Sex Difference in Risk of Second but not of First Venous Thrombosis:
Paradox Explained

Running title: Roach et al.; Higher risk of first VT in men than women

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Abstract

Background—The risk of recurrent venous thrombosis is twofold higher in men than in women. In contrast, no such sex difference in the risk of first venous thrombosis has been reported. We hypothesized that, for a first event, a risk difference between the sexes is masked by female exposure to reproductive factors (oral contraception, pregnancy/puerperium and postmenopausal hormone therapy).

Methods and Results—From the MEGA study, a population-based case-control study on risk factors for venous thrombosis, 2915 patients with a first venous thrombosis, and their partners as control subjects, were included. Odds ratios and 95% confidence intervals (95%CI) for first venous thrombosis were assessed in men compared with women without reproductive risk factors by use of conditional logistic regression. Analyses were stratified in 10-year age categories to account for the variation in exposure to reproductive risk factors over different age groups, and adjusted for body mass index and smoking. Overall, men had a 2.1-fold (95%CI, 1.9-2.4) increased risk of first venous thrombosis compared with women without reproductive risk factors. Similar results were found when 10-year age categories were viewed separately. Adjustment for BMI and smoking, and exclusion of cancer patients, did not materially affect the results.

Conclusions—When female reproductive risk factors are taken into account, the risk of a first venous thrombosis is twice as high in men as in women. These findings are in line with previous studies on recurrent venous thrombosis and may have implications for future treatment and prevention strategies.

Key words: sex, hormones, epidemiology, venous thrombosis, risk factors
The incidence of first venous thrombosis has been assessed for men and women separately in many large cohort studies.1-7 Some studies have shown a slightly higher risk of venous thrombosis in men than in women,1-2 with a male to female ratio of 1.2:1, whereas others have shown the incidence of venous thrombosis to be up to 1.3-fold higher in women than in men.3-7 Nevertheless, in the absence of a consistent difference, the incidence of first venous thrombosis is thought to be approximately equal among the sexes.8,9 In contrast, recurrent venous thrombosis has consistently been shown to occur at a clearly higher rate in men than in women: up to 10% per year versus 2-5% per year.10-14 Although several explanations for this sudden risk increase in men have been postulated, such as sex-differential treatment strategies after a first venous thrombosis or a lower threshold for recurrence diagnostics in men than in women,10 up to now the reason for the sex difference between the risk of first and recurrent venous thrombosis remains unknown.

Approximately 50% of women of reproductive ages who experience a first venous thrombosis are exposed to reproductive risk factors (oral contraception, postmenopausal hormone therapy or pregnancy) at the time of the event.12,15 As there is no such male-specific transient risk factor,1-7 we hypothesized that female exposure to reproductive risk factors masks an intrinsically higher risk of venous thrombosis in men, because the incidence of first venous thrombosis is still similar in men and women. We therefore set out to formally assess the risk of first venous thrombosis in men compared with women with and without reproductive risk factors.

Methods

This analysis was performed in the MEGA case-control study, details of which have been
described previously. Briefly, 4956 consecutive patients with a first venous thrombosis were included, with their partners as control subjects, all aged 18-70 years. In total, 3732 partners were eligible, of whom 3039 participated. Three thousand age- and sex-matched population controls were additionally recruited by random digit dialing but are not included in this analysis since, due to the matching on sex, they are uninformative to detect sex differences. Participants completed a detailed questionnaire shortly (median 2.4 months, interquartile range 1.7-3.4 months, maximum 33.8 months) after the thrombotic event on demographic and lifestyle-related factors, as well as risk factors for venous thrombosis. Items covered in the questionnaire included oral contraception and postmenopausal hormone therapy use in the year before the index date, pregnancy or childbirth in the three months before the index date, and malignancy in the five years before the index date. The index date was defined as the date of diagnosis of venous thrombosis for patients and their partners and the date of completing the questionnaire for the random control subjects. The MEGA study was approved by the medical ethics committee of the Leiden University Medical Center and all participants provided written informed consent.

**Statistical analysis**

For the current analyses, only couples were included in whom information on reproductive risk factors (oral contraception use, postmenopausal hormone therapy or pregnancy) was available for the woman, which was the case for 2915 couples. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for venous thrombosis in men and in women with reproductive risk factors, compared with women without reproductive risk factors. This method uses the information of the ‘discordant’ couples; couples in which the patient and the partner are of the opposite sex.

Female reproductive factors are well-known provoking risk factors for venous
thrombosis.\textsuperscript{18-20} To determine the odds ratio for venous thrombosis associated with being male versus being female (without the effect of reproductive risk factors), the number of couples with a male patient and a female partner without reproductive risk factors is compared with the number of couples with a female patient without reproductive risk factors and a male partner (Table 1). If male sex is not a risk factor for venous thrombosis, one would expect a similar number of each type of couple and an odds ratio close to 1. A larger number of couples with a male patient than couples with a female patient without reproductive risk factors would indicate a higher risk for males, and yield an odds ratio >1. This concept is further explained in the Statistical Appendix that accompanies this manuscript. To assess the risk of venous thrombosis in women with reproductive risk factors compared with women without reproductive risk factors, the ratio between the number of female patients with and without reproductive risk factors is compared in a similar manner. Conditional logistic regression fully takes matching into account and implicitly adjusts for all unmeasured factors in which couples tend to be similar (e.g. socioeconomic class).\textsuperscript{17} To account for the variation in exposure to reproductive factors over different age groups, analyses were stratified according to age by adding interaction terms between age, sex and hormone use to the model. In addition, risk estimates were adjusted for body mass index [BMI] (categorical: $<25$ kg/m\textsuperscript{2}, 25-30 kg/m\textsuperscript{2} and $\geq30$ kg/m\textsuperscript{2}) and smoking history as men and women tend to differ in these risk factors for venous thrombosis. The overall risk estimate was also adjusted for age. Finally, a sensitivity analysis was performed in which all participants with active malignancy, or malignancy within the five years before the index date, were excluded. A detailed description of the assessment of sex-specific risk factors in data in which patients and controls are mostly of the opposite sex can be found supplemental tables 1 and 2. All statistical analyses were performed with SPSS for Windows, release 20.0 (SPSS Inc,
Chicago, Ill).

Results

A total of 5830 participants, 2915 patients and their partners, were included in this study. Their clinical characteristics can be seen in Table 2. The mean age at enrolment was 48 years (range, 18-70) in both patients and controls. In female patients, 740 (51% of all women) used oral contraception, 73 (5% of all women) used postmenopausal hormone therapy and 129 (9% of all women) were pregnant or within three months postpartum at the time of their thrombotic event. For the female partner controls these numbers were 250 (17%), 87 (6%) and 28 (2%), respectively.

In total, 99% of partners were of the opposite sex to the patient. There were 1093 couples in which the patient was a man and the partner was a woman without reproductive risk factors, and 516 couples in which the patient was a woman without reproductive risk factors and the partner was a man (Table 1). This yields a crude odds ratio of 1093/516 = 2.1, implying that men had a 2.1-fold (95%CI, 1.9-2.4) increased risk of venous thrombosis compared with women without reproductive risk factors (Table 3 and Figure 1). When 10-year age categories were viewed separately, the effect of male sex was most pronounced in the age group 18-30 years: OR 3.3 (95%CI, 1.3-8.3). This was slightly lower, OR 2.6 (95%CI, 1.8-3.7), in the age group 30-40 years. Men retained an approximately 2-fold increased risk of venous thrombosis compared with women in all age groups after 40: OR 1.7 (95%CI, 1.4-2.2) in 40-50 year olds, OR 2.0 (95%CI, 1.7-2.4) in 50-60 year olds and OR 2.0 (95%CI, 1.7-2.5) in 60-70 year olds. Adjustment for BMI and smoking history did not affect these results. Including BMI as a continuous variable also yielded similar risk estimates. In all age categories women with reproductive risk factors had a
higher risk of first venous thrombosis than women without reproductive risk factors (overall odds ratio 5.5, 95%CI 4.7-6.5). The sensitivity analysis in which all participants with malignancy were excluded yielded similar risk estimates to the overall analyses: crude and adjusted ORs both 2.3 (95%CI, 2.0-2.6).

Discussion

In this study we found that the risk of a first venous thrombosis is two-fold higher in men than in women once female reproductive risk factors for venous thrombosis are taken into account. These results were found in all age categories and were not affected by adjustment for body mass index and smoking, or by excluding participants with malignancy.

To our knowledge, this is the first study to assess the risk of first venous thrombosis in men compared with women with and without reproductive risk factors separately. We found a relative risk of 2 when comparing men with women without reproductive risk factors, which indicates that the intrinsic risk of venous thrombosis is higher in men than in women. Until now, this higher intrinsic risk of venous thrombosis in men has mostly been noted in recurrence research.10-14 Studies have shown that men have a twofold higher risk of recurrent venous thrombosis than women.10-14 It was hypothesized that this could be explained by a reduction in exposure to reproductive risk factors in women,10,11-13,15 as women who experience a first venous thrombosis are encouraged to discontinue the use of hormonal preparations or to use thromboprophylaxis in future pregnancies.21-23 However, population based studies that compared men with women who had a first venous thrombosis that was not related to reproductive risk factors still showed a twofold higher risk of recurrence in men.10-12

As far as we know, the effect of female and male sex on the risk of first venous
thrombosis has not been studied before whilst taking female reproductive risk factors into account. Studying this research question would be very time-consuming in a cohort study, as information on exposure to reproductive risk factors would need to be collected for all women throughout the observation period. The advantage of a case-control study is that it is much easier to collect information on exposure in all participants. However, most case-control studies include sex-matched controls, and so the effect of sex on venous thrombosis cannot be assessed. In this case-control study with partner controls, most partners were of the opposite sex to the patient. This enabled us to accurately compare the risk of venous thrombosis in men and women with and without reproductive risk factors for the first time.

In addition, as partners generally share the patients’ lifestyle, they are likely to have a similar socioeconomic status, diet and other unknown factors which may affect the risk of venous thrombosis, reducing the likelihood that our results can be explained by residual confounding.

The reason why men have a higher risk of (recurrent) venous thrombosis than women is as yet unknown. Risk factors for venous thrombosis can be genetic or acquired, and it is possible that either or both of these factors differ between men and women. Although we found no differences in the prevalence of known acquired and genetic risk factors for venous thrombosis between men and women in our study (Table 1), from our results, a genetic difference in risk of venous thrombosis between men and women is plausible, as the risk difference was present in all age groups and seemed to be highest in the youngest age categories (which are not yet affected by other, age-related causes of venous thrombosis). A previous genome-wide gene-centric study found that the G>A variant of the rs6048 SNP in Factor 9 (also known as F9 Malmö) is associated with an up to 30% increased risk of first venous thrombosis.
in men, but not in women. As this SNP is located on the X-chromosome, a larger proportion of men will carry only variant alleles (all carriers are hemizygous) than women (only a minority are homozygous carriers). Certain genetic variants on the Y-chromosome were recently associated with a 1.6-fold increased risk of coronary artery disease which is also more common in men than in women. The Y-chromosome has not yet been studied in relation to venous thrombosis, but it, or other genetic differences, could hold part of the explanation. Alternatively, a difference in lifestyle-related risk factors for venous thrombosis could underlie the difference in risk between men and women.

Although the pathophysiology underlying the higher risk of venous thrombosis in men is as yet unknown, male sex can be used as a proxy through which high risk individuals can be identified. Prediction models for recurrent venous thrombosis - the Vienna prediction model, the DASH and the HERDOO-2 prediction score – already include male sex as an independent predictor of recurrent venous thrombosis and advocate differential treatment strategies for men and women after a first venous thrombosis. More specifically, the paper on the HERDOO2 score recommends that anticoagulation therapy should be continued beyond 6 months after a first episode of venous thrombosis in all men with an unprovoked first event. Whether the same holds for the prevention of first venous thrombosis in men and women is as yet unknown. From our results, it is possible that men may benefit from a lower threshold for prophylactic treatment than women without reproductive risk factors when encountering high risk situations (e.g. when undergoing surgery or during non-surgical hospitalization). The ACCP guidelines for surgical patients currently include female oral contraceptive use as a ‘mild’ risk factor for venous thrombosis. Including male sex in a similar manner may help to reduce the number of venous thrombotic events that occur in men. Alternatively, men may require a higher dose of
prophylactic anticoagulation therapy than women without exposure to reproductive risk factors in order to reduce their venous thrombosis risk to the same extent. It is important that future studies focus on the sex-specific risk and prevention of first venous thrombosis in order to identify which factors can be targeted to reduce the higher risk of venous thrombosis in men.

The strength of our study is that data were collected in the same manner for all participants and all venous thrombotic events were objectively diagnosed. Another strength is the inclusion of partner controls (who share a similar lifestyle to the patients) in the MEGA study, which enabled us to assess the risk of venous thrombosis in men and women whilst reducing the risk of residual confounding. A potential limitation is that patients included in the MEGA study had to survive long enough for a first visit to the anticoagulation clinic. Therefore, individuals who died shortly after the venous thrombotic event were not included in our study. However, we consider it unlikely that this affected our results as no difference in the immediate venous thrombosis death rate between men and women has been reported.\(^{30-33}\) Another potential limitation was that information on reproductive risk factors was self-reported. As female reproductive risk factors were already known to increase the risk of venous thrombosis when the MEGA study was performed, female patients could have reported hormone use more accurately than female controls. However, as 39% of the female partner controls aged 18-50 years reported the use of oral contraceptives, and this percentage is 40% in the Dutch population,\(^{34}\) it seems unlikely that such misclassification occurred in our study. Finally, not all patients who were included in the MEGA study had a partner and not all partners were eligible to participate as control subjects. As no eligible data were kept on non-participants, we cannot rule out the possibility that our results were influenced by a differential participation rate for male and female partner controls. However, considering that the male/female ratio in the patients who did not
have a partner or whose partner was not eligible to participate was nearly 50/50 (52% were female and 48% were male), we consider a sex difference in the partner participation rate unlikely.

In summary, in our study, men had a higher risk of first venous thrombosis than women once reproductive risk factors had been taken into account. Although the pathophysiology behind these observations has yet to be unraveled, this risk difference may have implications for future sex-specific treatment and prevention strategies for venous thrombosis.

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**Conflict of Interest Disclosures:** None.

**References:**


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16. Bezemere ID, Bare LA, Doggen CJ, Arellano AR, Tong C, Rowland CM, Catanese J, Young BA, Reitsma PH, Devlin JJ, Rosendaal FR. Gene variants associated with deep vein


1025.


Table 1. All possible combinations of sex and exposure to reproductive risk factors in couples

<table>
<thead>
<tr>
<th>Patients</th>
<th>Man</th>
<th>Woman with reproductive rf</th>
<th>Woman without reproductive rf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>23</td>
<td>352</td>
<td>1093</td>
</tr>
<tr>
<td>Woman with reproductive rf</td>
<td>913</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Woman without reproductive rf</td>
<td>516</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

Rf denotes risk factors. The analysis is based on comparing the number of discordant couples. For example, there are 1093 couples in which the case is a man and the partner is a woman without reproductive risk factors, while there are only 516 such couples in which the woman without reproductive risk factors is the case. If male sex was not a risk factor for venous thrombosis these numbers would have been similar. This indicates that the odds for thrombosis is about 1093/516 = 2.11 times higher for men compared with women. Similarly the odds for thrombosis is 913/352 = 2.59 times higher for women who use reproductive risk factors compared to man. This yields an odds ratio for women with reproductive risk factors compared with women without risk factors of 2.59 * 2.11 = 5.46. Actually the conditional logistic regression also uses the information from the three female couples in which only one of the women was exposed to reproductive risk factors, but the estimates of the odds ratios in this analysis were similar.
**Table 2.** Clinical Characteristics

<table>
<thead>
<tr>
<th>General Characteristics</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women without reproductive rf</td>
</tr>
<tr>
<td>Number</td>
<td>1468</td>
<td>524</td>
</tr>
<tr>
<td>Age</td>
<td>53 (18-70)</td>
<td>53 (21-70)</td>
</tr>
<tr>
<td>Normal weight (BMI &lt;25kg/m2)</td>
<td>417 (30)</td>
<td>179 (37)</td>
</tr>
<tr>
<td>Overweight (BMI 25-30kg/m2)</td>
<td>734 (53)</td>
<td>177 (37)</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30kg/m2)</td>
<td>230 (17)</td>
<td>124 (26)</td>
</tr>
<tr>
<td>Non-smoking</td>
<td>368 (27)</td>
<td>188 (38)</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>1023 (73)</td>
<td>301 (62)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT only</td>
<td>871 (59)</td>
<td>264 (50)</td>
</tr>
<tr>
<td>PE +/- DVT</td>
<td>597 (41)</td>
<td>260 (50)</td>
</tr>
<tr>
<td>Provoking risk factors*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>804 (62)</td>
<td>256 (60)</td>
</tr>
<tr>
<td>Present</td>
<td>502 (38)</td>
<td>173 (40)</td>
</tr>
<tr>
<td>Reproductive risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraception</td>
<td>/40 (80)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal hormone therapy</td>
<td>73 (8)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy/ puerperium</td>
<td>129 (14)</td>
<td></td>
</tr>
</tbody>
</table>

Data were missing for some participants in some subgroups. Rf denotes reproductive risk factors; DVT, deep vein thrombosis; PE, pulmonary embolism.
Continuous variables are denoted as mean (range), categorical variables as number (percent).
*Defined as malignancy, surgery, hospitalisation, plaster cast immobilization or long haul travel.
Table 3. Risk of venous thrombosis in men and women with and without reproductive risk factors

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients, n (%)</th>
<th>Partners, n (%)</th>
<th>Crude OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All age groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women without reproductive risk factors</td>
<td>524 (18)</td>
<td>1104 (38)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Men</td>
<td>1468 (50)</td>
<td>1452 (50)</td>
<td>2.1 (1.9-2.4)</td>
<td>1.9 (1.7-2.2)</td>
</tr>
<tr>
<td>Women with reproductive risk factors</td>
<td>923 (32)</td>
<td>359 (12)</td>
<td>5.5 (4.7-6.5)</td>
<td>6.0 (5.0-7.1)</td>
</tr>
<tr>
<td><strong>18-30</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women without reproductive risk factors</td>
<td>6 (2)</td>
<td>32 (14)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Men</td>
<td>39 (16)</td>
<td>143 (60)</td>
<td>3.3 (1.3-8.3)</td>
<td>2.5 (1.0-6.4)</td>
</tr>
<tr>
<td>Women with reproductive risk factors</td>
<td>207 (82)</td>
<td>62 (26)</td>
<td>18.9 (7.4-48.4)</td>
<td>17.9 (6.7-47.6)</td>
</tr>
<tr>
<td><strong>30-40</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women without reproductive risk factors</td>
<td>51 (10)</td>
<td>130 (26)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Men</td>
<td>189 (38)</td>
<td>287 (57)</td>
<td>2.6 (1.8-3.7)</td>
<td>2.5 (1.7-3.6)</td>
</tr>
<tr>
<td>Women with reproductive risk factors</td>
<td>264 (52)</td>
<td>90 (18)</td>
<td>7.8 (5.2-11.7)</td>
<td>7.7 (4.9-12.1)</td>
</tr>
<tr>
<td><strong>40-50</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women without reproductive risk factors</td>
<td>138 (19)</td>
<td>245 (33)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Men</td>
<td>304 (41)</td>
<td>388 (52)</td>
<td>1.7 (1.4-2.2)</td>
<td>1.7 (1.3-2.2)</td>
</tr>
<tr>
<td>Women with reproductive risk factors</td>
<td>289 (40)</td>
<td>108 (15)</td>
<td>4.7 (3.5-6.4)</td>
<td>5.0 (3.6-6.9)</td>
</tr>
<tr>
<td><strong>50-60</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Women without reproductive risk factors</td>
<td>191 (23)</td>
<td>420 (46)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Men</td>
<td>477 (58)</td>
<td>402 (45)</td>
<td>2.0 (1.7-2.4)</td>
<td>2.1 (1.7-2.6)</td>
</tr>
<tr>
<td>Women with reproductive risk factors</td>
<td>152 (19)</td>
<td>80 (9)</td>
<td>4.1 (3.0-5.7)</td>
<td>4.7 (3.3-6.6)</td>
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<tr>
<td><strong>60-70</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Women without reproductive risk factors</td>
<td>138 (23)</td>
<td>277 (53)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Men</td>
<td>459 (75)</td>
<td>232 (44)</td>
<td>2.0 (1.7-2.5)</td>
<td>2.1 (1.6-2.6)</td>
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<tr>
<td>Women with reproductive risk factors</td>
<td>11 (2)</td>
<td>19 (4)</td>
<td>1.2 (0.5-2.5)</td>
<td>1.2 (0.5-2.9)</td>
</tr>
</tbody>
</table>

OR denotes odds ratio

*Adjusted for partnership, body mass index and smoking. The overall risk estimate was additionally adjusted for age.
Figure Legend:

**Figure 1.** Adjusted risk of venous thrombosis in men compared with women without reproductive risk factors.
Adjusted* OR with 95% CI

*Adjusted for BMI and smoking

OR=1

Age groups (years)
Supplemental Methods

Estimating the effect of sex as an exposure in a case-control study with partners as matched controls

In general, it is not possible to directly estimate the effect of variables which are used as matching variables in a case-control study.\(^1\) This is the reason why many people refrain from estimating sex effects in case-control studies in which partners (who are usually of the opposite sex) are included as controls. This is a misunderstanding, as we will show here.

The analysis of a case-control study with partner controls uses information from the couples which are of the opposite sex, i.e. couples with one man and one woman. If sex is not a risk factor for venous thrombosis, we would expect the same number of couples in which the case is male -and the partner is female- as couples in which the case is female. If male sex is a risk factor for thrombosis, we would expect more couples in which the case is male, than couples in which the case is female. To illustrate this we consider 100 cases with venous thrombosis and 100 partner controls. For simplicity, we assume that all couples are of the opposite sex, in which case the sample consists of 100 males and 100 females. If the risk of venous thrombosis is not influenced by sex, we expect 50\% of both the cases and the controls to be men. The male versus female ratio in the cases is then equal to 1 (Supplemental Table 1).

If the men have a higher risk of venous thrombosis than the women, there will be more couples in which the case is male and the control is female, than couples in which the case is female and the control is male. Supplemental Table 2 shows the expected numbers if the odds ratio for venous thrombosis for men versus women is 3. In this situation, the probability that the case of the couple is male is 0.75, and the probability that the control is male is 0.25. It can be shown that the odds ratio for venous thrombosis equals the ratio of male-case to female-case matched pairs, in our example 75/25 = 3.

In general a case-control study with partner controls is not different from other 1:1 matched case-control studies.\(^2\) In 1:1 matched case-control studies, only discordant pairs (i.e pairs with only the case or only the control exposed) provide information, and the estimated odds ratio is the number of exposed cases divided by the number of unexposed cases. In the partner case-control study, all couples in which the partner is of the opposite sex are discordant and the odds ratio is estimated by the ratio of case-male to case-female matched pairs. Data from partner case-control studies can therefore be analyzed in the same way as other 1:1 matched case-control studies.\(^2\) Adjustment for confounding can be done by performing conditional logistic regression.
Supplemental Tables

Supplemental Table 1. Expected numbers if sex is not related to the occurrence of venous thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Partner</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-</td>
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Supplemental Table 2. Expected numbers if the odds ratio of venous thrombosis for men versus women is 3

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Supplemental References
