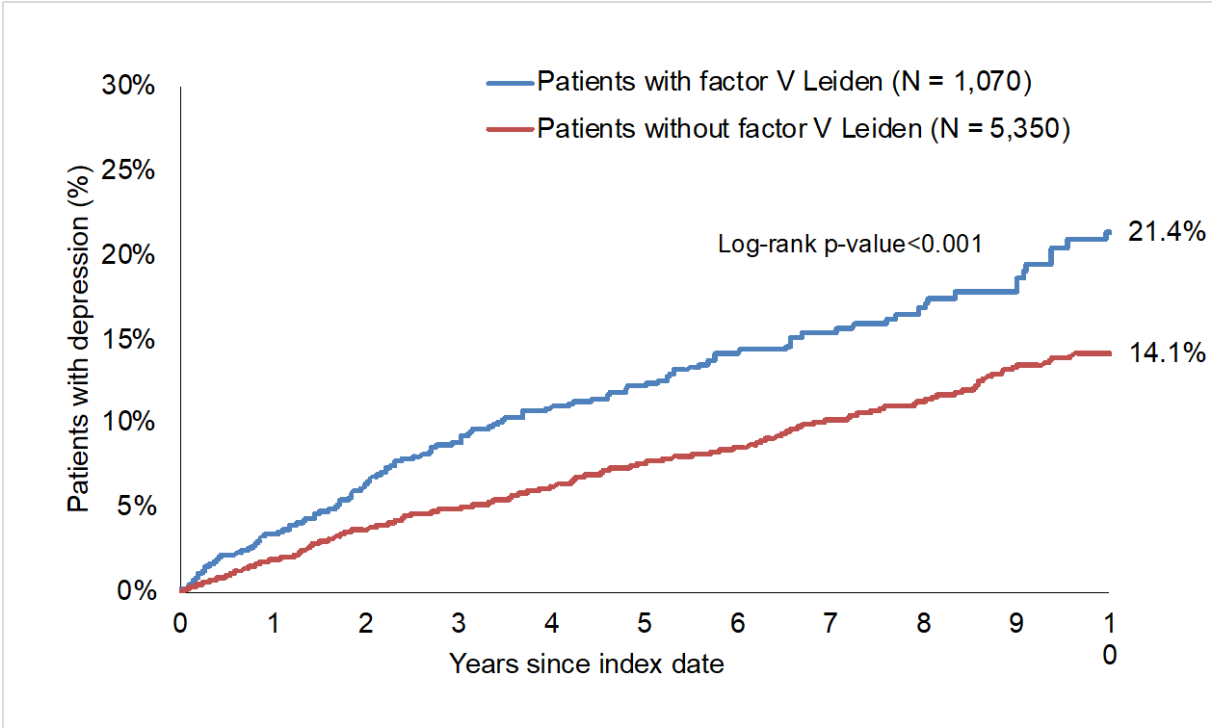


**Figure 2.** 10-year cumulative incidence of depression in patients with and without factor V Leiden (Kaplan-Meier curves)

**Table 1.** Baseline characteristics of study patients after 1:5 matching

| Variable | Patients with factor V Leiden (N = 1,070) | Patients without factor V Leiden (N = 5,350) | P-value |
|---|---|---|---|
| *Sex* | | | |
| Women | 64.9 | 64.9 | 1.000 |
| Men | 35.1 | 35.1 | |
| *Age (in years)* | | | |
| Mean (standard deviation) | 46.0 (16.5) | 46.0 (16.5) | 1.000 |
| 18-30 | 20.7 | 20.7 | |
| 31-40 | 21.6 | 21.6 | |
| 41-50 | 18.4 | 18.4 | 1.000 |
| 51-60 | 18.2 | 18.2 | |
| >60 | 21.1 | 21.1 | |
| Average number of consultations per year, mean (standard deviation) | 3.1 (4.0) | 3.1 (4.0) | 1.000 |

Data are percentages unless otherwise specified.

**Table 2.** Association between factor V Leiden and the incidence of depression

| Population | Incidence in patients with factor V Leiden[a] | Incidence in patients without factor V Leiden[a] | Crude HR (95% CI) | P-value | Adjusted HR (95% CI)[b] | P-value |
|---|---|---|---|---|---|---|
| Overall | 26.5 | 16.5 | 1.79 (1.45-2.21) | <0.001 | 1.61 (1.33-1.95) | <0.001 |
| Women | 30.4 | 19.1 | 1.72 (1.35-2.19) | <0.001 | 1.58 (1.26-1.99) | <0.001 |
| Men | 20.4 | 12.2 | 1.80 (1.18-2.75) | 0.006 | 1.65 (1.16-2.34) | 0.006 |
| Age 18-30 years | 28.0 | 13.8 | 2.18 (1.32-3.60) | 0.002 | 2.05 (1.28-3.28) | 0.003 |
| Age 31-40 years | 33.8 | 19.6 | 1.73 (1.14-2.62) | 0.011 | 1.71 (1.16-2.51) | 0.007 |
| Age 41-50 years | 28.7 | 19.8 | 1.69 (1.10-2.60) | 0.018 | 1.43 (0.96-2.13) | 0.082 |
| Age 51-60 years | 22.2 | 14.7 | 1.40 (0.83-2.35) | 0.206 | 1.50 (0.96-2.36) | 0.077 |
| Age >60 years | 20.8 | 13.9 | 1.91 (1.13-3.24) | 0.016 | 1.57 (1.00-2.46) | 0.052 |

Abbreviations: HR hazard ratio; CI confidence interval.
[a] Number of individuals diagnosed with depression per 1,000 patient-years.
[b] Adjusted for thromboembolic disorders (i.e., pulmonary embolism, phlebitis and thrombophlebitis, varicose veins of lower extremities, and other disorders of veins).