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Crystal Rae Dunn

AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Epidemiology)

GRADE / DEGREE

Department of Epidemiology and Community Medicine

FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

An Exploratory Study of the Psychological and Behavioural Impacts of Genetic Testing for Thrombophilia among Asymptomatic First-degree Relatives of Patients with Venous Thrombosis

TITRE DE LA THÈSE / TITLE OF THESIS

Brenda Wilson

DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

Phil Wells

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Ian Graham

Julian Little

Gary W. Slater

Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

An exploratory study of the psychological and behavioural impacts of genetic testing for thrombophilia among asymptomatic first-degree relatives of patients with venous thrombosis

by

Crystal R. Dunn

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfilment of the requirements for the MSc degree in Epidemiology

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ABSTRACT

Objective: To conduct a preliminary exploration of psychological outcomes and health behaviour in individuals undergoing testing for genetic mutations associated with thrombophilia.

Methods: Subjects were 57 carriers and 54 non-carriers identified through an existing pilot study. Part I analyzed perceived risk and psychological data collected at baseline, 1 week and 12 months post-test. Part II used a cross-sectional survey to collect data regarding: test implications, perceived causes and control, and behaviour change post-test.

Results: Accuracy of risk perception improved post-test due to decreased risk perception among non-carriers. No major psychological harms were identified, but a subgroup of carriers may experience distress. Participants had a high sense of control over their risk of venous thromboembolism and had a good understanding of risk factors. Many tried to change their behaviours post-test, but did not report doing this specifically to reduce their risk of a blood clot.

Conclusions: This exploratory study suggests no major psychological harm arising from genetic testing, but its findings need replication with larger samples.

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LIST OF ABBREVIATIONS

AD	Alzheimer Disease
BDI	Beck Depression Inventory
BSE	Breast Self Examination
C	Carrier
CES-D	Center for Epidemiological Studies Depression Scale
CBE	Clinical Breast Examination
DVT	Deep Vein Thrombosis
FAP	Familial Adenomatous Polyposis
FDR	First-Degree Relative
FH	Familial Hypercholesterolemia
FVL	Factor V Leiden
GHQ-28	General Health Questionnaire
HADS	Hospital Anxiety and Depression Scale
HBOC	Hereditary Breast and Ovarian Cancer
HD	Huntington Disease
HNPCC	Hereditary Non-polyposis Colorectal Cancer
HRT	Hormone Replacement Therapy
HSCL-25	Hopkins Symptom Checklist
IES	Impact of Event Scale
NC	Non-Carrier
PE	Pulmonary Embolism
POMS-SF	Profile of Mood States – Short Form
QLI	Quality of Life Index
SCL-90	Symptom Checklist
STAI	State-Trait Anxiety Inventory
TMD	Total Mood Disturbance
TVU	Transvaginal Ultrasound
VTE	Venous Thromboembolism

CHAPTER I

INTRODUCTION

With the completion of the human genome project, the boundaries of genetic medicine are expanding beyond the realm of rare, monogenic disorders. We are gradually shifting along a continuum from medical genetics to 'genomic medicine', requiring a reassessment of the traditional genetic services model (See Table 1).[1] No longer are we merely concerned with 'genetics', the study of single genes and their effects, but we have entered the era of 'genomics', which is the study of the functions and interactions of all the genes in the genome.[2] The term 'genomics' is considered a more appropriate term than 'genetics' when the focus of study is on how interactions of multiple genes and environmental factors increase one's risk of common ('complex') diseases.[2] As the genetic basis for these multifactorial disorders is established, testing for relevant susceptibility genes (singly or in combination) may become a legitimate element of clinical diagnosis and management for a broader segment of the population. However, as this situation evolves, it is still important to consider and examine the implications of genetic testing from the perspectives of patients and their families. It is also important to ensure that there are benefits of genetic testing for these conditions, that these benefits outweigh the harms and that they are worth the costs and impacts on the broader health care system.

To date, the majority of studies that have investigated the impacts of genetic testing have focused on single gene disorders (e.g., Huntington disease (HD), hereditary breast/ovarian cancer (HBOC)) (see reviews[3-5]). As we shift further along the genetic-genomic

continuum, there is a growing need to characterize the impacts that genetic testing for multifactorial conditions may have on patients, families and the health care system. Genetic testing for thrombophilia (i.e. the predisposition to venous thrombosis) presents a useful opportunity for a case study of these potential impacts, particularly those beyond the strictly clinical domain. We present an exploratory study that identifies and quantifies some of these impacts, with a view to defining important areas for future substantive research and, possibly, identifying issues of immediate relevance for the clinical management of patients and their families.

Table 1: Continuum from genetics to genomics in practice

Type of genetic variation	Examples	Practice Model
Single gene disorders, High penetrance; No effective interventions	Huntington disease	Genetic services; nondirective counselling
Single gene disorders; High penetrance; Effective interventions	Phenylketonuria	Population screening (e.g., newborn screening)
Single gene disorders; Low or variable penetrance; Intervention: variable	Hereditary breast/ovarian cancer, hemochromatosis	Genetic services; counselling may or may not be directive
Genetic variation at one or multiple loci	Pharmacogenetic traits; factor V Leiden, MTHFR	Communicating genetic information re: future risk of disease and intervention; counselling may be directive
Genetic variation at multiple loci in somatic cells (e.g., tumours)	Gene expression profiles; serum proteomic patterns	Using genetic information in early diagnosis, classification, prognosis, and treatment; genetic services/counselling model does not apply

Source: Khoury (2003)[1]

Background

Thrombophilia

In developed countries, the annual incidence of venous thromboembolism (VTE) is approximately 1 per 1000 people, ranging from 1 per 100,000 during childhood to nearly 1 per 100 in old age.[6] Most commonly, the disorder is manifest as deep-vein thrombosis of the leg (DVT), or as pulmonary embolism (PE), with complications ranging from post-thrombotic syndrome to acute death from PE.[7] While treatment with oral anticoagulation is extremely effective in treating VTE, this treatment does carry a significant risk of hemorrhagic complications (1-3%)[8;9] and recurrence rates are high after cessation of initial therapy (24.8% at 5 years and 30.3% at 8 years).[10]

Although the pathogenesis of this serious disorder is not fully understood, it has been postulated that the development of VTE is influenced by the complex and dynamic interaction of genetic, acquired and 'mixed' (genetic and acquired) risk factors (Table 2).[7;11;12] The multigenic, multifactorial nature of VTE and the recent establishment of several inherited factors have caused it to be viewed as a prototype of a complex disorder.[11]

Table 2: Established genetic, acquired and 'mixed' risk factors for VTE

Inherited	Acquired	Mixed
Antithrombin deficiency	Age	Hyperhomocysteinemia
Protein C deficiency	Immobilization	Increased factor VIII levels
Protein S deficiency	Surgery	Increased fibrinogen levels
Factor V Leiden	Malignancy	Increased factor XI levels
Factor II G20210 A	Pregnancy and puerperium	Increased factor IX levels
	Oral Contraceptives	
	Hormone replacement	
	Antiphospholipid syndrome	
	Myeloproliferative disorders	

Source: Franco and Reitsma (2001)[11]

Inherited thrombophilia is the term used to describe a genetically determined predisposition to VTE. Interest in inherited thrombophilia has grown after the discovery of two gain-of-function mutations prevalent in white populations: the factor V Leiden (FVL) mutation[13] and the prothrombin G20210A mutation.[14] While earlier loss-of-function mutations (e.g. deficiencies of antithrombin, protein C, and protein S) were detectable in only a small percentage of the general population (0.02-0.4%) and among patients with VTE (1-5%), FVL and prothrombin mutations are much more prevalent in both populations (1-15%, and 6-50% respectively) (Table 3).[15] Kearon *et al.*[16] describe that the common mutations (i.e. FVL and prothrombin) are associated with a modest risk of VTE and the uncommon mutations (i.e. antithrombin, protein C and S) are associated with a higher risk. However, the high prevalence of FVL and prothrombin lead to a high population attributable risk (PAR), thus they are more important when considering the impacts of genetic testing at the population level. For example, Rosendaal[17] reports a PAR equal to 20-25% for FVL, while that for protein C or antithrombin deficiencies is reported as less than 2%. Interest in 'mixed' risk factors is also growing, with several studies reporting relatively high

Table 3: Prevalence of genetic and 'mixed' risk factors involved in the aetiology of venous thromboembolism (VTE)

Risk Factor	General Population[d]	Patients with VTE[d]	Relative Risk of VTE[e]
Antithrombin deficiency	0.02%	1-3%	25
Protein C deficiency	0.2-0.4%	3-5%	10
Protein S deficiency	0.03-0.13%	1-5%	10
Factor V Leiden	1-15%	10-15%	4
Factor II G20210 A	2-5%	6-18%	2.5
Hyperhomocysteinemia	~5%	~10%	
High plasma factor VIII level[a]	11%	25%	
High plasma factor IX level[b]	3%	7.5%	
High plasma factor XI level[c]	10%	19%	

[a]Factor VIII levels ≥ 150 IU/dl (Rosendaal *et al.* 1999)[18]
[b]Factor IX levels > 90th percentile, i.e. 129 IU/dl (van Hylckama Vlieg *et al.* 2000)[19]
[c]Factor XI levels > 90th percentile, i.e. 120.8 IU/dl (Meijers *et al.* 2000)[20]
[d]Source: Franco and Reitsma (2001)[11]
[e]Source: Kearon *et al.* (2000)[16]

prevalence of elevated levels of factors VIII, IX and XI among both the general population and patients with VTE (see Table 3).[18-20]

As the genetic basis for inherited thrombophilia is established, one or more genetic mutations will be detectable in an increasing number of VTE patients.[21] While the capacity for genetic testing is present, one must ask whether there is a clear rationale for thrombophilia testing among patients with VTE and/or their families. Genetic testing for thrombophilia would be helpful if it led to a change in the type or duration of initial anticoagulant therapy or the use of long-term prophylactic anticoagulation to prevent recurrences.[22] However, there is currently no evidence that those with an inherited thrombophilia should be managed any differently than VTE patients without identifiable abnormalities.[22-25] While the benefits for the patients themselves may be limited, a major argument in favor of testing is the potential benefit for the patient's family through the identification of other first-degree relatives (FDRs) with inherited thrombophilia.[22] The identification of these unaffected individuals may have important implications for primary prevention and risk-reducing behaviours during periods of increased VTE risk (e.g. surgery, immobilization, pregnancy), and may ultimately reduce mortality among FDRs who would otherwise be unaware of their predisposition to VTE.[26]

Several studies have investigated the clinical validity of genetic testing for thrombophilia among asymptomatic FDRs. To determine the likelihood that testing could lead to improved health outcomes, these studies have assessed the incidence of VTE among carriers of FVL[27-29] and antithrombin, protein C or protein S deficiencies.[29;30] All four studies found a low absolute risk of VTE per year among asymptomatic carriers of these mutations and concluded that the low incidence of spontaneous VTE does not warrant

continuous anticoagulant prophylaxis.[27-30] Three of the four studies do, however, indicate that routine testing of FDRs does have the potential to identify those who might benefit from anticoagulant prophylaxis during high risk periods.[28;30;30] While the authors acknowledge this potential benefit of testing relatives, there is no evidence that a more stringent policy of thromboprophylaxis in high risk situations could further reduce the risk of thrombosis.[29;30] Furthermore, Simioni *et al.*[28] state that an accurate evaluation of the cost-benefit ratio of testing selected family members should be performed before this is recommended as a routine approach. While further research is needed to resolve the clinical benefits of genetic testing for thrombophilia, there is a need to concurrently examine the broader impacts that testing may have on the individual, their family and the health care system. We must ask if genetic testing is worth the cost, not only in terms of financial costs, but also in terms of the psychosocial and non-clinical costs of identifying a genetic trait with a low penetrance for a late onset disease in a large number of individuals.[31]

Multiple impacts of genetic testing

Apart from issues for clinical management, there are several potential psychological and non-clinical impacts of genetic testing. For those receiving both positive and negative results, genetic testing may have beneficial and/or detrimental consequences with respect to: 1) individual psychological functioning; 2) health behaviour and perceptions of control over one's health; 3) family dynamics and communication; 4) socio-legal issues (e.g. increased insurance premiums); and 5) health services utilization. These consequences are mediated by various cognitive appraisals, including one's own perception of risk and one's perceived seriousness and control over the disorder in question.

Regardless of the potential clinical benefits provided by a genetic test, these must be balanced against the emotional and psychological risks that may be encountered. The impact of genetic testing on psychological distress, anxiety, and depression could have serious consequences for the individual and the health care system. Furthermore, the potential value of detecting mutations in asymptomatic individuals and estimating their personal susceptibility to disease will only be realized if these individuals adopt risk-reducing behaviours in response to their genetic status. Finally, the impact of genetic testing on the individual and his/her response to it will depend upon cognitive appraisals of the situation that may or may not be modified by the genetic testing and counselling process.

Several studies have examined the cognitive, psychological and/or behavioural impacts of genetic testing and/or counselling within the past ten to fifteen years. Many of these studies have previously been reviewed and the main findings from six relevant systematic reviews are summarized in Table 4. Two of these reviews focused on the impacts of testing and/or counselling for hereditary breast cancer,[5;32;33] one focused on the impacts of genetic counselling for familial cancer,[4] one focused on the impacts of predictive genetic testing for any disorder[3] and one reviewed the predictors of perceived breast cancer risk and its relation to prevention and early detection.[34]

In general, the authors of these reviews found that genetic testing or counselling does not increase distress, and that some studies report short-term reductions in general anxiety or disease-specific worry. Broadstock *et al.*[3] report that both carriers and non-carriers showed decreased distress after predictive genetic testing, but that this decrease was greater and more rapid among non-carriers. They also found that pre-test distress was

Table 4: Summary of findings from systematic reviews of the cognitive, psychological and/or behavioural impacts of genetic testing

Review	Objective	Main Conclusions
Broadstock *et al.* (2000)[3] 11 studies 1990-1998	• Systematic review of the psychological consequences of ***predictive genetic testing*** (including Huntington's disease, breast/ovarian cancer, familial adenomatous polyposis and speinocerebellar ataxia)	• No increase in distress (general and situational distress, anxiety and depression) in carriers or non-carriers during the 12 months following testing. • Carriers and non-carriers showed decreased distress after testing; greater and more rapid decrease among non-carriers. • Pre-test distress often a predictor of subsequent distress; test result rarely a predictor • Most studies were of Huntington's disease
Meiser & Halliday (2002)[32] 12 studies 1980-2000	• Systematic review/meta-analysis of the psychological and behavioural impacts of ***genetic counselling*** for hereditary breast cancer	• Genetic counselling leads to statistically significant decreases in generalized anxiety, but not in psychological distress • Counselling improves the accuracy of perceived risk • Few studies of behavioural outcomes; two found improvements in breast cancer screening relative to baseline and one found reduced mammography use among less-educated participants.
Butow *et al.* (2003)[5] 19 studies 1980-2001	• Systematic review of the effects of ***genetic counselling and testing*** for familial breast cancer on women's perspective of risk and psychological morbidity	• Testing and counselling appear to produce psychological benefits and to improve accuracy of risk perception. • Carriers did not experience increased anxiety/depression and non-carriers experienced relief • Improvements in accuracy of perceived risk were observed immediately after counselling, although 22-50% of women still overestimated their risk at this time.
Katapodi *et al.* (2003)[34] 42 studies 1985-2002	• Systematic review/meta-analysis of predictors of perceived breast cancer risk and the relation between perceived risk and prevention/early detection	• Women do not have accurate perceptions of their breast cancer risk • Overall, women have an optimistic bias about their personal risk • There is an association between perceived risk and mammography screening, but it is not clear whether perceived risk influences adherence to breast self-examination • Women who perceive a higher breast cancer risk were more likely to pursue genetic testing and to undergo prophylactic mastectomy
Braithwaite *et al.* (2004)[4] 21 studies 1980-2001	• Systematic review/meta-analysis of the psychological outcomes of ***genetic counselling*** for familial cancer	• Genetic counselling did improve knowledge of cancer genetics • Counselling did not alter the level of short-term perceived risk, and had no effect on long-term general anxiety or cancer-specific worry • Some studies reported short-term reductions in general anxiety or cancer-specific worry
Wainberg & Husted (2004)[33] 7 studies 1996-2003	• Systematic review of the utilization of screening and preventive surgery among unaffected carriers of a BRCA1/2 mutation	• Considerable variability between countries in risk reduction strategies used by healthy mutation carriers • Proportion of mutation carriers who chose preventive surgery over screening ranges: 0% to 54% for prophylactic masectomy and 13% to 53% for prophylactic oophorectomy • Significant minority of subjects who chose surveillance failed to comply with recommended schedule

often a predictor of subsequent distress, while test result was rarely a predictor. Both Meiserand Halliday[32] and Butow *et al.*[5] reported that genetic counselling improves the accuracy of perceived risk of hereditary breast cancer, while Braithwaite *et al.*[4] found that counselling did not alter the level of short-term perceived risk. Butow *et al.*[5] did note, however, that 22-50% of women still overestimated their risk following counselling. Katapodi *et al.*[34] found that those with higher breast cancer perceived risk were more likely to pursue genetic testing and to undergo prophylactic masectomy, and that there was also an association between perceived risk and mammography screening. Finally, Wainberg *et al.*[33] reported considerable variability between countries with respect to risk reduction strategies used by healthy carriers of BRCA1/2 mutations. The proportion of carriers choosing prophylactic surgery ranged from 0-54%, and a substantial minority of those choosing surveillance failed to comply with the recommended schedule.

While several studies have examined and reviewed the multiple impacts of genetic testing and counselling, this field has been rapidly evolving since the late 1990's. Until then, genetic testing was only available in research settings and was not conducted on a routine clinical basis. Furthermore, new genetic discoveries have expanded the realm of testing from 'predictive' testing (e.g. HD) to 'predispositional' testing (e.g. familial cancers) and finally to 'susceptibility' testing (e.g. thrombophilia). In order to provide an overview of the recent developments in this field and to provide a solid foundation for the present study, the cognitive, psychological and behavioural impacts of genetic testing are systematically reviewed in the following chapter.

Rationale

The purpose of this study is to begin the process of quantifying the psychological and non-clinical impacts of genetic testing among unaffected individuals. Apart from previous work in cancer, there are little published data on these broader impacts of genetic testing for complex, less penetrant conditions. An ongoing study of first-degree relatives presented an excellent opportunity to explore these impacts in the context of thrombophilia, a complex, multifactorial condition. While a single study cannot examine the full range of potential impacts as outlined in Table 5 (overleaf), we have begun filling in the gaps by focusing on emotional and behavioural impacts. Longitudinal and cross-sectional data collected from first-degree relatives were used to report preliminary estimates of benefit and harm. The results of this study are important for generating knowledge valuable in the consideration of the wider impacts of genetic testing at both the level of the individual and the health care system.

Table 5: Framework for the potential consequences of genetic testing for thrombophilia. (Focus areas in the current study are denoted by *)

Potentially beneficial consequences	**FDR Positive Result**	**FDR Negative Result**
Clinical	-Prophylaxis recommended beyond standard of care	-No indication of prophylaxis except where standard of care
****Emotional***	-Relief of uncertainty -Reduced anxiety	-Relief of uncertainty -Reduced anxiety
****Health Behaviour***	-Increase in risk reducing behaviours	-Increase in risk reducing behaviours
Family	-Others at risk may be identified	-Other family members can be reassured about risk status
Socio-legal	?	-Higher insurance premiums should be avoided
Health Services	-Avoidance of health care costs through more effective prevention efforts	-Avoidance of health care costs through avoidance of unnecessary procedures or prophylaxis
Potentially harmful consequences	**FDR Positive Result**	**FDR Negative Result**
Clinical	-Prophylaxis carries risks (i.e. bleeding)	-Treated as having no risk, while residual risk exists
****Emotional***	-Increased anxiety -Somatization	-Survivor guilt
****Health Behaviour***	-Decreased perceived control (fatalistic attitude) -No increase in risk reducing behaviours	-Increased complacency towards health -No increase in risk reducing behaviours
Family	-Other family members distressed on patient's or own behalf	-Family dysfunction as a result of challenging family beliefs about disease
Socio-legal	-Insurance premiums may increase	?
Health Services	-Increased service use for unspecified symptoms -Insufficient knowledge/confidence on part of physicians with respect to clinical management	-Continued or increased service use due to failure to reassure -Complacency on part of physicians with respect to clinical management

Objectives

The current study aims to improve our understanding of the psychological and behavioural impacts of genetic testing in people with a family history of thrombophilia. These impacts are compared between two groups of asymptomatic first-degree relatives of patients with VTE (hereafter referred to as 'FDRs') who are either carriers or non-carriers of a thrombophilic mutation. The primary objectives are as follows:

1. To conduct a systematic review of the cognitive, psychological and behavioural impacts of genetic testing among those at risk for multifactorial genetic disorders.
2. To compare, between carriers and non-carriers, psychological distress, somatization, and perceived risk of thrombosis subsequent to receiving either positive or negative genetic test results.
3. To compare, between the two groups of FDRs:
    a) perceived causes of VTE and perceived control over the factors that may cause VTE;
    b) self-reported prevalence of health behaviours following genetic testing;
    c) perceived control over developing VTE; and
    d) self-reported use of primary health care services following genetic testing.
4. To describe the relationships between risk perception, psychological outcomes and health behaviours.

CHAPTER II

A SYSTEMATIC REVIEW OF THE COGNITIVE, PSYCHOLOGICAL AND BEHAVIOURAL IMPACTS OF GENETIC TESTING

Objective

The aim of this systematic review is to summarize empirical data, published between 2000 and 2005, that describes the cognitive, psychological and behavioural impacts of predispositional and susceptibility testing among those at risk for multifactorial genetic disorders. Since this systematic review is meant to provide a solid foundation for the current study, focusing on the impacts of susceptibility testing for thrombophilia, the most recent literature is the most relevant. While we are most interested in susceptibility testing, it is not expected that many studies will have been published assessing the impacts of this type of testing, so the impacts of both predispositional and susceptibility testing will be reviewed here.

Methods

Search Strategy

Five electronic databases were searched using the OVID search interface, namely: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and PsycINFO. Each database search was conducted during the week of November 13th, 2005, and all search results were limited to the years 2000-2005. This timeline was deemed appropriate for the reasons described above. A detailed search strategy was developed for use in MEDLINE and then adapted for each database. Search

terms were based on the general categories of genetics and genetic testing, psychological factors and behavioural factors. Descriptions of the database search strategies are presented in Appendix 1.

The reference lists of all relevant articles (including reviews) were examined for reports of additional studies, and retrieved by searching bibliographic databases and electronic journals. Also, the Science Citation Index (via Web of Science) was searched to find reports that had cited relevant studies. Key authors in this subject area were identified from the relevant studies and used as search terms in the five electronic databases listed above (See Appendix 1 for a complete list of authors included).

Inclusion/Exclusion Criteria

Studies were included in this review if they: (1) were published in a peer-reviewed journal in English; (2) included adult, human subjects; (3) evaluated the cognitive, psychological and/or behavioural impacts of genetic testing on individuals with a family history of any multifactorial adult onset genetic disorder; and (4) included separate results for carriers and/or non-carriers. Studies were excluded if they: (1) assessed only the intention to undergo genetic testing; (2) assessed the impacts of genetic counselling where subjects did not receive genetic test results; (3) assessed the impacts of genetic testing or counselling where subjects were already affected with the disorder in question (or where results were combined for affected and unaffected subjects); (4) assessed the impacts of testing for single gene disorders (e.g. HD); (5) were studies of prenatal or childhood genetic testing.

Controlled trials and prospective studies were included in the review, while qualitative studies and case reports were excluded. Outcomes of interest included cognitive outcomes (e.g. perceived risk), affective outcomes (e.g. general distress, anxiety, depression and disorder-specific worry) and behavioural outcomes (e.g. surveillance, screening uptake, lifestyle changes). With respect to cognitive and affective outcomes, pre and post-test data were required for inclusion. Post-test behavioural data was sufficient for inclusion.

Study Selection

All relevant citations, including titles and abstracts, were imported into a reference database (Reference Manager 10). Duplicates were identified and removed using the batch duplicate search operation using several different fields for comparison. A manual check was completed to remove the remaining duplicates. All reviews, editorials, letters to the editor, book reviews, and commentaries were immediately excluded based on citation notes and indications of such in the title and/or abstract. A single reviewer (CD) independently screened the titles and abstracts of each remaining citation, and excluded studies based on the inclusion/exclusion criteria. If it was unclear whether the study met these criteria, then the reviewer obtained the full text of the report for independent assessment. Two reviewers (CD, HH) independently assessed the eligibility of all potentially eligible full-text studies, and any discrepancies were resolved through discussion and/or a third reviewer (BW). With respect to the full-text reports that were screened, all excluded studies and reasons for exclusion were documented.

Quality Assessment

A formal quality assessment was not performed, as most studies were prospective, non-randomized studies, and all well-validated quality assessment tools are intended for use with

randomized controlled trials. Instead, one reviewer (CD) summarized the strengths and weaknesses of included studies.

Data abstraction

Two reviewers (CD, HH) independently abstracted data from all studies meeting the inclusion/exclusion criteria using an information extraction sheet (See Appendix 2). Any discrepancies were resolved through discussion. Information was collected regarding study characteristics (e.g. year published, publication status, source of funding), study design (e.g. RCT, prospective, etc), population (e.g. participant characteristics), and outcomes (e.g. cognitive, affective, behavioural). The reviewers were not blinded to the names of authors, journal or institutions.

Data analysis

Data were qualitatively synthesized to examine each included study with respect to study design, population, and outcomes. Sources of clinical and methodological heterogeneity were identified and reported.

Results

Study Characteristics

A flow diagram of the search results, as described in the QUOROM statement,[35] is illustrated in Figure 1. The electronic database searches generated 941 citations, including 278 duplicates, resulting in the identification of 663 unique citations for the initial screening of titles and abstracts. Following this initial screening, 99 potentially eligible studies were retrieved. In addition, 12 citations were identified through reference list

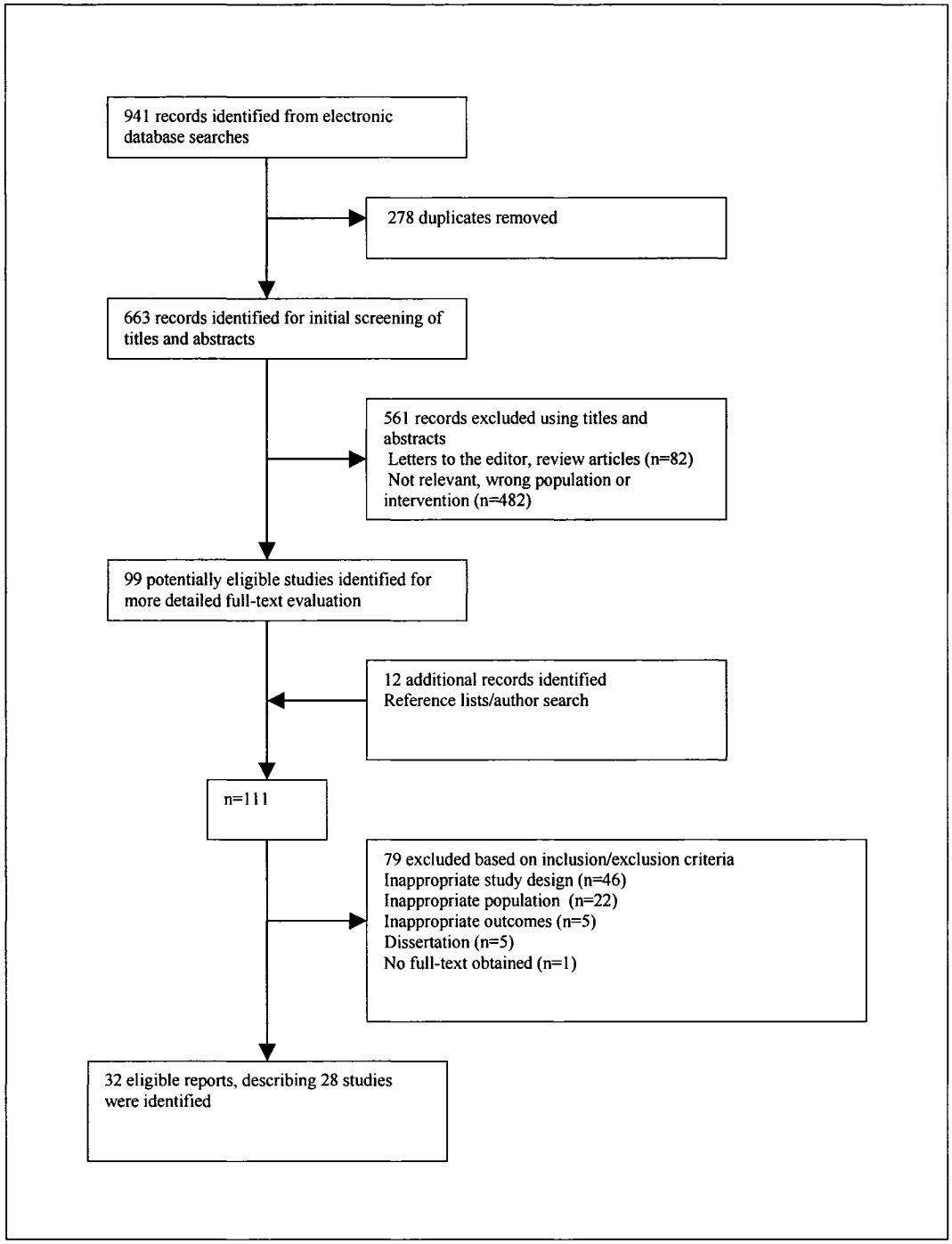


Figure 1: QUOROM[35] flow diagram outlining the results of the literature search and the selection of studies for inclusion in the review.

searching and searching for key authors. Therefore, 111 reports were determined to be potentially relevant.[36-85;86-113;114-146]

Further inspection revealed that five of these reports were dissertations,[71;89;90;102;111] thus not meeting the eligibility criteria of being published in a peer-reviewed journal. Full-text reports were obtained for 105 of the 106 remaining studies and two reviewers independently applied inclusion/exclusion criteria to these reports (a single study was not readily available,[60] but both reviewers determined that it was most likely ineligible on the basis of the title and abstract). After independent review, the two reviewers further discussed 16 reports to reach consensus, and two of these studies were also assessed by a third reviewer.

Of the 105 full-text reports assessed, 73 were excluded on the basis of: inappropriate study design (n= 46), inappropriate population (n=22), or inappropriate outcomes (n=5). Those studies excluded due to study design were qualitative (n=2),[44;101] were assessments of pre-test counselling only or studies where subjects did not receive a genetic test (n=27),[37;38;41;42;49;51;52;54-56;59;62-66;72;75;76;82;92;96-98;107;108;112] did not provide pre-test (n=13),[40;43;47;48;50;57;79;80;83;95;104;110;113] or post-test disclosure data (n=3).[67;68;73] Studies excluded based on inappropriate population utilized subjects affected with the disorder in question (n=2),[36;58] combined results for affected and unaffected individuals (n=13),[45;46;53;77;78;81;87;94;99;100;105;109;145] combined results for carriers and non-carriers (n=3),[39;74;130] assessed the impact of testing for single gene disorders (n=2)[88;103] or a fictitious disorder (n=1),[61] or included individuals with no family history of the disorder (n=1).[93] Those studies excluded based on inappropriate outcomes assessed the intention to

test (n=1)[69] or intended behaviours (n=4).[84-86;106] See Appendix 3 for a complete list of these excluded studies and reasons for exclusion.

Thus, a total of 32 reports, describing 28 studies fulfilled the inclusion criteria.[114-129;131-144;146] The relevant studies are summarized in Table 6. There were three sets of companion studies included.[1] Both reports by Aktan-Collan *et al.*[114;115] describe the same study participants and methods, but report different outcomes in the two publications. Also, the two reports by Lodder *et al.*[131;132] and Van Oostrom *et al.*[143] describe short and long-term follow-up data for the same population. Finally the reports published by Claes *et al.*[119;120] describe the same population and outcomes at 1 month and 1 year follow-up.

In total, fifteen studies assessed the impacts of genetic testing for HBOC,[116;118;121;127-129;131-134;136;138;140;142-144;146] ten for hereditary nonpolyposis colorectal cancer (HNPCC),[114;115;119;120;122-126;135;137;139] one for both HBOC and HNPCC,[117] and one for Alzheimer disease (AD).[141] Ten studies were conducted in Europe,[114;115;117;119-121;131-133;139;140;144;146] twelve studies in North America,[118;123-129;136;138;141;142] four in Australia[116;122;134;135] and one in Japan.[137] The length of follow-up ranged from 1-week to five years post-test. Twenty-two studies (73.3%) followed subjects for one year or more. Seven studies assessed at least one cognitive outcome,[115;119-121;123;127;142;146] fifteen assessed at least one affective outcome,[114-116;119-121;123;131;132;134;135;137;140-142;144;146] and fourteen assessed at least one behavioural outcome.[118;120;122;124-126;128;129;132;133;136;138;139;146]

[1] Companion studies are counted as one 'study', as they utilize the same population and methodology.

Table 6: Summary of included studies (n=28)

Authors	Condition[a]	Country	Assessment timepoints[b]	Outcomes[c]
Aktan-Collan *et al.* [114;115]	HNPCC	Finland	Base, DS, 1m, 12m	*Cognitive:* Perc risk; *Affective*: State Anx, Worry
Andrews *et al.*[116]	HBOC	Australia	Base, 7-10d, 1m, 12m	*Affective*: Spec dist, State Anx, Dep
Arver *et al.* [117]	HBOC, HNPCC	Sweden	Base, 1w, 2m, 6m, 12 m	*Affective*: Anx, Dep
Botkin *et al.* [118]	HBOC	USA	Base, 1-2w, 4-6m, 12m, 24m	*Behaviour*: Surv, Surg
Claes *et al.* [119;120]	HNPCC	Belgium	Base, 12m	*Cognitive*: Perc risk; *Affective*: Spec dist, State Anx; *Behaviour*: Surv
Claes *et al.* [121]	HBOC	Belgium	Base, 12m	*Cognitive*: Perc risk; *Affective*: Spec dist, State Anx
Collins *et al.* [122]	HNPCC	Australia	Base, 2w, 4m, 12m	*Behaviour*: Surv, Surg
Gritz *et al.* [123]	HNPCC	USA	Base, 2w, 6m, 12m	*Cognitive:* Perc risk; *Affective:* State Anx, Dep, Worry
Hadley *et al.* [124]	HNPCC	USA	Base, 6m, 12m	*Behaviour*: Surv
Halbert *et al.* [125]	HNPCC	USA	Base, 1m, 6m, 12m	*Behaviour*: Surv
Johnson *et al.* [126]	HNPCC	USA	Base, mean 12m (±3m)	*Behaviour:* Surv
Kelly *et al.* [127]	HBOC	USA	Base, 1-2d, 1w	*Cognitive*: Perc risk
Lerman *et al.* [128]	HBOC	USA	1m, 6m, 12m	*Behaviour:* Surv & Surg
Liede *et al.* [129]	HBOC	Canada/ USA	Mean 2.2y post-test	*Behaviour*: Surv
Lodder *et al.* [130]	HBOC	Netherlands	Base, 1-3w	*Affective*: Spec dist, Anx, Dep
Lodder/van Oostrom *et al.* [131;132;143]	HBOC	Netherlands	Base, 1-3w, 6m, 12m, 5y	*Affective*: Spec dist, Anx, Dep, Worry; *Behavior:* Surv, Surg
Meijers-Heijboer *et al.* [133]	HBOC	Netherlands	Median 26m post-test	*Behaviour:* Surg
Meiser *et al.* [134]	HBOC	Australia	Base, 7-10d, 4 m, 12m	*Affective*: Spec dist, State Anx, Dep
Meiser *et al.* [135]	HNPCC	Australia	Base, 7-10d, 4m, 12m	*Affective*: Spec dist, State Anx, Dep
Metcalfe *et al.* [136]	HBOC	Canada /USA	Mean 42.6m post-test	*Behaviour*: Medication use, Surg
Murakami *et al.* [137]	HNPCC	Japan	Base, 1m	*Affective*: Presence/absence mental disorder
Peshkin *et al.* [138]	HBOC	USA	1m, 6m, 12m	*Behaviour*: Surv
Ponz de Leon *et al.* [139]	HNPCC	Italy	1-2y	*Behaviour:* Surv
Reichelt *et al.* [140]	HBOC	Norway	Base, 6w	*Affective*: Anx, Dep, Gen distr, Hopelessness
Romero *et al.* [141]	AD	USA	Base, 1m, 4m, 10m	*Affective*: Mood state, emotional reactions
Schwartz *et al.* [142]	HBOC	USA	Base, 6m	*Cognitive*: Perc risk; *Affective*: Spec dist, Gen distr
Van Roosmalen *et al.*[144]	HBOC	Netherlands	Base, 2w	*Affective*: Spec dist, State Anx, Dep
Watson *et al.* [146]	HBOC	UK	Base, 1m, 4m, 12m	*Cognitive*: Perc risk; *Affective*: Spec dist, Worry, Gen dist; *Behaviour*: Surv, Surg

[a]HBOC: hereditary breast and ovarian cancer; HNPCC: hereditary nonpolyposis colorectal cancer; AD: Alzheimer Disease
[b]DS: disclosure session; d: days; w: weeks; m: months; y: years
[c]Perc risk: perceived risk; Spec dist: disorder-specific distress; Anx: anxiety; Dep: depression; Gen dist: general distress; Worry: cancer worry, Surv: surveillance, Surg: prophylactic surgery

The only cognitive outcome included in this review was perceived risk. While some studies assessed other cognitive outcomes (e.g. perceived seriousness, perceived control), these were not assessed at multiple time points and often reported as predictors of other outcomes. Affective outcomes included are disorder-specific distress, general and state anxiety, depression, mood state, cancer worry, general distress and psychiatric diagnosis. Behavioural outcomes included are surveillance behaviours (e.g. mammography, transvaginal ultrasound, colonoscopy), prophylactic surgery (e.g. bilateral mastectomy or oophorectomy) and other preventive behaviours (e.g. diet, exercise). Table 7 summarizes the general and specific outcomes used in the included studies.

Table 7: General and specific outcomes used in the included studies.

General Outcome	Specific Outcome
Cognitive	Perceived risk
Affective	Disorder-specific distress or worry General or State Anxiety Depression General Distress General Health Status Psychiatric Diagnosis
Behavioural	Surveillance behaviours Prophylactic surgery General preventive behaviours (i.e. lifestyle)

Cognitive Outcomes: perceived risk

The eight studies that assessed the impact of genetic testing on perceived risk are summarized in Table 8. The included studies assessed the impact of genetic testing for HBOC (n=4),[121;127;142;146] and HNPCC (n=3).[115;119;120;123] These studies were prospective, longitudinal studies with length of follow-up ranging from one week to one year. Most studies of HBOC included female subjects only, while one study included women specifically from the high-risk Ashkenazi Jewish community.[127] Studies of HNPCC

Table 8: Summary of studies describing risk-perception outcomes of genetic testing

Study (year)	Design, sample size	Outcome measures	Main Results and Conclusions
HBOC (BRCA1/2)			
Claes *et al.* (2005)[121]	Prospective 1 year follow-up 34 C; 34 NC 100% Female	Two items (breast and ovarian); absolute; verbal	→ *Breast & ovarian cancer PR:* C significantly higher than NC for breast cancer but not ovarian cancer distress; both decreased for NC over time; non-significant decrease for C → Both C & NC: Breast cancer PR higher than ovarian cancer PR
Kelly *et al.* (2004)[127]	Prospective 1 week follow-up 46 affected; 40 unaffected 19 C; 7 NC; 60 U 100% Female	One item (breast); absolute; numerical; risk accuracy	→ *Risk accuracy:* C more accurate from pre- to post-test, while NC did not demonstrate significant change
Schwartz *et al.* (2002)[142]	Prospective 6 month follow-up 35 C; 58 NC 100% Female	Two items (breast and ovarian); comparative; verbal	→ *Breast and ovarian cancer PR:* No difference between C and NC (pre-test); C significantly higher than NC (post-test) → Most women thought they were at higher than average risk at pre-test → Difference between C and NC at post-test mainly due to decreased PR among NC over time
Watson *et al.* (2004)[146]	Prospective 1 year follow-up 91 C; 170 NC 77% Female	Two items (breast/ovarian); absolute and comparative; verbal	→ *Breast/ovarian PR:* No difference between C and NC (pre-test); C higher than NC (post-test) → Most women thought they were at higher than average risk at pre-test; at post-test, ~2% of NC and 100% of C thought they were at higher than average risk → Difference between C and NC at post-test due to decreased PR among NC over time and increase among some C, particularly those < 50 years old
HNPCC (hMLH1/2)			
Aktan-Collan *et al.* (2001)[115]	Prospective 1 year follow-up 84 C; 187 NC	One item (colorectal cancer); absolute; verbal; risk accuracy	→ *Risk accuracy:* NC understood post-test risk of colorectal cancer more often than C; 48 and 35% of C and 92 and 90% of NC were accurate in their PR at 1 month and 12 months respectively; accuracy decreased for C from 1 month to 12 months
Claes *et al.* (2004)[119]	Prospective 1 month follow-up 19 C; 21 NC 42.5% Female	Two items (colorectal cancer); absolute; verbal	→ *Colorectal cancer PR:* non-significant decrease among C from pre- to post-test; significant decrease among NC from pre- to post-test
Claes *et al.* (2005)[120]	1 year follow-up 36 C; 36 NC 40.3% Female	Two items (colorectal and endometrial cancer); absolute; verbal	→ *Colorectal & endometrial cancer PR:* No difference between C and NC at 1 year post-test
Gritz *et al.* (2005)[123]	Prospective 1 year follow-up 19 C; 47 NC 64% Female	One item (colorectal cancer); comparative, verbal	→ *Colorectal cancer PR:* scores remained high for carriers from pre- to post-test; scores decreased for NC from pre- to post-test

HBOC: Hereditary breast/ovarian cancer; HNPCC: Hereditary nonpolyposis colorectal cancer; C: Carriers; NC: Non-carriers; PR: perceived risk

testing included both men and women. There was considerable variability between studies with respect to the wording of the questions used to assess perceived risk (Table 9). Each study used one to three items to assess either one's absolute risk of developing the disorder, or one's risk compared to that of other people. Most response scales were verbal (i.e. non-numerical responses) and presented as a Likert scale, and only one study assessed strictly numerical estimates of risk.[127] The two studies by Kelly *et al.*[127] and Aktan-Collan *et al.*[115] reported risk accuracy based on the discrepancy between one's perceived risk of developing the disorder and one's objective risk (as determined by the genetic counsellor).

Based on the studies reported here, carriers and non-carriers do not differ in their estimates of risk at baseline (pre-test). Post-test, three studies that compared carriers and non-carriers of BRCA1/2 mutations found that carriers had higher perceptions of risk than non-carriers for breast and/or ovarian cancer at post-test.[121;127;142;146] The studies reported by Claes *et al.*[119-121] did not find a significant difference between carriers and non-carriers for ovarian, colorectal or endometrial cancer perceived risk at post-test. In general, the differences observed between carriers and non-carriers at follow-up were due to decreased perceived risk among non-carriers from pre- to post-test. The response of carriers to genetic testing varied between studies. Carriers either experienced a non-significant decrease in perceived risk from pre- to post-test[119;121] or they experienced a slight increase, particularly for those under 50 years of age.[146] The two studies that reported risk accuracy differed in their findings. While Kelly *et al.*[127] found that carriers became more accurate in their perceived risk of breast cancer from pre- to post-test, Aktan-Collan *et al.*[115] reported a significant decrease in accuracy of colorectal cancer perceived risk.

Table 9: Measures of perceived risk used in included studies.

Author	Question(s)	Response categories	Valid[a]
Aktan-Collan *et al.* [115]	"What does your risk of developing colorectal cancer look like after testing? In this connection, the risk refers to what the cancer risk would be without regular cancer surveillance aimed at prevention of cancer."	1 = 'the risk is high, close to 100%' 2 = 'the risk is approximately50%' 3 = 'the risk is quite low, corresponding to that of the general population' Labeled 'understanding' if carriers chose 1 and non-carriers chose 3	No
Claes *et al.*[119-121]	"Independent of their actual risk, some persons feel they will develop breast cancer while others feel they will not develop breast cancer. How do you feel about your risk?"	1,2 = 'I am convinced that I will (probably) not develop cancer' 3 = 'My risk of developing cancer is as high as my risk of not developing cancer' 4,5 = 'I am convinced that I will (probably) develop cancer'	No
Gritz *et al.* [123]	"In your opinion, compared with other persons your age, would you say your chances of getting colorectal cancer are..."	1 = 'much lower' 2 = 'a little lower' 3 = 'about the same' 4 = 'a little higher' 5 = 'much higher'	Yes
Kelly *et al.* [127]	"What do you think the chances are that you will get breast cancer before age 70?"	0-100%	No
Schwartz *et al.*[142]	"In your opinion, compared with other women your age, what are your chances of getting breast/ovarian cancer?"	1 = 'Much lower' to 5 = 'Much higher'	Yes
Watson *et al.*[146]	Baseline: Perceived risk of developing breast/ovarian cancer Baseline and 1 month: Perceived risk relative to the general population 1 and 12 months: "What risk figure have you been given for developing breast/ovarian cancer?"	1 = 'Not very likely' to 3 = 'Very likely' 1 = 'Very much lower than average' to 5 = 'Very much higher than average' 'Less than average woman', 'Same as average woman', '50:50 chance', '85% chance', 'Other', 'Can't remember'	No

[a]Report indicates that measure was validated in current or previous study

Affective Outcomes

The fifteen studies that assessed the impact of genetic testing on affective outcomes are summarized in Table 10. The included studies assessed the impact of genetic testing for HBOC (n=8),[116;121;131;132;134;140;142-144;146] HNPCC (n=5),[114;119;120;123;135;137] both HBOC and HNPCC (n=1),[117] and AD (n=1).[141] These studies were prospective, longitudinal studies with length of follow-up ranging from two weeks to five years. Most studies of HBOC included women subjects only, while studies of HNPCC and AD included both men and women. The outcomes assessed in each study are summarized in Table 11. Cancer-

Table 10: Summary of studies describing affective outcomes of genetic testing

Author (year)	Design, sample size, follow-up	Outcome measures	Main Results and Conclusions
HBOC (BRCA1/2)			
Andrews *et al.*[116] (2004)	Prospective 1 year follow-up 4 C; 28 NC 100% Female	IES, STAI-State, BDI	→ *Cancer-specific distress:* Non-significant decrease at 7-10 days; significant decrease at 1 and 12 months compared to baseline irrespective of carrier status → *State anxiety and depression:* No significant changes relative to baseline → Genetic testing in Ashkenazi Jewish women does not lead to adverse psychological outcomes
Claes *et al.*[121] (2005)	Prospective 1 year follow-up 34 C; 34 NC 100% Female	IES, STAI-State, SCL-90	→ *Cancer-specific distress:* Significant decrease in breast and ovarian distress for NC; significant decrease in ovarian cancer distress for C; ovarian cancer distress higher among C than NC at post-test; breast cancer distress higher than ovarian cancer distress in both C and NC → *State anxiety & general distress:* No differences between C and NC; significant decrease in anxiety for NC only; no change in general distress for C or NC → All scores within normal range for C and NC → No adverse effects of predictive testing
Lodder *et al.*[131] (2001) Lodder *et al.*[132] (2002) Van Oostrom *et al.*[143] (2004)	Prospective 1-3 week follow-up 25 C; 53 NC 1 year follow-up 26 C; 37 NC 5 year follow-up 23 C; 42 NC 100% Female	IES, HADS	→ *Cancer-specific distress:* Scores decreased for NC, and increased for C from pre-test to 1-3 weeks; no change for C and decrease for NC from pre-test to 1 year; no change for C or NC between 1 year and 5 year; C opting for mastectomy had highest distress pre-test and at 1-3 weeks, but similar to C opting for surveillance and NC by 1 year; no difference between C and NC at 5 years → *Anxiety:* Scores decreased for NC and increased slightly for C from pre-test to 1-3 weeks; no change for C and decrease for NC from pre-test to 1 year; significant increase for both C and NC from 1 year to 5 year; no difference between C and NC at 5 years → *Depression:* Scores decreased for NC and increased slightly for C from pre-test to 1-3 weeks; significant increase for both C and NC from 1 year to 5 year; no difference between C and NC at 5 years → Those with high anxiety and depression post-test had high levels at pre-test
Meiser *et al.*[134] (2002)	Prospective 1 year follow-up 22 C; 46 NC; 46 NT 100% Female	IES, STAI, HADS-Depression	→ *Breast cancer-specific distress:* Significantly higher for C vs. NT at 7-10 days and 12 months; scores increase for C and decrease for NC post-test; C higher than NC at all follow-up points → *State-anxiety:* C showed significant decrease at 12 months post-disclosure compared to NT; NC showed trend for lower scores than NT at 4 months; similar scores for C and NC; no apparent trends over time for C or NC → *Depression:* NC showed significant decrease at 4 months post-disclosure; similar scores for C and NC; no apparent trends over time → NC derive psychological benefits from genetic testing; C may experience sustained increase in breast-cancer distress following disclosure, although no other adverse outcomes observed

Table 10 continued

Author (year)	Design, sample size, follow-up	Outcome measures	Main Results and Conclusions
Reichelt *et al.*[140] (2004)	Prospective 6 week follow-up 80 C; 164 NC 100% Female	IES, HADS; GHQ-28	→ *Cancer-specific distress, Anxiety, Depression, General distress, hopelessness:* No significant differences between C and NC for any measure; no significant change in mean scores from baseline to follow-up → Pre-test levels of anxiety contributed to post-test levels → Genetic testing not associated with increased levels of psychological distress in short-term
Schwartz *et al.*[142] (2002)	Prospective 6 month follow-up 78 C; 58 NC 100% Female	IES, HSCL-25	→ *Cancer-specific distress:* NC decreased significantly from baseline to 6 months; no change for C → *General distress:* No change for C or NC from baseline to 6 months; however, after adjusting for family clustering, NC also experienced decrease in general distress → No evidence for adverse psychological effects among C or NC; psychologic benefits observed among NC
Van Roosmalen *et al.*[144] (2004)	Prospective 2 week follow-up 66 C; 0 NC 100% Female	IES, STAI-State, CES-D	→ *Cancer-specific distress, State anxiety, Depression:* Significantly increased among C at 2 weeks after disclosure → Mean levels of cancer-specific distress, state anxiety, and depression were below clinically significant levels
Watson *et al.*[146] (2004)	Prospective 1 year follow-up 91 C; 170 NC 77% Female	IES, CWS-R, GHQ-28	→ *Cancer-specific distress:* C had more avoidant and intrusive thoughts than NC at all time points; C showed no significant increase in avoidant thoughts, but there was an increase in intrusive thoughts at 1 month compared to baseline (female only) → *Cancer worry:* C reported higher levels of cancer worry than NC at all follow-up points; worry increased among C at 1 month compared to baseline and decreased among NC at all time points (female only) → *Mental health:* C had significantly higher scores than NC at 1 month and 4 months, but not at 12 months; C scores were higher at 1 and 4 months compared to baseline, but returned to baseline levels by 1 year; no significant changes for male C or NC
HNPCC (hMLH1/2)			
Aktan-Collan *et al.*[114] (2001)	Prospective 1 year follow-up 84 C; 187 NC 57% Female	STAI-State	→ *State anxiety:* C and NC similar at baseline; C scores higher than NC at disclosure session due to increase among C and decrease among NC; scores returned to baseline levels for C and NC at 1 month and 1 year → No harmful emotional impact was detectable at 1 year follow-up
Claes *et al.*[119] (2004) Claes *et al.*[120] (2005)	Prospective 1 month follow-up 19 C; 21 NC 42.5% Female 1 year follow-up 36 C; 36 NC 40.3% Female	IES, STAI, SCL-90	→ *Cancer-specific distress:* No significant difference between C and NC at 1 month; higher among C vs. NC at 1 year; colorectal specific distress decreased for NC at 1 month and for NC and C at 1 year; endometrial specific distress decreased for NC at 1 year → *State anxiety and general distress:* No differences between C and NC at 1 month or 1 year; state anxiety decreased at 1 month and 1 year for NC but not for C; no change in general distress for C or NC → Mean scores on all scales lower or same as normative samples → Predictive genetic testing did not induce major psychological problems when offered in the context of a multidisciplinary approach

Table 10 continued

Author (year)	Design, sample size, follow-up	Outcome measures	Main Results and Conclusions
Gritz *et al.*[123] (2005)	Prospective 1 year follow-up 19 C; 47 NC 64% Female	Cancer worry; STAI-State; CES-D; QLI	→ *State anxiety and depression:* C showed significant increase from pre-test to 2 weeks and significant decrease from 2 weeks to 6 months; No change for NC from pre-test to 1 year → *Cancer worry:* C showed significant increase and NC significant decrease from pre-test to 2 weeks → No long-term adverse psychological effects of testing, but C may experience increased distress immediately post-disclosure
Meiser *et al.*[135] (2004)	Prospective 1 year follow-up 32 C; 82 NC 60.5% Female	IES, STAI-State, HADS-Depression	→ *Cancer-specific distress:* Significantly higher for C vs. NC at 2 weeks and 12 months post-test; C showed significant increase 2 weeks, but returned to baseline at 4 and 12 months; NC showed significant decreases at 2 weeks, 4 and 12 months → *State anxiety:* Significantly higher for C vs. NC at 2 weeks post-test; no significant changes observed for carriers; significant decreases for NC at 2 weeks → *Depression:* No significant differences between C and NC at any time point; significant decreases for NC from baseline at 2 weeks and 12 months → Predictive genetic testing for HNPCC leads to psychological benefits among NC, and no adverse psychological outcomes were observed among C
Murakami *et al.*[137] (2004)	Prospective 1 month follow-up 5 C; 10 NC 52.4% Female	Major and minor clinical depression (DSM-III-R); Acute stress disorder or Post-traumatic stress disorder (DSM-IV)	→ No unaffected C or NC met criteria for major or minor depression, acute stress disorder, or posttraumatic stress disorder at follow-up; only one unaffected participant met the criteria for posttraumatic stress symptoms at 1 month post-test (a carrier) → Disclosure of genetic test results for HPNCC may not cause significant psychological distress in Japanese probands or relatives
HBOC and HNPCC			
Arver *et al.*[117] (2004)	Prospective 1 year follow-up 31 C; 56 NC 100% Female	HADS	→ *Anxiety:* Significant decrease in mean scores measured over time for C and NC; scores in normative range → *Depression:* Levels in C decreased over time while levels increased in NC (non-significant); scores in normative range → *QoL*: No significant changes in QoL, although vitality dropped significantly in hMLH1/2 C at 2-6m, but then increased to baseline levels at 1 year → No significant differences between those tested for breast cancer and those tested for colorectal cancer → Healthy self-referred women going through predictive cancer testing will not experience adverse psychological outcomes
AD (APOE)			
Romero *et al.*[141] (2005)	Prospective 27 High risk; 49 Low risk 65.2% Female	Emotional reactions (author defined questions)	→ *Emotional reactions:* No significant changes for C in feeling sad or depressed; NC felt significantly less depressed at 1 month; NC and C showed significant decrease in worry from baseline to 1 month, but no significant changes in emotional responses occurred past 1 month → For emotionally stable persons, high risk subjects did not report more depression or worry and low risk subjects felt relieved knowing their results

HBOC: Hereditary breast/ovarian cancer; HNPCC: hereditary nonpolyposis colorectal cancer; AD: Alzheimer Disease; C: Carriers; NC: Non-carriers; IES: Impact of Events Scale; STAI-State: State anxiety subscale of State-Trait Anxiety Inventory; HADS: Hospital Anxiety and Depression Scale; BDI: Beck Depression Inventory; SCL-90: The Symptom Checklist; CES-D: The Center for Epidemiologic Studies Depression Scale; SDS: Self-rating Depression Scale; QLI: Quality of Life Index; POMS: Profile of Mood States; HSCL-25: Hopkins Symptom Checklist; GHQ-28: General Health Questionnaire; CWS: Cancer Worry Scale.

Table 11: Summary of psychological outcomes assessed in included studies.

Outcome	Scale, number of studies
Cancer-specific distress	Impact of Event Scale (n=10)[116;119-121;131;132;134;135;140;142-144;146]
Cancer worry	Cancer Worry Scale (Revised) (n=1)[146] Author defined question (n=1)[123]
Anxiety	State-Trait Anxiety Scale (n=8)[114;116;119-121;123;134;135;144] Hospital Anxiety and Depression Scale (n=3)[117;131;132;140;143]
Depression	Hospital Anxiety and Depression Scale (n=5)[117;131;132;134;135;140;143] Beck Depression Inventory (n=1)[116] Centre for Epidemiological Studies Depression Scale (n=2)[123;144]
General Distress/Health	Symptom Checklist (n=2)[119-121] General Health Questionnaire (n=2)[140;146] Hopkins Symptom Checklist (n=1)[142] Quality of Life Index (n=1)[123] Emotional reactions (author defined) (n=1)[141]
Clinical Diagnosis	Based on DSM-III-R and DSM-IV (n=1)[137]

specific distress was assessed in the majority of studies using the Impact of Event Scale (IES). Anxiety was also commonly assessed using either the State-Trait Anxiety Inventory (STAI) or the Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A). Depression was measured using several scales, including the Hospital Anxiety and Depression Scale, Depression subscale (HADS-D), the Beck Depression inventory (BDI), and the Center for Epidemiological Studies Depression Scale (CES-D). Many studies assessed general distress or general health outcomes using the Symptom Checklist (SCL-90), the General Health Questionnaire (GHQ-28), the Hopkins Symptom Checklist (HSCL-25), the Quality of Life Index (QLI), emotional reactions (author defined), and Profile of Mood States (POMS). One study by Murakami *et al.*[137] measured clinical diagnoses of major or minor depression, acute distress disorder, and posttraumatic stress symptoms/disorder based on DSM-III-R and DSM-IV criteria.

With respect to cancer-specific distress, the studies reviewed here suggest that carriers may experience a short-term increase with respect to baseline levels. Four studies reported that cancer-specific distress levels increased at 1-3 weeks,[131] 2 weeks,[135;144] or 1 month (intrusive subscale only),[146] as compared to baseline. For intermediate and long-term

follow-up, carriers tended to show no change in cancer-specific distress as compared to baseline levels. Five studies reported no change at 1 month,[119;146] 6 weeks,[140] 6 months,[142] 1 year[132] and 5 years.[143] Only two studies, both by Claes *et al.*, reported a significant decrease in cancer-related distress among carriers, specifically for ovarian cancer distress[121] and colorectal cancer distress[120] (both at 1 year follow-up). Most studies reported a significant decrease in cancer-specific distress among non-carriers at short and long-term follow-up. Seven studies reported a significant decrease in cancer-specific distress at 1-3 weeks,[131] 1 month,[116;119;132] 6 months[142] and 1 year.[116;120;121;132] Only one study found no significant change in cancer-specific distress among non-carriers as compared to baseline (measured at 6 week follow-up).[140] While some studies report greater cancer-specific distress levels among carriers as compared to non-carriers at 2 weeks and 1 year,[120;135] others report no differences between the two groups at 1 month,[119] 6 weeks,[140] 1 year[132] or 5 years.[143]

The two studies measuring cancer worry reported a short-term increase in worry for carriers and a short and long-term decrease among non-carriers.[123;146] Furthermore, Watson *et al.*[146] reported that carriers had higher levels of cancer worry than non-carriers at all follow-up points up to 1 year post-disclosure.

With respect to anxiety (both state and general), four studies found increased levels among carriers within three weeks following test result disclosure.[114;123;131;144] Three of these studies assessed long-term outcomes and found that anxiety returned to baseline levels at 1 month, 6 months and 1 year.[114;123;132] Several other studies found no change at all in anxiety levels from pre-test to 2 weeks,[135] 1 month,[119] 6 weeks,[140] and 1 year[120;121] post-test disclosure. Two studies showed a significant decrease in anxiety among carriers

at 1 year.[117;134] Several studies found that anxiety decreased among non-carriers from pre-test to immediately following disclosure,[114] and at 1-3 weeks,[135] 1 month,[119] and 1 year[120;121;132] post-disclosure. Three studies found that anxiety did not change significantly from pre-test to 6 weeks[140] or 1 year[116;123] post-disclosure for non-carriers. While two studies reported that carriers had higher anxiety than non-carriers at the disclosure session[114] and 2 weeks post-disclosure,[135] most studies reported no differences between the two groups at 1 month,[119] 6 weeks,[140] 1 year[120;121] and 5 years.[143] Mean anxiety scores for both carriers and non-carriers were within the normative ranges.

Results from the included studies varied with respect to depression scores. Three studies reported increased scores amongst carriers within the first three weeks post-disclosure.[123;131;144] While Gritz *et al.*[123] reported a subsequent decrease from 2 weeks to 6 months post-disclosure, Van Oostrom *et al.*[143] reported a subsequent increase in depression scores from 1 year to 5 years for the same sample of carriers reported by Lodder *et al.*[131;132] Meiser *et al.*[134;135] found that depression scores did not change significantly for carriers of either BRCA1/2 or hMLH1/2 from baseline to 1 year post-disclosure, whereas non-carriers of both mutations experienced a significant decrease in depression at 1 year post-disclosure. Four additional studies reported no change in depression scores for carriers and non-carriers from pre-test to 6 weeks[140] and 1 year[116] post-disclosure, and for non-carriers alone from pre-test to 2 weeks[144] and 1 year.[123] One study found that depression scores decreased for carriers and increased for non-carriers at 1 year[117] post-disclosure, attributing this to possible survivor guilt. Reichelt *et al.*,[140] Meiser *et al.*[135] and Van Oostrom *et al.*[143] reported no differences between carriers and non-carriers at 6 weeks, 1year and 5 years post-disclosure.

Most studies reporting general distress outcomes found no significant changes among carriers or non-carriers at 1 month,[119] 6 weeks,[140] 6 months,[142] or 1 year[120] relative to baseline. Only one study by Watson *et al.*[146] reported increased scores for carriers at 1 and 4 months, but these scores returned to baseline by 1 year post-disclosure. While Gritz *et al.*[123] reported no change in quality of life scores, Arver *et al.*[117] found a short-term decrease in the vitality subscale for carriers that later returned to baseline levels. Regarding AD testing, Romero *et al.*[141] found that carriers experienced no change in sadness or depression, while non-carriers were significantly less depressed at 1 month post-disclosure. Also, carriers and non-carriers were significantly less worried at 1 month, and non-carriers were more relieved. Finally, Murakami *et al.*[137] found that no carriers or non-carriers met the criteria for major or minor depression, acute stress disorder, or posttraumatic stress disorder, and only one carrier met the criteria for posttraumatic stress symptoms at 1 month post-test.

Behavioural Outcomes

The twelve studies that assessed the impact of genetic testing on behavioural outcomes are summarized in Table 12. The included studies assessed the impact of genetic testing for HBOC (n=7), and HNPCC (n=5). Ten studies were prospective, longitudinal studies with length of follow-up between 1 and 2 years.[118;120;122;124-126;128;133;138;146] Two studies were cross-sectional with a single assessment point at 2.2 years[129] and 3.6 years[136] post-test. All studies used self-reported measures of health behaviour, while two studies indicated that they confirmed results with medical records.[126;133]

Table 12: Summary of studies describing behavioural outcomes of genetic testing

Study (year)	Design, sample size, % female	Outcome measures	Main Results and Conclusions
HBOC (BRCA1/2)			
Botkin *et al.*[118] (2003)	Prospective 2 year follow-up 37 C; 92 NC 100% Female	Self-reported screening behaviours and prophylactic surgery	→ *Mammography:* Increased for C and NC from pre-test to 1 and 2 years post-test; no significant difference between C and NC; 62% of C and 57% of NC at 1 year; 53% of C and 49% of NC at 2 years
Lerman *et al.*[128] (2000)	Prospective 1 year follow-up 84 C; 83 NC; 49 NT 100% Female	Self-reported screening behaviour and surgery	→ *Mammography:* C (68%) had higher rates than NC (44%) at 12 months; no change in C, decrease among NC from pre- to post-test → *TVU and CA-125:* 21% and 15% of C respectively; 6% and 5% of NC respectively at 12 months → *Mastectomy and Oophorectomy:* 3% and 13% of eligible C respectively at 12 months post-test
Liede *et al.*[129] (2000)	Cross-sectional 59 C (mean 2.2 years post-test) 0% Female	Self-reported screening behaviours	→ *PSA screening:* About 50% adhered to guidelines; 78% of these received annual testing → *BSE and CBE:* 15% had ever performed BSE; 11% had had a CBE → Overall, 43% of men stated that their cancer-surveillance practices had changed after they had received positive results
Meijers-Heijboer *et al.*[133] (2000)	Prospective 2 year follow-up 68 C eligible for mastectomy 45 C eligible for oophorectomy 100% Female	Self-reported surgery and medical records	→ *Mastectomy:* at 9m, 1 year and 2 years, 46%, 51% and 55% of eligible C women had surgery → *Oophorectomy:* at 9m, 1 year and 2 years, 47%, 53% and 59% of eligible C women had surgery → The majority of women who undergo prophylactic surgery do so in the first 9 months post-disclosure
Metcalfe *et al.*[136] (2005)	Cross-sectional 81 C; 0 NC (mean 3.6 years post-test) 100% Female	Self reported use of tamoxifen and prophylactic surgery	→ *Chemopreventive drug use:* current or previous use of tamoxifen and raloxifene reported by 12.3% and 9.9% of women; 35.3% of these women discontinued taking these prior to five year duration → *Mastectomy and Oophorectomy:* 27.2% and 66.7% of women respectively → Women carriers are more likely to undergo surgery than to take tamoxifen to prevent breast cancer
Peshkin *et al.*[138] (2002)	Prospective 41 C; 66 NC 1 year follow-up 100% Female	Self reported use of mammography and clinical breast examination	→ *Mammography:* 59% of C and 47% of NC had a mammogram during the year after testing; Older C were more likely to have a mammogram post-test (74%≥40 vs. 39% 25-39); 23% of NC women under 40 obtained a mammogram post-testing, suggesting they did not feel reassured → *CBE:* 95% of C had obtained a CBE within the year after test result disclosure vs. 77% of NC
Watson *et al.*[146] (2004)	Prospective 91 C; 170 NC 1 year follow-up 100% Female (for behavioural outcomes)	Self reported breast/ovarian cancer screening and prophylactic surgery	→ *Mammography:* Rates significantly different between C (92%) and NC (30%) at 12 months where there had previously been no difference at baseline → *CBE:* Rates were similar for C (90%) and NC (89%) → *BSE:* Rates slightly higher for C (91%) as compared to NC (84%) → *Ovarian ultrasound:* Rates higher for C (59%) as compared to NC (8%) → *Mastectomy and Oophorectomy:* 28% and 31% of C respectively

Table 12 continued

Study (year)	Design, sample size, % female	Outcome measures	Main Results and Conclusions
			→ 52% of female C, 43% of female NC, 44% of male C and 44% of male NC reported having done something else to help them stay healthy and/or avoid cancer (e.g. change diet, exercise, quit smoking)
HNPCC (hMLH1/2)			
Claes *et al.*[120] (2005)	Prospective 1 year follow-up 36 C; 36 NC 40.3% Female	Self-reported screening behaviour	→ *Colonoscopy:* 77% of C had colonoscopy in 1 year post-test; 100% of C were adherent to recommendations of having a colonoscopy within 2-year interval; No NC had a colonoscopy in the 1 year post-testing
Collins *et al.*[122] (2005)	Prospective 1 year follow-up 32 C; 82 NC 58.5% Female	Self-reported screening behaviour and surgery	→ *Colonoscopy:* C (71%) more likely than NC (12%) to have had a colonoscopy in 12 months post-test; significant decrease in screening behaviour for NC pre- to post-test → *TVU and Endometrial sampling:* C more likely than NC to report both procedures post-test → *Colectomy and Hysterectomy:* No C or NC had undergone either procedure 12 months post-test
Hadley *et al.*[124] (2004)	Prospective 1 year follow-up 17 C; 39 NC 71.4% Female	Self-reported screening behaviour	→ *Colonoscopy:* C (58%) more likely than NC (8%) to have had a colonoscopy in 12 months post-test; significant decrease in screening behaviour pre- to post-test for NC → 35% of C and 13% of NC were not adherent to screening recommendations in 12 months post-test
Halbert *et al.*[125] (2004)	Prospective 1 year follow-up 45 C; 56 NC; 33 D 68% Female	Self reported screening behaviour	→ *Colonoscopy:* C (73%) more likely than NC (16%) and D (22%) to have had a colonoscopy in 12 months post-test; significant increase among C in screening behaviour pre- to post-test, but no change for NC or D
Johnson *et al.*[126] (2002)	Prospective Mean 12.7m follow-up 7 C; 37 NC; 21 NT 50.8% Female	Self reported screening behaviour (confirmed with medical records)	→ *Colonoscopy:* C (100%) more likely than NC (40.5%) and NT (57.1%) to have had colonoscopy within 12 months post-test; NC significantly more likely to be overdue for screening than C and NT

HBOC: hereditary breast/ovarian cancer; HNPCC: hereditary nonpolyposis colorectal cancer; C: Carriers; NC: Non-carriers; NT: Not tested; D: Decliners; CBE: Clinical Breast Exam; BSE: Breast Self Exam; TVU: Transvaginal Ultrasound

Two studies assessing mammography screening behaviour found that rates among carriers were significantly higher than rates among non-carriers at 1 year post-disclosure,[128;146] while two studies found that carriers and non-carriers did not differ significantly during the same time frame.[118;138] Proportions of carriers obtaining a mammogram within 1 year following testing range from 59% to 92%, while proportions for non-carriers range from 30% to 53%. Breast self-examination (BSE) and clinical breast examinations (CBE) were common among both carriers and non-carriers following testing, as 90-95% of carriers

and 77-89% of non-carriers reported these behaviours during the year following testing.[138;146] In their study of male mutation carriers of BRCA1/2 genes, Liede *et al.*[129] found that BSE and CBE were only reported by 15% and 11% of at risk males, and that only about 50% of these males adhered to prostate-specific antigen screening guidelines.[129] Two studies found that carriers were more likely than non-carriers to report ovarian cancer screening (transvaginal ultrasound (TVU) and CA-125 screening) at one year post-test.[128;146] Metcalfe *et al.*[136] found tamoxifen and raloxifene use by carriers to be low, and suggested that women are more likely to opt for prophylactic surgery. Rates of mastectomy and oophorectomy were reported in four studies. At one year post-disclosure, rates of mastectomy ranged from 3% to 51% among carriers, while rates of oophorectomy ranged from 13% to 53%.[128;133;146] Meijers-Heijboer *et al.*[133] reported rates of both surgeries at 9 months, 1 year and 2 years post-disclosure. They found that most women who decided to have surgery had done so within the first 9 months post-disclosure. While these studies reported slightly higher rates of oophorectomy versus mastectomy, Metcalfe *et al.*[136] reported the largest difference, as 27.2% of carriers had a mastectomy and 66.7% had an oophorectomy post-test (mean 3.6 years).

All five studies reporting colonoscopy rates following testing for HNPCC found that carriers were more likely than non-carriers to obtain colonoscopy in the 1 year following testing.[120;122;124-126] While three studies mainly attribute this to a significant decrease in screening behaviour for non-carriers,[120;122;124] one study attributes the difference to a significant increase in screening behaviour among carriers.[125] Rates of colonoscopy screening during the 1 year post-disclosure ranged from 58-100% among carriers and 0-40.5% among non-carriers. Collins *et al.*[122] also report that carriers were more likely than

non-carriers to obtain TVU and endometrial sampling in the one year following testing, while no carriers or non-carriers obtained prophylactic colectomy or hysterectomy within this time frame.

Only one study reported on general health behaviours in response to genetic testing. Watson *et al.*[146] found that 43-52% of subjects reported having done something else to help them stay healthy and/or avoid cancer since their genetic test (e.g. change diet, exercise, quit smoking). Responses were similar for carriers and non-carriers and for males and females.

Methodological Quality of Included Studies

Most of the studies included in this review acknowledged several limitations. Most study populations included small, self-selected samples that were not representative of all individuals eligible for testing. Claes *et al.*[119] suggest that those individuals presenting for genetic testing may have a higher perceived ability to cope with their test result and that this may explain the relatively low distress levels found among study participants.[119] Also, several studies that assessed the behavioural impacts of genetic testing noted that the study sample was highly motivated and already involved in pre-test surveillance and/or likely to adhere to screening recommendations.[117;120;126] Many studies reported homogenous samples that included predominantly white individuals with high levels of education.[118;124;125;128;142] Some studies also had several participants from the same family, possibly producing family specific effects.[119-121;127]

As part of the research protocol, most studies included extensive pre and post-test counselling and education, such that results may not be generalizable to a routine clinical

setting.[114;115;120;121;125;142] Genetic testing was usually offered free of charge, thus observed rates of testing may be higher than expected routinely.[124;137;138] Finally, outcome measures for perceived risk were often not validated and those for behaviours were based on self-report (potential for recall bias). Claes *et al.*[119] suggest that distress measures used in the majority of these studies focus largely on detecting clinical disorder or psychopathology and may not be sensitive enough to capture the occurrence of negative emotional reactions in a 'non-clinical' population.[119]

Strengths and Limitations of this Review

A major strength of this review is the provision of a detailed and replicable search strategy. Another strength is that two reviewers independently screened all potentially eligible reports for inclusion and independently abstracted the data for each included study. This minimized the risk of selector bias, as disagreements could be resolved by discussion or a third reviewer.[147]

A major limitation that may affect this review is publication bias. A search of the grey literature, particularly conference abstracts, was not conducted. It is possible that other eligible studies have been conducted, but that these were not published. Evidence exists suggesting that the exclusion of grey literature may lead to exaggerated estimates of effects.[148;149] One study reports that only about half of the studies presented as summaries or abstracts at professional meetings are subsequently published as peer-reviewed journal articles, and that the most important factor influencing whether a study is published in full is the presence of significant results in the abstract body.[150] Ideally, abstracts from relevant conferences would have been scanned and experts in the field would have been

contacted to obtain information about unpublished or ongoing studies, but this was not within the scope of the thesis.

Finally, the narrow inclusion/exclusion criteria meant that several studies examining psychosocial impacts of genetic testing and/or counselling were not included. However, the objective of this review was to focus on the most relevant studies and to lay the foundation for the work presented in this thesis. While meta-analysis may have been possible for some psychological outcomes, a qualitative synthesis of the data was deemed appropriate and in line with the objectives of the thesis.

Conclusions

In summary, while carriers and non-carriers do not differ in their perceived risk before receiving genetic test results, they often differ at follow-up because of decreased perceived risk among non-carriers. With respect to affective outcomes, most reports conclude that genetic testing appears to have beneficial consequences for non-carriers and to produce no major harms for carriers, though short-term increases in distress are possible. Behavioural outcome data were mainly limited to breast, ovarian and colorectal cancer screening and prophylactic surgery. The included studies suggest that breast cancer screening rates are high and similar among carriers and non-carriers, while ovarian and colorectal cancer screening rates appear to be higher among carriers post-test compared with non-carriers. Rates of prophylactic mastectomy and oophorectomy varied between studies, and women tended to opt for oophorectomy slightly more often than mastectomy.

In their review, Broadstock *et al.*[3] found that most studies focused on the impacts of genetic testing for HD and only five studies examined the impacts of testing for hereditary

cancers; however, the current review reveals that psychosocial genetics research focusing on hereditary cancers has expanded over the past 5-6 years. While the results of this systematic review continue to suggest that the negative psychosocial impact of genetic testing may not be significant, one cannot assume that these results are generalizable to all other conditions.

Implications for the current study

The present review included very few studies examining the impacts of genetic testing for common, multifactorial conditions beyond cancer. A single included study looked at the emotional impacts of genetic testing for AD, concluding that testing for this susceptibility gene produces no harmful effects and also shows a decrease in worry among both carriers and non-carriers at one month.[141] Other studies have examined the impacts of testing for multifactorial disorders, but were excluded from the present review because they did not meet the inclusion criteria (e.g. Marteau *et al.*[78] examined the impacts of testing for familial hypercholesterolemia (FH), but combined results for carriers and non-carriers in their analyses). While these studies do provide very tentative evidence that genetic testing for multifactorial disorders may produce similar impacts to those seen for hereditary cancers, there is a need to confirm these findings in studies of different disorders.

The psychological aspects of genetic testing for thrombophilia have not been widely studied, and were excluded from the present review since they did not meet the inclusion criteria. One published study was qualitative and examined the experiences of seventeen asymptomatic carriers of FVL with respect to the procedure of testing.[151] This study found that carrying FVL has the potential to affect daily life by inducing concerns,

stigmatization and insurance problems. Another published study used a cross-sectional design to examine the knowledge and educational needs of affected and unaffected individuals with the FVL mutation.[152] They conclude that there is a lack of available information about FVL and that additional educational resources are needed. They also note that 43% of individuals reported increased worry following testing and that 51% had made positive lifestyle changes, including avoiding immobility, increasing exercise and altering dietary habits, due to genetic test results.[152] Two unpublished studies conducted by researchers in Italy assessed the emotional impact of predictive genetic testing for thrombophilia.[153;154] They found no short or long-term negative impacts in those with positive or negative results.

Further research is required in this area due to the lack of published, quantitative studies, and the absence of data on risk perception, disorder-specific worry and behavioural outcomes. The comparability of cognitive, psychological and behavioural outcomes for multifactorial disorders (e.g. thrombophilia) and previously studied disorders (e.g. HD, hereditary cancer) is important in determining whether a generalizable model of the multiple impacts of genetic testing exists.

CHAPTER III

METHODS

This exploratory study consisted of two parts (described in detail below):

PART 1: Secondary analysis of FDR pilot study data (psychological outcomes)

Design

Objective 1 was addressed through the secondary analysis of data collected as part of a pilot study for a randomized controlled trial.[2] The pilot study was designed to examine two approaches to managing asymptomatic FDRs who were carriers of thrombophilic mutations. Carriers were randomized to either a novel care strategy or to standard care (Figure 2; See description of intervention, Appendix 4), and non-carriers were followed-up as a comparison group. Data on psychological distress, somatization (i.e. the physical expression of psychological needs), and perceived risks were collected over a one-year period from carriers in the intervention and control arms and also from non-carriers (See schedule, Appendix 5).

Subjects and Recruitment

Subjects were recruited through multiple centers (Halifax, Nova Scotia; Montreal, Quebec; London, Ontario), although this thesis includes data on only those subjects recruited in Ottawa. Subject recruitment and follow-up was completed at the Ottawa Hospital-Civic Campus in Ottawa, Ontario. Subjects with VTE were screened for

[2] For the purposes of this thesis, analyses presented in Part 1 are considered 'secondary' since the author did not personally collect the data.

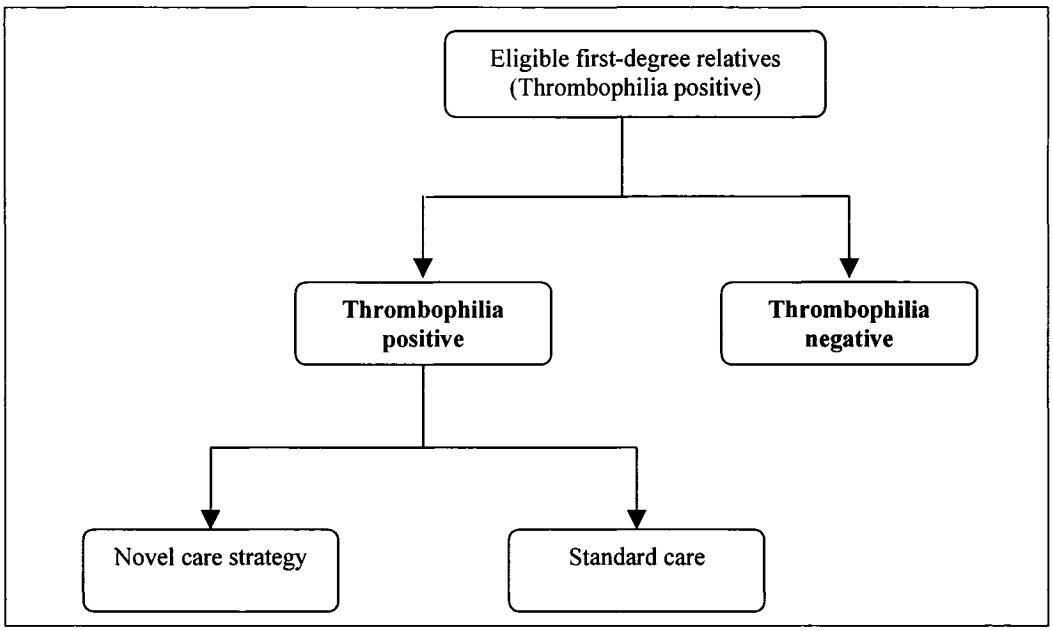


Figure 2: Flow of first-degree relatives through pilot study. For the present study, thrombophilia positive and negative first-degree relatives are compared.

thrombophilia as part of usual care. Eligible probands (i.e. individuals affected with VTE through whom a family with inherited thrombophilia was ascertained) were invited to participate in the pilot study, and consenting individuals constructed a family tree with a genetic counsellor (see Appendix 6 for inclusion/exclusion criteria for probands). Probands were contacted specifically to identify eligible FDRs, and were not further involved in the pilot study. Potentially eligible FDRs were sent a letter describing the study, and within two weeks were contacted by a genetic counsellor and asked to participate (see Appendix 6 for inclusion/exclusion criteria for FDRs). Those agreeing to participate attended 'Visit 1', where the study was explained, questions were answered, and those interested in continuing signed the consent form. Recruitment began in 2003 and was completed in 2005. A total of 111 FDRs, including non-carriers and carriers in both the intervention and control arms of the pilot study, were available for inclusion in this thesis project.

Outcomes and Study Instruments

Four outcomes collected during the pilot study were analyzed in the present study: psychological distress, somatization, perceived risk, and VTE-specific worry.

Psychological distress was measured with the Profile of Mood States-Short Form (POMS-SF) (See Appendix 7).[155] The POMS-SF is a 36-item self-report measure designed to assess subjective mood states. Respondents indicate the degree to which each adjective describes themselves during the last week using a 5-point Likert scale format. Standard scoring of the POMS-SF yields a global distress score referred to the Total Mood Disturbance (TMD) as well as scores for six subscales: Fatigue-Inertia, Vigor-Activity, Tension-Anxiety, Depression-Dejection, Anger-Hostility, and Confusion-Bewilderment. To obtain a score for each subscale (each has a maximum possible score of 24), the sum of the responses is obtained for the adjectives defining each domain as described by Shacham.[155] The TMD is computed as indicated below:[156]

Depression-Dejection + Tension-Anxiety + Anger-Hostility + ...
...Fatigue-Inertia + Confusion-Bewilderment + (24 – Vigor-Activity)

The possible range of values for the TMD score is 0-144, where a higher score reflects greater mood disturbance. Internal consistency of the overall POMS-SF and each of the subscales has been shown to be acceptable, with Cronbach's α values ranging from 0.76 to 0.95.[156] The original POMS has been demonstrated to be sensitive to changes over a short time span.[156-158] This instrument takes approximately five minutes to administer.

Somatization was measured using the Somatization subscale of the SCL-90-R (See Appendix 8). This subscale contains 14 items that evaluate distress arising from

perceptions of bodily dysfunction. To obtain the total subscale score, item scores are summed and divided by the total number of items. Scores range from 0-4 where a higher score indicates higher levels of somatization. The SCL-90-R subscales as well as the abbreviated forms of the SCL-90-R have been shown to be both reliable and valid.[159;160;160]

Perceived risk and VTE-specific worry were measured using a questionnaire developed by the authors of the pilot study (See Appendix 9). Two items assess perceived personal risk of having a blood clot, and two items assess concern/worry about personal chances of having a blood clot.

Data Collection

Demographic data were collected at the first clinic visit during an interview with a genetic counsellor. Data collection included: age, gender, ethnicity, height, weight, highest level of education, household income, and FDR's relationship with the proband. Subjects were also questioned about current medications and risk factors (e.g. smoking status, history of varicose veins, cardiovascular disease, cancer, and diabetes) and were screened for past VTE events using a standardized questionnaire.[161]

The POMS-SF, Somatization Subscale, and Perceived risk questionnaire were administered to all FDRs at baseline (i.e. 'Visit 1' where blood was drawn), one week, and 12 months after receiving their thrombophilia test results. These questionnaires were also administered to mutation carriers at 6 months (see Appendix 5 for the schedule). Baseline questionnaires were self-completed at the clinic. One-week, 6-month and 12-month questionnaires were mailed in a self-addressed, stamped envelope for self-completion. If

questionnaires were not received within two weeks, the genetic counsellor contacted the subject by telephone as a reminder, and offered an additional questionnaire if required.

PART 2. Cross-sectional survey of FDRs (causes of VTE, health behaviour, perceptions of control, use of health services)

Design

Objective 2 was addressed through a cross-sectional survey of FDRs (carriers and non-carriers) who had previously participated in the pilot study described above.

Subjects and Recruitment

A list of FDRs included in the pilot study and their contact information was obtained from the research coordinator for the pilot study. All potential subjects (n=107) were mailed a letter and information sheet describing the current study, and invited to participate by completing the questionnaire enclosed with the letter (See Appendix 10 and 11 for a copy of the letter and information sheet).

Outcomes and Study Instruments

The 'Causes & Prevention of Blood Clots' questionnaire was developed in consultation with clinical experts in the field of thrombosis (See Appendix 12). Various outcomes were assessed in the survey, including:

- general reactions to receiving a genetic test for thrombophilia;
- perceived causes of blood clots;
- perceived control over the factors that may cause blood clots;
- self-reported prevalence of health behaviours;
- perceived control over developing blood clots; and
- self-reported use of primary health care services.

Section I of the survey assessed respondents' general reactions to their genetic test for thrombophilia. Respondents were first asked to indicate whether they remembered their genetic test result, and were then given two familiar questions assessing absolute and relative risk from the 'Perceived Risk' questionnaire used in the FDR pilot study. Five additional questions were adapted from a questionnaire developed by Michie *et al.*[162] for use in adults receiving predictive genetic testing for familial adenomatous polyposis (FAP). These questions measured the following: perceived seriousness of blood clots, perceived accuracy of the genetic test, perceived certainty of test result, perceived likelihood of developing a blood clot, and regrets about having the genetic test. A final question was formulated by the authors of this study to assess respondents' confidence in their ability to identify the symptoms of a blood clot.

Section II of the survey assessed respondents' perceived causes of blood clots, perceived control over the factors that may cause blood clots, and self-reported prevalence of health behaviours. To assess perceived causes of blood clots, respondents were presented with 19 factors and asked to indicate how much they agreed or disagreed that the factor would increase a person's risk of developing a blood clot (Table 13). Generic factors were taken from the 'possible causes' section of the Illness Perception Questionnaire-Revised,[163] which is an instrument that measures five components that make up a person's perception of their illness (identity, cause, timeline, consequences and cure/control). Condition-specific factors were chosen in collaboration with thrombosis clinicians and researchers. For each factor, respondents were also asked to indicate how much they agreed or disagreed that the factor 'is something that some people can control' and 'is something

Table 13: Factors that may or may not increase one's risk for developing a blood clot and specific behaviour changes related to each factor. Respondents were asked to comment on these factors in relation to their own risk and behaviours in the 'Causes & Prevention of Blood Clots' cross-sectional survey.

Risk factor	**Specific behaviours**
Not enough exercise*	Tried to exercise more
Stress, worry or depression*	Tried to decrease stress levels
Infection with a germ or virus*	Tried to avoid infection
Poor diet or eating habits*	Tried to improve diet
Lack of access to high quality medical care*	N/A
The effects of aging*	N/A
Exposure to chemicals*	Tried to limit exposure to household chemicals
Over-exertion*	Tried not to work as hard
Family history of blood clots	Tried to inform relatives
A positive test for thrombophilia	N/A
Smoking*	Tried to quit smoking
A generally negative attitude*	Tried to adopt more positive attitude
Being overweight*	Tried to lose weight
Injury requiring hospitalisation	Tried to avoid injury Informed doctor when/if injury occurs Wore compression stockings during recovery Got back on feet as soon as possible
Major surgery	Informed doctor before surgery Wore compression stockings after surgery Got back on feet as soon as possible
Prolonged immobility	Tried to avoid long trips Discussed genetic test result with physician before long trip Wore compression stockings during long trip Took frequent breaks while on long trip
Pregnancy/childbirth (women only)	Discussed genetic test result with physician once pregnant Wore compression stockings during pregnancy and/or after childbirth
Taking birth control pills (women only)	Stopped taking birth control pills
Taking HRT (women only)	Stopped taking HRT

* Taken from the Illness Perception Questionnaire-Revised[163]

that I feel I can control.' Finally, participants were asked to indicate whether they had made specific changes in their behaviour with respect to each factor, and whether they made these changes specifically to reduce their risk of developing a blood clot (Table 13).

Section III of the survey assessed respondents' perceived control over developing a blood clot. Respondents were asked to indicate how much they agreed or disagreed with eight statements concerning the importance of genes, behaviours and chance in controlling one's risk of developing a blood clot.

Section IV of the survey assessed respondents' self-reported use of primary health care services. Participants were asked whether they had a physician with whom they could regularly schedule appointments (e.g. a family doctor) and whether they felt they had visited this physician more often since receiving their genetic test result. Also, they were asked if they had discussed their genetic test result with this physician and whether they felt that their physician had an adequate understanding of the test result and if this physician had given them any advice. Finally, respondents were asked how satisfied they were with the amount of information they had received from any health professional about thrombophilia and their risk of developing a blood clot.

The questionnaire was first tested among a convenience sample of University of Ottawa employees (n=5) (two stages/revisions). These individuals were asked to comment on clarity, formatting, length and any complications with the survey. Following revisions, the questionnaire was included in the submission to The Ottawa Hospital Research Ethics Board.

Data Collection

The questionnaire was mailed to all eligible FDRs, including carriers and non-carriers, along with a stamped self-addressed envelope for return. The questionnaire was accompanied by a cover letter, signed by the Principal Investigator for the original pilot study (Dr. Phil Wells), stating instructions for completion and a patient information form providing detailed information about the study. If the questionnaire was not returned within 2 weeks, subjects were contacted by telephone as a reminder, and sent an additional copy if required. If subjects who had indicated that they would return the survey after the first phone call had not done so within one month, they were contacted a second time by telephone for a final reminder.

Statistical Analysis Strategy & Methods

The data analysis strategy was largely exploratory in nature and mainly consisted of descriptive statistics and univariate comparisons to provide quantitative estimates of benefit and harm in regards to genetic testing for thrombophilia. Descriptive statistics were calculated to characterize the sample in terms of sociodemographics, risk factors, and medical conditions. Carriers and non-carriers were compared on each of these baseline variables using chi-square tests for categorical variables and independent t-tests for continuous variables.

With regards to psychosocial and behavioural data, differences between groups (carriers and non-carriers) or associations between variables were analyzed by means of non-parametric tests either because of categorical or ordinal data or because of non-normality of continuous data and small sample size. This report focuses on psychological outcomes

at the 1-week and 12-month follow-up assessment. Missing values for continuous psychosocial variables (POMS-SF TMD score and SCL-90-R somatization subscale score) were imputed using the 'person mean substitution' method (if three or more items were missing for a single case, this case was excluded from the analyses). Using this method, the imputed value for a variable with missing data is derived from the non-missing items for the case. For the POMS-SF, missing data were derived from the items from the corresponding subscale. For the SCL-90-R, the missing data were derived from the total somatization subscale. For example, where a scale (or subscale) score (Y) is summed from 5 items (Y_1 to Y_5) and, for case i, Y_{i3} is missing. The value for Y_i (i.e. Y for case i) is calculated:

$$Y_i = 5 \times \frac{Y_{i1} + Y_{i2} + Y_{i4} + Y_{i5}}{4}$$

According to Hawthorne and Elliot,[164] this method of imputation is preferred because it is computationally simpler and similar in its efficiency to other methods, it is advocated by other researchers and it is more likely to be an option on statistical software packages. Following imputation, these psychological variables were compared between carriers and non-carriers at baseline, 1-week and 12 months using the Mann-Whitney rank-sum test. Comparisons between baseline and 1-week and baseline and 12-month scores were computed for carriers and non-carriers separately using the Wilcoxon signed-rank test. Tests for overall trends in these two variables from baseline to 12 months were computed separately for carriers and non-carriers using the Friedman test.

Categorical psychosocial variables (perceived risk compared to most people, perceived absolute risk, concern about one's chances of developing a blood clot, worry about one's

chances of developing a blood clot, and the extent to which worry about getting a blood affects one's daily life) were compared between carriers and non-carriers using the chi-square test. Due to small sample sizes, categories for the two perceived risk variables were dichotomized for analysis. For perceived risk compared to most people, the two categories were: 'lower or same as most people' versus 'little higher or much higher than most people'. For perceived absolute risk, the two categories were: '1 in 10, 1 in 100 or 1 in 500' versus '1 in 1000 or 1 in 5000'. Categories for the three questions related to VTE-specific worry were also collapsed for analysis. For concern about one's chances of developing a blood clot, the three categories were: 'not at all concerned', 'somewhat concerned' versus 'moderately or very concerned'. For worry about one's chances of developing a blood clot, the two categories were: 'rarely or never worry' versus 'sometimes or often worry'. For the extent to which worries about getting a blood clot affect one's daily life, the two categories were: 'not at all' versus 'sometimes or very much'. When an expected cell frequency was still less than five after collapsing the categories for these variables, Fisher's exact test was used to compare proportions.

Descriptive statistics were used to characterize the participants in Part II of this study ('Causes and Prevention of Blood Clots' questionnaire). Differences between survey respondents and non-respondents and also between carrier and non-carrier participants were assessed using the chi-square test. The chi-square test was also used to compare responses of carriers and non-carriers to questions regarding perceived risk factors for blood clots, perceived control over these risk factors (general and personal), self-reported health behaviours and high-risk situations, perceptions of control over developing blood clots, and self-reported interactions with health care professionals since their genetic test.

Because of the small sample size, the response categories were collapsed into two or three new categories for questions regarding perceived risk factors and general and personal control over these risk factors. In most cases, the response categories were dichotomized: 'agree or strongly agree' versus 'strongly disagree, disagree, or neither agree nor disagree'. When possible, 'neither agree nor disagree' was a separate category. When an expected cell frequency was still less than five after collapsing the categories for these variables, Fisher's exact test was used to compare proportions.

Bivariate associations between psychosocial, behavioural and sociodemographic variables were assessed by means of chi-square or Fisher's exact tests. To assess associations with behaviour change, one dichotomous variable was derived from all the variables assessing specific behaviours. The two categories were: 'tried to change at least one behaviour' and 'did not try to change at least one behaviour'.

All statistical tests were two-tailed and the significance level was α=0.05. All analyses were conducted using a statistical software program (SPSS 12.0).

Ethics Approval

The Ottawa Hospital Research Ethics Board (OHREB) had previously approved Part 1 of this study. The protocol and study instruments for Part 2 were submitted to the OHREB and approved.

CHAPTER IV

RESULTS

Response Rates

Part I

Completion rates of baseline and follow-up questionnaires are shown in Table 14. While high response rates were observed for baseline questionnaires, one-week response rates were higher for carriers than non-carriers. Rates of completion at 12 months reflect the proportion of participants who had reached this follow-up point due to the staggered recruitment to the pilot study. When this is taken into account, the response rates for those who had actually been sent 12-month questionnaires were 73.7-77.2% for carriers and 64.8% for non-carriers. Complete data were therefore only available for a proportion of participants.

Table 14: Number and percentage of carriers and non-carriers completing questionnaires at baseline, 1 week and 12 months after receiving their genetic test result.

	Carriers (n=57) n (%)	Non-carriers (n=54) n (%)
Baseline		
Demographic Information	56 (98.2)	52 (96.3)
Medical Conditions and Risk factors	56 (98.2)	51 (94.4)
Participation questionnaire[a]	45 (78.9)	50 (92.6)
POMS-SF[b]	46 (80.7)	51 (94.4)
Somatization[c]	47 (82.5)	51 (94.4)
1 Week		
Perceived risk	47 (82.5)	32 (59.3)
POMS-SF[b]	47 (82.5)	32 (59.3)
Somatization[c]	47 (82.5)	32 (59.3)
12 Months[d]		
Perceived risk	30 (52.6)	25 (46.3)
POMS-SF[b]	28 (49.1)	25 (46.3)
Somatization[c]	28 (49.1)	25 (46.3)

[a]Participation questionnaire includes perceived risk questions.
[b]Profile of Mood States – Short Form
[c]Somatization subscale of the SCL-90-R
[d]14 (24.6%) carriers and 10 (18.5%) non-carriers had not yet been sent 12 month follow-up questionnaires because they were not due for completion at the time of analysis.

The perceived risk questionnaire was completed at all three time points by 17 (29.8%) carriers and 19 (35.2%) non-carriers. The POMS-SF was completed at all three time points by 18 (31.6%) carriers and 20 (37.0%) non-carriers. The somatization subscale was completed at all three time points by 21 (36.8%) carriers and 20 (37.0%) non-carriers.

Part II

In total, 70 FDRs completed the 'Causes & prevention of blood clots' questionnaire, including 44 carriers and 26 non-carriers. While 107 surveys were mailed (55 to carriers and 51 to non-carriers),[3] the denominator was adjusted to account for mail returned to sender (n=2), indication that the FDR had moved upon follow-up phone call (n=5), indication that the person was out of the country (n=1), or indication that the person did not receive the survey after two attempts to mail it (n=1). Therefore, the response rates were 44/51 (86.3%) for carriers, 26/47 (55.3%) for non-carriers, and 70/98 (71.4%) overall.

Description of participants

Part I

The dataset for the FDR pilot study contained observations on 118 subjects. Of these, seven observations were excluded from all analyses (1 duplicate; 4 missing test result and/or no records found; 2 no data collected for relevant outcomes). The remaining 111 participants belonged to 73 different families and included 57 carriers and 54 non-carriers of a thrombophilic mutation.

[3] While 111 subjects were included in Part 1, surveys were only mailed to 107 individuals. Some addresses were not available and some subjects had withdrawn during follow-up and did not wish to be contacted.

The sociodemographic variables measured at baseline are shown in Table 15. Participants ranged in age from 21-82 years, where the average age of carriers was 48.6 and that of non-carriers was 47.5. The majority of participants were female and were of Northern European descent. There were also several participants of French Canadian descent. Most participants reported having at least some post-secondary education. A small proportion of participants reported having a household income less than $40,000 per year.

Table 15: Sociodemographic characteristics of study participants in FDR pilot study.

	Carriers	**Non-carriers**
Total, N	57	54
Mean age (years) (sd)	48.6 (14.9)	47.5 (14.9)
Age range (years)	22-78	21-82
	n (%)	**n (%)**
Gender		
Male	24 (42.1)	17 (31.5)
Female	33 (57.9)	36 (66.7)
Not Stated	0	1 (1.9)
Self-identified ethnicity[b]		
French Canadian	19 (33.3)	17 (31.5)
Northern European	44 (77.2)	44 (81.5)
Southern European	3 (5.3)	2 (3.7)
Aboriginal	2 (3.5)	0
Middle Eastern	1 (1.8)	0
Not Stated	1 (1.8)	2 (3.7)
Education		
Did not finish high school	5 (8.8)	9 (16.7)
Completed high school	7 (12.3)	6 (11.1)
Some post-secondary	9 (15.8)	6 (11.1)
Graduated post-secondary	31 (54.4)	25 (46.3)
Advanced degree	3 (5.3)	4 (7.4)
Not Stated	2 (3.5)	4 (7.4)
Household income		
<$40,000	11 (19.3)	7 (13.0)
$40,000-$79,999	18 (31.6)	16 (29.6)
>$80,000	20 (35.1)	19 (35.2)
Not stated	8 (14.0)	12 (22.2)
Relationship to index patient		
Parent	13 (22.8)	7 (13.0)
Sibling	27 (47.4)	23 (42.6)
Child	16 (28.1)	22 (40.7)
Not Stated	1 (1.8)	2 (3.7)

[b]Respondents could select more than one ethnic background

Table 16 summarizes the clinical characteristics and potential risk factors for VTE among the study population. Varicose veins were the most common medical condition reported by participants. Most participants had never smoked cigarettes or were previous smokers. The most commonly used medications were ACE inhibitors, antiplatelet agents and statins. Use of hormone replacement therapy and oral contraceptives was very low, as only one participant was taking HRT and four participants were taking oral contraceptives at baseline.

Table 16: Medical conditions and potential risk factors for VTE.

	Carriers n (%)	**Non-carriers** n (%)
Total, N	57	54
Ever had:		
Varicose veins	9 (15.7)	10 (18.5)
Heart disease	2 (3.5)	2 (3.7)
Peripheral vascular disease	1 (1.8)	0
Transient ischemic attack	1 (1.8)	1 (1.9)
Diabetes	4 (7.0)	1 (1.9)
Cancer	1 (1.8)	2 (3.7)
Superficial vein thrombosis	6 (10.5)	1 (1.9)
Not Stated	2 (3.5)	3 (5.6)
Cigarette smoker:		
Never	28 (49.1)	27 (50.0)
Previous	15 (26.3)	18 (33.3)
Current	13 (22.8)	6 (11.1)
Not Stated	1 (1.8)	3 (5.6)
Currently taking:		
HRT	1 (1.8)	0
Oral contraceptives	0	4 (7.4)
ACE inhibitors	5 (8.8)	1 (1.9)
Antiplatelet agent	9 (15.8)	3 (5.6)
Statins	5 (8.8)	1 (1.9)
Not Stated	2 (3.5)	3 (5.6)

Before having their genetic test for thrombophilia, participants were asked general questions about their decision to have this test. The majority of participants either agreed (36.1%) or strongly agreed (20.6%) that they needed more advice and information about genetic testing for thrombophilia (n=97). Also, most participants either agreed (41.2%) or

strongly agreed (55.7%) that the decision to have genetic testing for thrombophilia was hard to make (n=97).

Part II

Sociodemographic characteristics of the Part II survey participants are shown in Table 17. There were no significant differences between those who completed the survey and those who did not.

Table 17: Sociodemographic characteristics of survey respondents (n=70).

	Carriers	**Non-carriers**
Total, N	44	26
Mean age (years) (sd)	49.0 (13.3)	47.4 (14.5)
Age range (years)	22-78	21-76
Time since genetic test		
Mean (months) (sd)	18.7 (9.4)	22.1 (6.5)
Range (months)	3.9-32.5	6.3-30.8
	n (%)	**n (%)**
Gender		
Male	18 (40.9)	8 (30.8)
Female	26 (59.1)	17 (65.4)
Not Stated	0	1 (2.5)
Self-identified ethnicity[b]		
French Canadian	14 (31.8)	5 (19.2)
Northern European	33 (75.0)	25 (96.2)
Southern European	3 (6.8)	0
Aboriginal	2 (4.5)	0
Middle Eastern	1 (2.3)	0
Not Stated	0	1 (2.5)
Education		
Did not finish high school	3 (6.8)	3 (11.5)
Completed high school	7 (15.9)	2 (7.7)
Some post-secondary	5 (11.4)	3 (11.5)
Graduated post-secondary	27 (61.4)	15 (57.7)
Advanced degree	1 (2.3)	2 (7.7)
Not Stated	1 (2.3)	1 (2.5)
Household income		
<$40,000	8 (18.2)	2 (7.7)
$40,000-$79,999	12 (27.3)	10 (38.5)
>$80,000	19 (43.2)	10 (38.5)
Not stated	5 (11.4)	4 (15.4)
Relationship to index patient		
Parent	10 (22.7)	3 (11.5)
Sibling	20 (45.5)	9 (34.6)
Child	13 (29.5)	13 (50.0)
Not Stated	1 (2.3)	1 (2.5)

[b]Respondents could select more than one ethnic background

PART I Outcomes: Risk Perception and Affective Impacts

1. Risk Perception

Figure 3 summarizes carrier and non-carrier responses to the question 'Compared to most people, what do you believe is your chance of having a blood clot.' At baseline, there was no significant difference between the two groups, most reporting their risk as the same or a little higher than most people. The distribution of responses at 1-week post-testing showed a statistically significant difference between carriers and non-carriers. Most carriers reported a personal risk of VTE a little higher than most people, and most non-carriers reported a personal risk as the same as most people. This persisted at 12 months. Over time, the proportion of carriers who believed that their risk was much higher than that of most people increased, as did the proportion of non-carriers who believed that their risk was lower than most people. Though not significant, those who had completed the 12-month follow-up questionnaire were slightly less likely to perceive their risk as higher than that of most people compared to those who had not completed 12-month follow-up (completed versus not completed, 52.3% v 62.0%, p=0.341).

Figure 4 summarizes responses to the question, 'What do you think are your chances of developing a blood clot?' Carriers and non-carriers did not differ significantly in their estimates of absolute risk at baseline, 1 week or 12 months. Based on a known population risk of thrombosis of 1/1000, at baseline, most carriers (59.5%) believed that their risk was equal to or lower than that of the general population. After 1 week most carriers (67.4%) perceived their risk as being higher than 1/1000. However, this proportion decreased at 12 months and only 50.0% of respondents believed that their risk was greater

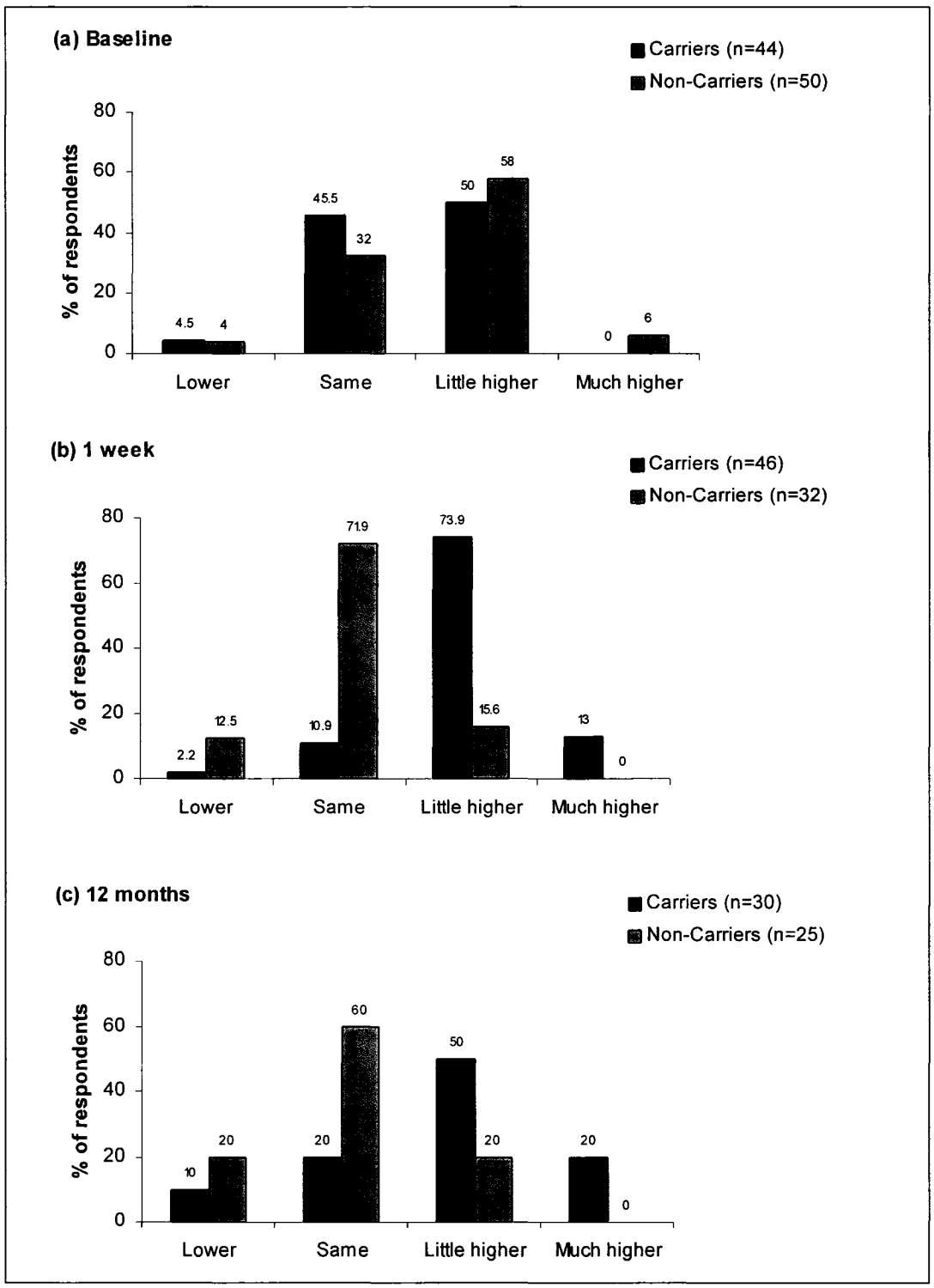


Figure 3: Perceived risk of VTE relative to the general population for carriers and non-carriers of a thrombophilia measured at a) baseline b) 1 week and c) 12 months after receiving genetic test results. Carrier v Non-Carrier: (a) $p=0.171$; (b) $p<0.001$; (c) $p=0.001$ (lower/same versus little higher/much higher).

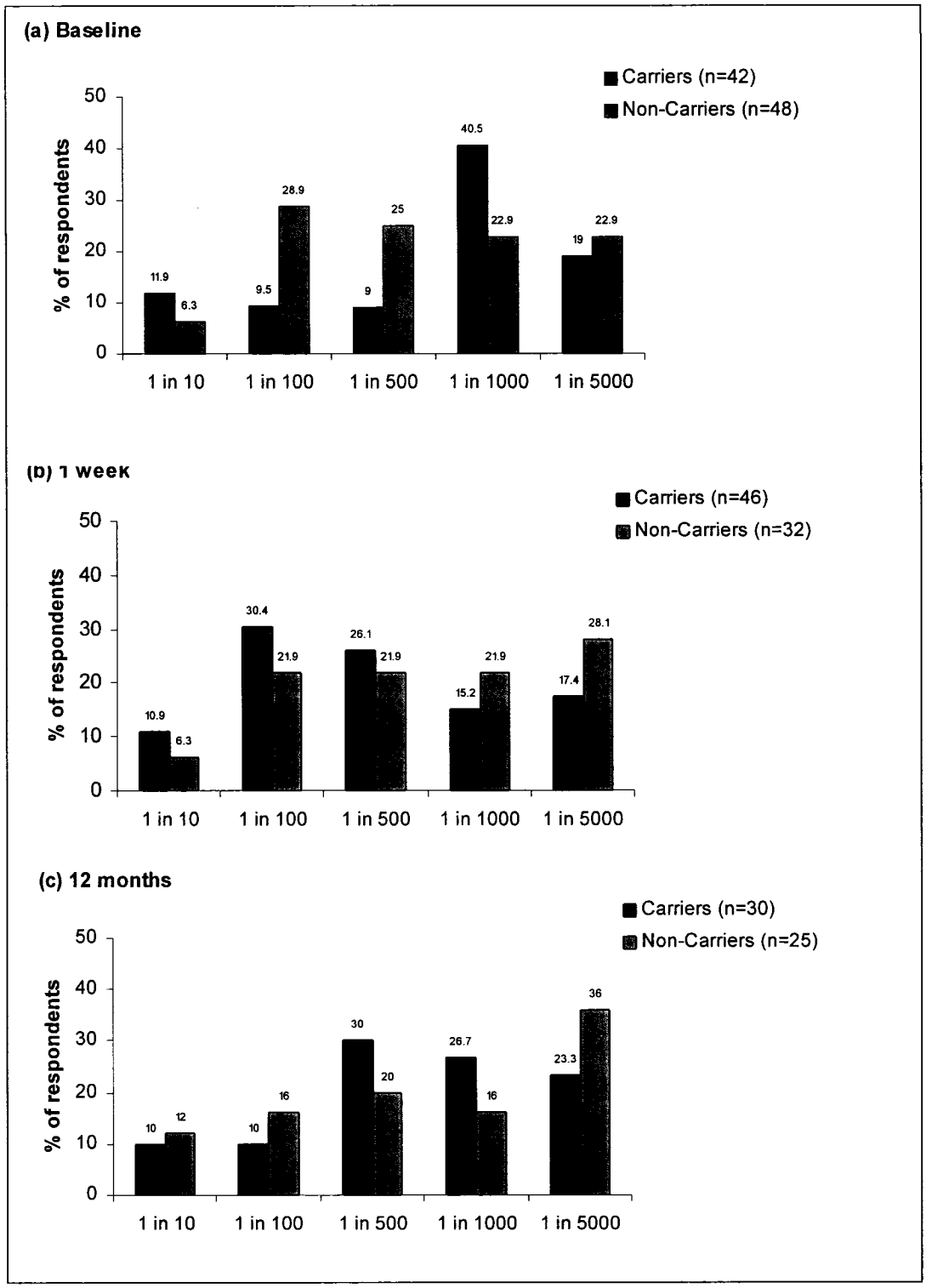


Figure 4: Perceived risk of VTE for carriers and non-carriers of a thrombophilia measured at a) baseline b) 1 week and c) 12 months after receiving genetic test results. Carriers v Non-Carriers: (a) p=0.195; (b) p=0.123; (c) p=0.883 (1 in 10, 100, 500 versus 1 in 1000, 5000).

than 1/1000. The distribution of responses by non-carriers did not vary greatly over the 12-month follow-up period, though the proportion of non-carriers who perceived their risk as being 1/5000 increased from 22.9% at baseline to 36.0% at 12 months. Overall, the proportion of non-carriers who believed that their risk was equal (1/1000) or less than (1/5000) that of the general population increased from 45.8% at baseline to 52.0% at 12 months. Though not significant, those who had completed the 12-month follow-up questionnaire were slightly less likely to perceive their risk as being higher than 1 in 1000 than those who had not completed follow-up (completed versus not completed, 39.1% v 56.8%, p=0.093).

2. Affective Impacts

a) VTE-specific worry

Responses to the questions on VTE-specific worry are summarized in Table 18. At baseline, most carriers and non-carriers were 'somewhat' concerned about their chances of having a blood clot, and there was no significant difference between the two groups. One week after testing, carriers and non-carriers showed significant differences, with a higher proportion of carriers reporting concern than non-carriers. The differences were still apparent at 12 months though they were not statistically significant. Most carriers and non-carriers reported that they 'rarely' or 'never' worried about their chances of developing a blood clot, and there was no significant difference between the two groups at baseline, 1 week or 12 months. Also, while most carriers and non-carriers reported that worries about blood clots did not affect the way they felt from day to day, the proportion of carriers who felt that worries did affect them at least 'somewhat' increased over the 12-

Table 18: VTE-specific worry as reported by carriers and non-carriers at baseline, 1 week and 12 months after receiving genetic test results.

	Carriers n (%)	Non-carriers n (%)	p-value[a]
How concerned are you about your chances of having a blood clot?			
Baseline, N[b]	45	50	
Not at all	13 (28.9)	13 (26.0)	0.580
Somewhat	28 (62.2)	29 (58.0)	
Moderate-Very	4 (8.9)	8 (16.0)	
1 week, N[b]	47	32	
Not at all	11 (23.4)	17 (53.1)	0.025
Somewhat	27 (57.4)	11 (34.4)	
Moderate-Very	9 (19.1)	4 (12.5)	
12 months, N[b]	30	24	
Not at all	12 (40.0)	13 (54.2)	0.581
Somewhat	15 (50.0)	9 (37.5)	
Moderate-Very	3 (10.0)	2 (8.3)	
How often do you worry about your chances of developing a blood clot?			
Baseline, N[b]	45	50	
Rarely or never	33 (73.3)	42 (84.0)	0.203
Sometimes/often	12 (26.7)	8 (16.0)	
1 week, N[b]	47	32	
Rarely or never	33 (70.2)	28 (87.5)	0.072
Sometimes/often	14 (29.8)	4 (12.5)	
12 months, N[b]	30	25	
Rarely or never	22 (73.3)	21 (84.0)	0.340
Sometimes/often	8 (26.7)	4 (16.0)	
How much do worries about blood clots affect the way you feel from day to day?			
Baseline, N[b]	45	50	
Not at all	41 (91.1)	42 (84.0)	0.298
Somewhat/very much	4 (8.9)	8 (16.0)	
1 week, N[b]	47	32	
Not at all	39 (83.0)	30 (93.8)	0.189
Somewhat/very much	8 (17.0)	2 (6.3)	
12 months, N[b]	30	25	
Not at all	22 (73.3)	24 (96.0)	0.031
Somewhat/very much	8 (26.7)	1 (4.0)	

[a] χ^2 test, carriers v non-carriers
[b] N=number of respondents to each question.

month period while the opposite pattern was seen in non-carriers. The difference at 12 months was statistically significant. With respect to baseline responses to these three questions, there were no statistically significant differences between those who completed 12-month follow-up questionnaires and those who did not (data not shown).

b) Psychological distress

Median psychological distress scores (POMS-SF, Total Mood Disturbance) are reported in Table 19. Lower TMD scores correspond to lower levels of distress. Subscale means were compared to population means reported in the POMS manual by McNair *et al.*[165] Baseline carrier and non-carrier scores were lower than population scores for depression-dejection, confusion-bewilderment, tension-anxiety, and anger-hostility subscales. Respondent scores were similar to population scores for the fatigue-inertia subscale and higher than population scores for the vigour-activity subscale. Differences between carriers and non-carriers regarding baseline, 1-week and 12-month TMD scores were not statistically significant (see Table 19). While there was a small increase in the TMD scores from baseline to one week for both carriers and non-carriers, these differences were not statistically significant (carriers: p=0.102, non-carriers: p=0.259). Less than 60% of carriers and non-carriers who had completed baseline POMS-SF questionnaires had also completed the 12-month follow-up POMS-SF. While median TMD scores at 12 months were slightly lower than baseline and 1-week scores, these differences were not statistically significant for either carriers or non-carriers (baseline-12 months: carriers, p=0.858; non-carriers, p=0.389; 1 week-12 months: carriers, p=0.389; non-carriers, p=0.191). To check for potential selection bias at 12 months, baseline TMD scores were compared for those who had completed the 12-month POMS-SF and those who had not.

While those completing follow-up had slightly lower TMD scores at baseline, this difference was not significant (completed versus not completed, 24.5 v 26.5, p=0.275).

Table 19: Median Total Mood Disturbance (TMD) scores for carriers and non-carriers as measured using the POMS-SF at baseline, 1 week and 12 months after receiving genetic test results for thrombophilia. (TMD range: 0-144)

	Carriers			Non-carriers			
	n	Median TMD	IQR	n	Median TMD	IQR	p-value[a]
Baseline	46	25.0	21.3	48	25.4	24.0	0.949
1 week	43	27.0	21.0	32	26.0	22.8	0.936
12 months	27	21.0	40.0	25	21.0	11.8	0.978

IQR – Interquartile Range
[a]Mann-Whitney test, carriers v non-carriers

Only 39.1% of carriers and 41.7% of non-carriers who had completed baseline POMS-SF questionnaires had completed the POMS-SF at all three time points. For this subset of participants, there were no statistically significant changes in TMD scores over the 12-month period in carriers or non-carriers (carriers: p=0.594, non-carriers: p=0.148). To more closely scrutinize whether TMD scores tended to 'track' over time (i.e. those with initial higher scores tended to remain at the top of the score distribution over follow-up points, and vice versa), individual scores were plotted as shown in Figures 5a-5c. From baseline to one week, changes in TMD scores for most carriers and non-carriers were minimal, except for two carriers and one non-carrier (Figure 5a). One week following genetic testing the average carrier score was 3.0 points higher than baseline, and the average non-carrier score was 1.2 points higher (see Table 20). On average, TMD scores for both carriers and non-carriers decreased by 4.0 points between baseline and 12 months (Table 20), although Figure 5b shows that two non-carriers and four carriers had scores that increased by over 20 points.

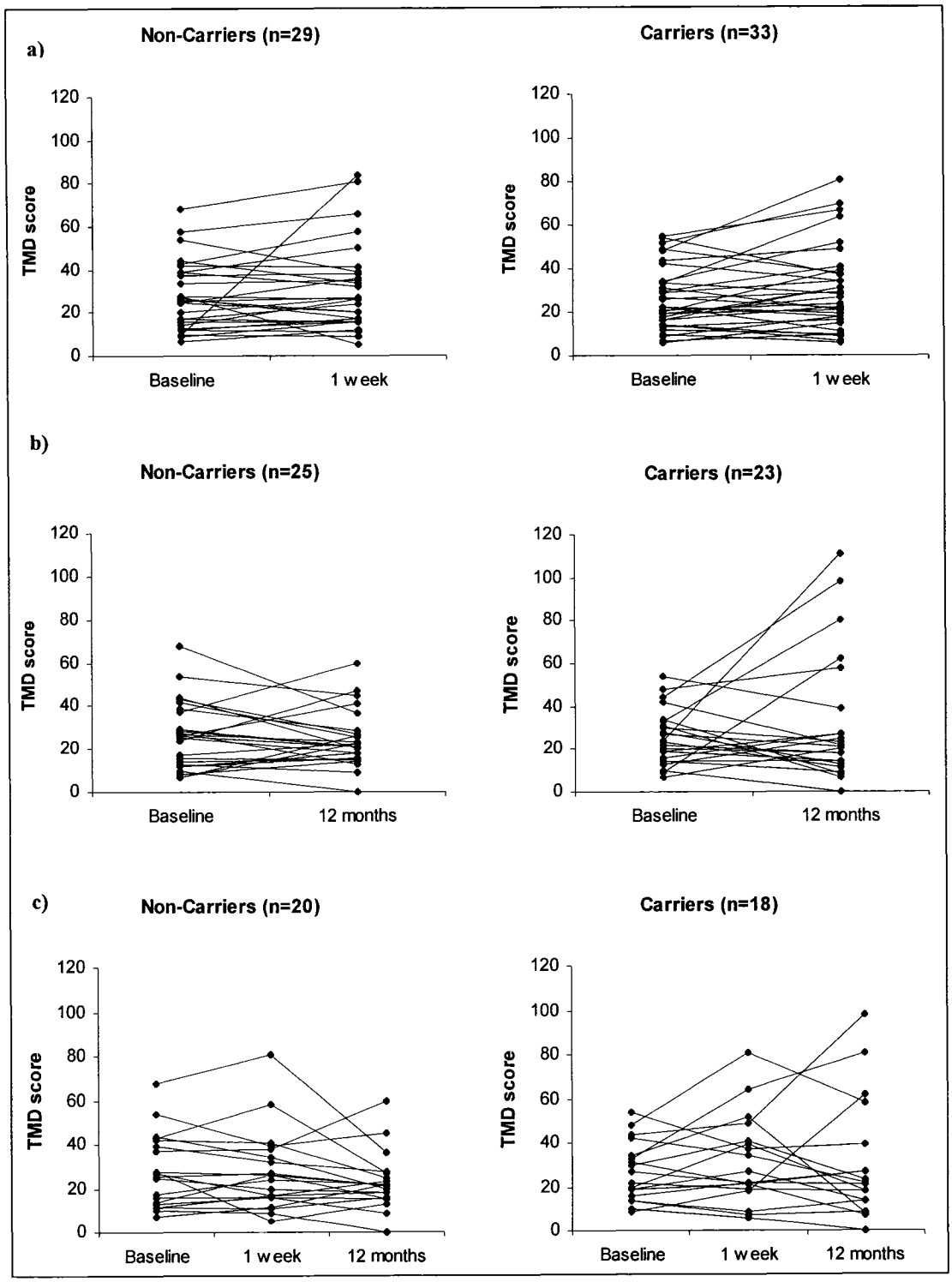


Figure 5: POMS-SF Total Mood Disturbance (TMD) scores for individual carriers and non-carriers showing changes between baseline, 1 week and 12 month scores. (Note: only individuals with complete data for each comparison are included).

Table 20: Differences between pre and post-test POMS-SF TMD scores for carriers and non-carriers at one week and 12 months after receiving a genetic test for thrombophilia.

	Carriers			Non-Carriers			
	n	Range	Median	n	Range	Median	P-value[a]
1-week - baseline	33	-17 to +33	+3.0	29	-23 to +74	+1.2	0.626
12-month - baseline	23	-26 to +87	-4.0	25	-32 to +23	-4.0	0.657

[a]Mann-Whitney test, carriers v non-carriers

Spearman rank correlation coefficients (Table 21) indicated statistically significant correlations between baseline and 1-week scores for both groups, and between baseline and 12-month scores for non-carriers, but not for carriers.

Table 21: Correlations between pre- and post-test POMS-SF TMD scores for carriers and non-carriers.

	Carriers			Non-carriers		
	n	r_s	P-value[a]	n	r_s	P-value[a]
Baseline-1 week	33	0.807	<0.001	29	0.671	<0.001
Baseline-12 months	23	0.246	0.259	25	0.518	0.008

r_s: Spearman rank correlation coefficient
[a]Spearman rank correlation, baseline v 1 week, baseline v 12 months

c) Somatization

Median somatization scores (SCL-90-R subscale) are reported in Table 22. Overall, median scores were very low for both carriers and non-carriers. There were no statistically significant differences between carriers and non-carriers at baseline, 1 week or 12 months (see Table 22). Also, there were no statistically significant changes in somatization scores over the 12-month period for either carriers or non-carriers (data not shown). Because somatization scores were very low and did not vary greatly between participants or over time, more detailed analyses were not conducted.

Table 22: Median somatization scores for carriers and non-carriers as measured using the SCL-90-R subscale at baseline, 1 week and 12 months after receiving genetic test results for thrombophilia. (Subscale range: 0-6)

	Carriers			Non-carriers			
	n	Median	IQR	n	Median	IQR	p-value[a]
Baseline	47	0.36	0.50	51	0.29	0.64	0.808
1 week	47	0.29	0.43	32	0.36	0.55	0.688
12 months	27	0.43	1.00	25	0.29	0.39	0.139

IQR: Interquartile range
[a]Mann-Whitney test, carriers v non-carriers

PART II Outcomes: Cognitive and Behavioural Impacts

3. Cognitive Impacts

a) Test implications

When Part II participants were asked if they remembered their genetic test result, 95.5% of carriers and 100% of non-carriers reported the correct result. Two (4.5%) carriers indicated that they did not remember their genetic test result. While not a significant difference, 23.1% of non-carriers and 6.8% of carriers believed that their genetic test results were only somewhat accurate, and one carrier felt that his/her test was not at all accurate. None of the respondents reported that they had regrets about having the genetic test for thrombophilia. While not statistically significant, non-carriers were more likely than carriers to report that a blood clot would be 'extremely' serious for their health (see Figure 6). A higher proportion of carriers than non-carriers reported confidence in being able to identify symptoms of a blood clot, and many respondents were slightly or not at all confident in their ability to identify the symptoms of a blood clot (see Figure 7).

b) Perceived risk/susceptibility

Most respondents indicated that their genetic test result meant that they 'may or may not get a blood clot' in their lifetime (76.9% of non-carriers and 88.6% of carriers); 23.1% of

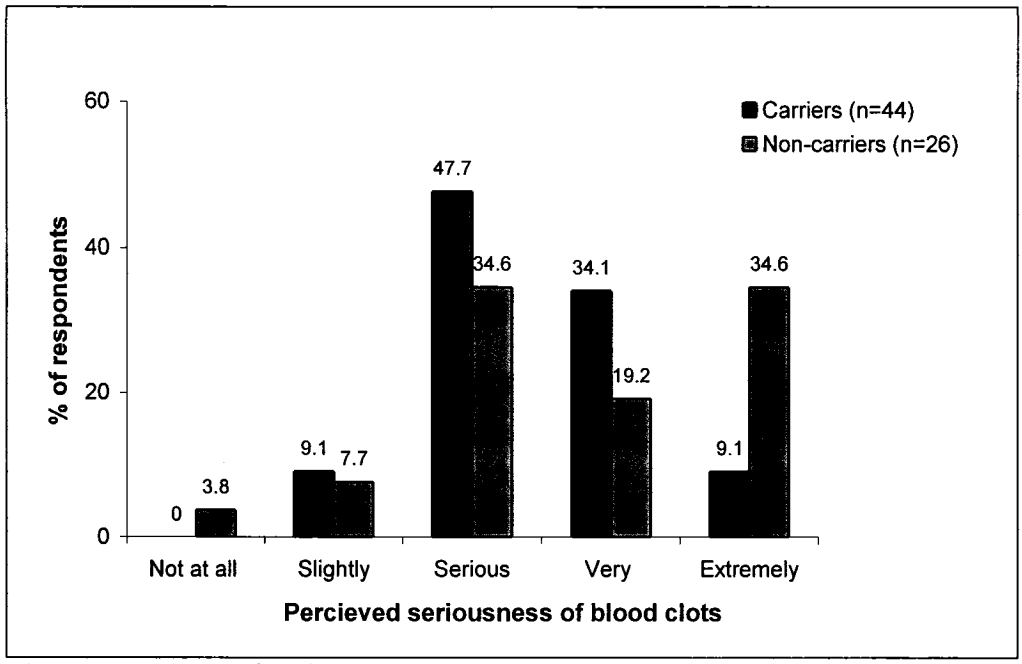


Figure 6: Cross-sectional survey responses to the question 'How serious for your health do you think it would be to get a blood clot?' Carriers v Non-Carriers: p=0.521 ('not at all/slightly serious' v 'serious/very/extremely serious').

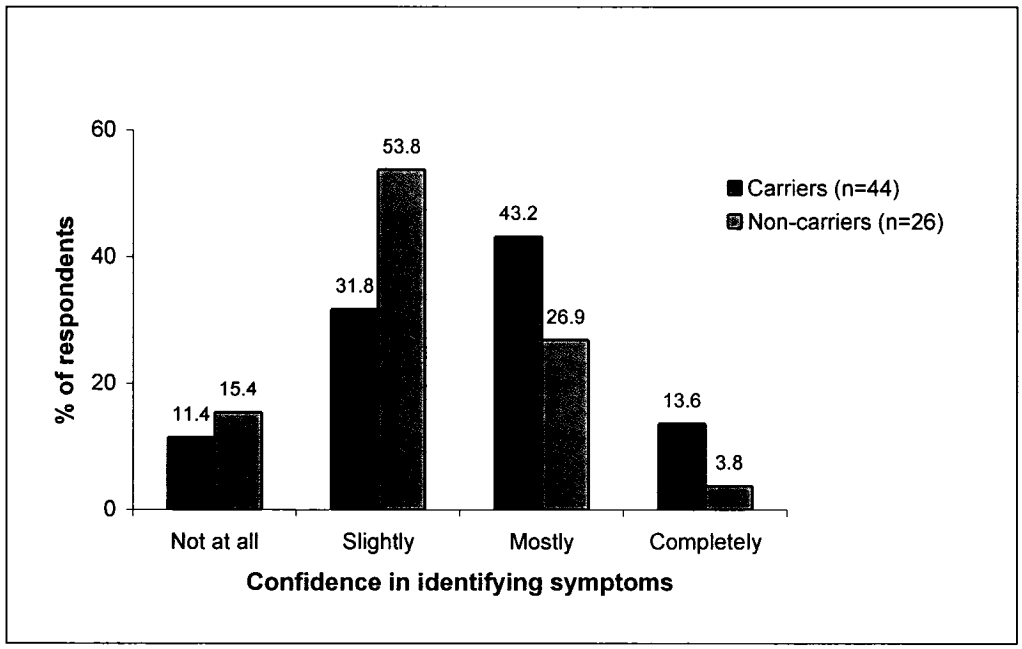


Figure 7: Cross-sectional survey responses to the question 'How confident are you in your ability to identify the symptoms of a blood clot?' Carriers v Non-Carriers: p=0.035 ('not at all/slightly confident v mostly/completely confident).

non-carriers and 4.5% of carriers felt that their result meant that they 'probably will not' get a blood clot; and 6.8% of carriers felt that their test result meant that they 'probably will' get a blood clot in their lifetime.

Participants were asked the same two questions that they were asked in Part I of this study (Figures 3 & 4) concerning perceived risk. Responses to these questions are summarized in Figure 8. The distribution of responses to both questions was similar to that seen at 1 week and 12 months. Carriers were more likely than non-carriers to believe that their risk of getting a blood clot is a little higher or much higher than most people. Some carriers continue to believe that their risk is the same as or lower than most people, and some non-carriers continue to report that their risk is a little higher or much higher than that of most people. Carriers were most likely to report that their risk was 1/1000, and non-carriers were most likely to report that their risk of ever developing a blood clot was 1/5000.

c) Perceived control over VTE

Respondents were asked about their general perceptions of control over developing a blood clot. These responses are summarized in Figure 9, a-c. There were no statistically significant differences between carriers and non-carriers for any of these questions. Most respondents believed that there was a lot that they could do to control whether or not they developed a blood clot. Respondents were not likely to report that chance or luck played a major role in controlling whether or not one gets a blood clot.

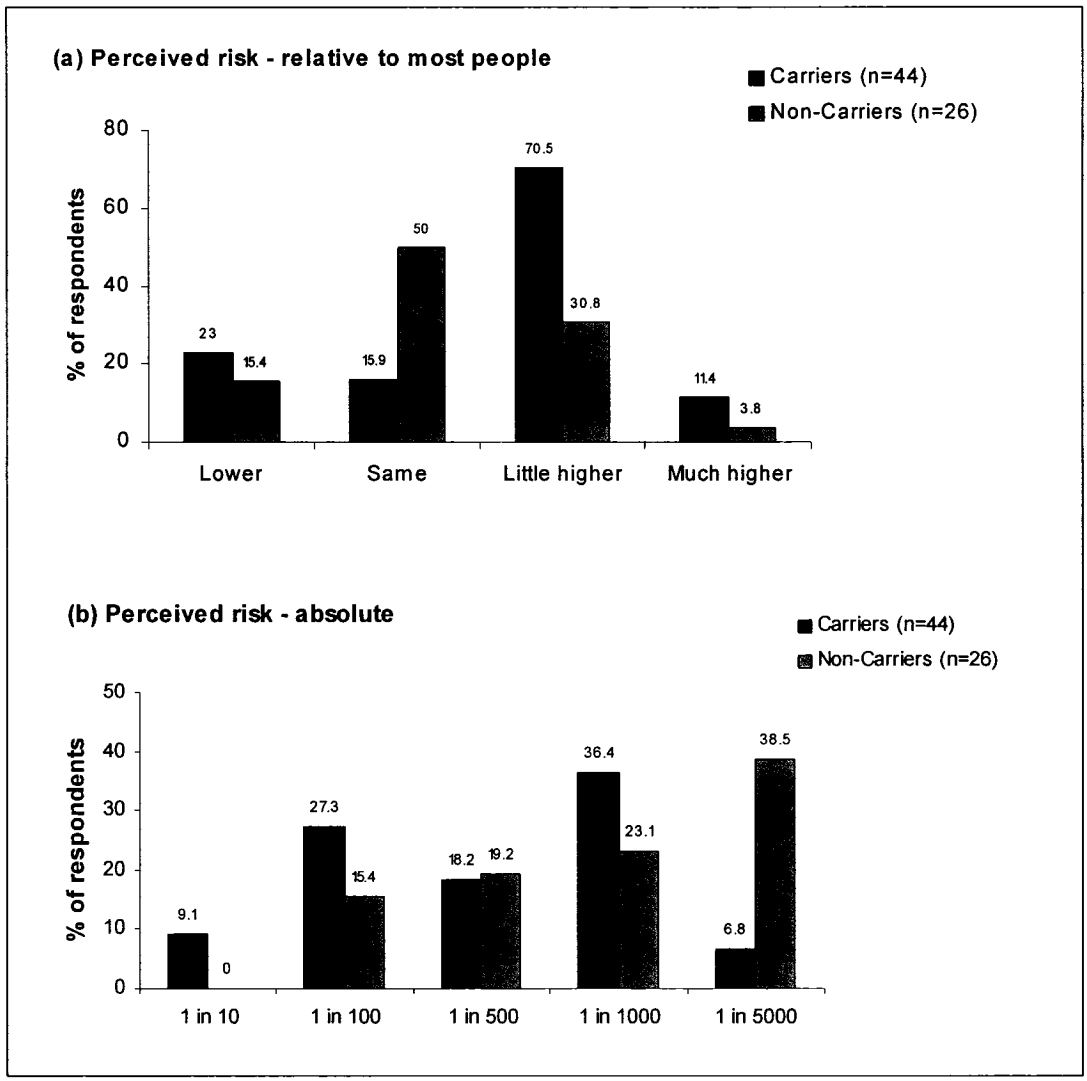


Figure 8: Responses of carriers and non-carriers to the questions (a) 'Compared to most people, what do you believe is your chance of ever having a blood clot?' and (b) 'Roughly, what do you think are your chances of ever developing a blood clot?' Carriers v Non-carriers: (a) $p<0.001$ (lower/same v little higher/much higher), (b) $p=0.115$ (1 in 10, 100, 500 v 1 in 1000, 5000).

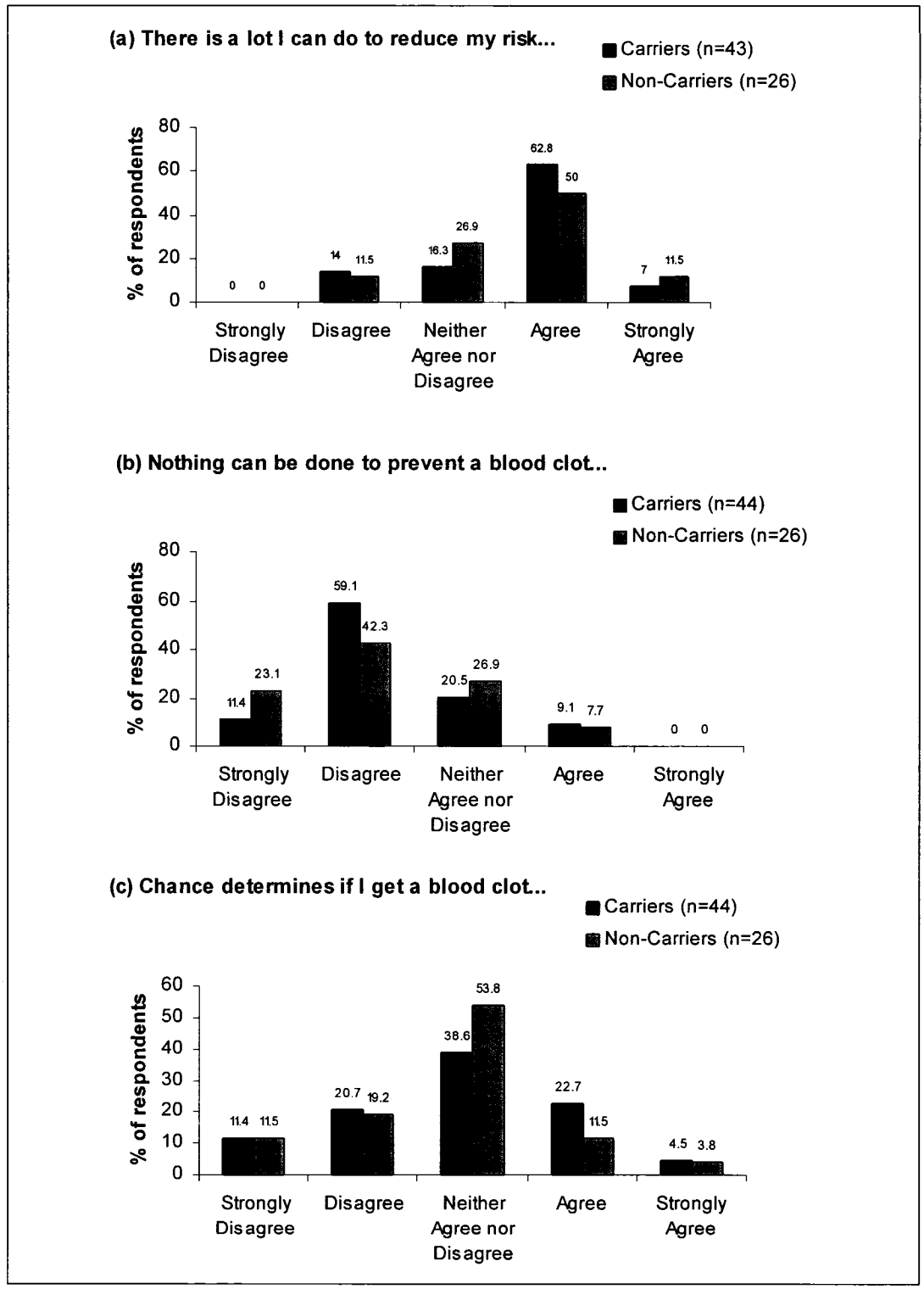


Figure 9: General perceptions of control over developing a blood clot for carriers and non-carriers of a thrombophilic mutation. Carriers v Non-carriers: (a) p=0.482 (b) p=0.606 (c) p=0.383 (strongly disagree/disagree/neither agree nor disagree v agree/strongly agree).

4. Perceived causes of VTE and behavioural impacts

For reporting and comparison purposes, the 19 potential risk factors were divided into three groups: specific risk factors, general risk factors and irrelevant risk factors.

a) Specific risk factors

Specific risk factors are those known to increase one's risk for VTE, and patients are given specific advice about these factors by their physician or genetic counsellor. These factors include both medical risk factors (injury, major surgery, prolonged immobility, pregnancy/childbirth, taking birth control pills, taking hormone replacement therapy (HRT)) and genetic risk factors (a positive genetic test for thrombophilia, a family history of blood clots).

Perceived causes: For each of these factors, carrier and non-carrier responses to the question '...will increase a person's risk getting a blood clot' are shown in Figure 10, a-h. In general, most carriers and non-carriers agreed or strongly agreed that the six medical risk factors and two genetic risk factors increased a person's risk of getting a blood clot. Carriers and non-carriers only differed significantly with respect to whether or not they felt that injury increased one's risk of getting a blood clot. Carriers were slightly more likely than non-carriers to agree/strongly agree that injury would increase one's risk ($p=0.039$). While not significant, carriers also appeared slightly more likely than non-carriers to agree/strongly agree that major surgery increased one's risk ($p=0.143$). With respect to medical risk factors, respondents were most likely to agree/strongly agree that prolonged immobility increases one's risk of getting a blood clot. Respondents appeared to be most uncertain (i.e. neither agreed nor disagreed) that HRT increased one's risk.

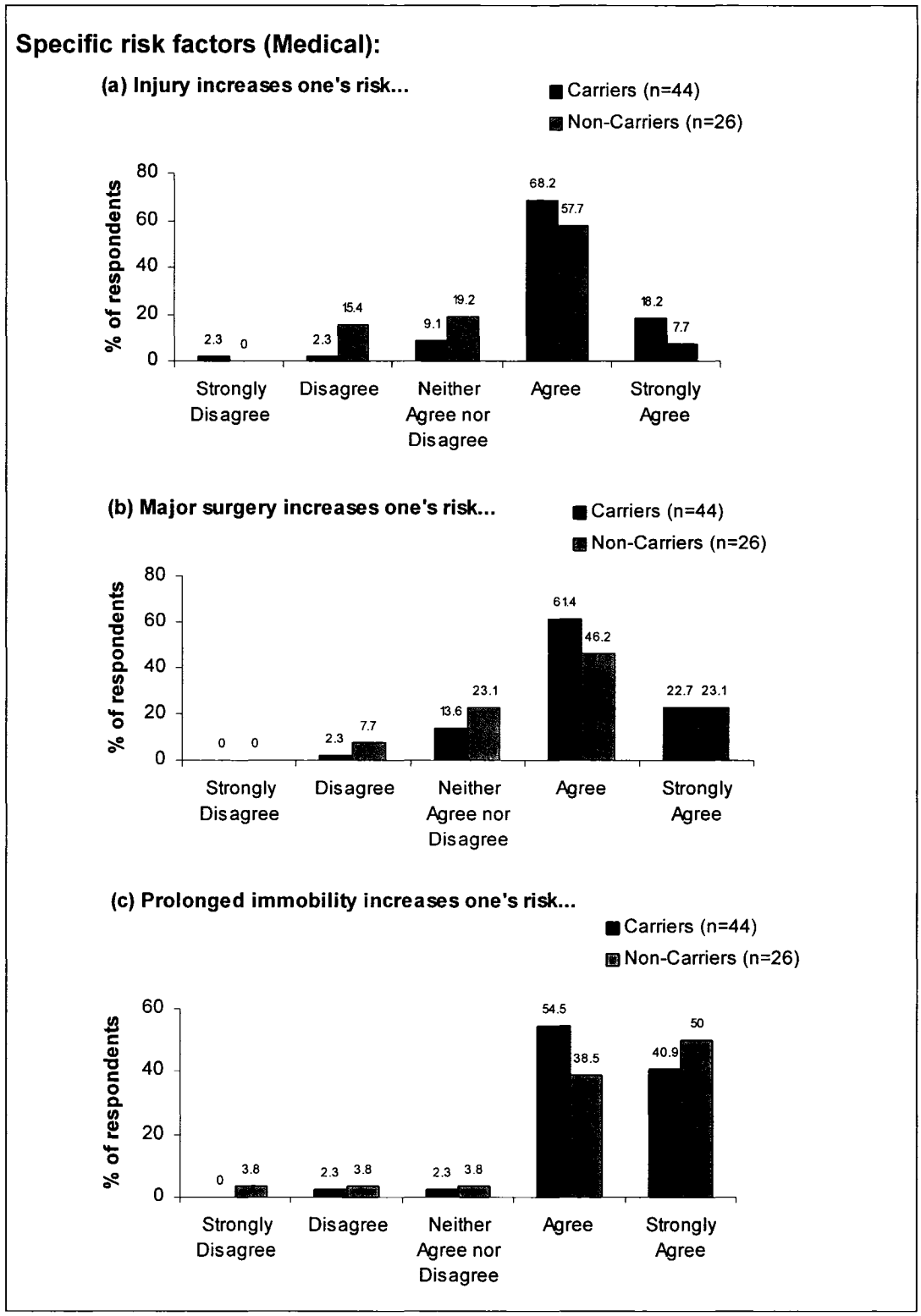
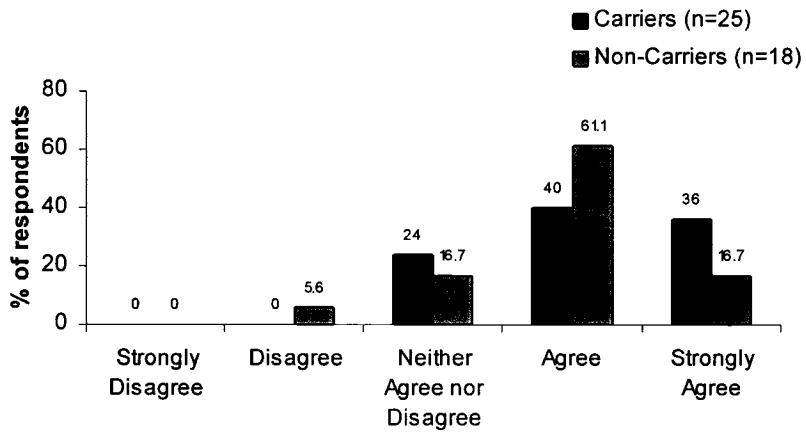

Specific risk factors (Medical):
(a) Injury increases one's risk...
Carriers (n=44)
Non-Carriers (n=26)
% of respondents
80
60
40
20
0
2.3
0
2.3
15.4
9.1
19.2
68.2
57.7
18.2
7.7
Strongly Disagree
Disagree
Neither Agree nor Disagree
Agree
Strongly Agree
(b) Major surgery increases one's risk...
Carriers (n=44)
Non-Carriers (n=26)
% of respondents
80
60
40
20
0
0
0
2.3
7.7
13.6
23.1
61.4
46.2
22.7
23.1
Strongly Disagree
Disagree
Neither Agree nor Disagree
Agree
Strongly Agree
(c) Prolonged immobility increases one's risk...
Carriers (n=44)
Non-Carriers (n=26)
% of respondents
60
40
20
0
0
3.8
2.3
3.8
2.3
3.8
54.5
38.5
40.9
50
Strongly Disagree
Disagree
Neither Agree nor Disagree
Agree
Strongly Agree

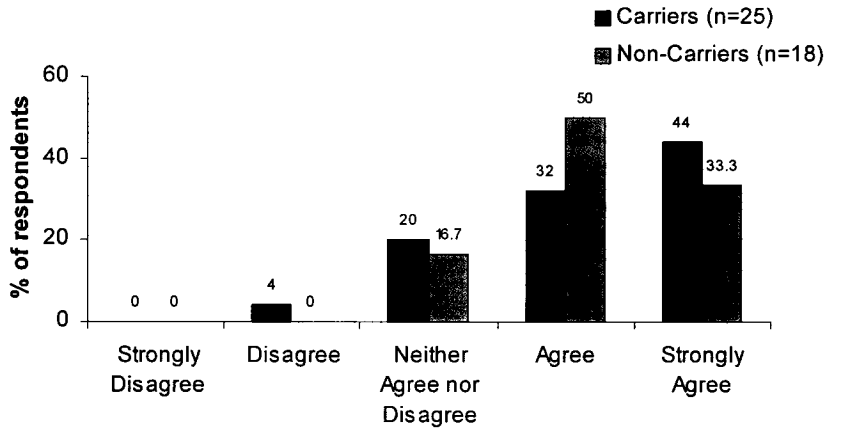
Figure 10 (a-c)

Specific risk factors (Medical):

(d) Pregnancy/Childbirth increases one's risk...



(e) Taking birth control pills increases one's risk...



(f) Taking HRT increases one's risk...

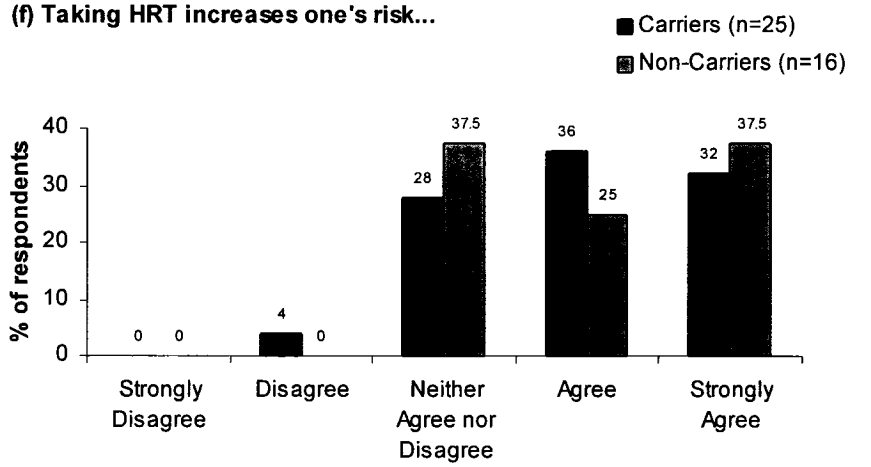


Figure 10 (d-f): Female respondents only.

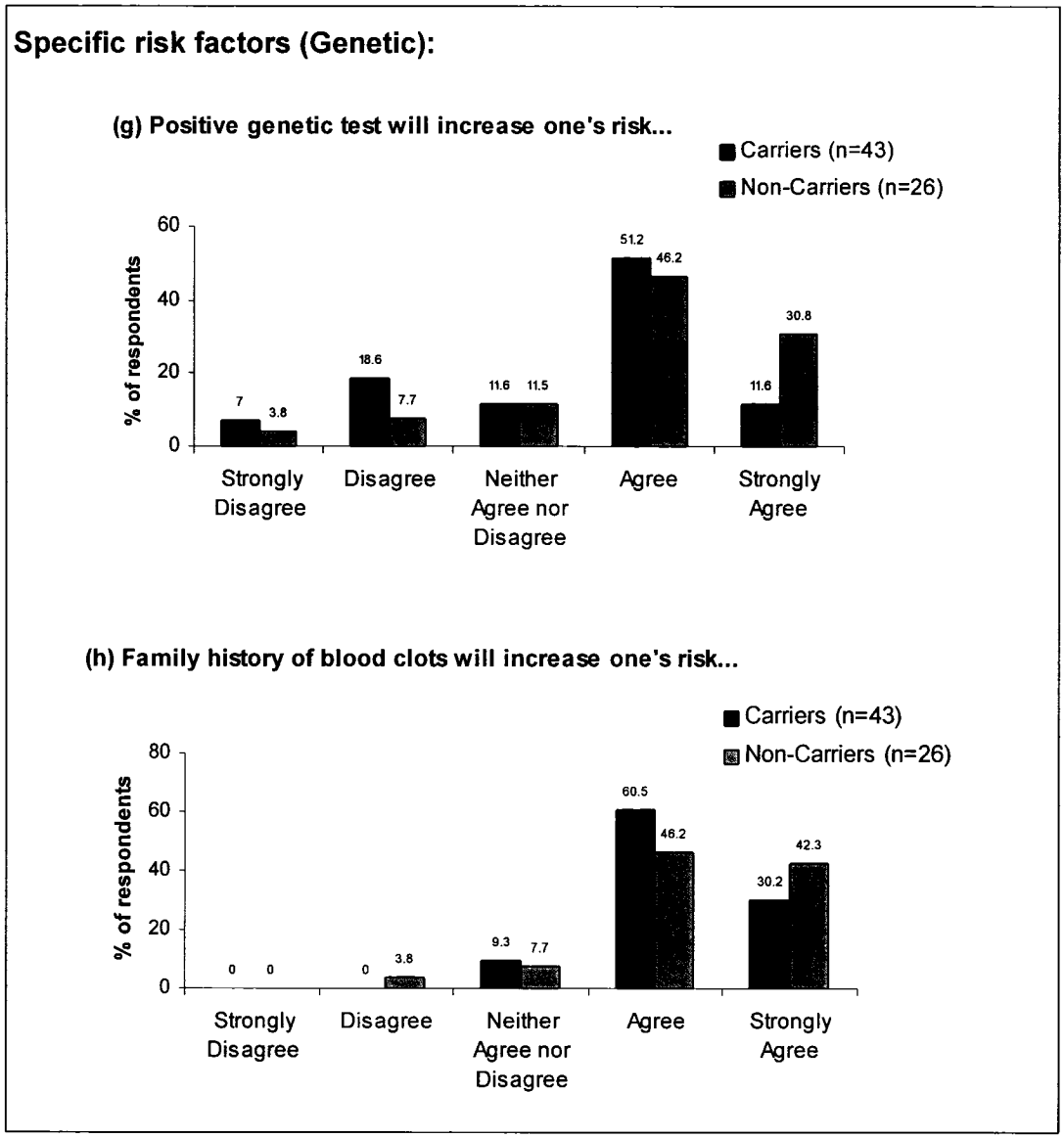


Figure 10: Carrier and non-carrier responses to the question '...will increase a person's risk of getting a blood clot' for various medical (a-f) and genetic (g-h) known risk factors for VTE. Carriers v Non-carriers: (a) p=0.039 (b) p=0.143 (c) p=0.263 (d) p=0.594 (e) p=0.425 (f) p=0.717 (g) p=0.222 (h) p=0.521 (strongly disagree/disagree/neither agree nor disagree v agree/strongly agree).

With respect to genetic risk factors, respondents were more likely to agree that a family history of blood clots would increase a person's risk of getting a blood clot as compared to a positive genetic test for thrombophilia. While 90.7% of carriers and 88.5% of non-carriers

agreed/strongly agreed that a family history of blood clots increases one's risk of VTE, only 62.8% of carriers and 77.0% of non-carriers agreed/strongly agreed that a positive genetic test increases one's risk.

Perceived control: Table 23 summarizes the responses of all first-degree relatives to questions regarding control over injury, prolonged immobility, taking birth control pills and taking HRT. (Respondents were not asked about control over the other specific risk factors, as they were considered uncontrollable factors). Since there were no significant differences between carriers or non-carriers for any of these questions, responses are combined for all respondents. The distribution of responses is similar for both general and personal control questions. Most respondents agreed/strongly agreed that prolonged immobility, taking birth control pills and taking HRT are controllable factors. Respondents were less likely to agree that injury is a controllable factor.

Table 23: Responses of all FDRs (carriers and non-carriers combined) to questions regarding general and personal control over four specific risk factors for VTE.

%	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Injury (n=69)					
...is something some can control	5.8	31.9	27.5	33.3	1.4
...is something I can control	5.8	27.5	30.4	34.8	1.4
Prolonged immobility (n=69)					
...is something some can control	0	10.1	13.0	62.3	14.5
...is something I can control	0	8.7	11.6	60.9	18.8
Taking birth control pills					
...is something some can control (n=42)	0	0	19.0	64.3	16.7
...is something I can control (n=4)	0	0	0	75.0	25.0
Taking hormone replacement therapy					
...is something some can control (n=40)	0	2.5	27.5	55.0	15.0
...is something I can control (n=8)	12.5	12.5	12.5	50.0	12.5

High-risk situations and behaviour change: Injury: Approximately 25% of all respondents reported that they had tried to reduce their risk of injury since their genetic test (see Figure 11). Five carriers and two non-carriers reported that they had done this specifically to reduce their risk of a blood clot. Only one carrier and two non-carriers reported being injured and admitted to hospital since their genetic test. The carrier and one of the non-carriers alerted their physician of their genetic test result shortly after he/she treated their injury. Following their injury, none reported that they had received blood thinners or wore compression stockings, and the one carrier and one non-carrier reported trying to get back on their feet as soon as possible. Surgery: Six carriers and one non-carrier reported having major surgery since their genetic test. Five of the carriers and the one non-carrier had discussed their genetic test result with their physician before surgery. Three of the six carriers were prescribed blood thinners to take before or after their surgery. One of the carriers reported wearing compression stockings following surgery. All respondents who reported having surgery indicated that they tried to get back on their feet as soon as possible. Immobility: Carriers were more likely than non-carriers to have tried to avoid long trips since their genetic test, as seven carriers (16.3%) and none of the non-carriers had tried to do so ($p=0.030$) (see Figure 11). Five of these carriers reported that they avoided these trips specifically to reduce their risk of a blood clot. Twenty-two carriers and 15 non-carriers reported that they had been on a long trip since their genetic test. Of these, five carriers and one non-carrier had discussed their genetic test result with their physician before going on this trip. None had been prescribed blood thinners, but three carriers and three non-carriers reported wearing compression stockings during their trip. Most respondents (21 carriers and

12 non-carriers) reported that they had taken frequent breaks to walk around and move their legs during their trip.

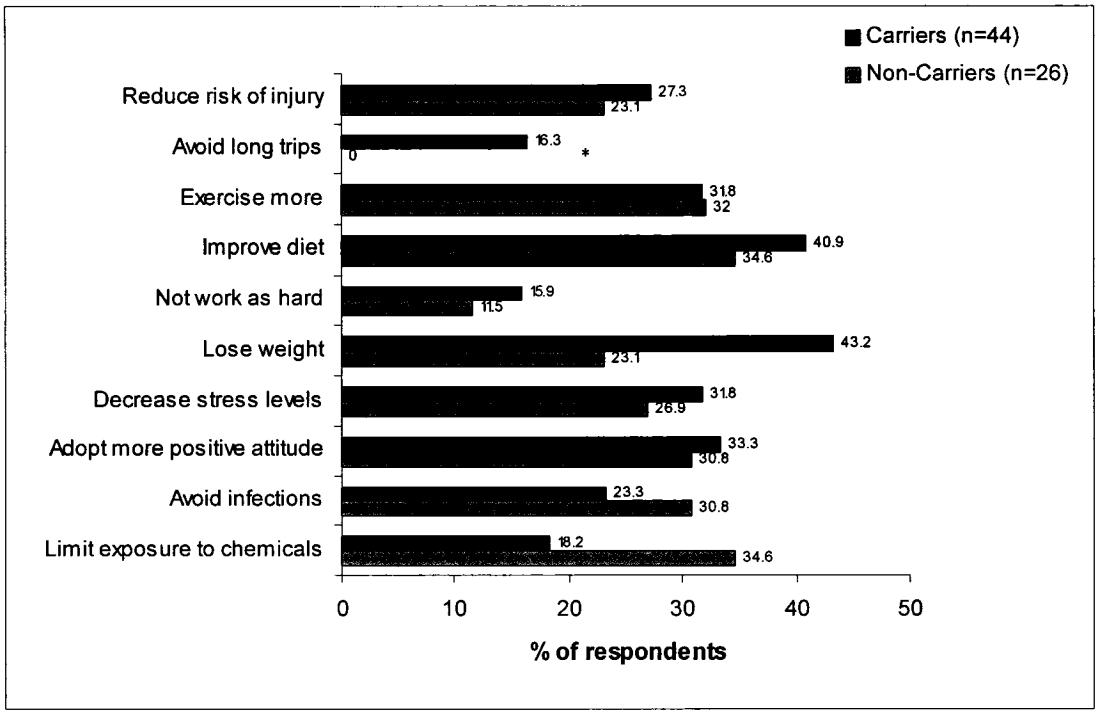


Figure 11: Percentage of carriers and non-carriers who reported that they had tried to change specific behaviours since receiving their genetic test result. (*$p<0.05$)

Pregnancy/childbirth: Two carriers and one non-carrier reported being pregnant and/or giving birth since their genetic test. One carrier and the non-carrier had discussed their genetic test result with their physician after finding out they were pregnant, one carrier was prescribed blood thinners to take during and/or after childbirth, and none of these women wore compression stockings during pregnancy or after childbirth. Birth control pills: Only three carriers and one non-carrier reported taking birth control pills at the time of their genetic test. Two of the carriers reported that they stopped taking the pills after their genetic test, and they reported doing this specifically to reduce their risk of a blood clot. Hormone Replacement Therapy: Four carriers and no non-carriers reported that they had been taking HRT at the

time of their genetic test. One carrier reported that she had stopped taking HRT after her test. Two carriers reported that the results of their genetic test had helped them to decide not to start taking HRT.

b) General risk factors

General risk factors are those known to be related to good health, but are not specifically linked to an increased risk of VTE. Physicians and genetic counsellors may advise patients to make changes related to these factors. General risk factors include lifestyle factors (not enough exercise, poor diet, smoking, being overweight) and also the effects of aging.

Perceived causes: For each general risk factor, carrier and non-carrier responses to the question '...will increase a person's risk getting a blood clot' are shown in Figure 12, a-e. There were no statistically significant differences between carrier and non-carrier responses for any of these factors. Over 70% of respondents agreed/strongly agreed that being overweight, smoking and not enough exercise increased a person's risk of getting a blood clot. Poor diet was less likely to be considered a risk factor for blood clots. In general, the effects of aging were seen to be a risk factor, as 76.9% of non-carriers and 65.9% of carriers agreed/strongly agreed that these effects would increase one's risk.

Perceived control: Responses to questions regarding control over the four factors discussed above are summarized in Table 24. There were no significant differences between carriers or non-carriers, and the distribution of responses is similar for both general and personal control questions. Most respondents agreed/strongly agreed that all four factors are controllable.

General Risk Factors (lifestyle & aging):

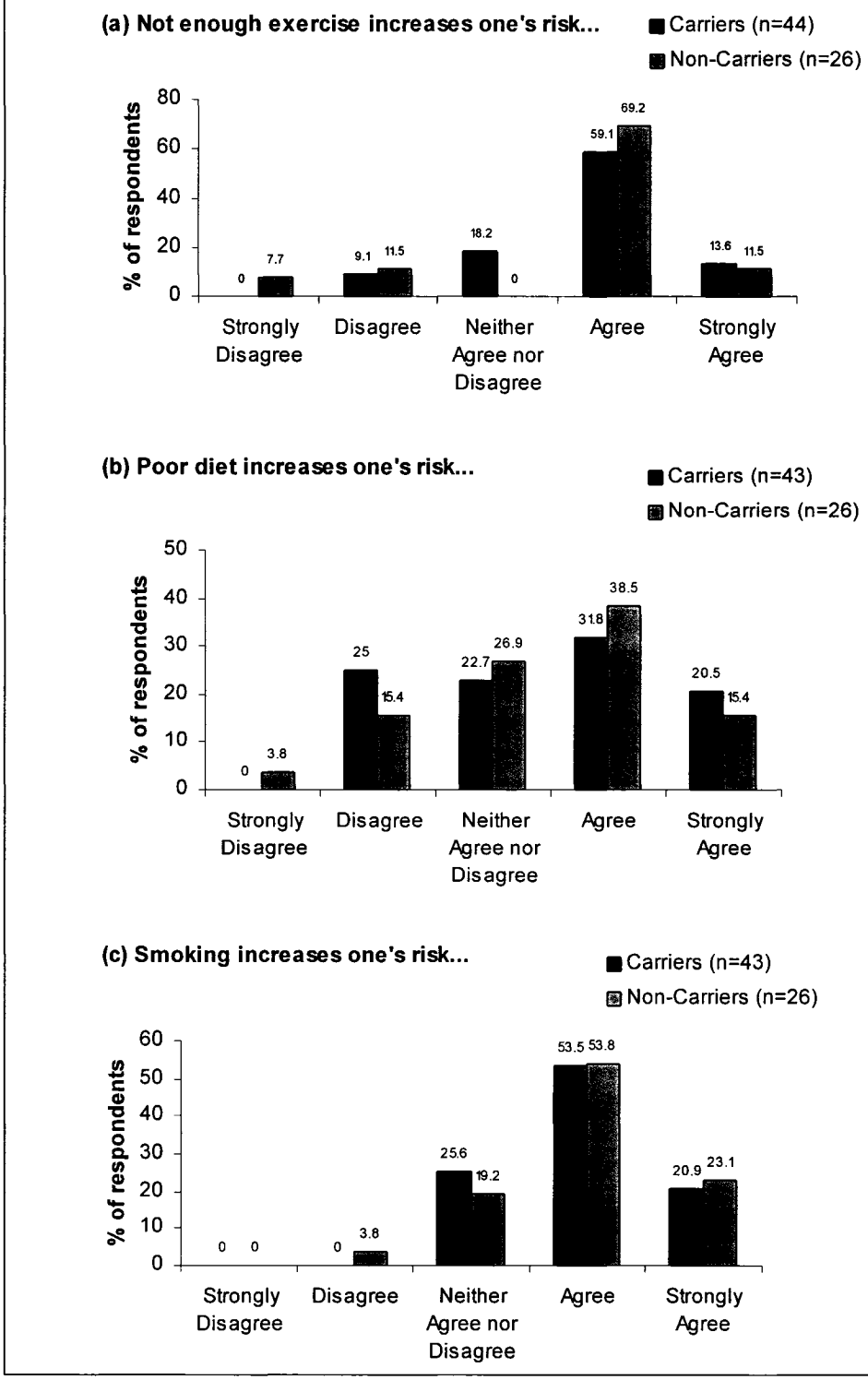


Figure 12 (a-c)

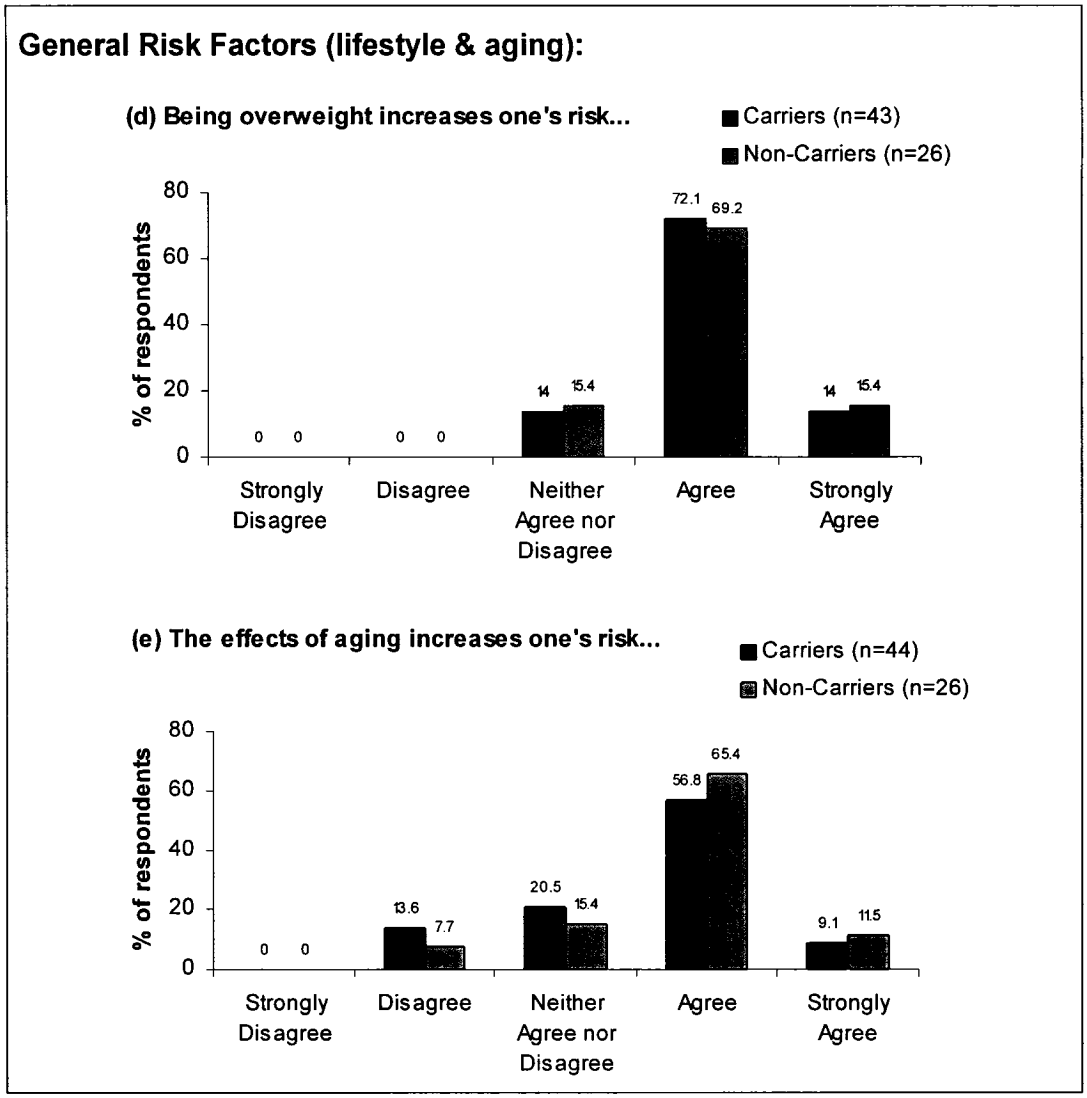


Figure 12: Carrier and non-carrier responses to the question '...will increase a person's risk of getting a blood clot' for various lifestyle general risk factors (a-d) and the effects of aging (e). Carriers v Non-carriers: (a) p=0.448 (b) p=0.834 (c) p=0.815 (d) p=0.566 (e) p=0.331 (strongly disagree/disagree/neither agree nor disagree v agree/strongly agree).

Table 24: Responses of all FDRs (carriers and non-carriers combined) to questions regarding general and personal control over five general risk factors for VTE.

%	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Not enough exercise (n=69)					
...is something some can control	1.4	2.9	17.4	53.6	24.6
...is something I can control	0	5.8	15.9	46.4	31.9
Poor diet (n=69)					
...is something some can control	0	4.3	7.2	60.9	27.5
...is something I can control	0	2.9	7.2	60.9	29.0
Smoking (n=68)					
...is something some can control	0	2.9	11.8	54.4	30.9
...is something I can control	0	4.4	11.8	42.6	41.2
Being overweight (n=69)					
...is something some can control	0	0	17.4	69.6	13.0
...is something I can control	0	10.1	10.1	63.8	15.9

Behaviour change: Carrier and non-carrier responses to questions asking whether they had tried to make changes related to three of the lifestyle factors are shown in Figure 11. There were no significant differences between carriers and non-carriers for responses related to behaviour change or to whether the change was made specifically to reduce one's risk of getting a blood clot. While 14 carriers and 8 non-carriers indicated that they had tried to exercise more since their genetic test, only two carriers reported doing this specifically to reduce their risk of a getting a blood clot. Similarly, 18 carriers and 9 non-carriers reported that they had tried to improve their diet since their genetic test, and only four carriers and three non-carriers had done so specifically to reduce their risk. While not statistically significant, almost twice as many carriers as non-carriers reported that they had tried to lose weight since their genetic test ($p=0.090$). Three carriers and two non-carriers had tried to lose weight specifically to reduce their risk. Ten carriers and four non-carriers reported smoking cigarettes at the time of their genetic test. Six carriers and two non-carriers had tried to quit smoking since their genetic test, but all had smoked within the past 30 days. Of those trying to quit, two carriers and one non-carrier did so to reduce their risk of getting a blood clot.

c) Irrelevant factors

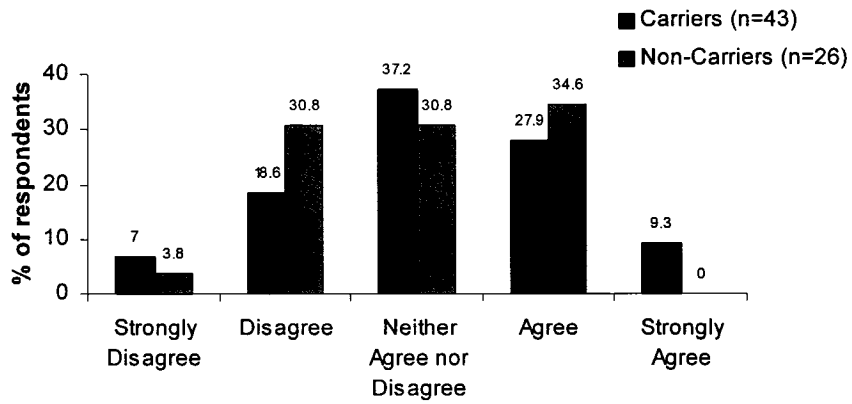
Irrelevant factors are those with no known link to VTE, and physicians and genetic counsellors do not regularly give advice about these factors to patients at risk. Irrelevant factors include emotional factors (stress, worry or depression, a general negative attitude in life), lifestyle factors (over-exertion) and external/environmental factors (lack of access to high quality medical care, infection with a germ or virus, chemical exposure).

Perceived causes: For each of these factors, carrier and non-carrier responses to the question '...will increase a person's risk getting a blood clot' are shown in Figure 13, a-f. There were no significant differences between carrier and non-carrier responses for any of these factors. Most respondents disagreed or were uncertain that these factors would increase one's risk of getting a blood clot. Of these six factors, respondents were most likely to agree that stress, worry or depression would cause a blood clot, and least likely to agree that infection would cause a clot.

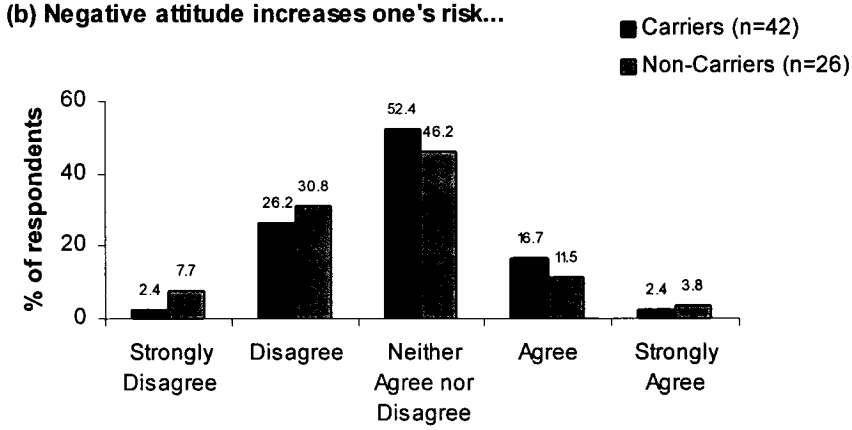
Perceived control: Responses to questions regarding control over the irrelevant factors discussed above are summarized in Table 25. There were no significant differences between carriers or non-carriers, and the distribution of responses was similar for both general and personal control questions. Most respondents agreed/strongly agreed that stress, worry or depression, a negative attitude, over-exertion and exposure to household chemicals are controllable factors. Respondents were less likely to agree that lack of access to high quality medical care and infection by a germ or virus are controllable.

Irrelevant/Unknown Factors (emotional, external, environmental):

(a) Stress, worry, depression increases one's risk...



(b) Negative attitude increases one's risk...



(c) Over-exertion increases one's risk...

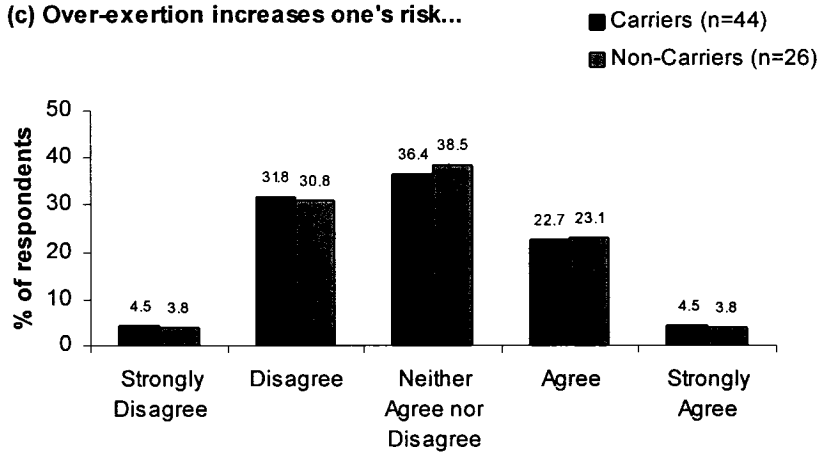


Figure 13 (a-c)

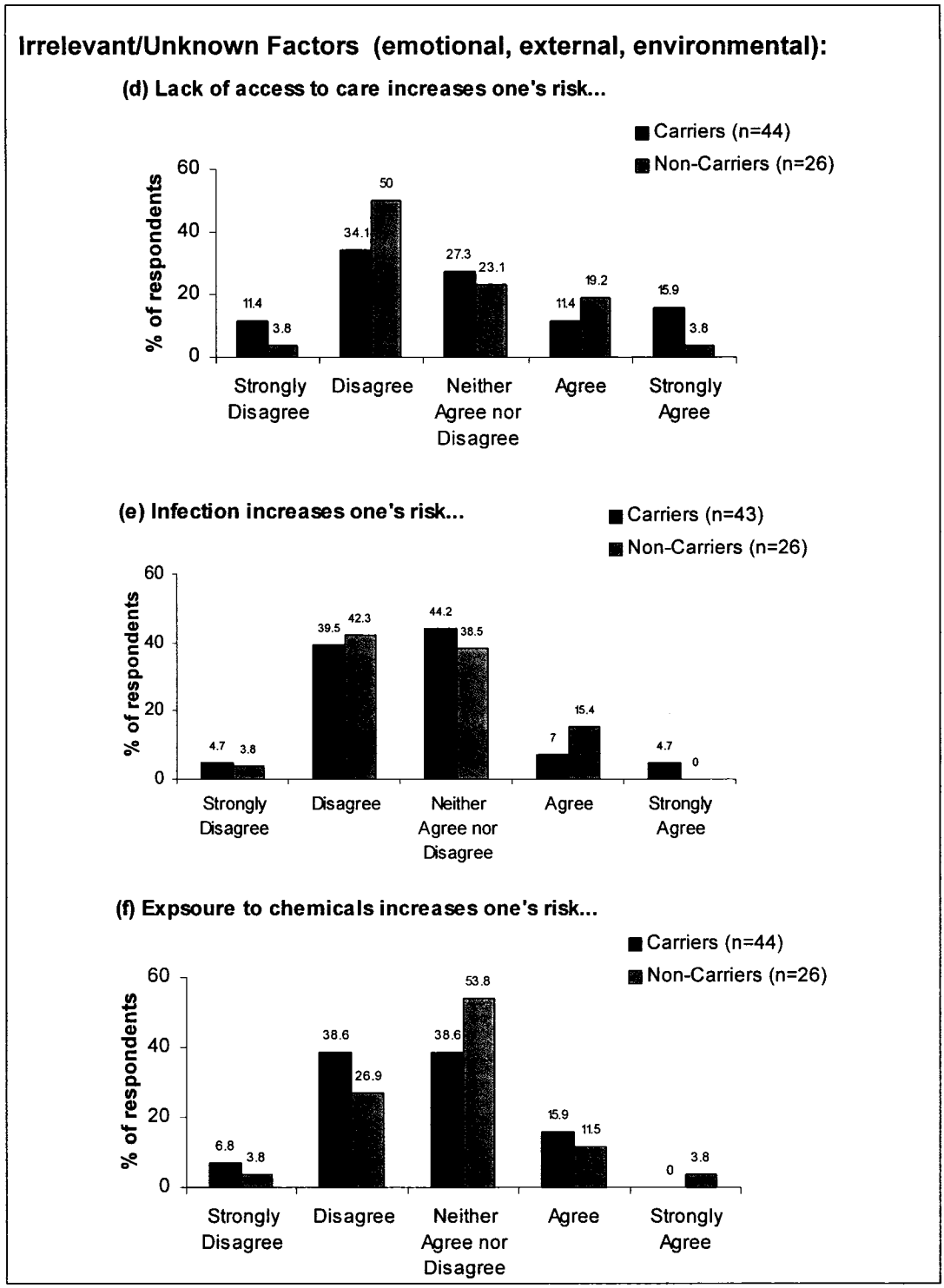


Figure 13: Carrier and non-carrier responses to the question '...will increase a person's risk of getting a blood clot' for 'irrelevant' emotional (a-b), lifestyle (c) and external/environmental factors (d-f). Carriers v Non-carriers: (a) p=0.712 (b) p=0.484 (c) p=983 (d) p=0.794 (e) p=0.459 (f) p=618 (strongly disagree/disagree/neither agree nor disagree v agree/strongly agree).

Table 25: Responses of all FDRs (carriers and non-carriers combined) to questions regarding general and personal control over six 'irrelevant' risk factors for VTE.

%	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Stress, worry or depression (n=68)					
...is something some can control	1.5	13.2	20.6	52.9	11.8
...is something I can control	0	8.8	20.6	54.4	16.2
A negative attitude (n=68)					
...is something some can control	0	2.9	25.0	60.3	11.8
...is something I can control	0	4.4	14.7	61.8	19.1
Over-exertion (n=69)					
...is something some can control	0	5.8	15.9	69.6	8.7
...is something I can control	0	7.2	14.5	65.2	13.0
Lack of access to care (n=69)					
...is something some can control	8.7	43.5	30.4	14.5	2.9
...is something I can control	8.7	23.2	43.5	23.2	1.4
Infection (n=68)					
...is something some can control	5.9	36.8	23.5	33.8	0
...is something I can control	7.4	30.9	30.9	29.4	1.5
Exposure to chemicals (n=68)					
...is something some can control	0	10.3	22.1	55.9	11.8
...is something I can control	0	10.3	19.1	57.4	13.2

Behaviour change: Carrier and non-carrier responses to questions asking whether they had tried to make changes related to four of the irrelevant factors are shown in Figure 11. There were no significant differences between carriers and non-carriers for responses related to behaviour change or to those related to whether the change was made specifically to reduce one's risk of getting a blood clot. Fourteen carriers and seven non-carriers reported that they had tried to reduce their stress levels since their genetic test. While none of the carriers indicated that they had done this specifically to reduce their risk of a blood clot, two non-carriers reduced stress in order to lower their risk. Fourteen carriers and eight non-carriers had tried to adopt a more positive attitude since their genetic test, and three carriers had done so in order to reduce their risk of a blood clot. Respondents were least likely to report trying to work less since their genetic test, as seven carriers and four non-carriers reported doing this (two carriers had tried to work less in order to reduce their risk of a blood clot). While ten carriers and eight non-carriers indicated that they had tried to avoid infection since their

genetic test, none of these reported that they did this to reduce their risk of a clot. While eight carriers and nine non-carriers tried to limit their exposure to household chemicals since their genetic test, only one carrier reported doing so specifically to reduce his/her risk.

d) Overall behaviour change and high-risk situations

While carriers were more likely than non-carriers to try to make at least one change in their behaviour or lifestyle since their genetic test,[4] this difference was not significant. In total, 70.5% of carriers and 61.5% of non-carriers had tried to make at least one change. However, only 12 carriers (27.3%) and 5 non-carriers (19.2%) indicated that they had made any of these changes specifically to reduce their risk of a blood clot.

More non-carriers (65.4%) than carriers (54.5%) reported being in a high-risk situation since their genetic test (been injured and admitted to hospital, had major surgery, been on a long trip, or been pregnant/given birth), but this difference was not significant. Carriers were more likely to have discussed their genetic test result with their physician before, during or after being in a high-risk situation (p=0.027). Of those who had been in one of these situations, 11 carriers and two non-carriers had discussed their genetic test result with their physician.

5. Overall perceptions of control and prevention

Figure 14 a-e summarizes carrier and non-carrier responses to questions regarding overall control and prevention of blood clots. Again, there were no statistically significant differences between carrier and non-carrier responses for any of these questions. In general,

[4] Including exercise less, decrease stress, avoid infections, improve diet, limit chemical exposure, not work as hard, quit smoking, adopt positive attitude, lose weight, reduce risk of injury, avoid long trips, stop taking birth control pills or HRT

most respondents agreed that taking blood thinners, wearing stockings, and informing their physicians when in high-risk situations can prevent them from getting a blood clot. Respondents were less likely to agree that their own behaviours or their genetic makeup determines whether or not they get a blood clot.

6. Experiences with health professionals

Carrier and non-carrier responses to various questions regarding their experiences with health professionals are summarized in Table 26. The majority of respondents indicated that they did have a physician with whom they could regularly schedule appointments (e.g. a family doctor). Since receiving their genetic test results, only one non-carrier and two carriers felt that they had visited this physician more often. Carriers were more likely than non-carriers to have discussed their genetic test result with their physician. Of those who had discussed their test result, most carriers and non-carriers felt their physician had an adequate understanding of what their genetic test result meant. Also, while not significant, carriers were more likely than non-carriers to report that this physician had given them advice about their risk for a blood clot. Overall, most carriers and non-carriers reported that they were either satisfied or very satisfied with the amount of information that they had received from any health professional about thrombophilia and their risk of developing a blood clot (see Figure 15). While carriers tended to report being 'very satisfied' more often than non-carriers, they were also slightly more likely to report being unsatisfied or very unsatisfied.

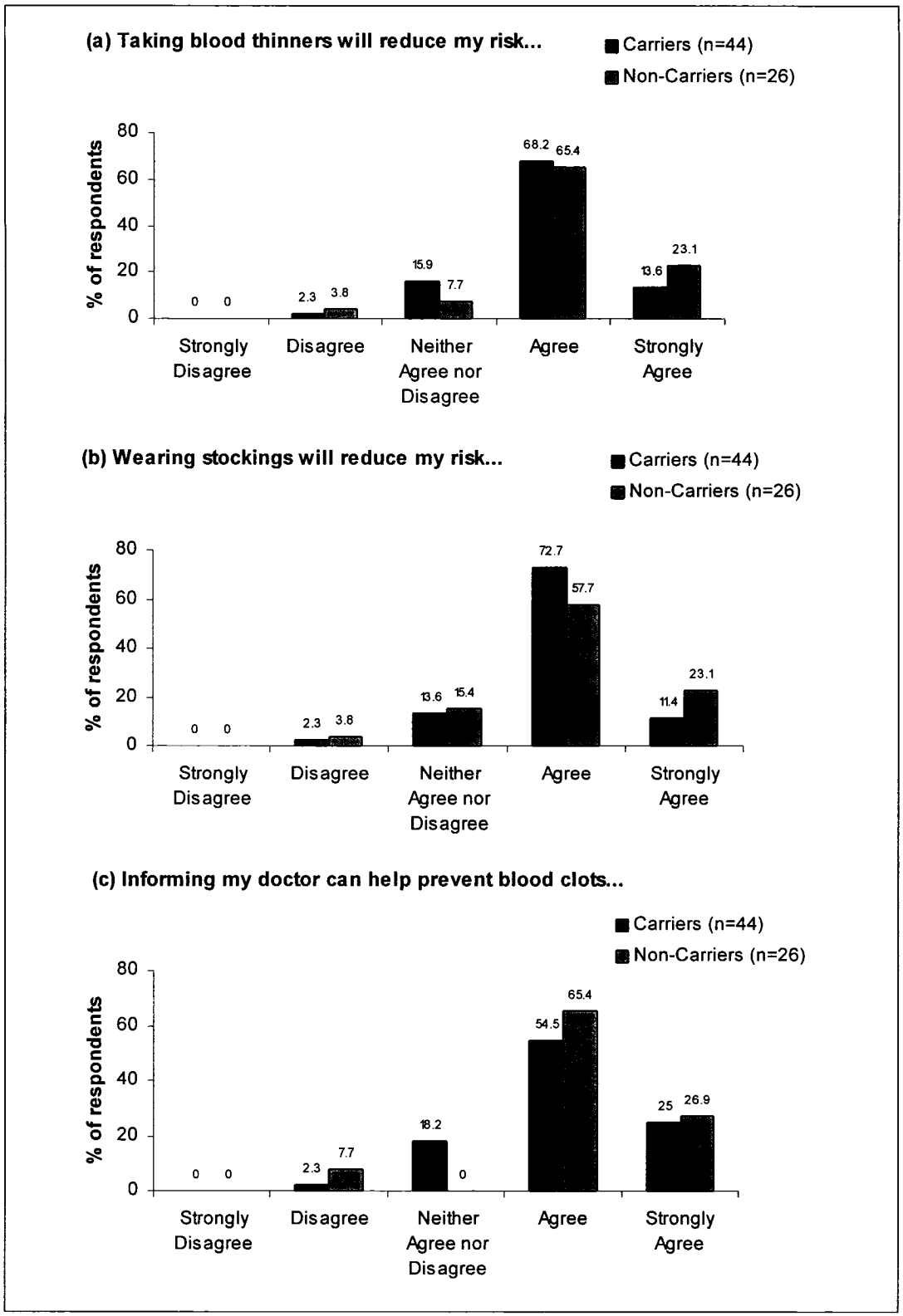

(a) Taking blood thinners will reduce my risk...
Carriers (n=44)
Non-Carriers (n=26)
% of respondents
80
60
40
20
0
0 0
2.3 3.8
15.9 7.7
68.2 65.4
13.6 23.1
Strongly Disagree
Disagree
Neither Agree nor Disagree
Agree
Strongly Agree
(b) Wearing stockings will reduce my risk...
Carriers (n=44)
Non-Carriers (n=26)
% of respondents
80
60
40
20
0
0 0
2.3 3.8
13.6 15.4
72.7 57.7
11.4 23.1
Strongly Disagree
Disagree
Neither Agree nor Disagree
Agree
Strongly Agree
(c) Informing my doctor can help prevent blood clots...
Carriers (n=44)
Non-Carriers (n=26)
% of respondents
80
60
40
20
0
0 0
2.3 7.7
18.2 0
54.5 65.4
25 26.9
Strongly Disagree
Disagree
Neither Agree nor Disagree
Agree
Strongly Agree

Figure 14 (a-c)

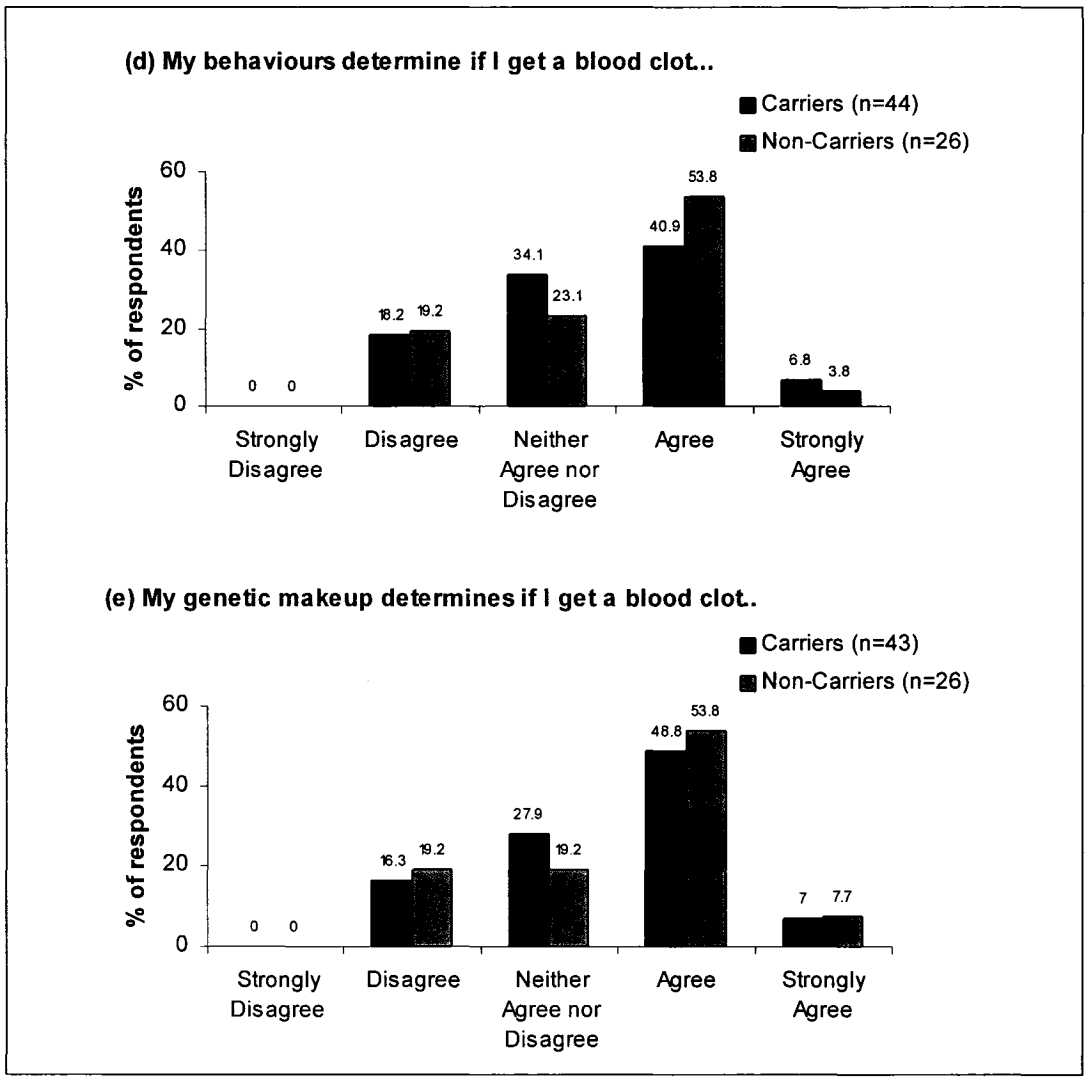


Figure 14: Carrier and non-carrier responses to various questions regarding overall control over developing a blood clot. Carriers vs. Non-carriers: (a) p=0.353 (b) p=0.481 (c) p=0.140 (d) p=0.420 (e) p=0.641 (strongly disagree/disagree/neither agree nor disagree v agree/strongly agree).

Table 26: Carrier and non-carrier experiences with health professionals since receiving their genetic test result.

	Yes	No	Don't know	p-value[a]
Have a family doctor				
Carriers	43 (97.7)	1 (2.3)	-	0.597[F]
Non-Carriers	24 (96.0)	1 (4.5)	-	
Visited doctor more often since test				
Carriers	2 (4.9)	39 (95.1)	0	0.709[F]
Non-Carriers	1 (4.3)	22 (95.7)	0	
Discussed test result with doctor				
Carriers	32 (78.0)	9 (22.0)	0	0.013
Non-Carriers	11 (47.8)	12 (52.2)	0	
Doctor understands test result				
Carriers	26 (81.3)	3 (9.4)	3 (9.4)	0.463
Non-Carriers[b]	10 (83.3)	0	2 (16.7)	
Doctor gave advice about risk				
Carriers	18 (56.3)	12 (37.5)	2 (6.3)	0.157
Non-Carriers[b]	3 (25.0)	7 (58.3)	2 (16.7)	

[a] χ^2 test, Fisher's exact test[(F)], carriers v non-carriers.

[b] 11 non-carriers reported discussing their test results with a doctor, but 12 reported answered subsequent questions about interactions with a doctor

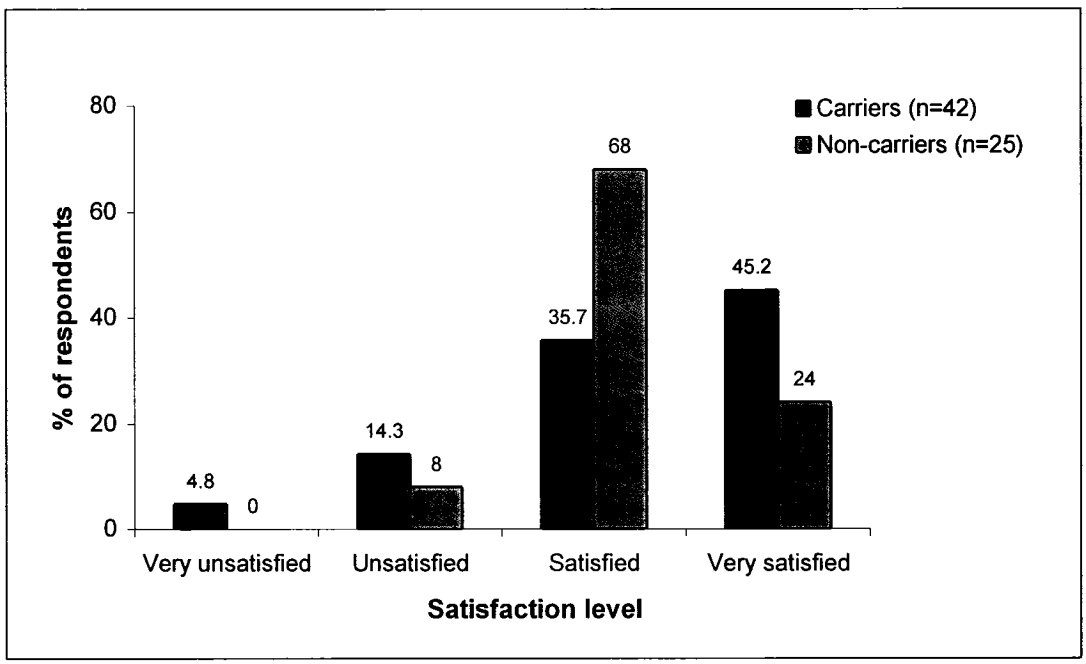


Figure 15: Cross-sectional survey responses to the question 'Overall, how satisfied are you with the amount of information you have received from any health professional about thrombophilia and your risk of developing a blood clot?' Carriers v Non-Carriers: p=0.194 (very unsatisfied/unsatisfied v satisfied/very satisfied).

Associations between cognitive, affective, behavioural & sociodemographic variables

Analyses were conducted to determine if there were any associations between the cognitive outcomes (perceived risk, perceived causes, perceived seriousness, perceived control), affective outcomes (TMD score, concern/worry about chances of getting a blood clot), behavioural outcomes (i.e. 'changed at least one behaviour') and sociodemographic variables (age, gender, education, income, and relationship to proband).

Perceived risk relative to the general population was related to concern about one's chances of developing a blood clot at 1 week and 12 months. Those who perceived their risk as being higher were more likely than those who perceived their risk as being the same or lower than most people to report being somewhat, moderately or very concerned as opposed to being not at all concerned (1 week: 81.8% v 34.5%, $p<0.001$; 12 months: 86.4% v 36.4%, $p=0.001$). Perceived risk was not significantly associated with TMD scores.

Perceived risk relative to the general population and concern about one's chances of developing a blood clot appear to be inversely related to age. Those less than 40 years of age were most likely to perceive their risk as higher than the general population and those 60 years and older were least likely to do so. This difference was only significant at baseline, but the trend was also apparent at 1 week and 12 months (Baseline: $p=0.033$; 1 week: $p=0.304$; 12 months: $p=0.386$). Those less than 40 years of age were most likely to report higher levels of concern and those 60 years and older were least likely to do so. While this difference was only statistically significant at 12 months, the trend was present from baseline onwards (Baseline: $p=0.165$; 1 week: $p=0.525$; 12 months: $p=0.009$).

Concern about one's chances of developing a blood clot appears to be related to gender, as females were more likely to report being somewhat/moderately/very concerned about their chances of getting a clot as compared to males. This difference was significant at 1 week and 12 months, but the trend was also present at baseline (Baseline: p=0.061; 1 week: p=0.034; 12 months: p=0.034). To examine whether the relationship between concern and gender was confounded by age, the association between age and gender was assessed and there was no significant association found between these variables (p=0.554). TMD score also appears to be related to gender. While males were more likely than females to have scores over 40, they were also more likely to have scores between 0 and 20. Females were most likely to have scores between 21 and 40 (Baseline: p=0.022; 1 week: p=0.003; 12 months: p=0.816).

Cognitive variables measured in Part II of this study were not related to psychological variables measured in Part I. Perceived seriousness, perceived control and perceived accuracy of one's test result were not related to concern over developing a blood clot or to TMD score.

Trying to change at least one behaviour appears to be related to gender, as 76.7% of females and 53.8% of males reported trying to make at least one change (p=0.048). It also appears that the children of a proband were less likely than parents or siblings to have tried to make at least one change since their genetic test, as 42.3% of children, 76.9% of parents and 86.2% of siblings tried to make at least one change (p=0.002). There was no apparent relationship between behaviour change and education, income or age.

There appears to be some association between behaviour change and perceived risk. Behaviour change was only measured at one timepoint (during the cross-sectional survey),

yet the associations between perceived risk at 1 week and 12 months were also assessed. There were no significant associations between comparative or absolute risk measured at 1 week and subsequent behaviour change. However, at 12 months, those who reported that their risk was higher than most people were more likely than those reporting their risk was the same or lower than most people to subsequently report at least one behaviour change (83.3% v 38.9%, p=0.006). While those reporting a perceived absolute risk between 1 in 10 and 1 in 500 were slightly more likely than those reporting a risk between 1 in 1000 and 1 in 5000 to report changing their behaviour, this association was not significant (66.7% v 54.5%, p=0.461). While the associations between behaviour change and perceived risk measured at the time of the cross-sectional survey show similar trends to those at 12 months, these associations were not significant (comparative risk: 73.3% v 56.0%, p=0.139; absolute risk: 78.8% v 57.1%, p=0.057). There were no significant associations between changing any behaviour and perceived seriousness or perceived control (i.e. feeling that there was a lot they could do to control whether or not they got a blood clot). There were also no associations between causal beliefs and behaviour change, such that those who agreed/strongly agreed that a factor increased one's risk of developing a blood clot were not more likely to report trying to change the corresponding behaviour.

There appears to be an association between VTE concern and behaviour change. Those who were somewhat concerned at 12 months were more likely than those who were not at all concerned to have tried to change at least one behaviour post-test (76.2% v 37.5%, p=0.018). A similar trend exists with respect to 1-week concern data (71.1% v 47.4%, p=0.081). While stratifying by mutation status suggests that this association may only be present for carriers,

the sample size was too small to confirm this. There were no significant associations between behaviour change and TMD scores.

There were no other statistically significant associations found, and even those significant relationships discussed above must be interpreted with caution due to the small sample sizes.

CHAPTER V

DISCUSSION

The current study provides information concerning the cognitive, psychological and behavioural impacts of genetic testing for thrombophilia among unaffected first-degree relatives of patients with VTE. The results presented here are meant to bring forth potential benefits and harms of genetic testing for this complex, multifactorial disorder, and to generate valuable knowledge in the consideration of the wider impacts of genetic testing on the individual and the health care system.

Before discussing the results of this study in detail, the methodological strengths and limitations must be outlined.

Strengths and Limitations

A major strength of this study is the broad range of outcomes collected from a single population. While the sample size was small, limiting the statistical power of this study, it was still able to provide a comprehensive picture of the multiple impacts of genetic testing for thrombophilia among unaffected individuals. Furthermore, this is the first known study to address this range of outcomes in the context of a multifactorial, complex disorder other than cancer.

A limitation of this study is that it was conducted within an ongoing randomized controlled trial assessing the effectiveness of two alternative models of care. Carriers of a thrombophilic mutation were randomized to either a novel care strategy or to standard care. This group assignment was not accounted for in any of the analyses presented here, as follow-up for this

trial is not complete and it was not the intent of this thesis to examine intervention effects. When interpreting the results presented here, one must consider the impact of not examining these effects. If this trial is a null trial, there will be no effect on the results of the current study. However, if there is a detectable difference between the two intervention groups with respect to the outcomes reported here, differences between carriers and non-carriers will change depending on whether the carriers are in the novel care or standard care group, and this difference would have to be controlled for.

It is also acknowledged that there is no control or comparison group representing first-degree relatives who have not received genetic testing. This limits conclusions regarding the actual impacts of genetic testing, and does not allow one to truly estimate the benefits and harms of testing versus not testing. Ideally, one would examine the impacts of genetic testing through a randomized trial that assigns subjects to either receive or not receive a genetic test. However, the purpose of the original pilot study, of which this thesis is only a part, was not to examine the impacts of genetic testing specifically, but to compare the two interventions as described above.

Another limitation is that the study population consisted of a self-selected and highly motivated group who were highly educated and mostly white. Furthermore, recruitment of relatives for Part I of this study was difficult, and baseline characteristics of non-respondents could often not be obtained for comparison purposes. There were instances in both parts of this study where non-response was due to low literacy levels (as communicated by the participants). Even after explanation and with assistance, some participants clearly did not understand the questions. Some suggest that disorder-specific distress is associated with interest in genetic testing and those who seek testing wish to obtain relief from uncertainty

and feel reassured. Thus, those presenting for testing may represent a psychologically vulnerable group.[116] On the other hand, Decruyenaere *et al.*[166] suggest that individuals with very high disorder-specific worry and low perceived control over the disease are not likely to attend genetics clinics or participate in research studies. The current study relied on volunteers and required multiple follow-up assessments, so selection bias is difficult to avoid. It is also difficult to ascertain the extent of this bias when the characteristics of non-respondents are not known. While the results presented here are likely representative of the population presenting for testing at specialized genetics clinics, they are not generalizable to all eligible relatives and not in the case where testing may be offered in other settings.

With respect to Part I of this study, analyses were limited by the fact that data were not available for several participants at one year post-test (either due to withdrawal from the study or because they were not due for follow-up at the time of analyses). Ideally, all analyses would be conducted when follow-up was complete, but the time constraints associated with this thesis did not allow for this. While not significantly different, those completing the POMS-SF at 12 months had slightly lower scores at baseline than those not completing 12-month follow-up. Also, for both measures of perceived risk in Part I, those completing 12-month follow-up had lower estimates of risk at baseline than non-respondents. Therefore, 12-month estimates of general distress and perceived risk are likely underestimates compared to what would be expected with complete follow-up and no dropouts.

Another limitation of this study is the low response rate to the cross-sectional survey among non-carriers. This may be due to the fact that non-carriers have less interest in the results of the study and in furthering research in this area. They may also have felt that the questions

regarding risk factors for blood clots and behaviour change were not applicable to them, or they may have felt overburdened with an additional questionnaire.

Finally, limitations may exist with respect to the outcomes used in this study. The cross-sectional collection of self-reported behavioural data limits conclusions regarding behaviour change as a result of one's genetic test result. Without pre-test behavioural data, one cannot conclude that participants have actually made the reported changes. This outcome is also subject to recall bias and social desirability bias, as some may report trying to change behaviours they know they should change. Nevertheless, these limitations were acknowledged when designing the questionnaire, and the questions were meant to elicit preliminary estimates of how many carriers and non-carriers personally felt that they had tried to make changes since their test. This outcome was considered important in itself, regardless of whether they were successful in actually changing the behaviour.

Cross-Sectional Survey Issues

There were several issues that arose while analyzing the cross-sectional survey data. These issues are discussed here in the event that researchers using this survey in the future may want to incorporate the recommended changes.

Most people indicated that they 'may or may not get a blood clot in their lifetime' when asked, "What does your genetic test result mean?" In other studies, respondents also seemed to favour this response category, though it was worded differently ('my risk of developing ... is as high as my risk of not developing ...').[119-121] These responses indicate a level of uncertainty, rather than a specific probability, and it has been suggested that respondents are

more likely to choose this uncertain option than to be forced to indicate a specific answer.[120] This question is not very informative and could be left out in the future.

The two questions exploring general and personal control over health related factors might not have been interpreted as intended. Several respondents disagreed that some people could control a factor, but they agreed that they could personally control the same factor. The first question was meant to address whether the factor was seen as controllable in general, but some respondents seemed to indicate whether they thought the factor was controllable by some, relative to themselves (i.e. they may respond as indicated above if they think that some people cannot control the factor, but they are personally able to control it). These questions showed little variability and I would not recommend using them to assess control in future studies. An alternative, but related concept one could measure is self-efficacy. Michie *et al.*[167] have used this concept in their research, asking subjects to answer questions beginning with, 'I am confident in my ability to...'followed by a specific behaviour (e.g. eat a healthy diet).

The questions asking respondents whether they had tried to make changes 'specifically to reduce their risk of getting a blood clot' may have been too narrowly interpreted. Respondents rarely answered 'yes' to these questions. This may mean that the behaviour change was influenced by several factors, but not 'specifically' their genetic test result. More informative results may be obtained by giving the respondents three options: 'yes, completely', 'yes, partially' and 'no, not at all', in response to the question, "Have you done this to reduce your risk of a blood clot?"

Also, it would have been helpful to ask a few open-ended questions regarding whether participants felt that anything else increased one's risk of developing blood clots, or if they had made any other changes in their lives as a result of genetic testing for thrombophilia.

Finally, one question that was included in the survey was not reported in this thesis (#10). This question listed all of the potential risk factors and participants were to put a check beside each factor that they thought was important for their own risk of developing a blood clot. Several respondents clearly checked off all the factors that they believed increased one's risk in general. It would have been more informative to ask the participants to list the three most important factors that they felt would increase their own risk of getting a blood clot.

The Multiple Impacts of Genetic Testing

Many theoretical models emphasize the role of cognitive variables (e.g. perceived risk, perceived seriousness, perceived control) as important in adopting risk reducing behaviours or in experiencing distress.[119] For example, Leventhal's self-regulation model of illness representations suggests that health related behaviour is influenced by a person's cognitive and emotional representation of a health threat. These representations, in turn, generate behaviours aimed at resolving objective health problems and reducing distress associated with the health threat.[166] Similarly, the transactional model posits that there are two appraisals that determine coping and consequent anxiety: the cognitive representations of the threat (e.g. perceived seriousness, accuracy of the test result, distress about the disease in the family); and the appraisal of the availability of resources to manage the threatening situation (e.g. optimism, self-esteem).

While this study was not designed according to a particular model, they are useful for interpreting the cognitive, psychological, and behavioural impacts of genetic testing and in understanding the interactions between these. This is especially important in the context of multifactorial conditions with genetic, environmental, and particularly behavioural risk factors.

Cognitive Impacts

Five attributes of cognitive illness representation are discussed here in relation to VTE: perceived causes, perceived seriousness, perceived accuracy of the genetic test result, perceived risk and perceived controllability.

Perceived Causes

While it is expected that an individual's perceived causes of blood clots will be influenced by information provided during genetic counselling and by other health professionals, causal beliefs also develop from general information one receives from other sources and from experiences with affected family members.[166]

Perceived causes of VTE were consistent with information that was provided during genetic counselling, though some discrepancies did exist, reflecting individual causal beliefs. In general, specific risk factors were seen as more important in increasing one's risk of VTE than general health factors, which were seen as more important than irrelevant factors. While not viewed as being quite as important as specific factors, respondents often indicated a belief that general health factors were risk factors for VTE. Subjects likely feel that an overall healthy lifestyle will decrease one's risk of most health conditions, including VTE. Also, it is clear that subjects do not believe that their genetic makeup/family history is the

sole, or even dominant determinant of risk. It is also possible that the role of lifestyle factors is emphasized due to their controllable nature.

Since one's causal beliefs will have implications for perceived risk and preventive behaviour, one must determine why some individuals maintain beliefs that differ from the medical model of the disease, even after consultation. This is important because for those subjects, particularly carriers, who disagree or are unsure that a 'specific' risk factor (e.g. prolonged immobility) increases risk, this will impact their behaviours and potentially their health in these situations. Similarly, those who believe 'irrelevant' measures increase one's risk may be taking unnecessary precautions.

Further research should also examine the distinction that some subjects make between the importance of having a family history of blood clots and of having a positive genetic test for thrombophilia. Respondents were more likely to agree that family history increases one's risk, rather than a positive genetic test result. This result may be due to a general lack of faith in the accuracy of the genetic test, or it may reflect the importance of personal family experiences with this disease and other lay representations of genes and inheritance. For example, one may believe that an individual closely resembling an affected relative is more likely to develop the disease, or that risk is associated with social closeness rather than genetic closeness.[166] This finding should be confirmed with larger samples and reasons should be elicited, possibly by means of a qualitative study.

Perceived seriousness

In this study, no significant differences in perceived seriousness of blood clots were found between carriers and non-carriers at post-test. Non-carriers were more likely than carriers to

report that blood clots would be extremely serious for their health, though this difference was not significant. According to Leventhal's self-regulation model, the perceived severity of a health threat is important in adjusting to the threat itself. It is proposed that individuals handle the health threat and negative emotions by minimizing the problem in order to keep stress and anxiety at an acceptable level.[166] This has led some to hypothesize that a disease or health threat will be perceived as most serious by non-carriers due to 'threat minimization' among carriers.[84;120;121;166] In their study of genetic testing for FAP, Michie *et al.*[84] concluded that a 'defensive bias' among carriers allows them to perceive the condition as less serious than non-carriers, minimizing the health threat and regulating distress. However, similar to the current study, Claes *et al.*[120;121] found no significant differences in perceived seriousness of HBOC and HNPCC between carriers and non-carriers post-testing. They suggested that this was due to a high sense of controllability in terms of early detection and curability that buffered against negative emotions, such that threat minimization was not necessary.

FAP is an autosomal dominant condition with high penetrance, whereas HBOC, HNPCC and VTE are more complex with multiple risk factors and incomplete penetrance. While controllability was not assessed in relation to FAP, it would be expected that FAP is seen as less controllable and therefore threat minimization is still necessary.

There may be some indication of slight defensive bias with respect to the current study, as carriers were less likely to report that getting a blood clot would be extremely serious for their health; however, further research with a larger sample is required to confirm this.

Perceived accuracy of test result

While most carriers and non-carriers believed that their genetic test result was completely accurate, non-carriers were more likely than carriers to believe that their risk was only somewhat accurate. Michie *et al.*[84] also report a 'failure to reassure' among some non-carriers, and they report that this may be associated with high anxiety and may lead to unnecessary screening or preventive behaviours. Overall, the number of subjects reporting 'somewhat accurate' was too small to make these comparisons.

Similar to perceived seriousness, one might expect that those at high risk perceive their test result as less accurate in an effort to buffer against negative emotional effects. However, this idea has not been supported by previous studies that showed no differences between carriers and non-carriers.[84] This idea is also not supported by the current study, where non-carriers were slightly more likely than carriers to perceive their test as less accurate. Again, this may be due to a failure to reassure or a general lack of confidence in genetic testing.

Perceived risk

Perceived risk compared to the general population was consistent with information communicated during genetic counselling. At 1 week and 12 months post-test, most carriers felt that their risk was higher, and most non-carriers felt that their risk was the same as the general population. These results are also in line with previous work concerning HBOC and HNPCC, and similar to these studies, this difference post-test was mainly due to a decrease in perceived risk among non-carriers.[119;123;142;146]

Similar trends in absolute perceived risk estimates were not observed and these estimates did not differ between carriers and non-carriers and did not change significantly over time. While

carriers' responses seemed to shift toward higher estimates of risk at 1 week, this was not significantly different from baseline, and had returned to lower levels by 12 months. While the distribution of responses for non-carriers did not vary greatly during the 12-month follow-up, the proportion reporting a perceived risk of 1 in 5000 increased over time. Based on a population risk of 1 in 1000, these non-carriers underestimated their risk of VTE. However, non-carriers were equally likely to overestimate their risk of VTE as being between 1 in 10 and 1 in 500. Approximately half of the carriers underestimated their risk at follow-up, reporting their risk to be 1 in 1000 or 1 in 5000.

These results indicated that the respondents did not have a very good understanding of numerical risk estimates. Others have noted the difficulties that subjects have with absolute or numerical risk estimates, and suggested that qualitative descriptions of risk do not always correspond to self-reported numerical risk.[63] However, this general difficulty is compounded in this study by the fact that the response options given for estimates of risk (1 in 10, 1 in 100, 1 in 500, 1 in 1000 and 1 in 5000) do not directly correspond with the actual risk estimates given during the genetic counselling sessions. For example, the genetic counsellor involved in this study told individuals with FVL that their background risk is 1 in 1000, but that this increases 5-fold to approximately 1 in 200. They were also told that this represents a 'small' or 'mild' increase in risk, and that only 20-30% of people with FVL develop blood clots. Therefore, it is not surprising that participants had difficulty answering these questions and providing 'accurate' estimates of risk, given that the numerical figures they were given were not options. In the future, answers to perceived risk questions should reflect the information given during counselling sessions more closely.

While the concept of risk accuracy was alluded to above in relation to absolute risk, the problems with this question make it difficult to define what the accurate response is for carriers, so risk accuracy is discussed further only with respect to comparative risk. If one assumes that the accurate response for carriers is a 'little higher' than most people, then the percentage of carriers overestimating their risk increases over time. The percentage of carriers underestimating their risk decreases from baseline to 1 week, but then increases at further follow-up. So, while carriers are equally likely to over and underestimate their risk immediately following test disclosure, they appear more likely to underestimate their risk as time goes by. Aktan-Collan *et al.*[115] have also noted a tendency of carriers to underestimate their risk, and suggested that this may reflect protective coping mechanisms, such as denial. It is important to address and understand the underestimation of risk among carriers because denial may also impact adherence to important protective behaviours.

If one assumes that the accurate response for non-carriers is the 'same' as most people, then the percentage of non-carriers who overestimate their risk decreased dramatically from baseline to 1 week, and then increased slightly at further follow-up. The percentage of non-carriers who underestimated their risk increased over time. While non-carriers are equally likely to over and underestimate their risk at 1 week, they appear more likely to overestimate their risk as time goes by. Walter *et al.*[168] explain that family members develop a personal sense of vulnerability or risk that is informed by the salience of their family history and interpreted within their personal models of disease causation and inheritance. Therefore, one might expect that some non-carriers hold on to previous feelings of risk despite being told that they are at the same risk as the general population.

Overall, risk accuracy improved from pre- to post-disclosure for both carriers and non-carriers. Both groups were most accurate in their comparative risk perceptions at 1 week, where 71.9% of non-carriers and 73.9% of carriers correctly estimated their risk. Risk accuracy may decrease as time progresses, but this may be a reflection of incomplete follow-up.

Reviews by Meiser & Halliday[32] and Butow *et al.*[5] also report improvements in risk accuracy after genetic testing and counselling for carriers and non-carriers. However, there is conflicting evidence regarding differences between carriers and non-carriers and in the proportion of each who over versus underestimate their risk. While Butow *et al.*[5] conclude that 22-50% of women still overestimate their risk of breast cancer after genetic counselling and testing, Katapodi *et al.*[34] suggest that overall optimistic bias (underestimation of risk) exists among high-risk subjects. Furthermore, a study by Kelly *et al.*[127] found that risk accuracy only increased among carriers, while Aktan-Collan *et al.*[115] found that non-carriers were more accurate than carriers in their risk estimates, and that accuracy decreased for carriers from 1 to 12 months. It is difficult to compare the results of different studies with respect to risk accuracy, since this concept is defined in several different ways. Many studies compare numerical risk estimates with objective estimates (based on statistical models), and this will likely differ from the simplistic definition of accuracy used here that is based on verbal risk estimates.

While it is not clear whether subjects are more likely to over or underestimate their risk of VTE, nor is it clear whether risk accuracy differs between carriers and non-carriers, it is true that several carriers and non-carriers have inaccurate perceptions of risk at some point during follow-up. Further research is required to examine why some individuals have these

inaccurate perceptions. One must examine whether carriers who underestimate their risk do so as a protective mechanism or because of their perceived healthy lifestyle and avoidance of risks. Also, one must determine whether non-carriers who overestimate their risk do so because of personal experiences with affected relatives and/or a lack of reassurance gained from testing. There may be other factors that play a role in determining one's perception of risk, and qualitative interviews with carriers and non-carriers, particularly those with inaccurate risk perceptions, may be the best way to elicit these reasons.

Perceived control

In general, carriers and non-carriers had a high sense of control over developing VTE, feeling that there was a lot they could do to prevent a blood clot, though over 30% of respondents were unsure or disagreed that there was a lot they could do. There were no significant differences between carriers and non-carriers with respect to perceived control over VTE, similar to other studies that reported that there are no theoretical grounds to expect these differences.[120;121]

While most reported that one's genetic makeup, behaviours and medical interventions (e.g. blood thinners, stockings, informing their physician) all play a role in whether or not one develops a blood clot, there was some suggestion that subjects viewed medical interventions as slightly more important in reducing one's risk. This finding is consistent with results presented by Marteau *et al.*[78] When comparing subjects with a genetic and non-genetic diagnosis of FH, they found that mutation carriers believed less strongly in the efficacy of diet in reducing their cholesterol level and believed more strongly in the efficacy of cholesterol lowering medications. They suggest that when a risk is modifiable, as it is for FH

and VTE, learning of a genetic risk does not reduce perceptions of control (i.e. lead to fatalistic thinking), but rather influences how the control is most effectively achieved. They raise the concern that genetic testing will reinforce biologically or medically based ways of reducing risk when behavioural or environmental change is equally if not more effective. While there was not a dramatic difference between behavioural and medical factors in the current study, the potential for this shift in thinking should be acknowledged. Further research comparing perceived control among those tested and not tested for thrombophilia should be undertaken.

Respondents also reported a high sense of general and specific control over most of the risk factors presented. Changes in behaviour are largely determined by perceptions that the behaviour is personally controllable.[169] Of the general and specific factors, prolonged immobility, taking birth control pills, taking hormone replacement therapy, exercise, diet, smoking and being overweight were all seen as being personally controllable by most subjects. Injury was seen as less controllable. The lack of variability in the responses to these questions makes it difficult to assess associations with other variables.

While most respondents feel control over their chances of developing VTE and over the factors that may increase risk, a lack of perceived control among a subgroup of participants may act as a barrier to behaviour change, and should be further investigated. Future studies may want to use more common approaches for studying controllability. Both the locus of control belief and self-efficacy belief have been described as the most important measures of control.[166] While the assessment of locus of control (using the Multidimensional Health Locus of Control scale) was considered for use in the present study, the questions asked here seemed more relevant to control specifically over VTE. The two measures could be used

together to gain an understanding of both general and specific control, and to include a known and validated estimate. As previously mentioned, using the concept of self-efficacy may also provide a more reliable and comparable estimate of control regarding specific health factors. These measures may help to more closely tease out the differences between subjects and to determine the impacts on behaviour. For example, Claes *et al.*[121] describe how people may feel responsible for their own health (internal locus of control), but feel incapable of performing the required activities (low self-efficacy), or the disease can be considered under the control of medical science (external locus of control), but people may have doubts about the efficacy of medical science.

Psychological Impacts

Similar to other studies of genetic testing for HBOC and HNPCC susceptibility, general psychological distress did not differ between carriers and non-carriers in the 12 months post-test and median scores did not reach clinical significance.[119-121;140;142] While there was a slight, non-significant increase in distress from baseline to 1 week for both carriers and non-carriers, scores at 12 months were slightly lower than both earlier scores, though this difference was also not significant. For participants completing all three assessments, there was no significant change in scores over the 12-month period for either carriers or non-carriers, consistent with the general finding that general distress scores do not change significantly following genetic testing.[4;32;119-121;140;142] Claes *et al.*[119] suggest that a self-selected group will come forward for testing, namely those with a high perceived ability to cope with their genetic test result, which can explain relatively low distress levels overall. They also suggest that general distress measures mainly focus on detecting clinical disorder

or psychopathology and may not be sensitive enough to capture negative emotional reactions in a 'non-clinical' population.

While mean general distress levels did not change, a closer examination of individual level data revealed that a small subgroup of carriers experienced large increases in distress at 12 months. Furthermore, those carriers who had high scores at 12 months varied in their scores at baseline and no significant correlation existed between baseline and 12-month scores. This finding contradicts the previous evidence of 'tracking' reported in several reviews and studies, where high post-test distress is predicted by high pre-test distress.[3;131;132;140;143;170] While tracking is apparent for the combined sample of carriers and non-carriers at 1 week and 12 months, pre- and post-test scores were not related for the subgroup of carriers at 12 months. One must interpret these results with caution due to the small number of carriers with baseline and 12 months scores (n=23), and the issue should be further investigated. If this is a real effect and it is a result of genetic testing, more comprehensive psychological counselling offered to those with high distress at baseline may not be as effective as expected.

This study provides no evidence that genetic testing for thrombophilia leads to somatization among tested individuals. Subjects had very low scores at all assessment timepoints, and there were no significant differences between carriers or non-carriers. While no other study was found that specifically examines this outcome as the result of genetic testing, other studies have used the full Symptom Checklist (SCL-90-R) to assess general distress, also finding that scores were lower or within normal range and that these scores did not change over time or differ between carriers and non-carriers.[120;121]

While concern over one's chances of developing a blood clot was significantly higher among carriers versus non-carriers at 1 week post-test, this difference was not significant at 12 months. The short-term difference was mainly due to a decrease in concern among non-carriers, and this difference was not apparent at 12 months due to a decrease in concern among carriers from 1 week to 12 months. When asked how often they worried about their chances of developing a blood clot, there were no significant differences between carriers and non-carriers at any time during follow-up, and most indicated that they were rarely or never worried. Furthermore, most carriers and non-carriers reported that worries about blood clots did not affect the way they felt from day to day at all. So, it appears that participants respond differently to questions regarding concern about one's chances of developing a blood clot and the extent and impact of worries about getting a blood clot. While carriers were somewhat to very concerned about their chances, this did not appear to be causing a significant degree of worry.

It is difficult to interpret measures of concern or worry, as the clinical significance of different levels of these variables remains unknown and normative data are not available. It is also difficult to compare results to studies of other disorders since different measures were used (e.g. Impact of Events Scale; Cancer Worry Scale). Nonetheless, in comparing concern about one's chances of getting a blood clot to reports of cancer worry or disorder-specific distress, there are some similarities. Some studies also noted a decrease in these measures among non-carriers post-test,[123;131;132;134;135;142] while others reported that carriers and non-carriers differed immediately post-test, but that these differences were not present at later follow-up assessments.[114;135]

Similar to general distress, a small subgroup of participants report higher levels of concern, worry and impact on their daily life. Carriers were slightly more likely than non-carriers to report these outcomes, particularly immediately following testing. A substantial proportion of carriers were not at all concerned about their chances of developing a blood clot. Future research should examine whether this lack of concern has implications for preventive behaviour. Also, non-carriers who reported being moderately or very concerned about their chances of getting a blood clot may be a target for further education and counselling.

It is difficult to draw meaningful conclusions regarding the associations between cognitive, psychological and sociodemographic variables due to the small sample size. Similar to the results reported by Rees *et al.*[96] in their study of illness perceptions and distress among women at increased risk of breast cancer, risk perception was found to be the only significant predictive cognitive variable. Higher perceptions of risk were associated with higher levels of concern about one's chances of developing a blood clot. Age likely confounds the relationship between perceived risk and concern, as younger participants (<40 years) were more likely than older participants to have higher risk estimates and to report higher levels of concern. While one's objective risk of VTE increases with age, those over 60 years old were least likely to have an elevated risk estimate and to have high levels of concern. It is possible that being faced with a potentially serious and fatal condition has a greater impact on someone who is younger, has a family, etc. Also, older participants may feel that they have lived the majority of their lives without developing symptoms, possibly remaining asymptomatic through high-risk periods, and are likely to remain unaffected.

Behavioural Impacts

Genetic testing for thrombophilia will only be helpful to at-risk relatives if the risk information has psychological benefits or if it is translated into effective preventive behaviours or treatments.[171] Ideally, carriers will receive better clinical management and adopt risk-reducing behaviours, particularly at times of high risk, and non-carriers will avoid unnecessary treatment, both for the sake of the individual and to avoid unnecessary costs to the health care system.[86]

Genetic testing for thrombophilia has different implications than testing for hereditary cancers. While a genetic predisposition to hereditary cancers requires enhanced surveillance and possibly prophylactic surgery, carriers of a thrombophilic mutation must be aware of the high-risk situations that may induce clotting (e.g. surgery, trauma, immobility, pregnancy/post-partum) and take the appropriate precautions (e.g. discussing their test result with their physician for optimal management, taking blood thinners or wearing compression stockings as directed, taking frequent breaks while traveling or limiting immobility). Behaviour change within this high-risk context is difficult to measure, particularly within a short timeframe.

While there is an indication that some subjects tried to reduce their risk while in high-risk situations, there were too few of these risk periods reported to draw meaningful conclusions. The most commonly reported high-risk situation was prolonged immobility due to a long trip. Carriers were no more likely than non-carriers to perform wear compression stockings during a long trip, suggesting that test result was not as important as other factors in prompting this behaviour. While half of the carriers who had surgery since their genetic test

had been prescribed blood thinners before or after surgery, this is not necessarily a result of their genetic status. It is standard procedure to prescribe prophylactic anticoagulation for patients undergoing surgery, and it would have been more relevant to ask whether prophylactic treatment was altered in response to their high risk status (though patients would be less likely to know this). Only one carrier had been pregnant since testing had been prescribed blood thinners before or after giving birth. Again, one cannot conclude that this was due to her test status. While only a few participants were taking birth control pills or HRT at baseline, there is some evidence that test status influenced decisions to stop taking these medications or to help them to decide not to take them.

Most often, people reported personal behaviours in response to high-risk situations (e.g. discussing their genetic test with their physician, getting back on their feet as soon as possible after injury or surgery, walking around and taking frequent breaks during long trips). Carriers were also more likely than non-carriers to avoid long trips post-test. This may be because these behaviours were more personally controllable and did not place great demands on the individual.

There were no differences between carriers and non-carriers with respect to trying to change any general health behaviours. While nearly 40% of respondents reported trying to change one of these factors, most did not report trying to change specifically to reduce their risk of getting a blood clot (though this may be due to limitations of these questions, as described above). Consistent with their causal beliefs, all participants were least likely to report trying to change 'irrelevant' health behaviours, and the majority of those who did, did not change specifically to reduce their risk of getting a blood clot.

While a large percentage of carriers and non-carriers reported trying to change at least one behaviour since their genetic test, most did not report doing so specifically to reduce their risk of getting a blood clot. Carriers appeared more likely than non-carriers to try to make at least one behaviour change since their genetic test, but this difference was not statistically significant. It is not known whether genetic testing influenced these behaviours, or whether subjects who knew they were at higher than average risk due to a family history of blood clots would have behaved the same if they had not been tested.

It is logical to think that one's causal beliefs are related to health behaviours. That is, one is expected to change their behaviours only when they believe that a certain factor increases their risk of VTE and the corresponding behaviour will be effective in reducing their risk. However, the results of this study suggest that those who agree that particular health factors increase one's risk of getting a blood clot do not differ from those who are unsure or disagree with respect to trying to change the corresponding behaviour (e.g. those who believe that exercise increases one's risk of VTE are not more likely to report trying to exercise more than those who do not believe it increases risk). A likely explanation for these findings is that most reported behaviours included in these analyses were 'general' or 'irrelevant' factors, since these associations could not be determined with respect to 'specific' factors (due to the small number of subjects reporting high risk situations). Therefore, it could be expected that even those who did not agree that a factor increased one's risk for a blood clot, they had tried to make changes with respect to the corresponding behaviour in response to more general health beliefs. However, it has also been noted that the influence of causal beliefs seems to depend on intermediating cognitive variables, including perceived risk and perceived controllability of the disease.[166]

While there was no association between perceived control and behaviour change, those who had higher risk perceptions were more likely to have tried to change their behaviour than those with lower risk estimates. It has been suggested that studying the relationship between risk perception and health behaviour raises major methodological problems because people who have a particular behaviour interpret their risk according to that behaviour (e.g. people may think they have lower risk because they take preventive measures).[172;173] Gerrard *et al.*[173] suggest that cross-sectional studies of the relation between perceived risk and preventive behaviour are based on the incorrect assumption that feelings of vulnerability motivate individuals to engage in preventive behaviour. They suggest that an individual reporting a preventive behaviour post-test will have lowered perceived risk resulting in a negative correlation between behaviour and perceived risk. However, examining the relationships between perceived risk and behaviour in this study, the opposite was true. As time progressed, a positive relationship developed. At 1 week, those with high perceived risk were no more likely to report subsequent behaviour change, whereas at 12 months and at the time of the cross-sectional survey, those with high perceived risk were more likely to report changing at least one behaviour. There may be several reasons for this finding, including: subjects continued to report risk based on counselling estimates without incorporating the effects of any change in behaviour; subjects did not make changes in their behaviours specifically to reduce their risk of a blood clot, so their behaviours were not seen to reduce their risk; and/or, behaviours associated with high-risk periods were underrepresented in these analyses due to a small number of these situations reported by participants.

Since behaviours that are relevant to thrombophilia are risk reducing actions, rather than disease detecting, they are expected to be facilitated by some degree of distress because of

their potential for risk reduction and control, and thus anxiety reduction.[166] While behaviour change was not significantly associated with general distress, it does appear to be associated with VTE concern. Those who were somewhat concerned at 12 months were more likely than those who were not at all concerned to have tried to change at least one behaviour post-test. Lerman *et al.*[174] also found that disorder-specific distress was more associated with health behaviour than general distress. While some suggest that moderate levels of anxiety are optimal for adherence to screening behaviours,[175;176] others suggest that adherence increases with higher levels of worry.[177] Still others have found that general or disorder-specific distress do not influence adherence at all among carriers.[118] This inconsistency between studies was also reported by Decruyenaere *et al.*[166] who described possible causes for discrepancies as differences in sample characteristics, the conceptualization or measurement of distress, or in the type of behaviour assessed (i.e. risk reducing or disease detecting).

With respect to interactions with health care professionals, neither carriers nor non-carriers reported visiting their family physicians more often since their genetic test. However, carriers did report discussing their genetic test result with this physician and receiving advice about reducing their risk more often than non-carriers. While there is some suggestion that adopting certain lifestyle behaviours will reduce one's risk of getting a blood clot, there is no clear evidence linking these behaviours with risk reduction. Important behaviours involve one's interaction with the health care system (i.e. informing physicians of their test status, wearing stockings, getting back on feet after injury or surgery as soon as possible, taking precautions while pregnant). These behaviours depend not only on the patient themselves, but also on their attending physician, implying that inadequate knowledge on the part of physicians will

limit the overall goals of genetic testing and risk assessment for VTE. The current study only touched the surface of these interactions with health professionals, and more substantive research is necessary. Future research should focus on these interactions from the perspective of both the patient and the physician, and seek to understand how one's genetic test result affects their use of health services and influences their clinical management. Even if genetic testing for thrombophilia is neutral with respect to psychological consequences, it might incur unnecessary use of health services, thus creating unnecessary costs for the health care system.

Conclusions & Implications

Of those individuals who carry predisposing mutations, many will never become affected, but they may suffer the consequences of knowing that they carry a mutation. Col *et al.*[178] state that given the competing demands for limited health care resources, decisions to test for genetic susceptibility to common diseases takes on heightened importance. They suggest that the availability of genetic tests appears to be more driven by technical feasibility and commercial potential than by evidence-based medicine, and that tests have often proceeded into clinical practice with little understanding of the broader implications.[178]

The results of this study suggest that neither carriers nor non-carriers experience significant harms as a result of genetic testing for thrombophilia, while non-carriers tend to experience a decrease in perceived risk and VTE concern. There is no conclusive evidence concerning impacts on behaviour change, and while several carriers and non-carriers report trying to change their behaviours since genetic testing, few report doing this specifically to reduce their risk of VTE.

Some believe that the success of genomic medicine will depend largely on finding effective ways of communicating genetic risk in order to induce desirable behaviour change.[179] In the case of thrombophilia and one's risk of VTE, many important behaviour changes must occur in the context of high-risk situations. This will often require an awareness and understanding on the part of both the patient and their physician. There are several 'risk-reducing' behaviours that individuals can perform in high-risk situations and as general precautions (i.e. wearing stockings, losing weight). However, the evidence that these behaviours reduce one's risk of VTE is not indisputable. Since these behaviours generally do not carry significant risks, yet provide overall health benefits, one might suggest that all relatives adopt these behaviours regardless of genetic test status. It is the use of prophylactic anticoagulation that causes some to believe in the added benefits of knowing one's mutation status. Since this behaviour carries risks of bleeding, it is thought that the identification of carriers can lead to targeted prophylaxis among carriers, and non-carriers will not have to accept this unnecessary risk. However, the clinical evidence for the effectiveness of prophylactic measures among asymptomatic relatives is not strong. Sanson *et al.*,[30] Simioni *et al.*[28] and Tormene *et al.*[180] indicate that it is theoretically warranted to identify asymptomatic carriers of thrombophilic mutations who might benefit from anticoagulant prophylaxis during high-risk periods, though there is no evidence that this information will offer a real advantage in the prevention of VTE. Sanson *et al.*[30] also note that it remains unknown whether higher dosages of anticoagulation are necessary during high-risk periods, whether the prophylaxis should be continued for a longer period of time, or whether there should be a lower threshold for the administration of anticoagulant prophylaxis in comparison to patients without a mutation. Middeldorp *et al.*[27] do not advocate for testing relatives for the purpose of targeted

anticoagulant treatment, except possibly among pregnant women to allow consideration of postpartum prophylaxis.

The uncertainties surrounding the clinical management of asymptomatic first-degree relatives must be addressed in order to realize potential benefits with respect to morbidity and mortality. This exploratory study suggests no major psychological harm arising from genetic testing, but its findings need replication with larger samples. It is also necessary to determine whether the benefits of genetic testing, in terms of emotional relief for non-carriers and more effective clinical intervention for carriers, justifies the direct and opportunity costs of routine testing for inherited thrombophilia.

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APPENDICES

Appendix 1 – Systematic Review Search Strategy

MEDLINE/ CENTRAL	EMBASE	CINAHL	PSYCINFO	AUTHORS*
1. genetic diseases, Inborn/	1. exp human genetics/	1. Genetics, Medical/	1. genetic counseling/	1. bleiker e.au.
2. genetics, medical/	2. genetic disorder/	2. Hereditary Diseases/	2. Genetic Disorders/	2. braithwaite d.au.
3. genetic screening/	3. exp genetic service/	3. Genetic Screening/	3. Genetic Testing/	3. broadstock m.au.
4. exp Genetic Services/	4. genetic analysis/	4. Genetic Counseling/	4. genetic disorder$.tw.	4. brodersen nh.au.
5. genetic disorder$.tw.	5. genetic disorder$.tw.	5. genetic disorder$.tw.	5. genetic test$.tw.	5. butow pn.au.
6. genetic test$.tw.	6. genetic test$.tw.	6. genetic test$.tw.	6. genetic screen$.tw.	6. claes e.au.
7. genetic screen$.tw.	7. genetic screen$.tw.	7. genetic screen$.tw.	7. genetic risk$.tw.	7. codori am.au.
8. genetic risk$.tw.	8. genetic risk$.tw.	8. genetic risk$.tw.	8. genetic counsel$.tw.	8. collins v.au.
9. genetic counsel$.tw.	9. genetic counsel$.tw.	9. genetic counsel$.tw.	9. PSYCHOLOGY/	9. croyle rt.au.
10. psychology/	10. psychology/	10. PSYCHOLOGY/	10. DISTRESS/	10. davey a.au.
11. adaptation, psychological/	11. mental stress/	11. ANXIETY/	11. ANXIETY/	11. decruyenaere m.au.
12. stress, psychological/	12. anxiety/	12. DEPRESSION/	12. "DEPRESSION (EMOTION)"/ or MAJOR DEPRESSION/	12. denayer l.au.
13. anxiety/	13. depression/	13. Somatoform Disorders/	13. SOMATIZATION/	13. emery j.au.
14. depression/	14. somatization/	14. "Psychosocial Aspects of Illness"/	14. anxiety.tw.	14. emmons km.au.
15. somatization/	15. anxiety.tw.	15. anxiety.tw.	15. depression.tw.	15. esplen mj.au.
16. anxiety.tw.	16. depression.tw.	16. depression.tw.	16. psychologic$ distress.tw.	16. evers-kiebooms g.au.
17. depression.tw.	17. psychologic$ distress.tw.	17. psychologic$ distress.tw.	17. somatiz$.tw.	17. gurmankin ad.au.
18. psychologic$ distress.tw.	18. risk management/	18. somatiz$.tw.	18. Risk Management/	18. halliday j.au.
19. somatiz$.tw.	19. risk reduction/	19. Risk Management/	19. Health Behavior/	19. hopwood p.au.
20. Risk Management/	20. health behavior/	20. Health Behavior/	20. Coping Behavior/	20. julian-reynier c.au.
21. Risk Reduction Behavior/	21. coping behavior/	21. Behavioral Changes/	21. Risk Perception/	21. katapodi mc.au.
22. Health Behavior/	22. health behavio$.tw.	22. Adaptation, Psychological/	22. health behavio$.tw.	22. kristeller jl.au.
23. health behavio$.tw.	23. perceived risk$.tw.	23. health behavio$.tw.	23. perceived risk$.tw.	23. lerman c.au.
24. perceived risk$.tw.	24. perceived control$.tw.	24. perceived risk$.tw.	24. perceived control$.tw.	24. lemon sc.au.
25. perceived control$.tw.	25. fatalis$.tw.	25. perceived control$.tw.	25. fatalis$.tw.	25. lobb ea.au.
26. fatalis$.tw.	26. adult/	26. fatalis$.tw.	26. or/1-8	26. marteau tm.au.
27. adult/	27. or/1-9	27. ADULT/	27. or/9-17	27. meiser b.au.
28. or/1-9	28. or/10-17	28. or/1-9	28. or/18-25	28. michie s.au.
29. or/10-19	29. or/18-25	29. or/10-18	29. 26 and 27	29. rees g.au.
30. or/20-26	30. 27 and 28	30. or/19-26	30. limit 29 to yr="1999 - 2006"	30. senior v.au.
31. 28 and 29	31. limit 30 to yr="1999 - 2006"	31. 28 and 29	31. limit 30 to human	31. sutton s.au.
32. limit 31 to yr="1999 - 2005"	32. limit 31 to human	32. limit 31 to yr="1999 - 2005"	32. 26 and 28	32. vadaparampil st.au.
33. limit 32 to humans	33. 32 and 26	33. 32 and 27	33. limit 32 to yr="1999 - 2006"	33. van maarle mc.au.
34. 33 and 27	34. 27 and 29	34. 28 and 30	34. limit 33 to human	34. walter f.au.
35. 28 and 30	35. limit 34 to yr="1999 - 2006"	35. limit 34 to yr="1999 - 2005"	35. 31 or 34	35. watson m.au.
36. limit 35 to yr="1999 - 2005"	36. limit 35 to human	36. 35 and 27	36. prenatal diagnosis/	36. weinman j.au.
37. limit 36 to humans	37. 36 and 26	37. 33 or 36	37. 35 not 36	37. weinstein nd.au.
38. 37 and 27	38. 33 or 37			38. zapka jg.au.
39. 34 or 38	39. prenatal diagnosis/			39. or/1-38
40. prenatal diagnosis/	40. 38 not 39			40. limit 39 to yr="1999 - 2005"
41. 39 not 40				41. remove duplicates from 40
Total retrieved: 316/19	407	68	251	

Appendix 2 – Systematic Review Data Abstraction Forms

DATA ABSTRACTION FORM 1: Study and Population Characteristics

Author Year	Source of Funding	Study Design	Recruitment	Setting	Condition	Comparison groups	Inclusion/ Exclusion Criteria	Description of counselling	Data Collection Methods	Sample	Participant characteristics
				Location/ Country:						-# approached: -response rate: -# carriers: -# non-carriers:	-Mean age: -% female: -% > high school:

DATA ABSTRACTION FORM 2 – Outcomes

Study ID	Cognitive Outcome Measure(s)	Affective Outcome Measure(s)	Behavioural Outcome Measures	Assessment time-points

DATA ABSTRACTION FORM 3 – Results

Study ID	Main Results	General Conclusions

Appendix 3 – Excluded Studies from Systematic Review

Author (year)	Reason for exclusion
Bish *et al.* (2002)	Affected only
Brain *et al.* (2000)	No genetic test
Brain *et al.* (2002)	No genetic test; impact of genetic counseling
Brain *et al.* (2005)	Carriers and non-carriers combined data
Brandberg *et al.* (2004)	No pre-test data; does not assess impacts of genetic testing
Broadstock et al. (2000)	No genetic test among unaffected relatives; psychological consequences of waiting for results of mutation search of probands
Codori *et al.* (2005)	No genetic test; impact of genetic counseling
Dagan & Gil (2004)	No pre-test data; retrospective design
Daly *et al.* (2003)	Qualitative; no relevant outcomes
Delatycki *et al.* (2005)	Affected and unaffected results combined; assesses impact of population screening program (not predictive genetic testing)
Di Prospero *et al.* (2001)	Affected and unaffected results combined; Very small unaffected sample size (n=6)
DiCastro *et al.* (2002)	No pre-test data; Retrospective design; no pre-test data
Dorval *et al.* (2000)	No pre-test data: Compares anticipated emotional reactions to actual
Esplen *et al.* (2000)	No genetic test; impact of genetic counseling
Esplen *et al.* (2001)	No pre-test data; retrospective self reports; cross sectional design
Fang *et al.* (2003)	No genetic test
Franco *et al.* (2000)	No genetic test
Fries *et al.* (2004)	Affected and unaffected results combined; Only 2 unaffected subjects were tested
Fry *et al.* (2003)	No genetic test
Geirdal *et al.* (2005)	No genetic test; cross-sectional design
Gurmankin *et al.* (2005)	No genetic test; impact of genetic counseling
Hagoel *et al.* (2003)	No pre-test data; Cross sectional design
Halbert *et al.* (2004)	Affected only
Halbert *et al.* (2005)	No genetic testing or counseling
Hendriks *et al.* (2005)	Full text could not be obtained; based on abstract study was deemed ineligible
Hicken (2002)	Assesses impact of fictitious disorder
Holloway *et al.* (2004)	No genetic test
Hopwood *et al.* (2003)	No genetic test
Hopwood *et al.* (2004)	No genetic test
Huiart *et al.* (2002)	No genetic test
Hurley *et al.* (2001)	No genetic test
Isaacs *et al.* (2002)	No post-test data
Kelly *et al.* (2003)	No post-test data
Kelly *et al.* (2004)	Assess intention to undergo genetic testing
LaRusse *et al.* (2005)	No pre-test data
Lesniak (2001)	Dissertation
Liden *et al.* (2003)	No genetic test; only 2 received genetic test results
Liljegren *et al.* (2004)	No post-test data; mandatory surveillance program for participants
Loader *et al.* (2004)	Carriers and non-carriers combined data
Lobb *et al.* (2004)	No genetic test
Lobb *et al.* (2005)	No genetic test
Manne *et al.* (2004)	Affected and unaffected results combined
Marteau *et al.* (2004)	Affected and unaffected results combined
Marteau *et al.* (2005)	No pre-test data
Matthews (2002)	No pre-test data; Not directly looking at impact of genetic testing
McInerney-Leo *et al.* (2004)	Affected and unaffected results combined
Meiser *et al.* (2001)	No genetic test; impact of genetic counseling
Michie *et al.* (2001)	No pre-test data
Michie *et al.* (2002a)	Cross-sectional design; expectations to attend screening, not actual behaviour
Michie *et al.* (2002b)	Cross-sectional design; expectations to attend screening, not actual behaviour
Michie *et al.* (2002c)	Cross-sectional design; expectations to attend screening, not actual behaviour
Miller *et al.* (2005)	Affected and unaffected results combined
Molinuevo *et al.* (2005)	Single gene disorders (single gene form of AD)
O'Neill (2004)	Dissertation

Author (year)	Reason for exclusion
Ozakinci (2005)	Dissertation
Palmer & Hadley (2005)	Same data as Hadley (2004); assesses different methods of analyses
Pieterse *et al.* (2005)	No genetic test; impact of genetic counseling
Plon *et al.* (2000)	No family history of cancer; community based screening
Power *et al.* (2001)	Affected and unaffected results combined
Prevost *et al.* (2004)	No pre-test data
Rees (2004)	No genetic test
Ritvo (2000)	No genetic test
Ritvo *et al.* (2002)	No genetic test
Rouleau *et al.* (2004)	Affected and unaffected results combined
Schwartz *et al.* (2003)	Affected and unaffected results combined
Sheinfeld & Albert (2003)	Qualitative
Smith (2003)	Dissertation
Smith *et al.* (2004)	Single gene disorders
Steinbart *et al.* (2001)	No pre-test data; n=11
Tercyak *et al.* (2001)	Affected and unaffected results combined
Tiller (2005)	Assessed intentions to have surgery, not actual behaviour
Tinley et al. (2004)	No genetic test for unaffected group
van Dijk *et al.* (2003)	No genetic test
Van Dijk *et al.* (2004)	Affected and unaffected results combined
van Dooren *et al.* (2004)	No pre-test data; subjects part of trial assessing surveillance
Wade Walsh (2001)	Dissertation
Wagner et al. (2000)	Affected and unaffected results combined
Watson *et al.* (2005)	No genetic test
Wylie *et al.* (2003)	No pre-test distress data

Appendix 4 – Description of Intervention for FDR pilot study

FDRs Thrombophilia (-): No counselling following disclosure of genetic test results.

FDRs Thrombophilia (+) *Standard Care*: Counselling at one week following disclosure of genetic test results; received no additional information after counselling session; follow-up only occurred when requested by the FDR or by a medical referral, as is the current standard.

FDRs Thrombophilia (+) *Novel Care*: Counselling at one week following disclosure of genetic test results; received Learning Module Booklet after the counselling session, a magnet with the clinic's contact information on it, a sticker on their health card stating thrombophilia status, Dr.'s name and clinic's number; follow-up visits in Thrombosis clinic every four months for review of learning modules and discussion of signs and symptoms of DVT and PE, and risk factors for VTE; new or upcoming risk factors were assessed and prophylactic treatment will be recommended when appropriate.

Appendix 5 – Schedule for all consenting FDRs screened for thrombophilia

	Assessment	*T'Phila (-)*	*T'Phila (+)* **Standard Group**	*T'Phila (+)* **Novel Care Group**
Baseline	POMS	X	X	X
	Somatization	X	X	X
	Perceived Risks	X	X	X
Results	Demographic & Clinical data	X	X	X
	Counselling		X	X
1 Week	POMS	X	X	X
	Somatization	X	X	X
	Perceived risks	X	X	X
4 Months	Visit/Call			X
6 Months	POMS		X	X
	Somatization		X	X
	Perceived Risks		X	X
8 Months	Visit/Call			X
12 Months	Visit/Call	X	X	X
12 Months	POMS	X	X	X
	Somatization	X	X	X
	Perceived Risks	X	X	X

Appendix 6 – Inclusion/Exclusion Criteria for pilot study

	Inclusion Criteria	Exclusion Criteria
Probands	1. VTE with thrombophilia. 2. Diagnosis of PE confirmed with spiral CT with contrast, pulmonary angiography, or a high probability ventilation perfusion scan combined with a moderate or high clinical probability; OR diagnosis of DVT confirmed with compression ultrasonography or contrast venography 3. Provide written consent and the names and contact information of relatives in the area of one of the study sites (Ottawa, Montreal, Halifax, London, Hamilton)	1. Do not have eligible FDRs living near study site or unwilling to provide names and contact information of relatives
FDRs	1. Parent, child, or sibling of an eligible proband 2. At least 18 years of age 3. Able to communicate comfortably in either English or French 4. Live in close geographical proximity to one of the study sites 5. Written consent to participate.	1. Adoptive rather than biological relationship with proband 2. Personal history of VTE (confirmed by objective diagnostic methods) 3. Currently on long-term oral anticoagulants 4. Previously diagnosed with thrombophilia.

Appendix 7 - POMS-SF

1483

FAX TO: (613) 761-4874 when completed

Centre # | Proband # | FDR # | FU Month | FDR Initials | Date: / /

○ Baseline ○ 1 week ○ 6 months ○ 12 months

Profile of Mood States – Short Form (POMS-SF)

Please indicate the degree to which each of the adjectives below describes how you have been feeling OVER THE PAST WEEK, including today.

		Not at all				Extremely
1.	Unhappy	0	1	2	3	4
2.	Lively	0	1	2	3	4
3.	Confused	0	1	2	3	4
4.	Tense	0	1	2	3	4
5.	Angry	0	1	2	3	4
6.	Worn-out	0	1	2	3	4
7.	Sad	0	1	2	3	4
8.	Active	0	1	2	3	4
9.	Unable to concentrate	0	1	2	3	4
10.	On edge	0	1	2	3	4
11.	Peeved	0	1	2	3	4
12.	Fatigued	0	1	2	3	4
13.	Blue	0	1	2	3	4
14.	Energetic	0	1	2	3	4
15.	Bewildered	0	1	2	3	4
16.	Uneasy	0	1	2	3	4
17.	Annoyed	0	1	2	3	4
18.	Exhausted	0	1	2	3	4
19.	Hopeless	0	1	2	3	4
20.	Cheerful	0	1	2	3	4
21.	Forgetful	0	1	2	3	4
22.	Restless	0	1	2	3	4
23.	Resentful	0	1	2	3	4
24.	Weary	0	1	2	3	4
25.	Discouraged	0	1	2	3	4
26.	Full of pep	0	1	2	3	4
27.	Uncertain about things	0	1	2	3	4
28.	Nervous	0	1	2	3	4
29.	Bitter	0	1	2	3	4
30.	Bushed	0	1	2	3	4
31.	Miserable	0	1	2	3	4
32.	Vigorous	0	1	2	3	4
33.	Anxious	0	1	2	3	4
34.	Furious	0	1	2	3	4
35.	Helpless	0	1	2	3	4
36.	Worthless	0	1	2	3	4

Appendix 8 - Somatization subscale of the SCL-90-R

41273

FAX TO: (613) 761-4874 when completed

Centre #	Proband #	FDR #	FU Month	FDR Initials	Date: / /
					O 1 week O 6 months O 12 months

FDR Somatization Subscale of the SCL-90-R

INSTRUCTIONS:

I will be reading to you a list of problems people sometimes have. I want you to rate HOW MUCH THAT PROBLEM HAS STRESSED OR BOTHERED YOU DURING THE PAST 7 DAYS INCLUDING TODAY. Please rate if it distressed you: Not at all, A little bit, Moderately, Quite a bit, or Extremely.

	Not at all	A little bit	Moderately	Quite a bit	Extremely
Headaches	0	1	2	3	4
Faintness or dizziness	0	1	2	3	4
Pains in heart or chest	0	1	2	3	4
Poor appetite	0	1	2	3	4
Pains in lower back	0	1	2	3	4
Heart pounding or racing	0	1	2	3	4
Nausea or upset stomach	0	1	2	3	4
Soreness of your muscles	0	1	2	3	4
Trouble falling asleep	0	1	2	3	4
Trouble getting your breath	0	1	2	3	4
Hot or cold spells	0	1	2	3	4
Numbness or tingling in parts of your body	0	1	2	3	4
Feeling weak in parts of your body	0	1	2	3	4
Heavy feelings in your arms or legs	0	1	2	3	4

Appendix 9 - Perceived Risk Questionnaire

24504

FAX TO: (613) 761-4874 when completed

Centre # | Proband # | FDR # | FU Month | FDR Initials | Date: YYYY / MM / DD

○ 1 week ○ 6 months ○ 12 months

FDR Perceived risk Questionnaire

Shade circles like this: ●
Not like this: ⊠ ∅

1. Compared to most people, what do you believe is your chance of having a blood clot?

○ Lower ○ Same ○ Little higher ○ Much higher

2. What do you think are your chances of developing a blood clot?

○ 1 in 10 ○ 1 in 100 ○ 1 in 500 ○ 1 in 1000 ○ 1 in 5000

3. How concerned are you about your chances of having a blood clot?

○ Not at all ○ Somewhat concerned ○ Moderately concerned ○ Very concerned

4. How often do you worry about your chances of developing a blood clot?

○ Rarely or ever ○ Sometimes ○ Often ○ All the time

5. How much do worries about having a blood clot affect the way you feel from day to day?

○ Not at all ○ Somewhat ○ A fair bit ○ Very much

6. How treatable are blood clots?

○ Rarely or never ○ Somewhat ○ A fair bit ○ Very much

7. Do you feel that it is possible to prevent a blood clot?

○ Definitely ○ Probably ○ Not sure ○ Probably not ○ Definitely not

24504

Appendix 10 – Cover letter for potential survey participants

Ottawa Health Research Institute
OHRI IRSO
Institut de recherche en santé d'Ottawa

Dear Study Participant,

I would like to thank you for participating in our ongoing study of the impact of screening family members of people with thrombophilia. As it progresses, it is providing us with useful information that will help us improve our clinical services. I am writing to invite you to participate in an extension of this study, which focuses on the impacts of testing that go beyond clinical care. This specific project has been developed in collaboration with Dr Brenda Wilson, Associate Professor, and Ms Crystal Dunn, Graduate Student, of the University of Ottawa, Department of Epidemiology and Community Medicine.

We are contacting you as a first-degree relative who has been a participant in our previous study. We invite you to complete the enclosed questionnaire survey. We are interested in hearing from you regardless of the results of your genetic test (positive or negative). We hope that you will provide important information about whether your genetic test result has had an impact on how you live your life, how much control you feel you have over developing a blood clot, and your use of health services.

Enclosed is an information sheet that provides more detailed information about the project and the questionnaire survey. Please read the information sheet before deciding whether or not you would like to participate.

If you **do** wish to participate, simply fill in the questionnaire, seal it in the self-addressed, stamped envelope provided and place it in the regular mail. **Please keep the Participant Information Form for your personal files.**

If you **do not wish to participate**, simply seal the blank questionnaire in the self-addressed, stamped envelope provided and place it in the regular mail. We will know that you do not wish to be contacted again and we will remove your details from the files for this specific project. **Please keep the Participant Information Form for your personal files.**

You are under no obligation to take part in this study. Your decision, either to participate or not, will not affect the care that you receive now or in the future at The Ottawa Hospital.

Thank you for taking the time to read this letter.

Sincerely,

Dr. Phil Wells, MD,
Principal Investigator
Chief, Division of Hematology, Ottawa Hospital;
Canada Research Chair in Thromboembolic Diseases

Civic Campus
Campus Civic
1053 Carling
Ottawa, ON
Canada K1Y 4E9
WWW.OHRI.CA

Appendix 11 – Information sheet for potential survey participants

Ottawa Health Research Institute
OHRI IRSO
Institut de recherche en santé d'Ottawa

PATIENT INFORMATION FORM

(Please keep for your records)

THE IMPACTS OF GENETIC TESTING FOR THROMBOPHILIA ON HEALTH BEHAVIOURS AND HEALTH SERVICES USE

Investigators: Dr. Phil Wells, Dr. Brenda Wilson, Crystal Dunn

You are being asked to participate in a research project. This participant information form describes the study and outlines what will be asked of you if you decide to take part.

Purpose of this Research Study: We would like to study the impacts of genetic testing for thrombophilia. You have already provided information on the psychological impacts of testing and your perceived risk of developing a blood clot. We would now like to know whether receiving a genetic test for thrombophilia has caused you to change your behaviours. We would also like to know whether or not you feel that you have control over developing a blood clot. Finally, we are interested in whether receiving a genetic test result has affected your use of health services.

Your participation in this study will contribute to our growing knowledge about the impacts of genetic testing for thrombophilia on first-degree relatives of patients with blood clots. It will also be important in directing and improving counselling, educational, and clinical services.

Study Procedures: If you agree to participate in this study, we ask that you complete the single enclosed survey. It should take you no more than 15 minutes to complete. You should then seal the questionnaire in the self-addressed, stamped envelope provided and place it in the regular mail.

Potential Risks or Benefits: There are no risks or benefits to you participating in this study. However, the knowledge we gain from this study may improve the clinical management of patients with a genetic predisposition to blood clots, and aid in the development of counselling and educational interventions.

Voluntary Participation: You may choose not to participate in this study. Whether or not you participate will not, in any way, affect the treatment that you receive now or at any time in the future from The Ottawa Hospital or from the study investigators.

Withdrawal: You may decide to withdraw from this study at any time without it affecting your care at The Ottawa Hospital. If you withdraw, all information you provided for the research study will be destroyed.

Compensation: You will not be compensated for participating in this study. Completing and mailing the questionnaire will not involve any monetary costs to you.

Confidentiality: Your personal information will be kept confidential. Your name will not be recorded on any of the study documents, but instead a study identification number and initials will be used. Any personal information about you that leaves the hospital will be anonymous so that you cannot be identified by name.
If you choose to participate, when your questionnaire is received, your replies will be entered onto a computer database for analysis. The questionnaires will be kept in a secure location, only accessible to the investigators and their research team.

Representatives of the Ottawa Hospital Research Ethics Board may review your records under the supervision of Dr. Wells' staff for audit purposes.

Questions:

If you have any questions or would like to speak to the investigators of this study, you are free to call Crystal Dunn at the University of Ottawa at (613)-562-5800 ext. 8716. She will be happy to talk to you or direct your call without any obligation on your part.

The Ottawa Hospital Research Ethics Board (REB) is a group of people from scientific and non-scientific backgrounds that reviews research studies. Its goal is to ensure the protection of the rights and welfare of people involved in research. You may contact the Chair of the REB for information regarding patients' rights in research studies at (613) 798-5555 ext. 14902, although this person cannot provide any health-related information about the study.

Appendix 12 – Cross-sectional survey 'Causes & Prevention of Blood Clots'

Questioning & Evaluating Genetic, Clinical
& Social Outcomes in Thrombophilia

uOttawa

L'Université canadienne
Canada's university

Causes & Prevention of Blood Clots Questionnaire

This questionnaire is for people who have had a genetic test for thrombophilia, whatever the result. We wish to understand how you reacted to the result of this genetic test. In particular, we are interested in knowing what you think causes blood clots, how someone might prevent them, and if you've tried to reduce your risk.

DATE COMPLETED: _____ **STUDY ID #:** _____
(mm/dd/yyyy)

If you have any questions/concerns please contact Crystal Dunn
at the University of Ottawa at (613)-562-5800 ext. 8716

Section 1
Reactions to your genetic test

While some people are at higher risk than others, anyone could potentially develop a blood clot during his or her lifetime. We are interested in finding out more about your reactions to your genetic test, whether you tested positive or negative.

1. Do you remember your genetic test result?

   - ❒ Yes, it was positive
   - ❒ Yes, it was negative
   - ❒ No, I don't remember

2. Compared to most people, what do you believe is your chance of ever having a blood clot?

   - ❒ Lower
   - ❒ Same
   - ❒ Little higher
   - ❒ Much higher

3. Roughly, what do you think are your chances of ever developing a blood clot?

   - ❒ 1 in 10
   - ❒ 1 in 100
   - ❒ 1 in 500
   - ❒ 1 in 1000
   - ❒ 1 in 5000

4. How serious for your health do you think it would be to get a blood clot?

   - ❒ Not at all serious
   - ❒ Slightly serious
   - ❒ Serious
   - ❒ Very serious
   - ❒ Extremely serious

5. How confident are you in your ability to identify the symptoms of a blood clot?

- ❒ Completely confident
- ❒ Mostly confident
- ❒ Slightly confident
- ❒ Not at all confident

6. How accurate do you think your genetic test was?

- ❒ Not at all accurate
- ❒ Somewhat accurate
- ❒ Completely accurate

7. What does your genetic test result mean?

- ❒ You definitely will get a blood clot in your lifetime
- ❒ You probably will get a blood clot in your lifetime
- ❒ You may or may not get a blood clot in your lifetime
- ❒ You probably will not get a blood clot in your lifetime
- ❒ You definitely will not get a blood clot in your lifetime

8. Do you have any regrets about having the genetic test for thrombophilia?

- ❒ Yes
- ❒ No
- ❒ Don't know

Section 2
Causes and Prevention of Blood Clots

9. Please check the appropriate boxes to let us know what you think about the following factors that might be related to blood clots:

Not enough exercise...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to exercise more since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Stress, worry or depression...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to decrease my stress levels since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Infection with a germ or virus...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to avoid infections by a germ or virus since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Poor diet or eating habits...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to improve my diet since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Not having access to high quality medical care...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

The effects of aging...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

Exposure to chemicals (e.g. in your home or garden)...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to limit my exposure to chemicals around the home and garden since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Over-exertion (e.g. lack of rest/relaxation)...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried not to work as hard since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Family history of blood clots...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒

I have tried to inform my relatives of my genetic test result ❒ Yes ❒ No

↳IF YES, which relative(s) have you informed? *(check all that apply)*

❒ Mother ❒ Father
❒ Brother(s) ❒ Sister(s)
❒ Son(s) ❒ Daughter(s)
❒ Aunt/Uncle(s) ❒ Cousin(s)
❒ Grandparent(s)
❒ Other Specify:_____

A positive genetic test for thrombophilia...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒

Smoking...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I smoked cigarettes at the time of my genetic test ❒ Yes ❒ No

↳IF YES, did you try to quit smoking since your genetic test? ❒ Yes ❒ No

↳IF YES, during the past 30 days have you smoked cigarettes, even a puff? ❒ Yes ❒ No

↳Did you try to quit smoking specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

A negative attitude in life...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to adopt a more positive attitude since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Being overweight...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to lose weight since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Injury requiring hospital admission...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to reduce my risk of injury since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

I have been injured and admitted to hospital since my genetic test ❒ Yes ❒ No

↳IF YES...

Did you alert the doctor of your genetic test results shortly after he/she treated your injury? ❒ Yes ❒ No ❒ Don't know

Did your doctor prescribe blood thinners to take shortly after treating your injury? ❒ Yes ❒ No ❒ Don't know

Did you wear compression stockings while recovering from your injury? ❒ Yes ❒ No ❒ Don't know

Did you try to get back on your feet as soon as possible after your injury? ❒ Yes ❒ No ❒ Don't know

Having major surgery (e.g. requiring general anaesthesia)...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒

Have you had major surgery since your genetic test? ❒ Yes ❒ No

↳IF YES...	Did you discuss your genetic test results with your doctor before surgery?	❒ Yes	❒ No	❒ Don't know
	Did your doctor prescribe blood thinners to take before or after your surgery?	❒ Yes	❒ No	❒ Don't know
	Did you wear compression stockings following surgery?	❒ Yes	❒ No	❒ Don't know
	Did you try to get back on your feet as soon as possible after surgery?	❒ Yes	❒ No	❒ Don't know

Prolonged immobility (e.g. during long trips)...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a person's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that I feel I can control	❒	❒	❒	❒	❒

I have tried to avoid long trips since my genetic test ❒ Yes ❒ No

↳IF YES, have you done this specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

Have you been on a long trip since your genetic test? ❒ Yes ❒ No

↳IF YES...	Did you discuss your genetic test result with your doctor before going on this trip?	❒ Yes	❒ No	❒ Don't know
	Did your doctor prescribe blood thinners to take before your trip?	❒ Yes	❒ No	❒ Don't know
	Did you wear compression stockings during your trip?	❒ Yes	❒ No	❒ Don't know
	Did you take frequent breaks, walk around, and move your legs during your trip?	❒ Yes	❒ No	❒ Don't know

WOMEN ONLY: (Men proceed to question 10 at the bottom of the next page)

Pregnancy or childbirth...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a woman's risk of getting a blood clot	❒	❒	❒	❒	❒

Have you been pregnant and/or given birth since your genetic test? ❒ Yes ❒ No

↳IF YES...

Did you discuss your genetic test result with your doctor after you found out you were pregnant?	❒ Yes	❒ No	❒ Don't know
Did your doctor prescribe blood thinners to take during pregnancy and/or after childbirth?	❒ Yes	❒ No	❒ Don't know
Did you wear compression stockings during your pregnancy and/or after childbirth?	❒ Yes	❒ No	❒ Don't know

WOMEN ONLY:

Taking birth control pills...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a woman's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that applies to me	❒ Yes	❒ No	→If no, proceed to top of next page		
is something that I feel I can control	❒	❒	❒	❒	❒

Were you taking birth control pills at the time of your genetic test? ❒ Yes ❒ No

↳IF NO, did the results of your genetic test help you to decide not to start taking birth control pills? ❒ Yes ❒ No

↳IF YES, did you stop taking birth control pills after your genetic test? ❒ Yes ❒ No

↳ IF YES, did you stop specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

WOMEN ONLY:

Taking hormone replacement therapy (HRT)...	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
will increase a woman's risk of getting a blood clot	❒	❒	❒	❒	❒
is something that some people can control	❒	❒	❒	❒	❒
is something that applies to me	❒ Yes	❒ No	→If no, proceed to question 10		
is something that I feel I can control	❒	❒	❒	❒	❒

Were you taking HRT at the time of your genetic test? ❒ Yes ❒ No

↳IF NO, did the results of your genetic test help you to decide not to start taking HRT? ❒ Yes ❒ No

↳IF YES, did you stop taking HRT after your genetic test? ❒ Yes ❒ No

↳ IF YES, did you stop specifically to reduce your risk of a blood clot? ❒ Yes ❒ No ❒ Don't know

10. The following is a list of all the factors we have asked about. Please put a check beside every factor you think is important for <u>your</u> risk of developing a blood clot in the future:

- ❒ Stress, worry or depression
- ❒ Poor diet or eating habits
- ❒ Exposure to chemicals
- ❒ The effects of aging
- ❒ Being overweight
- ❒ Family history of blood clots
- ❒ A generally negative attitude
- ❒ Having major surgery
- ❒ Pregnancy or childbirth
- ❒ Taking HRT
- ❒ Infection with a germ or virus
- ❒ Not enough exercise
- ❒ Lack of access to high quality medical care
- ❒ A positive test for thrombophilia
- ❒ Over-exertion
- ❒ Smoking
- ❒ Injury requiring hospitalization
- ❒ Prolonged immobility
- ❒ Taking birth control pills
- ❒ Other *Specify:* _____

Section 3
Overall, can you control whether or not you get a blood clot?

11. Please indicate how much you agree or disagree with the following statements:

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
There is a lot I can do to control whether or not I develop a blood clot	❒	❒	❒	❒	❒
Taking blood thinners (anticoagulants) if and when directed by my doctor is an effective way to prevent me from getting a blood clot	❒	❒	❒	❒	❒
Wearing compressions stockings if and when directed by my doctor is an effective way to prevent me from getting a blood clot	❒	❒	❒	❒	❒
My behaviours can determine whether or not I get a blood clot	❒	❒	❒	❒	❒
My genetic makeup controls whether or not I get a blood clot	❒	❒	❒	❒	❒
There is nothing that can be done to prevent me from getting a blood clot	❒	❒	❒	❒	❒
Informing my doctor when I might be in a high risk situation would help to prevent me from getting a blood clot	❒	❒	❒	❒	❒
Chance or luck controls whether or not I get a blood clot	❒	❒	❒	❒	❒

Section 4
Experiences with health professionals

12. Do you have a physician with whom you can regularly schedule appointments (e.g. a family doctor)?

- ❒ Yes
- ❒ No **→Proceed to question 15**

13. Since receiving your genetic test result, do you feel that you have visited your physician more often?

- ❒ Yes
- ❒ No
- ❒ Don't know

14. Since receiving your genetic test result, have you discussed your genetic test result with your physician?

- ❒ Yes
- ❒ No
- ❒ Don't know

↳**IF YES**:

Do you feel that your physician has an adequate understanding of what your genetic test result means?

- ❒ Yes
- ❒ No
- ❒ Don't know

Has your physician given you advice about your risk for a blood clot?

- ❒ Yes
- ❒ No
- ❒ Don't know

15. Overall, how satisfied are you with the amount of information that you have received from **any** health professional about thrombophilia and your risk of developing a blood clot?

- ❒ Very unsatisfied
- ❒ Unsatisfied
- ❒ Satisfied
- ❒ Very satisfied

THANK YOU!

Please enclose this questionnaire in the envelope provided and place it in the regular mail.