Abstract Background. Previous studies have suggested that hyperhomocysteinemia may be a risk factor for venous thrombosis. To assess the risk of venous thrombosis associated with hyperhomocysteinemia, we studied plasma homocysteine levels in patients with a first episode of deep-vein thrombosis and in normal control subjects.

Methods. We measured plasma homocysteine levels in 269 patients with a first, objectively diagnosed episode of deep-vein thrombosis and in 269 healthy controls matched to the patients according to age and sex. Hyperhomocysteinemia was defined as a plasma homocysteine level above the 95th percentile in the control group (18.5 μmol per liter).

Results. Of the 269 patients, 28 (10 percent) had plasma homocysteine levels above the 95th percentile for the controls, as compared with 13 of the controls (matched odds ratio, 2.5; 95 percent confidence interval, 1.2 to 5.2). The association between elevated homocysteine levels and venous thrombosis was stronger among women than among men and increased with age. The exclusion of subjects with other established risk factors for thrombosis (e.g., a deficiency of protein C, protein S, or antithrombin; resistance to activated protein C; pregnancy or recent childbirth; or oral-contraceptive use) did not materially affect the risk estimates.


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a conditional logistic-regression algorithm by the maximum-likelihood method, with Egret software. We also investigated a possible dose–response relation by calculating odds ratios for several ranges of homocysteine concentrations in a conditional logistic model. In addition, we calculated odds ratios for men and women separately and for several age groups in order to study possible differences in risk among these subgroups.

We further explored the differences in risk between men and women by taking risk factors specific to women into account — specifically, the use of oral contraceptives, pregnancy, and recent childbirth. We analyzed the risk of thrombosis among women less than 50 years old, both with and without the inclusion of women with these risk factors, by calculating unmatched odds ratios. The use of unmatched odds ratios was necessary because in the restricted groups many matched pairs would not have been complete. Since the matched and unmatched odds ratios did not differ substantially in any of our analyses, we considered this approach justified.

We also assessed whether the increased risk associated with hyperhomocysteinemia in both sexes was confounded by other risk factors, such as a deficiency of protein C, protein S, or antithrombin. We repeated the analysis after excluding subjects with abnormally low levels of these proteins (measured, as previously reported, with a single test) and estimated the risk associated with hyperhomocysteinemia in persons with normal protein C, protein S, and antithrombin levels.

Finally, we looked at the possibility of an interaction between hyperhomocysteinemia and heterozygosity (carrier status) for factor V Leiden, a rather common defect that causes resistance to activated protein G. We analyzed this interaction by calculating univariate odds ratios for thrombosis in persons with both or either of these risk factors, as compared with persons with neither risk factor.

**RESULTS**

The ratio of male to female subjects among both the case patients and the controls was 1:1.3, and the mean age was 44 years (range, 16 to 70 for the case patients and 16 to 71 for the controls); both these variables were used in matching the case patients and the controls.

The median plasma homocysteine level in the patients was 12.9 μmol per liter (range, 4.8 to 60.2), and that in the controls was 12.3 μmol per liter (range, 6.4 to 37.5). The homocysteine concentrations of individual case patients and controls are shown in Figure 1.

![Figure 1. Plasma Homocysteine Levels in 269 Patients with Deep-Vein Thrombosis and 269 Controls. Values shown have been rounded.](image-url)

The 95th percentile of the homocysteine levels in the control group was 18.5 μmol per liter. Of the 269 patients, 28 (10 percent) exceeded this cutoff, as compared with 13 (5 percent, by definition) in the control group. The matched odds ratio for deep-vein thrombosis in subjects with a homocysteine concentration above the 95th percentile, as compared with those whose homocysteine levels were at or below that value, was 2.5 (95 percent confidence interval, 1.2 to 5.2). When the cutoff was set at the 90th percentile, the matched odds ratio was 1.9 (95 percent confidence interval, 1.1 to 3.3); it was 4.0 (95 percent confidence interval, 1.4 to 12.0) when the cutoff was the 97.5th percentile (Table 1).

In order to evaluate the possibility of a dose–response relation, we stratified the patients and controls according to their homocysteine concentrations and calculated odds ratios for thrombosis in the patients at the higher levels as compared with those at the lowest level. As Figure 2 shows, the risk of thrombosis did not increase among subjects with homocysteine levels up to 18 μmol per liter; the risk was greatly increased above 22 μmol per liter, however, indicating a threshold effect rather than a continuous dose–response relation.

Odds ratios for several age groups and for men and women separately are shown in Table 2. For both sexes, there was a sharp increase in the risk of thrombosis associated with hyperhomocysteinemia at increasing ages. The overall odds ratio for thrombosis associated with hyperhomocysteinemia in women was 7.0 (95 percent confidence interval, 1.6 to 30.8), and in men it was 1.4 (95 percent confidence interval, 0.6 to 3.4), with the cutoff set at the 95th percentile of the homocysteine levels in the control group (P = 0.067 for the comparison between the sexes). When we calculated the 95th percentile of the distribution of homocysteine levels for men and women separately, we found a 95th percentile of 17.1 μmol per liter among women and 20.0 μmol per liter among men in the control group. Using these cutoffs for hyperhomocysteinemia, we found an odds ratio for thrombosis of 3.8 (95 percent confidence interval, 1.4 to 10.2) for women and 1.8 (95 percent confidence interval, 0.6 to 5.4) for men.

The higher rate of hyperhomocysteinemia in women than in men was present at all ages, making it unlikely that the difference was due to risk factors specific to women, such as the use of oral contraceptives, recent childbirth, or pregnancy. Indeed, when we excluded women with these risk factors, the unmatched odds ratio for thrombosis that was associated with hyperhomocysteinemia (with the 95th percentile for both sexes — 18.5 μmol per liter — as the cutoff for hyperhomocysteinemia) among women under the age of 50 was 11.3 (95 percent confidence interval, 2.7 to 46.0), whereas it was 2.8 (95 percent confidence interval, 0.9 to 8.7) for all women, both those with and those without these risk factors, under the age of 50.

Of the 269 patients, 15 had protein C deficiency, 7 had protein S deficiency, and 10 had antithrombin deficiency. In the control group, four had protein C deficiency,
Hyperhomocysteinemia as a Risk Factor for Deep-Vein Thrombosis

Table 1. Pairwise Distribution of Plasma Homocysteine Values in 269 Case Patients and Their Matched Controls, According to Various Definitions of Hyperhomocysteinemia.

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>90th Percentile (16.6 μmol per liter)</th>
<th>Matched odds ratio for thrombosis, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above cutoff</td>
<td>Below cutoff</td>
<td>2.5 (1.2 to 5.2)</td>
</tr>
<tr>
<td>Above cutoff</td>
<td>6 pairs</td>
<td>38 pairs</td>
</tr>
<tr>
<td>Below cutoff</td>
<td>20 pairs</td>
<td>205 pairs</td>
</tr>
</tbody>
</table>

Our study shows that hyperhomocysteinemia is a risk factor for deep-vein thrombosis in the general population. Moreover, our results suggest that the association between mild hyperhomocysteinemia and venous thrombosis is similar in degree to that reported for hyperhomocysteinemia and arterial vascular disease. An unexpected finding was the substantial increase in the risk of thrombosis at the highest plasma homocysteine levels. Our data suggest that there may be a threshold level above which homocysteine has a thrombogenic effect.

Discussion

Our study shows that hyperhomocysteinemia is a risk factor for deep-vein thrombosis in the general population. Moreover, our results suggest that the association between mild hyperhomocysteinemia and venous thrombosis is similar in degree to that reported for hyperhomocysteinemia and arterial vascular disease. An unexpected finding was the substantial increase in the risk of thrombosis at the highest plasma homocysteine levels. Our data suggest that there may be a threshold level above which homocysteine has a thrombogenic effect.

When we analyzed men and women separately, we found a difference in the risk of thrombosis associated with hyperhomocysteinemia. Even when we used different cutoff points for hyperhomocysteinemia in men and women by calculating the 95th percentiles of their homocysteine distributions in the control group separately, we found that the odds ratio was roughly twice as high for women as for men. This suggests that women may be more susceptible to the pathologic effects of elevated homocysteine levels, even though their homocysteine levels are in general lower than those of men. This effect cannot be explained by risk factors specific to women (such as pregnancy, recent childbirth, and oral-contraceptive use); an effect of these risk factors was unlikely in any case because the difference between men and women who did not have such risk factors was even more pronounced.

Hyperhomocysteinemia remained a risk factor for
Table 2. Odds Ratios for Thrombosis Associated with Hyperhomocysteinemia, According to Age and Sex.*

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Men</th>
<th>Women</th>
<th>Both Sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>0.5 (0.1-5.1)</td>
<td>1.0 (0.1-16.0)</td>
<td>0.7 (0.1-4.0)</td>
</tr>
<tr>
<td>30–50</td>
<td>1.3 (0.3-4.6)</td>
<td>7.0 (0.9-56.9)</td>
<td>2.4 (0.8-6.8)</td>
</tr>
<tr>
<td>≥50</td>
<td>2.5 (0.5-12.9)</td>
<td>7.0 (1.6-30.8)</td>
<td>5.5 (1.2-24.8)</td>
</tr>
<tr>
<td>All ages</td>
<td>1.4 (0.6-3.4)</td>
<td>7.0 (1.6-30.8)</td>
<td>2.5 (1.2-5.2)</td>
</tr>
</tbody>
</table>

*Odds ratios were calculated as the risk of deep-vein thrombosis in subjects with hyperhomocysteinemia defined as a homocysteine level above the 95th percentile in the control group (18.5 μmol per liter) as compared with the risk in those without hyperhomocysteinemia. CI denotes confidence interval.

**The odds ratio was 12.0 (95% confidence interval, 1.6 to 92.3) when the cutoff used was the 90th percentile in the control group.

We conclude that mild hyperhomocysteinemia is a risk factor for deep-vein thrombosis in the general population. The next question to be answered is whether homocysteine-lowering therapy — folic acid, vitamin B₁₂, or vitamin B₉ — contributes to the prevention of recurrent venous thrombosis.

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References

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