

## ORIGINAL ARTICLE

# Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency

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**Summary.** *Background:* Little research has been performed regarding the psychological consequences of knowing that one is at an increased risk for venous thrombosis. *Objectives:* The aim of this study was to explore attitudes toward genetic testing for protein C deficiency. *Methods:* Questionnaires about genetic testing attitudes, dispositional anxiety, risk perception, and thrombosis-related worry were completed by 168 asymptomatic members of a North-American kindred with a high incidence of heritable protein C deficiency conferring a high lifetime risk of venous thrombosis. A total of 76 subjects (45%) had not been tested for protein C deficiency before participating in our study whereas the other 92 subjects (55%) had been tested prior to filling in the questionnaire, of whom 34 people had protein C deficiency, while 58 did not. *Results:* Family members with protein C deficiency perceived a higher risk of suffering venous thrombosis and scored higher on thrombosis-related worry than family members without protein C deficiency. Participants who had not been tested did not report excessive thrombosis-related worry. Participants with protein C deficiency reported a belief in the psychological and health benefits of testing, and felt that they experienced low psychological distress following the genetic test. High psychological distress following the test was related to dispositional anxiety and thrombosis-related worry. Participants without protein C deficiency were relieved after finding out that they did not have the deficiency.

*Conclusion:* There seem to be few negative psychological consequences of knowing that one is at an increased risk for venous thrombosis, except in vulnerable individuals.

**Keywords:** genetic testing, protein C deficiency, psychology, risk perception, screening, thrombophilia.

## Background

The number of inherited disorders and risk factors that can be detected through genetic testing is increasing rapidly, and genetic testing is becoming a common component of routine medical care. Recently, genetic testing is being applied to detect personal susceptibility to disease, in the belief that awareness of genetic risk will enhance informed medical decision making and have an impact on changing health behavior [1].

Quality of life in patients with venous thrombosis is impaired compared with a healthy population, especially in the presence of the post-thrombotic syndrome. This impairment encompasses the physical, social and psychological domains of quality of life [2,3]. Venous thrombosis is a multi-causal disease caused by both genetic and acquired risk factors [4,5]. Examples of acquired risk factors are older age, the use of oral contraceptives, hormone replacement therapy, pregnancy, and immobilization. The discovery of genetic risk factors for venous thrombosis, and the widespread clinical application of genetic screening, has engendered a debate regarding the pros and cons of thrombophilia testing [6,7]. Generally, it is believed that widespread screening for thrombophilia is not justified because it is not cost-effective. However, some believe screening of patients at a high risk of venous thrombosis is likely to be useful because it may improve clinical outcome through changes in the appropriate use and duration of therapy. It is reasoned that

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family screening of individuals with a close relative with thrombophilia can help optimize prophylactic treatment of asymptomatic carriers in high-risk situations (i.e. during surgery or pregnancy in which they would normally not receive treatment) [8]. To date, there are no data supporting this view. Opponents of widespread screening have pointed out that it may lead to psychological distress. However, little research has focused on the psychological consequences of knowing that one is at an increased risk for venous thrombosis. This is notable because carriership of a genetic deficit may influence daily life, as it can cause considerable distress. Research on the psychological influence of genetic testing has focused mainly on single gene conditions such as Huntington's disease, and on hereditary cancers. Findings suggest that individuals undergoing predictive genetic testing do not experience considerable long-term psychological distress [9,10]. However, individuals with a high predisposition to depression or anxiety may be more vulnerable to adverse effects [1,11]. Possible negative effects of a positive test result include anxiety and depression following the test, worry about the future and about the possibility of passing the genetic defect on to children. Furthermore, positive test results might cause stigmatization, problems with insurance, and they can interfere with medical decision making. To our knowledge, only three previous publications have dealt with the subject of the social and psychological impact of awareness of carriership of thrombophilia. The first study investigated women's reactions to awareness of activated protein C (APC) resistance carriership in 270 women [12]. In this study, women were asked to answer questions about the way their knowledge of APC resistance has affected them, in a yes/no format. The study concluded that most women were pleased with having been informed of their status. The majority of women (84%) found that their awareness of APC resistance might be an advantage in the event of future operations or accidents, and 69% reported that their lives were unaffected by the knowledge of APC resistance. However, 27% of the women reported that they had become more worried, and 10% was afraid to get pregnant again. The second study, by Hellmann *et al.* [13], used a questionnaire with a Likert scale to examine patient experience of genetic testing for factor V Leiden (FVL) in 110 patients and found that 43% of the patients experienced increased worry. In addition, they reported that patients indicated concern with the lack of available information about FVL. The discrepancy in the reported worry rates of these two studies might be explained by the difference in methodology between the two studies. A Likert scale allows participants to be more specific in their responses, rather than having to choose between two endpoints in a yes/no format.

The third study on this subject explored the psychological and social aspects of asymptomatic carriership of the FVL mutation in a qualitative study. After interviewing 17 individuals, the authors concluded that carriership of FVL has the potential to influence daily life by inducing concerns, stigmatization and problems with insurance eligibility [14].

The results of these three studies need to be replicated and clarified in more structured studies, which assess the

psychological impact of genetic testing for thrombophilia and factors that might influence this impact.

Protein C is a vitamin K-dependent protein that, upon activation to APC, inhibits thrombus formation by inactivating the coagulation factors Va and VIIIa. Deficiency of protein C was one of the first genetic risk factors associated with hereditary thrombophilia [15]. The lifetime risk for venous thrombosis in protein C deficient individuals is about 10-fold increased compared with the normal population [16]. Protein C deficiency is caused by a wide variety of mutations in the protein C gene. The present study investigates a large kindred of French-Canadian descent with protein C deficiency caused by a 3363 C insertion mutation [17].

The aim of this study was to explore the attitudes of protein C deficient individuals about genetic testing and to assess their perception of their thrombotic risk and their thrombosis-related worry. Furthermore, we tried to establish the role of trait anxiety in these attitudes to test the hypothesis that, as in earlier research on predictive genetic testing, individuals with a higher psychological vulnerability experience more psychological distress following the genetic test. Age and sex differences were assessed because older age and female hormones are risk factors for venous thrombosis. In addition, we assessed the knowledge of participants about other risk factors for venous thrombosis, and the relationship of this knowledge with risk perceptions, thrombosis-related worry and attitudes about genetic testing.

## Method

### *Participants*

The ascertainment and evaluation of the family members participating in this study were described previously [18]. Members of the kindred were contacted by phone by one of the investigators (SN) and an appointment was made to meet with the investigators. At this appointment, several questionnaires were completed. All participating subjects gave informed consent. The study protocol was approved by the Human Experimentation Committee of the University of Vermont College of Medicine, Burlington (VT, USA). Inclusion criteria stipulated that participants had to be over age 18, and physically and mentally capable of completing the questionnaire. Participants were divided into three groups: participants who had not been tested before (group 1), participants with protein C deficiency (group 2), and participants without protein C deficiency (group 3). Most of the participants who were tested before (group 2 and 3) were tested in a previous study [18].

### *Measurements*

#### *All participants*

*Risk perception* Perceived risk of venous thrombosis was assessed with two items:

- (i) How likely do you think it is that, at some point in your life, you will get thrombosis?
- (ii) How vulnerable do you think you are to getting thrombosis at some point in your life? Each item was rated on a seven-point Likert scale ranging from one (*not at all*) to seven (*almost certain or extremely*) and summed to generate risk perception scores.

**Worry** Worry about venous thrombosis was assessed with two items: (i) To what extent are you worried about getting thrombosis? (ii) To what extent are you concerned about getting thrombosis? Each item was rated on a seven-point Likert scale ranging from one (*not at all*) to seven (*extremely*) and summed to generate worry scores.

**Trait anxiety** As a measure of dispositional anxiety, the trait form of the State-Trait Anxiety Inventory (STAI) (form Y-2) was included [19]. This is a 20-item questionnaire that measures relatively stable individual differences in anxiety proneness. All items are rated on a scale from one (*not at all*) to four (*very much so*).

**Knowledge about risk factors for venous thrombosis** To assess the knowledge of participants about the acquired risk factors for venous thrombosis, a scale with eight items was used, on which participants had to rate on a five-point Likert scale (ranging from strongly disagree to strongly agree) whether they believed this risk factor could cause venous thrombosis or not. The scale consisted of the following items: pregnancy or child birth, birth control pills, bed rest, lack of exercise, sitting for long periods, surgery, aging, accident or injury. To calculate a score for the knowledge about risk factors for venous thrombosis, we assigned one point to each item that participant agreed or strongly agreed with, and points were added (possible score range 0–8).

*Group 1: Participants who had not been tested before and group 2: Protein C deficient participants*

**Attitudes about testing** To assess the attitudes about getting a genetic test for protein C deficiency in both family members that had been tested positive for protein C deficiency and family members that had not been tested before, attitude scales were adapted from a study by Cameron *et al.* [20], in which the same attitude scales were being applied to assess beliefs about testing for breast cancer susceptibility. Both groups completed a similar set of the following items, appropriate to their status. For group 2, items referred to how individuals felt about the genetic test result now, rather than how they felt when they had just received the results.

**Health benefits beliefs** were assessed with a set of five items (e.g. knowing whether I have protein C deficiency or not would give me more control over my health; knowing that I have protein C deficiency gave me more control over my health). These items were all rated on a Likert scale ranging from zero

(*strongly disagree*) to six (*strongly agree*) and summed to generate health benefits beliefs scores.

**Psychological benefits beliefs** were assessed with four items (e.g. the test would reduce the anxiety of not knowing one's genetic background; the test reduced the anxiety of not knowing my genetic background). These items were all rated on a Likert scale ranging from zero (*strongly disagree*) to six (*strongly agree*) and summed to generate psychological benefits beliefs scores.

**Psychological distress beliefs** were assessed with five items (e.g. knowing that I have protein C deficiency would seriously harm my self-image; knowing that I have protein C deficiency seriously harmed my self-image). These items were all rated on a Likert scale ranging from zero (*strongly disagree*) to six (*strongly agree*) and summed to generate psychological distress beliefs scores.

Furthermore, participants who had not been tested before (group 1) filled in two items about their interest in getting a genetic test and their beliefs in the likelihood of receiving a positive test result.

**Testing interest** Interest about getting the genetic test for protein C deficiency was assessed with one item: how interested are you in getting a genetic test for protein C deficiency? This item was rated on a seven-point Likert scale ranging from one (*not at all interested*) to seven (*extremely interested*).

**Likelihood of having protein C deficiency** With one item, the belief in the likelihood of receiving a positive test result was assessed: if you would be tested, how likely do you think it is that you have protein C deficiency? This item was rated on a seven-point Likert scale ranging from one (*not at all*) to seven (*almost certain*).

**Group 3: Participants without protein C deficiency** Three additional items were added for participants who tested negative for protein C deficiency. All items were rated on a seven-point Likert scale ranging from one (*not at all*) to seven (*extremely*).

**Relief** One item assessed the amount of relief the participants felt after finding out that they did not have protein C deficiency: did you feel relieved after finding out that you do not have protein C deficiency?

**Guilt** One item assessed whether participants felt guilty about not having protein C deficiency: if other people in your family have protein C deficiency, did you feel guilty after finding out that you do not have it?

**Likelihood of having protein C deficiency if tested again** One item assessed the false or correct beliefs of participants about the likelihood of getting a positive test result, if they would be tested again: if you would be tested again, how likely do you think it is that you have protein C deficiency?

## Results

### Demographic variables

A total of 265 family members were invited to participate in the study. Of the non-responders, 30 (11.3%) refused to participate, 22 (8.3%) did not show up at their scheduled appointment, and 15 (5.7%) could not participate because of other reasons such as illness. A questionnaire was eventually filled out by 198 (74.7%) family members. Questionnaires of 24 participants who had already suffered from venous thrombosis were removed from the present analyses because the aim of this paper was to study attitudes about genetic testing in thrombophilic individuals without a history of venous thrombosis.

A further six questionnaires were removed because of incomplete data. The remaining database consisted of 168 participants. The mean age of the participants was 44.4 (SD 14.2) years with a range from 18 to 76 years. The sample consisted of 73 men (43%) and 95 women (57%). Of all participants, 92 subjects (55%) had been tested for protein C deficiency in a previous study [18], and 76 subjects (45%) had not been tested before and thus did not know their status when they completed the questionnaires. Of the tested participants, 34 people had protein C deficiency, and 58 participants had tested negative.

### Descriptive analyses

In further analyses, a distinction was made among the three groups of participants: participants who had not been tested (group 1), participants with protein C deficiency, and participants without protein C deficiency. Internal consistency of all attitude scales was satisfactory (Cronbach's alpha's > 0.70) and the items from the risk perception and worry scores were highly correlated ( $r = 0.90$  and  $r = 0.87$ ). To test for age differences, a median split of the sample was made (median = 45). To protect against inflation of type 1 error from multiple correlations and other statistical tests, we used  $P < 0.01$  as our critical value for all statistical tests.

#### Group 1: Participants who had not been tested before ( $n = 76$ )

Table 1 presents means, SDs and intercorrelations among all measures, for participants that had not been tested for protein C deficiency. Means for risk perception and thrombosis-related worry were 3.9 and 3.4 on scales ranging from 2 to 14, indicating that participants did not think it is very likely that they would ever get venous thrombosis or worry a lot about it. Mean scores on beliefs in the health benefits and psychological benefits of testing were 20.6 and 15.1 on scales ranging from 0 to 30 and 0 to 24, whereas the belief in psychological distress following the genetic test was 7.5 on a scale ranging from 0 to 30. This indicates that beliefs about the positive consequences of getting a genetic test were stronger than beliefs about the negative consequences of the test. For the benefits of testing,

the item with the highest mean score was 'I should get tested for the sake of my family and loved ones' (mean 4.7), indicating that deciding to have a genetic test for protein C deficiency is primarily a matter of concern for the family. The item with the lowest mean score was 'The test results would help me in making decisions about whether and when to have children' (mean 0.7). The mean score on the trait form of the STAI was 36.3 (SD 9.6). Participants were quite interested in getting a genetic test for protein C deficiency (mean 4.6 on a scale ranging from 1 to 7) and did not think it was very likely that they would have protein C deficiency (mean 2.6 on a scale from 1 to 7). Risk perception and worry were correlated ( $r = 0.51$ ,  $P < 0.01$ ). Higher trait anxiety was related to a higher belief in psychological distress following the test ( $r = 0.37$ ,  $P < 0.01$ ), but not to a higher interest in getting the test, or a higher belief that one will have protein C deficiency. Beliefs in higher health and psychological benefits of testing were correlated with more interest in getting the genetic test ( $r = 0.59$  and  $0.46$ ,  $P < 0.01$ ) and a belief that one will have protein C deficiency ( $r = 0.35$  and  $0.41$ ,  $P < 0.01$ ). Older participants had higher scores on thrombosis-related worry than younger participants ( $P < 0.01$ ). No sex differences could be detected.

#### Group 2: Participants with protein C deficiency ( $n = 34$ )

Table 2 presents means, SDs and intercorrelations among all measures for participants who previously had been tested positive for protein C deficiency. Risk perception and thrombosis-related worry were higher than risk perception and worry scores for participants who had not been tested (means 5.4 and 5.5 on scales ranging from 2 to 14). Beliefs in the health benefits, psychological benefits and psychological distress following the test were marginally lower than the beliefs of participants who had not been tested (means 19.4, 14.3 and 5.3 on scales ranging from 0 to 30, 0 to 24 and 0 to 30). For the health and psychological benefits of testing, the item with the highest mean score was again 'I got tested for the sake of my family and loved ones' (mean 4.6 on a scale ranging from 1 to 7). Furthermore, the item with the lowest mean score was again 'The test results helped me in making decisions about whether and when to have children' (mean 1.6 on a scale ranging from 1 to 7). The mean score on the trait form of the STAI was 32.9 (SD 9.0). Risk perception and worry were correlated ( $r = 0.70$ ,  $P < 0.01$ ). Beliefs in health benefits and psychological benefits following the genetic test were also related ( $r = 0.60$ ,  $P < 0.01$ ). Both thrombosis-related worry and trait anxiety were correlated with psychological distress following the genetic test ( $r = 0.52$  and  $r = 0.61$ ,  $P < 0.01$ ). There were no sex or age differences for any of the measures.

#### Group 3: Participants without protein C deficiency ( $n = 58$ )

Table 3 presents intercorrelations among all measures, means and SDs, for patients who had been tested negative for protein C deficiency. In this group, risk perception and thrombosis-related worry were lower than in the other groups

**Table 1** Intercorrelations, means, and SDs, for group 1: participants that had not been tested for protein C deficiency ( $n = 76$ )

| Measure                        | Risk perception | Worry | Trait anxiety | Health benefits beliefs | Psychological benefits beliefs | Psychological distress | Testing interest | Likelihood of having PC def |
|--------------------------------|-----------------|-------|---------------|-------------------------|--------------------------------|------------------------|------------------|-----------------------------|
| Risk perception                | –               | –     | –             | –                       | –                              | –                      | –                | –                           |
| Worry                          | 0.51*           | –     | –             | –                       | –                              | –                      | –                | –                           |
| Trait anxiety                  | –0.11           | –0.01 | –             | –                       | –                              | –                      | –                | –                           |
| Health benefits beliefs        | 0.21            | 0.30  | –0.08         | –                       | –                              | –                      | –                | –                           |
| Psychological benefits beliefs | 0.11            | 0.20  | 0.13          | 0.79*                   | –                              | –                      | –                | –                           |
| Psychological distress         | –0.13           | –0.10 | 0.37*         | 0.00                    | 0.19                           | –                      | –                | –                           |
| Testing interest               | 0.20            | 0.38* | –0.09         | 0.59*                   | 0.46*                          | –0.13                  | –                | –                           |
| Likelihood of having PC def    | 0.40*           | 0.50* | –0.04         | 0.35*                   | 0.41*                          | 0.01                   | 0.43*            | –                           |
| Mean                           | 3.9             | 3.4   | 36.3          | 20.6                    | 15.1                           | 7.5                    | 4.6              | 2.6                         |
| SD                             | 2.4             | 1.9   | 9.6           | 7.6                     | 6.1                            | 8.4                    | 2.4              | 1.6                         |
| Range                          | 2–14            | 2–14  | 20–80         | 0–30                    | 0–24                           | 0–30                   | 1–7              | 1–7                         |

\* $P < 0.01$ .**Table 2** Intercorrelations, means, and SDs for group 2: participants with protein C deficiency ( $n = 34$ )

| Measure                        | Risk perception | Worry | Trait anxiety | Health benefits beliefs | Psychological benefits beliefs | Psychological distress |
|--------------------------------|-----------------|-------|---------------|-------------------------|--------------------------------|------------------------|
| Risk perception                | –               | –     | –             | –                       | –                              | –                      |
| Worry                          | 0.70*           | –     | –             | –                       | –                              | –                      |
| Trait anxiety                  | 0.01            | 0.28  | –             | –                       | –                              | –                      |
| Health benefits beliefs        | 0.26            | 0.19  | –0.11         | –                       | –                              | –                      |
| Psychological benefits beliefs | 0.04            | 0.21  | 0.19          | 0.60*                   | –                              | –                      |
| Psychological distress         | 0.13            | 0.52* | 0.61*         | –0.05                   | 0.30                           | –                      |
| Mean                           | 5.4             | 5.5   | 32.9          | 19.4                    | 14.3                           | 5.3                    |
| SD                             | 2.9             | 2.7   | 9.0           | 5.8                     | 5.3                            | 6.9                    |
| Range                          | 2–14            | 2–14  | 20–80         | 0–30                    | 0–24                           | 0–30                   |

\* $P < 0.01$ .**Table 3** Intercorrelations, means, and SDs for group 3: participants without protein C deficiency ( $n = 58$ )

| Measure         | Risk perception | Worry | Trait anxiety | Relief | Guilty | Genetic retest |
|-----------------|-----------------|-------|---------------|--------|--------|----------------|
| Risk perception | –               | –     | –             | –      | –      | –              |
| Worry           | 0.62*           | –     | –             | –      | –      | –              |
| Trait anxiety   | –0.11           | 0.10  | –             | –      | –      | –              |
| Relief          | –0.05           | 0.07  | 0.07          | –      | –      | –              |
| Guilty          | –0.08           | 0.06  | –0.02         | 0.12   | –      | –              |
| Genetic retest  | 0.33            | 0.28  | 0.00          | –0.02  | 0.14   | –              |
| Mean            | 3.2             | 3.2   | 32.5          | 5.4    | 1.8    | 1.7            |
| SD              | 1.7             | 1.8   | 9.4           | 1.9    | 1.4    | 0.8            |
| Range           | 2–14            | 2–14  | 20–80         | 1–7    | 1–7    | 1–7            |

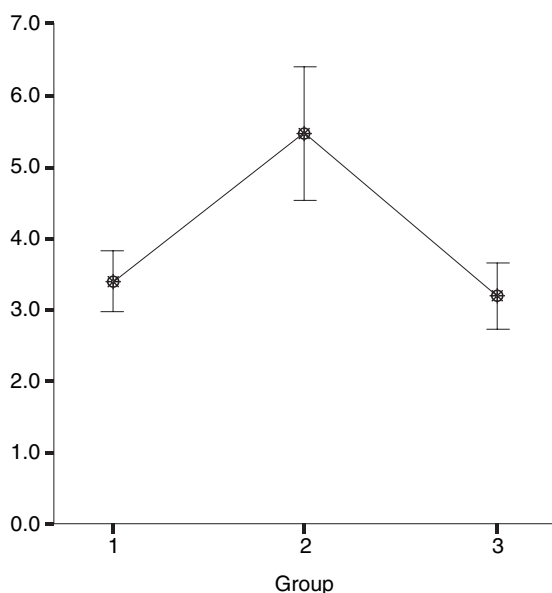
\* $P < 0.01$ .

and correlated as well (means 3.2 and 3.2 on scales ranging from 2 to 14,  $r = 0.62$ ,  $P < 0.01$ ). The mean score on the trait form of the STAI was 32.5 (SD 9.4). More than half of the participants (61%) reported that they felt relieved after finding out that they did not have protein C deficiency and the majority (81%) did not feel guilty when other family members were tested positive. Furthermore, most participants (87%) correctly assumed that a second test would still be negative. A higher risk perception or worry about getting thrombosis was associated with a higher belief that a second test would give a positive result ( $r = 0.33$  and  $0.28$ ), but these

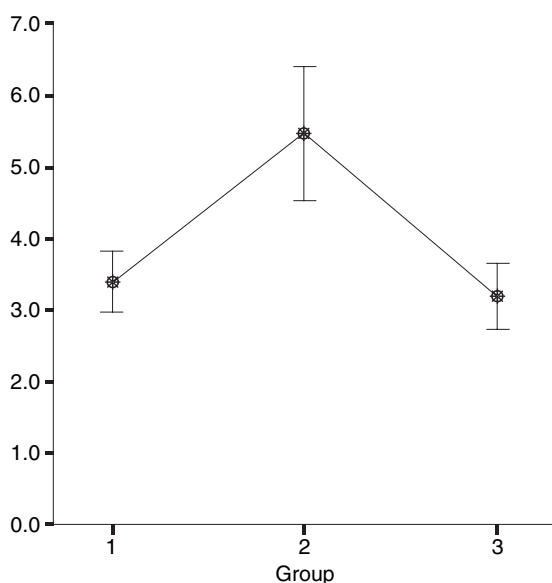
results did not reach statistical difference. There were no sex or age differences for any of the measures.

#### Between-group differences

$t$ -tests and ANOVAS with Scheffé's *post hoc* tests were used to test for differences between the three groups on the various measures. Scores for risk perception and worry were found to be significantly higher (ANOVA:  $F = 9.4$ ,  $P < 0.001$  and  $F = 15.8$ ,  $P < 0.001$ ) for the group with protein C deficiency compared with the group without protein C deficiency and



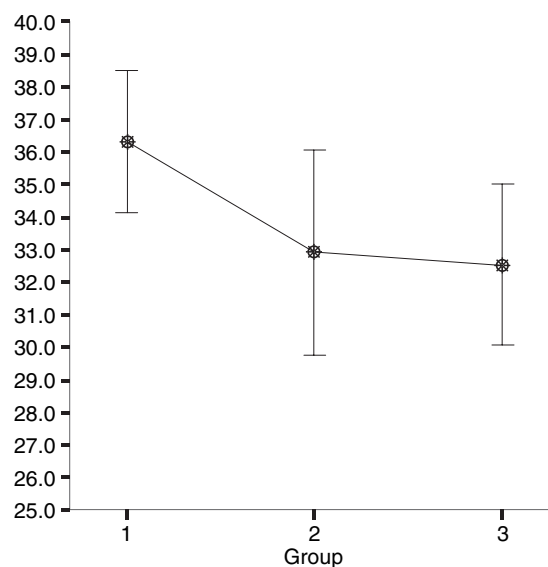
**Fig. 1.** Means for risk perception with 95% confidence intervals for means.



**Fig. 2.** Means for thrombosis-related worry with 95% confidence intervals for means.

those who had not been tested before (see Figs 1 and 2). Surprisingly, scores on the trait form of the STAI were highest for the group who did not know their protein C status (see Fig. 3), but this effect did not reach statistical significance (ANOVA:  $F = 3.2$ ,  $P = 0.45$ ).

*t*-tests demonstrate that, for attitudes about genetic testing, the individuals who had not been tested and individuals with known protein C deficiency did not differ significantly on any of the measures of psychological distress, psychological benefits and health benefits of receiving a genetic test result.



**Fig. 3.** Means for trait anxiety with 95% confidence intervals for means.

#### Knowledge about other risk factors for venous thrombosis

The risk factors that were believed to be most likely to cause venous thrombosis by the participants in our sample were lack of exercise (50% agreed or strongly agreed with the risk factor), aging (49% agreed or strongly agreed with the risk factor) and surgery (45% agreed or strongly agreed with the risk factor). No differences could be detected among the three groups or for younger and older participants. Women were more likely than men to agree with the risk factor birth control pills ( $t = -4.53$ ,  $P < 0.001$ ).

To assess whether knowledge about the risk factors for venous thrombosis was related to perceptions of risk, thrombosis-related worry and attitudes about genetic testing, we calculated correlations between the total knowledge scores and the other measures. The only significant correlation was found in the group that had not been tested between the knowledge and thrombosis-related worry scores ( $r = 0.33$ ,  $P < 0.01$ ).

#### Discussion

The results of this family study indicate that asymptomatic individuals with a family history of venous thrombosis perceive the psychological and health benefits of getting a genetic test for protein C deficiency as higher than the psychological distress following the test. Interestingly, it seems that attitudes about getting the genetic test did not differ significantly between the group with protein C deficiency and the group that had not yet been tested. This indicates that the expectations of the participants about getting the genetic test were realistic in terms of their expectations about the potential health and psychosocial benefits of testing as well as the psychological distress a positive test result might cause. However, it is possible that significant differences could not be detected because of the relatively small number of participants in each group.

Furthermore, as participants were not recently tested, it is possible that adverse psychological effects have arisen directly after receiving the test result but that individuals have adapted to their condition over the years, by giving the psychological effects of their condition a different meaning. This effect, which has been applied to some extent in quality of life research, is called response shift [21,22]. Therefore, these results should be taken with some caution.

For participants who had been tested positive for protein C deficiency, trait anxiety was highly correlated to psychological distress following the genetic test. As the same relationship can be noted for participants who had not been tested before, it seems that in general there are few adverse psychological effects of receiving a positive test result for protein C deficiency, but that certain vulnerable individuals, with a high predisposition to anxiety, might experience considerable distress following the positive test result. This is in line with the findings of Lindqvist *et al.* [12] who found that most APC resistant women reported that their lives were unaffected by the knowledge of being APC resistant, but that about a quarter of the women became more worried after getting the test. Additionally, this effect has been found in earlier research on predictive genetic testing [11]. In this light, it is also notable that a high score on trait anxiety does not predict interest in getting the genetic test or a higher belief in having protein C deficiency among the individuals who have not been tested before. This suggests that a high dispositional anxiety does not necessarily motivate one to have a genetic test performed or to believe they have a high likelihood of having an abnormal result. It is interesting to note that worry rather than risk perception was the only measure that correlates with the attitudes about the genetic test and interest in getting the genetic test. These findings are consistent with earlier research by Cameron *et al.* [20] and suggest that it is not the perception of risk that motivates people to take a genetic test, but the disease-specific worry people experience. As the lifetime risk for venous thrombosis in protein C deficient individuals is 50%, even the protein C deficient participants in this study slightly underestimate their risk for venous thrombosis. These relatively low risk perceptions could be because of people's tendency to underestimate their own risk, also called 'optimistic bias' [23].

Another interesting finding is that knowledge of risk factors for venous thrombosis does not differ between the three groups. However, only for the group that has not been tested, knowledge about the other risk factors for venous thrombosis is related to worry about venous thrombosis. This indicates that without knowing whether one has protein C deficiency or not, knowledge of other risk factors for venous thrombosis increases worry and that this knowledge does not influence worry in participants who have already been tested.

This study describes the results for the asymptomatic family members of one kindred only. It is possible that patients who have experienced an episode of venous thrombosis might react differently to getting a positive test result for protein C deficiency or another form of thrombophilia. Protein C deficiency is a disorder characterized by a 10-fold increased risk of developing

venous thrombosis and many family members have experienced the episodes of venous thrombosis in a close relative. This likely explains the fact that many family members consider getting tested as very important for their family. Patients with a different family history of venous thrombosis may express different emotional reactions to the knowledge of having thrombophilia. This study was not randomized, so there is a possibility that participants who decided to get tested differed from the other participants. In addition, because this is a family study in which most of the participants had already been tested previously (mostly around 10 years ago for the benefits of an earlier study), it was not possible to assess the reactions to the test, directly after receiving the test result. As discussed earlier, it is possible that adverse psychological effects have arisen directly after receiving the test result but that individuals have adapted to their condition over the years because of a response shift. This effect has been noted in earlier research on hereditary cancer as well [9,24], and should be acknowledged in further research on the psychological consequences of genetic testing for thrombophilia.

Taking the limitations of this study and their possible effect on the outcome of this study into account, we can conclude by saying that there do not seem to be many long-term negative psychological consequences of genetic testing for thrombophilia as measured by thrombosis-related worry and psychological distress following the test results. However, the short-term effects of testing deserve more attention in future studies. Future studies should investigate a more diverse group of thrombophilia patients with variation in risk factors. Ideally, such a study would have a randomized longitudinal design, with measurements of psychological distress immediately after receiving the test result and at a specified later time point, to investigate whether the duration and intensity of the perceived emotional impact of the test changes over time. In addition, it would be useful to include measures about state anxiety or depression following the genetic test result. From a clinical perspective, this study indicates that genetic testing for protein C deficiency does not have many adverse psychological effects in the long term. However, it is also important to note that non-tested individuals from a high-risk family do not worry excessively about developing venous thrombosis. To make a fully informed choice about genetic testing for thrombophilia, it is important that physicians inform patients in great detail about the other risk factors for venous thrombosis and the lack of treatment for thrombophilia.

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