Familial hypercholesterolemia screening in the Netherlands: psychological and social consequences
van Maarle, M.C.

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Familial Hypercholesterolemia Screening in the Netherlands: 
Psychological and Social Consequences

Merel C. van Maarle
Familial Hypercholesterolemia Screening in the Netherlands: Psychological and Social Consequences

ACADEMISCH PROEFSCHRIFT
Ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam, op gezag van de Rector Magnificus prof. mr. P.F. van der Heijden ten overstaan van een door het college voor promoties ingestelde commissie, in het openbaar te verdedigen in de Aula der Universiteit

op woensdag 7 mei 2003, te 12:00 uur

door
Merel Constantine van Maarle
Geboren te Leiden
Promotiecommissie

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Prof. dr. J.J.P. Kastelein
Prof. dr. L.P. ten Kate
Prof. dr. N.J. Leschot
Prof. dr. J. Passchier

Faculteit Geneeskunde
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Chapter 1

Introduction
Genetic screening

Testing for the presence of risk factors like high blood pressure or high cholesterol has been common practice for years now, the context varying from screening in an apparently healthy population to screening patients who suffered from an acute myocardial infarction or cerebrovascular accident. Tests for genetically mediated risk factors have emerged recently and their range of applications widens. Predictive testing in healthy people is likely to become more broadly available for an increasing number of genetically mediated risk factors [1]. The prerequisites for the success of a screening programme using genetic testing are a) the possibility to diagnose the disease early, b) the possibility to treat the disease and c) a high prevalence of the disease within a certain population [2]. However, empirical evidence of direct beneficial health effects of the screening does usually not suffice to achieve broad acceptance and successful implementation [3]. This acceptance of a screening programme by both screenees and government depends not only on the acceptability of the screening process itself, but also on the psychological and social consequences of being tested and of the follow-up [2,3]. Furthermore, the implementation of a screening programme depends on the prevailing organisational setting for genetic test services [2,3]. In the Netherlands, genetic test services are largely supplied by genetic centres related to teaching hospitals. These centres are put in charge of genetic testing and counselling [4]. Given their bounded size, the rising demand for genetic testing can no longer be met by geneticist-driven centres alone. It is expected that part of the testing will shift to genetic services supplied by non-geneticists; consequently new procedures have to be developed, in particular when a new programme is launched [5,6].

Experience and variety of considerations suggest that a genetic screening programme requires careful, guided implementation, which starts with a broad assessment with its pros and cons.

As a guideline to assess a genetic screening programme the criteria by Wilson and Jungner as adapted by the Crossroads 99 Group could be used (see table 1) [2,3].
Table 1 Criteria for assessment of screening adapted from the Crossroads 99 Group, based on the Wilson and Jungner criteria [2,3]

<table>
<thead>
<tr>
<th>1. Knowledge of population and disease</th>
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<tbody>
<tr>
<td>a. Important burden of the disease</td>
</tr>
<tr>
<td>b. Target population identifiable</td>
</tr>
<tr>
<td>c. Considerable level of risk</td>
</tr>
<tr>
<td>d. Preclinical phase of the disease existent</td>
</tr>
<tr>
<td>e. Natural course (from susceptibility to precursor, early disease, and advanced disease) understood</td>
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<tr>
<th>2. Feasibility of screening procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Suitable test or examination available</td>
</tr>
<tr>
<td>b. Entire screening procedure acceptable to population</td>
</tr>
<tr>
<td>c. Screening is a continuing process and encompasses all elements of screening procedures</td>
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<th>3. Interventions and follow up</th>
</tr>
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<tr>
<td>a. Physical net benefit of the intervention likely</td>
</tr>
<tr>
<td>b. Psychological net benefit of the intervention likely</td>
</tr>
<tr>
<td>c. Social net benefit of the intervention likely</td>
</tr>
<tr>
<td>d. Facilities for adequate follow-up available</td>
</tr>
<tr>
<td>e. Consensus on accepted management for those with a positive test result</td>
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<tr>
<th>4. Societal and health system issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Balanced economic and medical costs</td>
</tr>
<tr>
<td>b. Balanced psychological costs</td>
</tr>
<tr>
<td>c. Balanced societal costs</td>
</tr>
<tr>
<td>d. Appropriate screening services accessible to entire population without adverse consequences for non-participants</td>
</tr>
<tr>
<td>e. Appropriate confidentiality procedures and anti-discrimination provisions for participants and non-participants</td>
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</table>

Familial hypercholesterolemia (FH)

FH is an autosomal dominant disorder of lipoprotein metabolism with an estimated frequency of 1 in 500 persons (in Western countries). In the past, the diagnosis FH was only based on clinical signs and family history [7,8]. A definite clinical diagnosis (in adults) requires 1) a total cholesterol level above 7.5 mmol/l or low-density lipoprotein (LDL) cholesterol levels above 4.9 mmol/l, plus 2) tendon xanthomas in patient or in first- or second-degree relatives. A possible diagnosis of FH requires hypercholesterolemia (see 1 above) plus one of the following: 3) a family history of myocardial infarction (MI) before the age of 50 in second-degree relatives or before the age of 60 in first-degree relatives, and 4) a family history of raised cholesterol above 7.5 mmol/l in first-or second-degree relatives [8]. Patients with a clinical diagnosis experience an excess mortality from cardiovascular disease (CVD), in particular at a young age [7-10]. Clinical experience shows that most FH patients are still diagnosed after having their first cardiovascular event; at this stage damage to the vessels is already prevalent and at best only partially reversible. After characterising the genetic defect in FH in the seventies, the aetiology and pathophysiology
of the disease became gradually understood. It was shown that FH is characterised by a mutation in the low-density lipoprotein (LDL) receptor gene, resulting in LDL cholesterol accumulation and excess mortality from CVD [4]. Once the genetic defect could be diagnosed and effective lipid-lowering therapy (LLT) with HMG-CoA reductase inhibitors (statins) was available [11-16], early diagnosis and effective treatment was possible and genetic screening on FH in high-risk groups seemed feasible.

Screening for FH
With FH screening possible in high-risk groups, the ‘Foundation for tracing hereditary hypercholesterolemia’ (Dutch acronym: StOEH, ‘Stichting Opsporing Erfelijke Hypercholesterolemie’) was founded in 1994 to perform the FH screening in the Netherlands. Up to the beginning of 2002, 11613 persons were screened by the StOEH, of whom 4152 (36%) proved to be FH positive [17]. In this screening programme, first- and second-degree relatives of index patients (i.e. clinically diagnosed FH-patients with a known mutation) are actively approached by the StOEH using a pedigree investigation (‘cascade screening’) [18-20]. Relatives are tested for the mutation found in the index-patient only. Mutational analyses were performed on genomic DNA isolated from peripheral blood leucocytes using polymerase chain reaction (PCR) and restriction enzyme analysis as described by Jensen et al. [21]. By intent, cholesterol is not measured within this screening programme so far. If relatives test positive, their first- and second-degree relatives are approached and offered testing, etc. All test results are communicated to the screenee by mail only. Screen-positives get two additional letters: one directed to him/herself with the advice to consult the general practitioner (GP), and one to the GP, inviting the GP to refer the patient to a lipid clinic. This procedure requires the screen-positives to take the initiative to seek medical follow-up after receiving the letter. The StOEH is neither involved in the treatment phase of detected cases or the monitoring of the follow-up process.

Evaluation of the screening for FH
The main goal of the screening programme is to achieve health benefit for the screened persons. However, for some screenees the effects will not be exclusively positive, negative effects could occur. Henceforth, before implementing the screening programme, a broader evaluation is needed, as stated above. The evaluation of the FH-screening programme is based on the Dutch Health Council’s advice of what genetic screening programmes have to comply with in the Netherlands [22]. Their requirements are derived from Wilson and Junger’s criteria [2] while it is made clear that not only the achieved health benefit for the screenee should be evaluated, but the broader (psychological and societal) consequences including non-participants as well (see table 1).

In this thesis, we evaluate the provisional implementation of the Dutch FH-screening programme, focussing on the acceptability and feasibility of the implementation of the programme, in this thesis this is made operational as psychological and social consequences. Other components of the comprehensive evaluation, including the estimation of health benefits and financial burden, were published elsewhere [23]. In this evaluation the health benefits of early treatment of FH were estimated by using the Framingham function; by doing this it was assumed that the extra CAD risk in FH patients is caused completely by the raised serum cholesterol level and not by the mutation itself through another pathway [24].

As the combined results aimed to support decision-making on the future of the screening programme, the evaluation of the programme was organised separately from the actual
screening programme; this ‘third party’ approach is conform the set-up of major studies to evaluate screening programmes in the Netherlands [25,26].

The adapted Wilson and Jungner criteria (see earlier) provide a format to assess available knowledge on FH screening (see table 2) [2,3].

Table 2 Known and unknown factors for the assessment of FH screening

<table>
<thead>
<tr>
<th>1. Knowledge of population and FH</th>
</tr>
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<tbody>
<tr>
<td>a. Disease burden: In Western countries 1 in 500 persons has FH [7]</td>
</tr>
<tr>
<td>b. Target population: Family members of clinically diagnosed and genetically confirmed patients</td>
</tr>
<tr>
<td>c. Level of risk: Patients with a clinical diagnosis have an excess mortality from CVD, in particular at a young age [7-10]</td>
</tr>
<tr>
<td>d. Pre-clinical phase: Present [7]</td>
</tr>
<tr>
<td>e. Natural course of FH: Known [7], however in clinically diagnosed patients only, not in genetically identified patients without clinical signs of FH</td>
</tr>
</tbody>
</table>

The natural course of FH in genetically diagnosed patients was estimated in the evaluation study of the Dutch FH-screening programme using the Framingham function [24], assuming that the extra CAD risk in FH patients is caused completely by the raised serum cholesterol level [23].

<table>
<thead>
<tr>
<th>2. Feasibility of screening procedures</th>
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</thead>
<tbody>
<tr>
<td>a. Test: Feasibility of the mutation analyses within the Dutch screening programme is evaluated within the evaluation study of the Dutch FH-screening programme [23]</td>
</tr>
<tr>
<td>b. Acceptability of screening procedure to screened population: So far unknown, covered by Chapter 1 of this thesis</td>
</tr>
<tr>
<td>c. Screening process: In part covered by Chapter 6 of this thesis, the remainder is described in Chapter 2 &amp; 3</td>
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</table>

<table>
<thead>
<tr>
<th>3. Interventions and follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Physical effects: health effects of the FH-screening programme are estimated within the evaluation study [23]</td>
</tr>
<tr>
<td>b. Psychological effects: So far unknown, covered by Chapter 2 to 5 of this thesis</td>
</tr>
<tr>
<td>c. Social effects: Described in Chapter 2 &amp; 3</td>
</tr>
<tr>
<td>d. Follow-up: Chapter 6</td>
</tr>
<tr>
<td>e. Consensus on management for those with FH: Present (cholesterol consensus) [27,28]</td>
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<tr>
<th>4. Societal and health system issues</th>
</tr>
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<tbody>
<tr>
<td>a. Economic and medical costs: estimated within the evaluation study [23]</td>
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<td>b. Psychological costs: Chapters 2 to 5</td>
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<tr>
<td>c. Societal costs: Chapters 2 to 5 and chapter 7</td>
</tr>
<tr>
<td>d. Appropriate screening services accessible to entire population: Chapter 6 for FH-positive screenees. FH-negative screenees and non-participants stay in regular clinical setting.</td>
</tr>
<tr>
<td>e. Confidentiality procedures and anti-discrimination provisions: Chapter 7</td>
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Contents of the thesis

Chapter 2  
This chapter focuses on the critical first stage of the screening. It describes the screenees’ view on and the short-term psychological and social impact of the approach of, until then, healthy persons for the FH-screening programme and evaluates non-participation to the screening programme.

Chapter 3  
In principle, long-term and substantial transient quality of life (QoL) effects of a screening programme are not acceptable. Thus, the principal objectives of this chapter are to establish whether transient and long-term QoL effects of the screening are present, with a focus on psychological effects. If significant adverse effects are present, we intend to describe here the change over time and its dependence on personal characteristics, perceived and observed risk status, and on perceived social pressure to participate. Given these effects, we may further optimise the FH-screening programme.

Chapter 4  
In this chapter we describe the possibility of inadequate or even paradoxical preventive behaviour in both FH-positive and FH-negative screenees. FH-positive screenees may think that hypercholesterolemia is inevitable, and resist treatment (‘fatalism’), while FH-negative screenees may think that they are ‘safe’ or protected against hypercholesterolemia (‘false reassurance’), and even show compensatory risk behaviour, e.g. smoking or eating less healthy.

Chapter 5  
The evaluation in this chapter focuses on the essential role of the individual’s risk perception and representation of information, the change of risk perception over time, as influenced by test result and other information/experience, and the consequential influence of risk perception on actual risk reduction (cholesterol-lowering medication use, stated attitude towards gene therapy, smoking cessation and losing weight).

Chapter 6  
Chapter 6 focuses on the compliance with preventive care in screenees who tested positive for FH, which ultimately determines the programme efficiency. Not all screenees were unaware of a cholesterol problem and since some screenees were already aware of clinical hypercholesterolemia and were already treated, we distinguished in this chapter between newly identified and confirmed screenees. For both groups we evaluated what screening actually offers. To determine the impact of screening, we assessed the quality of care before screening, and at two points in time after screening. Guideline-based procedural quality and clinical outcome quality were established, taking the key recommendations of the Dutch hypercholesterolemia guidelines as reference.

Chapter 7  
The participating in a genetic screening could have negative social consequences, such as problems with regard to the access to insurance. In this chapter we describe whether legislation protects participants of a genetic screening programme from experiencing problems in the access to insurance and make suggestions how to avoid problems.

With the information from this thesis the table based on the criteria of Wilson and Jungner (see above) can be filled out and makes a balanced assessment possible of the acceptability and feasibility of FH screening in the Netherlands. A quick balance will be given in the section ‘Summary and Discussion’ of this thesis.
Reference list


Chapter 2

How disturbing is it to be approached for a genetic cascade screening programme for Familial Hypercholesteroleemia?

‘Psychological impact and screenees’ views’

M.C. van Maarle$^{1}$, M.E.A. Stouthard$^{1}$, P.J. Marang-v.d. Mheen$^{1}$, N.S. Klazinga$^{1}$, G.J. Bonsel$^{1}$

$^{1}$ Department of Social Medicine, Academic Medical Centre, Amsterdam

Abstract

Objectives: To assess the screenees' views on, and the psychological impact of, a family-based genetic screening programme for familial hypercholesterolemia (FH) and to evaluate non-participation. Methods: Self-administered questionnaires were filled out at screening and after communication of the test result. Non-participants of the screening programme were interviewed by phone. Results: Of the people approached for screening 2% did not participate. This 2% was not interested, already clinically diagnosed, or afraid of insurance consequences. 677 screenees participated, of whom 215 (32%) tested FH-positive. Less than 5% of the screenees were critical of the approach and the information provided. 20% of the screenees expressed feelings of social pressure. Effects on mood were minimal to absent, as were general 'quality of life' effects. Conclusions: Screening for FH is highly acceptable to screenees, although social pressure is prevalent. Only a small percentage of people being approached did not participate.
Introduction

General introduction
For years people have been tested for the presence of risk factors like high blood pressure or high cholesterol. Tests for genetically mediated risk factors have emerged recently. Predictive testing in healthy people is likely to be more broadly available for an increasing number of genetically mediated risk factors, the testing often being organised formally within screening programmes.[1] Even if the empirical evidence of beneficial screening effects is convincing, the broader consequences ask for careful, guided implementation.[2]

The implementation depends on the prevailing organisational setting for genetic test services. In the Netherlands, genetic centres, related to teaching hospitals, are in charge of testing and counselling for genetic disorders.[3] However, the rising demand for genetic testing can no longer be met by geneticist-driven centres alone. Testing now partially shifts to genetic services supplied by non-geneticists with little experience in the entire screening process.[4;5] We investigated the provisional implementation of one specific genetic screening programme for familial hypercholesteroleemia (FH), focussing on the critical first stage of the screening as seen from the point of view of the screenees.

The Dutch screening programme for FH
Familial hypercholesteroleemia (FH) is a common inborn error of metabolism with an estimated prevalence of 1 in 500 persons in most Western countries.[6] FH is associated with elevated cholesterol and consequently associated with coronary heart disease.[6-9] Once the genetic defect could be diagnosed and effective lipid-lowering therapy with HMG-CoA reductase inhibitors (statins) was available, genetic screening for FH seemed feasible.[10-15] In 1994 a screening programme started in the Netherlands in a provisional setting. In this screening programme, relatives of index patients (i.e. clinically diagnosed patients with a known mutation) are actively approached and screened by a genetic service called the ‘Foundation for tracing hereditary hypercholesterolemia’ (Dutch acronym StOEH).[16] Based on information given by the participating index patient, a pedigree investigation –or so-called cascade screening– is started to identify the at-risk first- and second-degree relatives of an index patient. Consent for the release of the name of the index patient was obtained prior to the approach of his/her relatives. If these relatives test positive, they are asked to provide the addresses of their first-degree (and if not available second-degree) relatives to facilitate their approach and testing. The FH-positive screenees are requested to inform their relatives before the StOEH will approach them, but it is up to them whether they actually do this. All relatives are invited to participate in the screening programme by mail. A week after receiving the written invitation the relatives are phoned by a genetic field worker (GFW) to enquire whether the relative wishes to participate in the screening programme. If they decide to participate, the GFW visits them at home and a written informed consent is obtained prior to testing. The GFW provides more information about the consequences and treatment alternatives of FH and draws blood for genetic testing. After 4 to 6 weeks the test result is communicated by mail. People who test negative are reassured that they do not carry the mutation tested for. Persons with a positive test are advised to consult their general practitioner (GP). An accompanying letter to inform the participant’s GP is enclosed, which the participant is invited to give to the GP. Thus the GP is not informed directly. In this letter, the GP is advised to refer the patient to a lipid clinic. No further services are delivered by the StOEH. For financial reasons the current programme does not include a parallel cholesterol measurement. For further diagnosis and
treatment the screenee is reliant on follow-up care in the regular medical setting (follow-up care is described elsewhere).[17]

Evaluation of the genetic screening programme for FH
We have evaluated the family-based FH screening programme in the Netherlands on its cost-effectiveness. Part of this cost-effectiveness study is an evaluation of the psychosocial consequences of the screening. Reported here is the evaluation of the first stage of the screening programme, in particular the acceptability of the approach.

In the literature, examples of process evaluation of family-based screening programmes are few. The evaluation of the family-based screening programme on hereditary cranial aneurysms in the Netherlands e.g. shows that in general there was no negative attitude towards the approach for this programme.[18;19] More is known about the psychological impact of other -non-genetic-screening programmes. In these screening programmes it is seen that initially participants are very worried,[20-23] but no long term effects are shown.[24] Studies on the psychological consequences of predictive genetic testing on e.g. Huntington's disease and hereditary breast and ovarian cancer (HBOC) suggest that tested screenees do not experience adverse psychological consequences.[25]

From an evaluation point of view some transient effects may be acceptable —to an extent depending on the interests and consequences at stake—, but large and permanent impact on Quality of Life (QoL) may be regarded unacceptable.

The principal objectives of this paper are 1) to determine what the screenees' view was on being approached for the screening programme for FH, 2) to assess what the psychological impact of this approach was, measured in QoL and 3) to evaluate non-participation to the screening programme.
Material and Methods

Subjects
The study was conducted between March and September 1998 among a consecutive cohort of 1434 persons approached for genetic testing. The inclusion criteria for our survey were: consent to our survey, and age 18 years or over. Due to resource and time constraints, as well as analytical considerations, only one person per postal address was invited, to a maximum of 20 persons per family (total N=720). The study was approved by the medical ethical board of the Academic Medical Hospital of Amsterdam.

Non-participants of the screening programme
Reasons for not participating in the screening programme were asked by phone. The interview contained 4 predefined categories of reasons and a possibility to write down a specified reason, if none of the categories applied.

Methods
Data were collected by means of two sets of self-administered standard questionnaires. This first set was handed over by the GFW who visited the participant at home and was filled out by the participant after this visit but before knowing the test result.

The second set was sent by mail approximately three days after the respondents got their test result.

Questions to assess judgement of the screening approach
The first set included questions about age, sex, civil status, educational level, religion, cholesterol level, cardiovascular disease (CVD) in family and previously obtained information for FH. Furthermore, standard questionnaires to evaluate the intrusiveness of the approach, the information provided, the presence of social pressure, and QoL were added. An extra question was added to the end of the first set to evaluate whether the participant would recommend the screening programme to somebody who is in the same situation as the(screenee).

The second set contained, among other things, questions on the opinion of the respondents about the way they received the test result.

The intrusiveness of the approach, the information provided and the presence of social pressure were evaluated in the first set by means of 16 statements (see Table 2). These 16 statements were taken from the questionnaire developed for the MARS-study[18;19] and adjusted for the situation of the screening programme for FH. The respondents could agree or disagree with or have a neutral opinion about each statement. We specified a lower limit for the acceptability of the amount of negative answers of 5%, and of 50% for negative and neutral answers together; analogous to the interpretation applied in the MARS-study. In the second set, five statements from the same questionnaire were taken and adjusted.

Instruments to assess QoL impact
To assess QoL impact, global QoL measures were used to ensure the possibility to compare the results with other screening programmes and to make longitudinal measurements possible. For all QoL instruments Dutch normative data were available.[26-28] These normative data were collected in a similar way as data of the current study. The following QoL instruments were included: the Hospital Anxiety and Depression Scale (HADS)[29], the Medical Outcomes Study 36-item Short Form Health Survey (SF-36)[30;31] and the EuroQol.[32;33] The HADS is a domain...
specific instrument. The SF-36 and the EuroQol are generic QoL instruments, which means that they measure the QoL on three domains: physical, psychological and social functioning, without being disease-specific.[34]

The HADS measures anxiety and/or depression for use in the setting of physical care and/or illness.[29] The instrument consists of two scales of 7 items, for anxiety and depression respectively. The items score from 0 (best) to 3 (worst).

The SF-36 questionnaire contains 36 items on 8 scales: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). The SF-36 consists of a two-dimensional structure, a physical (PCS) and mental (MCS) component scale respectively.[35;36]

The standard EuroQol contains 5 items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each following the general form: no problems (=1), some problems (=2), extreme problems (=3).[27;28;37]

**Genetic test**

Genomic DNA was isolated from the leukocyte fraction of 10 ml blood, followed by DNA testing using the polymerase chain reaction (PCR) technique and restriction enzyme analysis as described by Lombardi et al.[38]

**Statistical Analysis**

For all data analyses we used the Statistical Package for Social Sciences (SPSS/PC, version 8.0). Descriptive analyses were conducted and the correlations of the tested variables were assessed by Pearson's chi-square statistics and Student's t-test. A standard multivariate multinominal logistic model was used to evaluate the association between age, sex, educational level, marital status, cholesterol level and having heard of FH before the screening with the judgement on the screening approach. Furthermore, the Sign Test was used to compare categorical variables of the same case at different points in time. To standardise the PCS and MCS, the scoring algorithm as described by Ware and colleagues,[36] and the factor score coefficients for the general Dutch population[27] were used. This enables direct comparison of the PCS and MCS of the studied population with those of the general Dutch population.
Results

Study Population
During the period in which the evaluation study was conducted, the StOEH approached 1434 people (relatives of index-patients) to participate in the screening programme (see Figure 1). In all, 34 people decided not to participate in the programme. Of the 1400 participants, 720 people met the inclusion criteria for our survey and were asked to participate. The 680 people, who did not meet the inclusion criteria, were mainly excluded because the number of family members already participating in the evaluation study exceeded 20. Of the 720 people who met our inclusion criteria, 43 people did participate in the screening programme but decided not to participate in our survey. This leaves 677 participants in the survey, of whom 647 (96%) sent back the first set of questionnaires. In total there were 73 non-respondents of the survey. The second set of questionnaires was returned by 606 respondents (90% overall response), 41 screenees did not return it. These 41 screenees did not differ significantly in sex, age and FH status from the 606 screenees who returned the second questionnaire.

Figure 1 Participation in screening programme and subsequent survey

*StOEH: Foundation for tracing hereditary hypercholesterolemia

The sex and age distribution of the non-participants of the screening programme did not differ from those of the respondents of the survey. Most non-participants were not interested in knowing whether they had FH or not—a more explicit reason was not given—(15 persons) or did already know they had FH due to clinical features like high cholesterol or evident cardiovascular
disease (6 persons). Three persons gave other medical reasons, another three were afraid for problems with insurance, one thought he was too old to participate, one was afraid of blood being drawn and, for one, the intention of the screening was not clear. The other four persons did not give a reason for their refusal.

Table 1 presents the main characteristics of the 647 people, who sent back the first set. Almost 80% of the study population were either married or living together with a partner, compared to 54% in the Dutch population. Of all respondents, 56% had not previously heard of FH either in general or as running in their family, although 65% knew of family members with CVD. Of our study population, 32% were FH positive after testing.

<table>
<thead>
<tr>
<th>Table 1 Characteristics of the respondents of the survey (N=647)</th>
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<td><strong>Sex</strong></td>
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<tr>
<td><strong>Mean age</strong></td>
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<td><strong>Marital status</strong></td>
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<td><strong>Educational level</strong></td>
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<tr>
<td><strong>Religious</strong></td>
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<tr>
<td><strong>Cholesterol (self reported)</strong></td>
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<tr>
<td><strong>Heard of FH (before screening)</strong></td>
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<td></td>
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<tr>
<td><strong>Information about FH through:</strong></td>
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<tr>
<td><strong>CVD in family</strong></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>Genetic test</strong></td>
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<td></td>
</tr>
</tbody>
</table>

*a Missings excluded in percentages  
*b In the first questionnaire the participants was asked whether they had a high cholesterol level. This level was not further specified.
Judgement on the screening programme

The opinion of the respondents about 4 process aspects of the approach of the screening programme, the information provided and presence of social pressure are shown in Table 2.

Table 2 Opinion on process aspects of the approach of the screening programme on FH (N=647)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approach</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. I didn’t mind being invited to participate in the screening programme</td>
<td>92 %</td>
<td>8 %</td>
<td>0 %</td>
</tr>
<tr>
<td>2. I’m satisfied about the way I was approached</td>
<td>91 %</td>
<td>6 %</td>
<td>3 %</td>
</tr>
<tr>
<td>3. <strong>The way I was approached for the screening programme could be improved</strong></td>
<td>11 %*</td>
<td>43 %</td>
<td>46 %</td>
</tr>
<tr>
<td>4. I think it was improper to be approached without asking</td>
<td>3 %</td>
<td>9 %</td>
<td>88 %</td>
</tr>
<tr>
<td><strong>Information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Actually, I would have liked to know more in advance</td>
<td>15 %</td>
<td>45 %</td>
<td>40 %</td>
</tr>
<tr>
<td>6. The written information I got beforehand was clear</td>
<td>86 %</td>
<td>11 %</td>
<td>3 %</td>
</tr>
<tr>
<td>7. I do understand why I was approached</td>
<td>93 %</td>
<td>6 %</td>
<td>1 %</td>
</tr>
<tr>
<td>8. From the written information beforehand I did understand that my blood was going to be taken</td>
<td>97 %</td>
<td>2 %</td>
<td>1 %</td>
</tr>
<tr>
<td><strong>Worries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. <strong>The written information I received did worry me</strong></td>
<td>7 %</td>
<td>13 %</td>
<td>80 %</td>
</tr>
<tr>
<td>10. I rather had not known that I might have FH</td>
<td>4 %</td>
<td>12 %</td>
<td>85 %</td>
</tr>
<tr>
<td><strong>Social Pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. The circumstances made me feel like I was more or less forced to participate in the screening programme</td>
<td>20 %</td>
<td>13 %</td>
<td>67 %</td>
</tr>
<tr>
<td>12. I participate in the screening programme out of solidarity with my family</td>
<td>53 %</td>
<td>15 %</td>
<td>32 %</td>
</tr>
<tr>
<td>13. I felt free to choose whether I would participate or not</td>
<td>89 %</td>
<td>9 %</td>
<td>2 %</td>
</tr>
<tr>
<td><strong>Anticipated regret</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Suppose I didn’t participate in the screening programme and I would have a heart attack later on in life: I would reproach myself for that</td>
<td>50 %</td>
<td>21 %</td>
<td>29 %</td>
</tr>
<tr>
<td>15. If it turns out I have FH, I want to be treated</td>
<td>86 %</td>
<td>13 %</td>
<td>1 %</td>
</tr>
<tr>
<td>16. I didn’t like the idea of my blood being taken</td>
<td>7 %</td>
<td>6 %</td>
<td>87 %</td>
</tr>
</tbody>
</table>

*In bold*: statements which exceed the lower limit for the acceptability of the amount of negative answers of 5%, and for negative and neutral answers of 50%.

Applying the above-described limits of 5% negative answers and 50% negative and neutral answers the following statements draw attention: 3, 5, 9, 11, 12, 14 and 16 (printed bold in Table 2).
Overall the respondents are very positive about the screening programme, with apparently room for improvement of the information provided. The current programme showed some degree of perceived social pressure. The older screenees (>60 years) differed from younger screenees in their responses to a number of questions (see figure 2). Besides age and gender, educational level also influenced responses. Males more often wanted to know more in advance and the lower educated participated more often out of solidarity (both: p<0.001).

Of the respondents to the second set of questionnaires, 93% of the screenees said they were satisfied with the way they received the test result, regardless of their FH-status. However, 11% thought that the way the information was delivered could be improved. Significantly more FH positive screenees who agreed with or were neutral towards this statement (13% versus 10%; p<0.05), also significantly more often judged that the information given was not clear (12% versus 3%; p<0.001).

For people tested positive for FH, the statements 'I rather had not known that I might have FH' and 'If it turns out I have FH, I want to be treated' in the first set, were rephrased in the second set as: 'I rather had not known that I have FH' and 'Now I have FH, I want to be treated'. Overall, the FH positive screenees did not change their mind about the first statement (p=0.60), before testing 4% rather not had known they (might) have FH compared to 3% after the test result (18 persons changed their opinion in a positive and 15 in a negative direction). Significantly more people were planning to seek treatment after they proved to be FH positive than before knowing the test result (82% versus 89%; p<0.05).

Figure 2 Opinion about the screening approach, according to age (N=647)

<table>
<thead>
<tr>
<th>Statement</th>
<th>18-40 year (N=227)</th>
<th>41-60 year (N=292)</th>
<th>&gt;60 year (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Ignorance preferred' (10)**</td>
<td>4</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>'Wanted to know more' (5)</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>'Forced by circumstances' (11)</td>
<td>10</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>'Anticipated regret' (14)</td>
<td>10</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>'Participation out of solidarity with family' (12)</td>
<td>10</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

* p<0.001
** numbers in parentheses refer to the statement number in table 2
Most people (88%) would recommend the screening programme to somebody who is in the same situation as the participant, 11% did not know. Only two persons (1%) would not recommend the screening programme.

**Quality of life impact**

Table 3 shows that the distribution of the scores of the screenees on the HADS is equivalent to available reference data from the general Dutch population [26] (Table 3). With the exception of respondents of 66 years and over on the anxiety scale, the respondents scored even lower (better). Both the physical and mental subscale scores of the SF-36 showed normal to slightly better results from the screenees.

| Table 3 Quality of life of screenees, after being approached, but prior to test result |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Mean            | 95% CI of the difference |
| HADS¹ Anxiety Score 18-65 year | FH screenees    | 3.7             | (-1.9; -0.8)    |
|                                 | DGP             | 5.1             |                 |
|                                 | 66 and over     | FH screenees    | 3.7             | (-0.5; 0.9)     |
|                                 | DGP             | 3.9             |                 |
|                                 | 18-65 year      | FH screenees    | 2.1             | (-1.8; -0.8)    |
|                                 | DGP             | 3.4             |                 |
|                                 | 66 and over     | FH screenees    | 2.7             | (-2.8; -1.1)    |
|                                 | DGP             | 4.6             |                 |
| SF-36² PCS¹                   | FH screenees    | 51.7            | (0.8; 2.6)      |
|                                 | DGP             | 50              |                 |
|                                  | FH screenees    | 53.3            | (2.4; 4.2)      |
|                                  | DGP             | 50              |                 |

¹ Hospital Anxiety and Depression Scale
² Medical Outcomes Study 36-item Short Form Health Survey
³ Physical Component Scale
⁴ Mental Component Scale
⁵ Dutch General Population

On the EuroQol 56 percent of the respondents scored the best possible profile (11111), other frequently reported health states were 11121 (10%), 11112, 21121 and 21221 (all 4%). The overall mean valuation of the reported health state was 82 (SD=14), which does not significantly differ from the Dutch population (valuation=83 with SD=15) (95% CI of the difference; -0.7 – 2.7).[28]
Discussion

We conducted a process-oriented study of the current provisional genetic screening programme for FH in a large, unselected cohort of Dutch FH-patient relatives. The current study will contribute to the governmental decision making on the screening programme for FH. Overall, the screening participation and the response to our survey were high, and the measured psychological impact of the being approached for the screening programme was minimal. There appeared to be a problem with providing the right amount of information and perceived social pressure to be screened was reported, as 20% of the screenees felt more or less forced by the circumstances to participate.

Although participation rate was high, selective participation still may be present. As those 2% non-participants declined screening due to either lack of interest in knowing one’s FH status or lack of relevance if one was already clinically diagnosed as FH-patient without genetic testing, we do not think that non-representativeness is an issue here.

Surprisingly, less than half of the respondents were aware of FH in their family before being tested. In previous research on subarachnoid aneurysm family screening, awareness was almost complete.[18;19] Although research on cystic fibrosis carrier testing showed that siblings rarely discuss testing with each other,[39] this lack of communication may even be more evident when screening in large families. Ignorance of the presence of the disease may have influenced the psychological perspective of the first approach of candidate participants. Without affected family members as point of reference, much of the rationale of genetic screening will not be directly obvious to the persons approached and the potential health benefit may not be easily explained. Consequently, the role of adequate information on the risk and consequences of FH in the very first step of approach is essential.

A method-related explanation of the degree of dissatisfaction with the information supplied could be the response-tendency to agree rather than disagree with questions of the type ‘the way I was approached for the screening programme/got the test result could be improved’.[40] Asked the other way (‘was information sufficient’), persons usually show more satisfaction.

Yet, the dissatisfaction in case of a FH positive test result deserves attention. In the current set-up, the participant has full responsibility of taking actions after knowing the test result. The responsibility of the StOEH is delivery rather than explaining the consequences of the test result, as no further counselling is provided. Screenees probably expect more counselling or care than provided, making it worthwhile to consider including more counselling as a part of the way information is provided in the screening programme.

Process-evaluation results depended on age. Older respondents were –to some extent maybe rightly– more critical about the assumed benefit of screening and perceived more social pressure than younger respondents, despite the fact that, in general, older people show higher levels of socially desirable response.[41] In depth interpretation of statements referring to social pressure is difficult. It could be that older people perceived participation in screening as primarily in the interest of their relatives, rather than for their own sake. Whether this is genuine altruism, and consequently not bothersome, or involuntary participation, which should be minimised, is difficult to establish. Other personal characteristics proved to be of limited importance.

Our study showed no relevant QoL impact, the QoL of the screenees was at least equal to the
general Dutch population. Given the use of three different instruments and the size of the sample, we do not think insensitivity of the instruments to be responsible for this finding. However, whether this observation holds in the long run remains to be established.

From the experience in non-genetic screening programmes, it could be hypothesised that there would be a decline in well-being immediately following notification.[20-23] In breast cancer screening anxiety and depression following screening were raised but at a sub-clinical level,[42] returning to normal in the long term.[24;43;44] Information about psychological impact of being genetically tested for predictive genetic testing for e.g. Huntington’s disease and hereditary breast and ovarian cancer (HBOC) outside a screening programme could also give an indication what the psychological impact could be. These studies suggest that tested people do not experience lasting adverse psychological consequences.[25] However, these studies are not comparable to the screening for FH. FH is a modifiable genetic disease with acceptable treatment options. Furthermore, the persons tested for Huntington’s disease and HBOC were self-selected and came forward for testing themselves. These people most likely anticipate an adverse test result, should this occur,[45;46] while in the FH screening programme people were actively approached by the screening service and selection on emotional ability to cope was less probable. We know from carrier screening for autosomal recessive disorders that after the test result carriers think less positively about themselves and are less optimistic about their future health, than non-carriers.[47;48] But these effects do not seem strong enough to have a negative influence on the self-image or mood of the tested people.[47] Furthermore, parental guilt for transmitting a defective gene and fear of the loss of interpersonal desirability when being a carrier may occur.[39]

The psychological impact of testing for FH outside a screening programme has been retrospectively studied in Denmark.[49] The attitudes towards detection of FH, and the present well-being were measured in persons with clinically diagnosed FH and in their hypercholesterolemic relatives, after they were offered genetic testing. In this study 13% of the respondents reported a diminished well-being related to having FH and 7% felt ill due to FH. Of the patients 4 to 6% regretted that they knew they had FH and 84% approved of screening for FH. The authors conclude that the reaction to the diagnosis does not contraindicate screening. However, to limit negative reactions, a molecular genetic diagnosis must be accompanied by individualised counselling about risk, modifying factors and treatment possibilities, supporting our results regarding aftercare after a positive test result.

Successful implementation of a screening programme depends, among other things, on the impact on the QoL of participant. Here QoL appears not impaired, but perceived social pressure may be of concern. Of the screenees, 20% felt more or less forced to participate by the circumstances and over 50% participated out of solidarity with the family. This has been observed in another family-based screening programme.[18;19] It may indicate that people, at least partially, participate for the well-being of their relatives. The most prevalent reported circumstances were: responsibility towards children and/or other family members, and high cholesterol and/or cardiovascular diseases in other family members. It is a matter of judgement whether such concern is wrong or should be valued negatively.

We conclude that with some minor organizational amendments, family screening in FH-relatives can be safely implemented, assuming a favourable balance of health benefits and costs of the screening programme.[5]
Acknowledgements

We thank the respondents of this study for their enthusiasm, Marina Umans-EckenhAUSEN and the Genetic Field Workers from the ‘Foundation for tracing hereditary hypercholesterolemia’ (StOEH) for their support and help with inclusion of the study population, and Chris Moran for his comments on the English in the paper. The study was funded by The Health Research and Development Council of the Netherlands (ZON; formerly Prevention Fund) (grant number: 28-2751).

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Chapter 3

‘Quality of Life in a family-based genetic cascade screening programme on Familial Hypercholesterolemia: A longitudinal study among participants’

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Summary

Background Familial hypercholesterolemia (FH) is a genetic disorder, predisposing for coronary artery disease, with an estimated frequency of 1 in 500 persons in Western countries. In the Netherlands, relatives of genetically confirmed FH patients are tested for FH within a genetic cascade-screening programme. Here, we describe the transient and permanent effects on quality of life (QoL) effects of the screening, with a focus on psychological effects.

Methods In four self-administered questionnaires (at screening, and at 3 days, 7 and 18 months after the test result), the QoL of a consecutive cohort of 677 screenees was assessed (response 76%: 513 screenees).

Results The QoL in FH-screenees remained essentially unchanged during FH-screening. No differences between FH-positive and FH-negative screenees were found. Some known small effects of age and gender on QoL-levels were confirmed, as well as an initial effect on QoL in some of the screenees. Furthermore, the more one experienced a feeling of social pressure, and the higher one perceived the chance of having a heart attack later in life, the lower the QoL; all these significant effects, however, were small or negligible relative to the scale.

Conclusion Overall, our longitudinal survey of an unselected cohort of FH-screenees showed on average no adverse effects both on short and long term QoL. Thus, the set-up of the screening programme seems adequate. Few screenees showed adaptive responses, within this group, responses were within acceptable limits; no obvious factors define these screenees. From this perspective the implementation of FH-screening may be generally advocated.

Keywords: • Familial Hypercholesterolemia,
• Genetic Screening
• Quality of Life
• Psychological impact
Introduction

Systematic testing for genetically mediated risk factors has emerged recently, including genetic testing of apparently healthy people. The testing will often be organised within screening programmes [1]. Although the empirical evidence of the health benefits of such screening can be convincing, the broader consequences of family screening demand guided implementation strategies, including considerations of the effects on quality of life (QoL) and psychological well-being [2;3].

Familial hypercholesterolemia (FH) is a genetic disorder, predisposing for coronary artery disease. The estimated frequency of the genetic factor in Western countries is 1 in 500 persons [4-6]. In about 90%, the associated metabolic defect results in an accumulation of plasma-cholesterol and consequent excess CAD mortality [4-8]. The availability of DNA diagnosis at an asymptomatic stage and of effective lipid-lowering therapy have called for cascade screening [9-14]. In 1994, an FH-screening programme started in the Netherlands in a provisional setting, including a parallel, independent evaluation study. The evaluation study addressed not only the uptake and diagnostic procedure, but also the short- and long-term impact on QoL and psychological well-being of the participants of the screening programme.

Some evidence on QoL effects of -non-genetic- screening programmes is available. Early studies on hypertension screening showed adverse effects, which were contradicted later, both on hypertension and cholesterol screening [15-23]. In non-genetic cancer screening programmes, participants showed a temporary decline of the psychological domain of QoL [24-26]. E.g. in breast cancer screening, anxiety and depression following screening were raised but at a sub-clinical level [27], without lasting adverse psychological effects [28-30]. Psychological disturbance of prostate cancer screening was even less [31].

In genetic testing, carriers of an autosomal recessive disorder sometimes grow pessimistic about themselves and could grow less optimistic about their future health after detection [32;33], although mood in general seems unaffected [32,34-36].

The current study considers effects of FH-screening, where evidence is scarce and inconclusive. Some anxiety has been reported [37], but other studies report normal QoL and unchanged psychosocial functioning [38;39]. Adverse psychological effects in genetic screening may not only originate from the screening procedure, but also from the induced awareness of one's genetic status [40]. The perceived consequences of having FH, whether based on reality or not, and the unchangeable genetic basis of FH may result in fatalism in FH-positive screenees [41], that in turn may affect the QoL.

The principal objective of this paper is to establish in a large cohort of FH-screenees the transient and long term QoL effects of the screening, with a focus on specific psychological effects. If significant adverse effects are present, we intend to describe the change over time and its dependence on personal characteristics, like sex and age, and specifically on perceived and actual risk status, and the perceived social pressure to participate. From this knowledge, we may further optimise the FH-screening programme.
Material and methods

Screening programme
The Dutch screening programme actively approaches first- and second-degree relatives of index patients (i.e. clinically diagnosed FH patients with a known mutation). The ‘Foundation for tracing hereditary hypercholesterolemia’ (Dutch acronym: StOEH) is responsible for this pedigree investigation (‘cascade screening’) [42;43]. Family members are informed about their possible risk by mail. A week after this notification a genetic field worker (GFW) phones and, if the family member agrees to participate, makes an appointment for testing. The family members are tested at home by a GFW, who gives them more information about the procedure and FH. Furthermore, before agreeing to give a sample for DNA-analysis, the aspirant screenee signs an informed consent form. If relatives test positive, their first- and second-degree relatives are approached and offered testing, and so on. Relatives are only tested for the mutation found in the index-patient, and cholesterol is not measured within this screening programme. All test results are communicated to the screenee by mail. Screen-positives get two additional letters: one directed to him/herself with the advice to consult the general practitioner (GP), and one to the GP, inviting the GP to refer the patient to a lipid clinic. This procedure requires the screen-positives to take the initiative to seek medical follow-up, no further counselling is given within the screening programme. The screening procedure is approved by the Ministry of Health.

Written information supplied in the screening program
Before screening, relatives of FH-patients are approached by mail. This letter also comprises a leaflet, which gives more information about FH. As no exact figures are known about the penetrance estimates and consequent CHD risk, only a general description of FH is given. The leaflet explains that FH causes hypercholesterolemia, which subsequently causes damage of the blood vessels, atherosclerosis, and eventually myocardial infarction (MI). Also, information about the chances of inheriting the gene defect is given: a parent with FH has a 50% chance of passing the gene defect to his or her child.
Additional to this leaflet, a specific booklet is included with the test result in the case that the screenee tests positive. This booklet provides a detailed description of the biochemical mechanism of FH, information about inheritance and the risk of MI. It is stated that FH-positive screenees have a high risk of MI. Furthermore, the leaflet reassures the reader that hypercholesterolemia is treatable and that most FH-patients can normalize cholesterol levels with medication and diet, thus lowering the chance of getting an MI.

Subjects
The inclusion of the subjects was between March and September 1998. The inclusion criteria were: 18 years of age or older, and informed consent to genetic testing and to our survey (98% of the invited family members consented to genetic testing). The screenees were asked to participate in the current study by the GFW and signed a separate informed consent for this study. With consent of the participants, their FH-status was disclosed to the researchers. The study was approved by the medical ethical board of the hospital (AMC).

Data collection
Data were collected by means of four self-administered questionnaire sets (T0: at screening, before knowing the test result; T1, T2, and T3: 3 days, 7 and 18 months after the test result, respectively; time between T0 and T1 was on average 35 days). QoL was assessed in all four questionnaires (see below for details). The first questionnaire also covered socio-demographic
data, last year's prevalence of cardiovascular disease (CVD) manifestations, familiarity with FH (having heard of FH before the screening), familial prevalence of CVD (a/o CVD death in the family before the age of 50), cholesterol level— if known-, cholesterol-lowering medication use, risk perception and perceived social pressure.

Quality of Life questionnaires
To assess QoL impact, generic and domain specific QoL measures were used, all with available Dutch reference data [44-46]. The generic QoL questionnaires were: the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) [47,48], and the EuroQol [49-51]. The Hospital Anxiety and Depression Scale (HADS) was added as a widely used domain specific questionnaire [52].

The SF-36 questionnaire contains 36 items on 8 scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. The SF-36 response can be projected into two core dimensions, a physical (PCS) and mental (MCS) component summary score [53;54]. We standardised the PCS and MCS as described by Ware and colleagues [54] with Dutch population data [45]. This procedure provides component scores with a mean of 50 and a standard deviation of 10 in the general Dutch population, taken as a reference. Higher scores imply better physical and mental health, respectively.

The EuroQol contains a global evaluation of own health using a visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [46;55].

The HADS measures anxiety and depression for use in the setting of physical care and/or illness [52]. The questionnaire consists of two scales of 7 items, for anxiety and depression respectively. The items score from 0 (best) to 3 (worst), this gives a minimal score of 0 and a maximal score of 21 per subscale. However, also the total HADS score (both subscales added up) is used, as this score is claimed to be sensitive for non-specific distress and adaptive disorders. A total score, a score of 13 and higher indicates that an adaptive disorder may exist [56].

Risk perception
The risk perception of the screenees was studied; the perceived probability of 1) having FH and 2) having a heart attack later in life without treatment. Risk response was pre-categorised and given both as numerical (1 in x) and verbal probability. The comparison of the expected test result with the true test result allowed for categorisation of the screenees into three groups: 1) concordant, 2) discordant and 3) screenees who had an indifferent expectation of the test result (neither high nor low expectation, irrespective of the test result).

We additionally distinguished between screenees aware and screenees unaware of a cholesterol problem at the time of screening. Unaware cases were defined as screenees with an unknown cholesterol level, or with a normal cholesterol level (cholesterol level < 6.5 mmol/l) without treatment, and aware cases as screenees with either known hypercholesterolemia (with and without treatment) or a normal cholesterol level under treatment, all at the time of screening.

Social pressure
The presence of social pressure was evaluated by means of 3 statements: 'The circumstances made me feel like I was more or less forced to participate in the screening programme', 'I participate in the screening programme out of solidarity with my family', and 'I felt free to choose whether I would participate or not'. These statements were taken from the questionnaire developed for the MARS-study [57;58]. The respondents could agree or disagree with or have a neutral opinion on each statement.
Data analysis
Descriptive analyses included conventional testing of differences between groups (FH-positive versus FH-negative, T0 versus T1) using the Pearson's chi-square statistic and the Student's t-test. The longitudinal QoL data were analysed using a repeated measurement linear mixed-effects model, with time modelled as a fixed effect and effects per screenee as random effect. In addition to 'time', the following variables were examined univariately as a fixed effect: test result, age, sex, marital status, being religious or not, being aware of a cholesterol problem at the time of screening, cholesterol level, having heard of FH before the screening, having CVD, hypertension, diabetes or having any other chronic disease, CVD in the family (first degree family members with CVD, premature CVD deaths in the family), the perceived risk of having a heart attack later in life (both verbal and numerical), social pressure statements and expected test result versus actual test result. If statistically significant, these variables were entered into a similar multivariate regression model. Estimation was performed using restricted maximum likelihood (REML) in the S-Plus 2000 statistical package [59], for all other preparing analyses the SPSS version 10.0.07 for Windows was used.
Results

Response
Within the time frame of the evaluation study, 720 people met the inclusion criteria for our survey and were asked to participate (see Figure 1). Of those, 43 people did participate in the screening programme but decided not to participate in our survey. This leaves 677 participants in the survey, of whom 513 (76%) sent back all four questionnaires.

Figure 1 Participation in survey

Lost to follow up
There was no significant difference in age, sex, marital status, FH-status and educational level between the screenees lost to follow-up (N=134) and the screenees who sent back all four questionnaires (N=513).

Basic characteristics of the screenees
Table 1 presents the basic characteristics of the screenees. Overall, 46% were men and the mean age was 47 years. Furthermore, 56% had not previously heard of FH either in general or as occurring in their family, still 45% of these screenees reported first-degree family members with CVD, and 15% reported family members (total family) who died of premature CVD. Of all screenees, 3% reported to have CVD, 36% reported being hypercholesterolemic, 26% reported a normal cholesterol level, and the remaining screenees did not know their cholesterol level. Of all screenees, 36% were aware they had a cholesterol problem. After testing, 32% of our study population proved to be FH-positive.
<table>
<thead>
<tr>
<th><strong>Table 1 Basic Characteristics of the screenees (N=647)</strong></th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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<td>Mean age</td>
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<td>Marital status</td>
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<td>Educational level</td>
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<td>Religious</td>
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<td>Cholesterol (self-reported)</td>
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<tr>
<td>Aware of a cholesterol problem</td>
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<tr>
<td>Heard of FH before screening</td>
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<td>Cardiovascular and related diseases</td>
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<tr>
<td>Other chronic diseases</td>
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<td>1st degree relatives with CVD</td>
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<tr>
<td>Premature CVD deaths in family</td>
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<td></td>
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<td>Participation out of solidarity with family</td>
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<td>Freedom of choice to participate</td>
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<tr>
<td>Genetic test</td>
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* Missings excluded in percentages
Quality of life

Figure 2 Quality of Life over time (SF-36 and Hospital Anxiety and Depression Scale)

Figure 2a

Figure 2b

Chapter 3
<table>
<thead>
<tr>
<th>Measure</th>
<th>SF-36 PCS</th>
<th>SF-36 MCS</th>
<th>EuroQol Health valuation</th>
<th>EuroQol Anxiety</th>
<th>HADS Depression</th>
<th>HADS Total</th>
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<td>Intercept</td>
<td>50.7 (0.77) ***</td>
<td>51.8 (0.79) ***</td>
<td>79.5 (1.6) ***</td>
<td>4.9 (0.32) ***</td>
<td>1.58 (0.33) ***</td>
<td>5.84 (0.67) ***</td>
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<td>Time</td>
<td>0.90 (0.60)</td>
<td>-0.42 (0.12) ***</td>
<td>-0.53 (0.17) **</td>
<td>-0.55 (0.17) **</td>
<td>-1.76 (0.17) ***</td>
<td>-1.15 (0.25) ***</td>
</tr>
<tr>
<td>Time2</td>
<td>-0.02 (0.11)</td>
<td>0.10 (0.03) **</td>
<td>0.03 (0.01) ***</td>
<td>0.22 (0.05) ***</td>
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<tr>
<td>Age</td>
<td>-0.10 (0.02) ***</td>
<td></td>
<td>0.033 (0.01) ***</td>
<td>0.033 (0.01) **</td>
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<td></td>
</tr>
<tr>
<td>Sex (0=male; 1=female)</td>
<td></td>
<td>-0.86 (0.27) **</td>
<td>0.27 (0.09) **</td>
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<tr>
<td>Hypertension (0=no; 1=yes)</td>
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<td>-1.88 (0.50) ***</td>
<td>-0.88 (0.43) *</td>
<td>-1.9 (0.81) *</td>
<td>0.30 (0.14) *</td>
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<tr>
<td>Diabetes (0=no; 1=yes)</td>
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<td></td>
<td>-3.5 (1.5) *</td>
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<tr>
<td>Chronic diseases (0=no; 1=yes)</td>
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<td>-3.08 (0.32) ***</td>
<td>-3.4 (0.51) ***</td>
<td>0.31 (0.09) ***</td>
<td>0.18 (0.07) *</td>
<td>0.46 (0.15) **</td>
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<td>Small</td>
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<td>0.44 (0.18) *</td>
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<td>Large</td>
<td>-0.95 (0.34) **</td>
<td>0.20 (0.06) ***</td>
<td>0.21 (0.10) *</td>
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<tr>
<td>Very large</td>
<td>-1.02 (0.29) ***</td>
<td>0.12 (0.05) *</td>
<td>0.21 (0.08) *</td>
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<td>Neutral</td>
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<td>-0.20 (0.06) ***</td>
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<tr>
<td>Agree</td>
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<tr>
<td>Neutral</td>
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<td>0.43 (0.27)</td>
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<tr>
<td>Disagree</td>
<td>-1.56 (0.59) **</td>
<td>0.62 (0.20) **</td>
<td>0.83 (0.33) *</td>
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</tbody>
</table>

*p<0.05; **p<0.01; ***p<0.001

#Category above as reference category
SF-36
The physical component score (PCS) of the SF-36 was within the normal range at screening compared to the general Dutch population [45], and did not change significantly over time (figure 2; table 2). On average, older screenees, and screenees having hypertension, and/or any other chronic disease reported a significantly worse physical condition. Neither risk perception nor perceived social pressure was associated with the PCS. The mental component score (MCS) was within the normal range at onset [45], but deteriorated slightly but significantly over time (figure 2; table 2). Women, screenees having hypertension and screenees, who did not feel free to choose whether to participate in the screening programme generally reported a worse mental condition. Risk perception did not influence the MCS.

EuroQol
The self-reported health valuation (VAS) of the EuroQol decreased significantly over time (from 82.8 at screening to 81.2). On all occasions, screenees with hypertension, diabetes and/or any other chronic disease valued their health worse (see table 2). Furthermore, screenees with a higher perceived chance of having a heart attack later in life valued their present health lower. Perceived social pressure was not associated with the VAS of the EuroQol.

None of the included explanatory factors were significantly associated with the deterioration over time in the MCS and VAS of the EuroQol.

HADS
The anxiety subscale, the depression subscale and the total scale of the HADS declined (=improved) over time, with the greatest decline occurring between T0 and T1 (see figure 2 and table 2). Overall, women, screenees with hypertension and/or any other chronic disease, and screenees with a higher risk perception showed more anxiety. Furthermore, screenees who did not feel free to choose whether to participate in the screening programme showed more anxiety. None of these variables were significantly associated with the change over time. On the depression scale and the overall score of the HADS, the older screenees and the screenees having a chronic disease scored worse (see figure 2 and table 2). Furthermore, on the depression scale, the screenees who felt more or less forced to participate in the screening programme scored worse, and on the overall HADS score, screenees with a higher risk perception. None of these factors, however, were significantly associated with the change over time.

In all analyses the test result was included as an independent variable, but appeared not have any influence on the QoL.

Individual changes
On the individual level, 4% of the screenees showed a positive and another 4% a negative change in PCS. In the MCS, HADS-anxiety and HADS-depression subscale these figures were 6% and 7%, 5% and 10%, and 2% and 11%, respectively. Only on the depression scale of the HADS we observed a tendency that a positive test result influenced the depression score negatively (logistic regression, data not shown).
Discussion

This study showed a small significant change in QoL in FH-screenees after screening for FH, however this change was not clinically relevant. No differences between FH-positive and FH-negative screenees were found, both in the starting level of and the change in QoL. Some known effects of age and gender on QoL levels were confirmed, although the absolute effects were negligible. Two other specific effects however, were established. First, the more one experienced a feeling of social pressure, and second, the higher the risk perception of having a heart attack, the lower the QoL, be it that again the absolute effects were small. Any interpretation of these reassuring results rests on the validity and reliability of the measurements, and the representativeness of the sample.

In detail, analysis of the performance of the questionnaires showed overall satisfactory quality of response and reliabilities (data not shown). Using a quantitative rather than a qualitative design may miss a very specific harmful effect, but due to the deliberately overlapping QoL measurements with different response modes we think the prior chance of spurious findings was much higher than the missing of some negative screen effects. Furthermore, the sensitivity of these questionnaires in picking up many disorders (even of minor impact) has been established [60]. Also, results from interviews with 15 FH-screenees (not published) confirm this finding [52;61]. As no selective non-response could be demonstrated on the person level and non-response per questionnaire was low (6% or less per item), our findings seem representative for the current cohort of FH-screenees. Furthermore, only 2% of the people invited for FH-screening refused the screening offer, thus the findings seem generally applicable for all people eligible for FH-screening.

Only a small percentage of the screenees showed any substantial QoL change upon FH-positive status notification, and changes were in both directions. Temporary QoL deterioration seems easy to explain, but an explanation for the paradoxical temporary improvement has also been reported [62]. At the time of screening, the majority of the FH-positive screenees was already aware of a cholesterol problem, and reliable information on one’s FH risk status may have resulted in relief from uncertainty. As a 35-year old female screenee expressed it: ‘So my high cholesterol is not caused by eating habits, it is not my fault’. Apart from relief, adaptive responses such as threat minimisation and unrealistic optimism may account for the on average silent passing by of the genetic test notification, regardless the FH-status [63-67].

It is noteworthy that the test results within this screening programme were sent by mail and no follow-up of the screenees was included in the screening programme. We are aware that this is not usual practice in other countries, but might become more common if more large scale genetic screening programmes are instituted. One could hypothesise that sending the test result by mail might have a more negative effect on QoL than giving the test result in a counselling session. However, our results did not show any important adverse effects on QoL, both in the short and in the long term, thus effects on QoL do not seem to be an impediment for presenting the test results in this way.

A factor that could influence the QoL of the screenees is the time they had been aware that they did, or could have, a cholesterol problem [37]. Unfortunately no exact data on this were available to the researchers.

Overall, our longitudinal survey of an unselected cohort of FH-screenees showed no important adverse QoL effects on both the short and the long term. Thus, the set-up of the screening programme seems adequate. From this perspective the implementation of FH-screening may be advocated.
Acknowledgements

We thank the respondents of this study for their enthusiasm, Marina Umans-EckenhAUSEn and the Genetic Field Workers from the ‘Foundation for tracing hereditary hypercholesterolemia’ (StOEH) for their support and help with inclusion of the study population, Rebecca Holman for her help with the statistical analyses, Mary Nicolaou for her English editing and Arja Aro for her useful comments on the last draft of the article. The study was funded by The Health Research and Development Council of the Netherlands (ZON; formerly Prevention Fund) (grant number: 28-2751).

Reference List


[34] Rowley PT, Fisher L, Lipkin M, Jr. Screening and genetic counseling for beta-thalassemia


Chapter 4

‘Genetic Testing for Familial Hypercholesterolemia: Fatalism and false reassurance’

M.C. van Maarle”, M.E.A. Stouthard”, G.J. Bonsel”

1) Department of Social Medicine, Academic Medical Centre, Amsterdam
Abstract

Familial hypercholesterolemia (FH) is a genetic disorder, predisposing for coronary artery disease. In the Netherlands, relatives of genetically confirmed FH-patients are tested for FH within a genetic cascade-screening program. The aim of this study is to describe FH-screenees’ perceived control on cholesterol level and subsequent preventive behavior after genetic risk notification.

Perceived control and preventive behavior of 556 (overall response rate: 82%) screenees were measured by postal questionnaires on 2 occasions (at screening and 7 months after the test result). Perceived control was evaluated both by using the Multi-Dimensional Health Locus of Control scale, and by a question on ‘fatalism’ in FH-positive and ‘false reassurance’ in FH-negative screenees.

Of the FH-positive screenees, 54% are labeled as ‘fatalistic’ and of the FH-negative screenees 23% as ‘falsely reassured’. Being ‘fatalistic’ or ‘falsely reassured’ was inversely related to clinical outcome quality. Almost all FH-positive screenees planned to have a cholesterol check in the future. The ‘falsely reassured’ FH-negative screenees planned this less often than other FH-negative screenees. Furthermore, both ‘fatalistic’ and ‘falsely reassured’ screenees externalized the locus of control of their cholesterol level more than the other screenees.

Overall, in people screened for FH, ‘fatalism’ and ‘false reassurance’ seem to be associated with worse clinical outcome quality. Consequently, explicit prevention of ‘fatalism’ and ‘false reassurance’ as part of screening care seems justified.
Introduction

Genetic risk assessment is increasingly used for multifactorial diseases and this will extend in the near future (1). The main goal of risk assessment is to reduce the actual risk by subsequent preventive measures (2). The individual decision to undertake preventive measures may be represented by a cost-benefit analysis, balancing the expected benefits and disadvantages of the preventive measures suggested (3,4). Although perceived net benefit of preventive measures is a natural incentive for healthy behavior, perceived control over one’s condition is also suggested to be important (5).

The goal of genetic risk information in preventive programs is to induce adherence to preventive behavior (6). However, at the same time the very nature of a genetic risk may discourage adherence, as its presence may be perceived as beyond one’s personal control, resulting in a sense of fatalism (7,8). Reluctance to comply with healthy behavior may even be aggravated if genetic risk disclosure induces fear (9).

In the Netherlands, a genetic family-based cascade-screening program on familial hypercholesterolemia (FH) was started in 1994. FH, with an estimated frequency of 1 in 500 persons (in Western countries), is a distinct genetic risk factor for coronary artery disease (CAD) (10-12). FH can result in an accumulation of plasma-cholesterol and consequently in excess CAD mortality (10-13).

Untreated, a delay between asymptomatic hypercholesterolemia and overt CAD exists (‘lead time’). Preventive measures are effective during lead-time (14-19). The availability of DNA diagnosis and effective lipid-lowering therapy initiated the Dutch FH-screening program, which started in a provisional setting for a period of 6 years. A parallel, independent evaluation study covered, among other things, preventive behavior of the screenees in response to genetic risk notification.

By the mechanisms explained, risk notification may lead to inadequate or even paradoxical preventive behavior in both FH-positive and FH-negative screenees. FH-positive screenees may think that hypercholesterolemia is inevitable, and resist treatment (‘fatalism’), while FH-negative screenees may think that they are ‘safe’ or protected against hypercholesterolemia (‘false reassurance’), and even show compensatory risk behavior, e.g. smoking or eating less healthy (20).

In our study we expected that both ‘fatalism’ and ‘false reassurance’ was present and would adversely influence outcome measures. If true, screening could gain from improving the information part of the screening procedure (e.g. by specific counseling to reduce ‘fatalism’ and ‘false reassurance’). The aim of this study is to describe the perceived control on cholesterol level and subsequent preventive behavior after genetic risk notification in a large cohort of FH-screenees. A mediating role of ‘fatalism’ in FH-positive and ‘false reassurance’ in FH-negative screenees, with its potential adverse effects on treatment quality, was specifically tested.
Material and methods

Screening program
The screening program actively approaches first- and second-degree relatives of index patients (i.e. clinically diagnosed FH patients with a known mutation). The ‘Foundation for tracing hereditary hypercholesterolemia’ (Dutch acronym: StOEH) executes this pedigree investigation (‘cascade screening’) (21). If relatives test positive, their first- and second-degree relatives are approached and offered testing, etc. Relatives are tested for the mutation found in the index patient only. Cholesterol level is not measured within this (pilot-)screening program. All screenees received their test result by mail. Screen-positives receive an information booklet and two additional letters: one directed to him/herself with the advice to consult the general practitioner (GP), and one to be presented to the GP by the screenee him/herself, inviting the GP to refer the patient to a lipid clinic. This procedure requires the screen-positives to take the initiative to seek medical follow-up.

Written information supplied in the screening program
Prior to screening relatives of FH patients are approached by mail. The mail comprises, among other things, a leaflet, which gives more information about FH, and explains that FH usually causes hypercholesterolemia, and subsequently may cause damage of the blood vessels, atherosclerosis, and eventually myocardial infarction (MI). The booklet accompanying the communication of a positive test result informs the FH-positive screenee that he/she has a high risk to get an MI, if left untreated. Furthermore, the leaflet reassures the reader that hypercholesterolemia is treatable and that most FH-patients can lower their cholesterol within normal levels with medication and diet, thus lowering the chance of getting an MI.

Subjects
Subjects were included in the study between March and September 1998. The inclusion criteria were: informed consent to genetic testing and to our survey, and age 18 years or over. With consent of the participants, their FH-status was disclosed to the researchers. The study was approved by the medical ethical board of the Academic Medical Center, Amsterdam.

Data collection
Data were collected by means of two self-administered questionnaires (T0: at screening, before knowing the test result; T1: 7 months after the test result). The first questionnaire covered socio-demographic data, last year’s prevalence of cardiovascular disease (CVD) manifestations, familial prevalence of CVD (among other things: CVD death before the age of 50), and familiarity with FH (having heard of FH before the screening). The second questionnaire contained questions about cholesterol-lowering medication use, body mass index (BMI), smoking status, the intention to have a cholesterol check in the future, considering gene therapy when this will become available in the future and the Multi Dimensional Health Locus of Control (MHLC) scale (see below). Cholesterol level was asked in both questionnaires.

Multi Dimensional Health Locus of Control scale
In the second questionnaire, the MHLC (form C) was used to measure to what extent people assign influence to themselves, doctors, others and ‘chance’ in modifying their cholesterol level. The MHLC is a so-called ‘condition-specific locus of control scale’, consisting of 18 items (structured questions). By device it can easily be adapted for use with any defined medical condition (here: hypercholesterolemia) by substitution of the term ‘disease’ by the condition of
interest (22). The original scale consists of four components or subscales reflecting 4 different control orientations: Internality (6 items; ‘self control’), Chance (6 items; ‘control by external circumstances’), Doctor as Powerful Other (3 items) and Other powerful Others (3 items). The answer format of all items is a 6-point Likert-type scale (‘strongly disagree’ to ‘strongly agree’). Since one item on the doctors subscale (‘whenever my condition worsens, I should consult a medically trained professional’) was not applicable here, this item was deleted and technically treated as missing in all screenees (23). For each subscale a total score was calculated, with high scores indicating a high perceived influence (ranging from 6 to 36 in the 6-item and from 3 to 18 in the 3-item subscales). The scale represents a personal trait, hence a threshold value indicating ‘abnormal’ or ‘pathological’ is not relevant here.

**Fatalism and false reassurance**
In the second questionnaire the FH-positive screenees were asked ‘Now that I have FH, my cholesterol level can never be low’ (to capture ‘fatalism’) and the FH-negative screenees: ‘Now that I don’t have FH, my cholesterol level can never be too high’ (to capture ‘false reassurance’). The answer format was: ‘agree’, ‘neutral’ and ‘disagree’. The answers ‘agree’ and ‘neutral’ were interpreted as generally incorrect from a medical perspective, therefore this variable was dichotomized into ‘agree/neutral’ (implying the presence of ‘fatalism’ or false reassurance’ respectively) and ‘disagree’.

**Quality of clinical outcome**
Quality of clinical outcome was measured at 7 months after the test result, taking the published and widely supported Dutch hypercholesterolemia guidelines as reference (24,25). A ‘good’ outcome quality was defined by all of the following: self-reported cholesterol of less than 6.5 mmol/l, BMI of less than 27 kg/m2 and non-smoking status. ‘Moderate’ outcome quality was defined by self-reported cholesterol less than 6.5 mmol/l, but BMI exceeding 27 kg/m2 and/or positive smoking status. If a person reported a cholesterol level of 6.5 mmol/l or higher or had an unknown cholesterol level, outcome quality was defined as ‘unsatisfactory’, regardless the other risk factors involved.

**Data Analysis**
Descriptive analyses were conducted and differences of the tested variables between groups were assessed by Pearson's chi-square statistics and Student's t-test. To confirm the assumed structure of different scales making up the MHLC questionnaire in this specific patient group, a factor analysis was performed, using a principal component analysis with Varimax rotation. The internal structure of the questionnaire of four factors (internal, chance, powerful others and doctors subscale) was confirmed, with 59% of total variance explained. The reliability of the scales was tested formally. The Cronbach's alphas of varied from 0.52 (powerful others; 3 item scale) to 0.88 (internal; 6 item scale), on average 0.69, which justified further use of the MHLC in this study.
First, the association of socio-demographic characteristics and MHLC subscales with ‘fatalism/false reassurance’ was assessed for FH-positive and FH-negatives screenees separately (see figure 1). Second, we assessed the association of ‘fatalism/false reassurance’, with 1) treatment outcome variables, 2) the intention to have a cholesterol check in the future, and 3) in FH-positive screenees whether the screenees would consider gene therapy when available in the future. After this preparatory analyses, we assessed the association between socio-demographic characteristics, MHLC subscales and ‘fatalism/false reassurance’, with 1) treatment outcome variables, 2) the intention to have a cholesterol check in the future, and 3) in FH-positive screenees whether they would consider gene therapy when available in the future. When the dependent variable was dichotomous a logistic regression model was applied, using the backward elimination method (pin=0.05; pout=0.1) to select predictors. When the dependent variables were polytomous, selected variables from univariate analysis (p<0.1) were offered to a standard multivariate multinominal logistic model. The adjusted R2 (logistic regression) and Nagelkerke’s R2 (multinominal logistic regression) of the used models represent the explained variance. These analyses followed from a pre-stated model of attitude and behavior.

All statistical evaluations were performed using the SPSS version 10.0.07 for Windows.
Results

Response
In the evaluation study period, 720 people met the inclusion criteria for our survey and were asked to participate (see Figure 2). Of those, 43 people did participate in the screening program but decided not to participate in our survey. This leaves 677 participants in the survey, of whom 556 (82%) sent back the questionnaire sent out 7 months after receiving the test result.

Figure 2 Participation in survey

58

Lost to follow up
There was no significant difference in age, sex, marital status, FH-status and educational level between the screenees lost to follow up (N=91) and the screenees who sent back both questionnaires (N=556).

Basic characteristics of the screenees
Table 1 presents the basic characteristics of the screenees. Overall 45% were men, the mean age was 47 years and 3% of all screenees reported to have CVD. Furthermore, 56% had not previously heard of FH either in general or as occurring in their family. After testing, 32% of our study population proved to be FH-positive. There were no statistically significant differences between FH-positive and FH-negative screenees, except for cholesterol level at screening (74% versus 20%; P<0.001), familiarity with FH before screening (58% versus 42%; P<0.001) and the ‘chance’ subscale of the MHLC (14.6 versus 16.4; p<0.01).
Table 1 Basic Characteristics of the screenees (N=647)

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<td>Women</td>
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<tr>
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*a Misssings excluded in percentages
b CVD death before the age of 50

* There were no statistically significant differences in basic characteristics between FH-positive and FH-negative screenees, except for cholesterol level at screening, familiarity with FH before screening and the chance subscale of the MHLC. The FH-positive screenees were more often hypercholesterolemic, had more often heard of FH before screening and thought less often that chance could influence their cholesterol level.

**Basic characteristics related to ‘Fatalism’ and ‘False Reassurance’**

Of all FH-positive screenees, 28% agreed with and 26% were neutral towards the statement ‘Now I have FH, my cholesterol level can never be low’. These screenees (54%), labeled as ‘fatalistic’ about their cholesterol level, were significantly older (mean age: 48 versus 43 years; p<0.01), more often had a high cholesterol level (59% versus 39%; p<0.01) and thought it more likely that chance could influence their cholesterol level (16.2 versus 12.8; p<0.001) than screenees who thought they could have a normal cholesterol level (see table 2).

Of all FH-negative screenees 7% agreed with, and 16% were neutral towards ‘Now I don’t have FH, my cholesterol level can never be too high’. These FH-negative screenees (23%), labeled as
'falsely reassured', more often were male (56% versus 41%; p<0.05), older (mean age: 52 versus 47 years; p<0.01), lower educated (p<0.001), more often had an unknown cholesterol level (68% versus 39%; p<0.001), less often had heard of FH before screening (29% versus 41%; p<0.05) and more often thought that chance (20.0 versus 15.3; p<0.001) and other people (7.6 versus 6.4; p<0.01) could influence their cholesterol level than screenees who thought they could have a high cholesterol level (see table 2).

| Table 2 Association between basic characteristics and ‘fatalism/false reassurance’ |
|---------------------------------|---------------------------------|
| FH+  | ‘Now I have FH, my cholesterol can never be low’ | FH-  | ‘Now I don’t have FH, my cholesterol can never be too high’ |
| Agree/Neutral | Disagree | Agree/Neutral | Disagree |
| N=96 | N=82 | N=85 | N=283 |
| %* | %* | %* | %* |
| Sex (% men) | 47 | 44 | 56 * | 41 * |
| Mean age | 48 year ** | 43 year ** | 52 year ** | 47 year ** |
| Marital status (% Married/living together) | 80 | 80 | 75 | 82 |
| Educational level |
| Elementary school | 21 | 14 | 28 *** | 15 *** |
| Lower secondary school | 43 | 30 | 51 *** | 37 *** |
| Higher secondary school | 22 | 38 | 16 *** | 32 *** |
| Higher vocational level/ University | 15 | 19 | 5 *** | 15 *** |
| Cholesterol at screening |
| High | 77 | 71 | 7 *** | 24 *** |
| Normal | 5 | 9 | 25 *** | 37 *** |
| Don’t know | 18 | 21 | 68 *** | 39 *** |
| Cholesterol 7 months after test result |
| High | 59 ** | 39 ** | 2 *** | 13 *** |
| Normal | 32 ** | 56 ** | 52 *** | 63 *** |
| Don’t know | 8 ** | 5 ** | 46 *** | 24 *** |
| Heard of FH before screening (% yes) | 57 | 61 | 29 * | 41 * |
| Cardiovascular and related diseases |
| CVD | 3 | 0 | 2 | 4 |
| Hypertension | 12 | 7 | 14 | 13 |
| Other chronic diseases | 53 | 55 | 54 | 56 |
| 1st degree relatives with CVD (% yes) | 46 | 46 | 42 | 52 |
| Premature CVD* deaths in family (% yes) | 18 | 16 | 14 | 23 |
| Multi Dimensional Health Locus of Control |
| Internal | 22.9 | 24.4 | 23.9 | 24.4 |
| Chance | 16.2 *** | 12.8 *** | 20.0 *** | 15.3 *** |
| Doctors | 9.1 | 9.1 | 9.1 | 8.7 |
| Other people | 6.7 | 6.1 | 7.6 ** | 6.4 ** |

*a Missings excluded in percentages  
b CVD death before the age of 50  
*p<0.05; **p<0.01; ***p<0.001
MHLC related to 'Fatalism' and 'False Reassurance'

Both FH-positive and FH-negative screenees showed a consistent response pattern; the 'fatalistic' and 'falsely reassured' screenees showed significantly more externalization of the locus of control of their cholesterol level. Both 'fatalistic' and 'falsely reassured' screenees scored significantly higher on the 'chance' scale of the MHLC, furthermore the 'falsely reassured' screenees scored significantly higher on the 'other people' scale (all: p<0.001), supporting the assumed psychological mechanism.

'Fatalism' and 'False Reassurance' related to outcome measures, in FH-positive and FH-negative screenees respectively

Of all FH-positive screenees, the screenees who were 'fatalistic' less often had a 'good' outcome quality (21% versus 33%; p<0.05). All but a few FH-positive screenees were planning to have their cholesterol checked in the future (97% of the screenees that were fatalistic about their cholesterol level and 99% of the remaining FH-positive screenees). Additionally, there was no fatalism-related difference in considering gene therapy in the future (see Table 3).

<table>
<thead>
<tr>
<th>Table 3 Association between 'fatalism/false reassurance' and outcome quality, considering cholesterol checks and gene therapy in the future</th>
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# For FH-negative screenees: screenees with known cholesterol level at T0 only
*p<0.05
n.a. Not applicable

Using regression analyses, the relation between MHLC, 'fatalism' and the outcome measures (quality of clinical outcome, cholesterol check and considering gene therapy in the future) was further explored. The FH-positive screenees with hypercholesterolemia at screening, who were 'fatalistic' had less often a 'good' outcome quality 7 months after screening (explained variance: 13%). Furthermore, the FH-positive screenees who were lower educated and who thought more strongly that they themselves and chance could influence their cholesterol level, considered less often gene therapy (explained variance: 19%). No regression model could be fitted for 'planning to have a cholesterol check in the future' as over 98% of the FH-positive screenees stated that they planned to have a cholesterol check in the future.

The 'falsely reassured' FH-negative screenees (who knew their cholesterol level at screening) less often had a 'good' outcome quality (37% versus 45%; p<0.05). Furthermore, the 'falsely reassured' FH-negative screenees were less often planning to have a cholesterol check in the future (40% versus 58%; p<0.01).
Regression analyses were used for further exploration of the relation between MHLC, ‘false reassurance’ and the two outcome measures (quality of clinical outcome and cholesterol check in the future). The FH-negative screenees with hypercholesterolemia or an unknown cholesterol level at screening, and those who were ‘falsely reassured’ had less often a ‘good’ outcome quality 7 months after screening (explained variance: 34%). Furthermore, the FH-negative screenees who were older, had a known cholesterol level, and who thought more strongly that doctors and less strongly that others could influence their cholesterol level were planning more often to have a cholesterol check in the future (explained variance: 40%).

Discussion

Our results show that 54% of the FH-positive screenees could be labeled as ‘fatalistic’ and 23% of the FH-negative screenees as ‘falsely reassured’. Being ‘fatalistic’ or ‘falsely reassured’ predicted lower clinical outcome quality, as we hypothesized at onset. Among the FH-negative screenees, the ‘falsely reassured’ screenees planned a cholesterol check less often than the screenees who were not ‘falsely reassured’ (the FH-positive screenees invariably planned a cholesterol check).

Among other things, ‘fatalism’ and ‘false reassurance’ were associated with the extent to which people assign influence to themselves, doctors, others and ‘chance’ in modifying their cholesterol level. The ‘fatalistic’ and ‘falsely reassured’ screenees externalize the locus of control of their cholesterol level more than the screenees who were not ‘fatalistic’ or ‘falsely reassured’, adding evidence to the proposed role of perceived control in the attitude towards preventive behavior.

Interpretation of these results rests on the representativeness of the sample, and the validity and reliability of the measurements. As no selective non-response could be demonstrated on the person level and non-response per questionnaire was low (3.5% or less per item), our findings seem representative for the current cohort of FH-screenees. Furthermore, only 2% of the people invited for FH-screening refused the screening offer (26), thus the findings seem generally applicable for all people eligible for FH-screening. The validity of the MHLC subscales was confirmed. However, the question on the intention to have a cholesterol check in the future was apparently not discriminatory for FH-positive screenees, possibly due to social desirable response, although to this date we have no evidence of failing compliance with cholesterol checks. Also, one must distinguish stated intention of behavior from actual behavior, which we could not verify at this stage.

As described elsewhere, the majority of the FH-positive screenees in the current screening program did not attain optimal risk reduction one year-and-a-half after screening (27). This failure of risk reduction in the long run might be related to the sense of ‘fatalism’: people who do not believe that their cholesterol level can be influenced, may be less willing to adhere to life long preventive behavior and medication use. However, in this study ‘fatalism’ and ‘false reassurance’ was not associated with stated medication use (data not shown). In addition, genetic risk notification could also backfire by inducing fear, which we did not record directly. This could result in denial or underestimation of the risk, and an increased resistance to behavioral change (9,28). As described elsewhere, risk perception in this cohort of FH-screenees was not associated with change in risk reducing behavior (29), hence less likely.
An adverse effect, which could easily escape clinical attention, is the effect of ‘false reassurance’ in FH-negative screenes. These screenees may have the feeling to have received a ‘certificate of health’ (20); as one of the FH-negative screenees stated: ‘the test said I don’t have cholesterol’, and this particular screenee was unwilling to give up his habit to eat three fried eggs for breakfast. In general, in this study, there was a relation between ‘false reassurance’ and both not knowing one’s cholesterol level and not having the intention to have a cholesterol check in the future. This implicates that, in a screening program like the one presented, much more effort should be put in specific, explicit counseling to prevent this phenomenon.

To prevent ‘fatalism’ and ‘false reassurance’ it could be helpful to have an indication of which subgroups of screenees are more susceptible to these phenomena. Our study indicated that older, lower educated screenees who externalize the control of their cholesterol level represent the most vulnerable group.

Combining the facts that ‘fatalistic’ FH-positive screenees have suboptimal clinical outcome quality and ‘falsely reassured’ FH-negative screenees are less willing to have a cholesterol check, with the knowledge of the most vulnerable groups for ‘fatalism/false reassurance’, we can conclude that, apart from further research into the causal chain linking ‘fatalism’/‘false reassurance’ and treatment quality, caregivers should put more effort in increasing compliance, bearing the most vulnerable groups into mind, as compliance decides on the ultimate effectiveness of the screening program. The current evidence of the overall performance of this program justifies an active clinical attitude to these psychological mechanisms to improve effectiveness and efficiency (27,30).

Acknowledgements

We thank the respondents of this study for their enthusiasm, Marina Umans-Eckenhause and the Genetic Field Workers from the ‘Foundation for tracing hereditary hypercholesterolemia’ (StOEH) for their support and help with inclusion of the study population. The study was funded by The Health Research and Development Council of the Netherlands (grant number: 28-2751).
Reference List


Chapter 5

Risk Perception of Participants in a Family Based Genetic Screening Program on Familial Hypercholesterolemia

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Affiliation: 1) Department of Social Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

Abstract

The aim of this article is threefold. First, we describe the accuracy people's risk perception who have been screened on Familial Hypercholesterolemia (FH) in a family-based screening program. Second, we identify factors that modify risk perception. Finally, we show the influence of risk perception on subsequent preventive behavior.

The risk perception of 556 (677 participants, overall response = 82%) screenees was measured by postal questionnaires on 3 occasions: at screening, 3 days and 7 months after the test result was reported to the patient. Presentation of the risk was pre-categorized and given both as numerical (1 in x) and as verbal probability. In addition, medication use and attitudes towards gene therapy were determined 7 months after screening.

On average, the screenees underestimated their numeric risk of having FH and getting a myocardial infarction (MI). Furthermore, FH-positive screenees perceived they were at greater risk of MI than FH-negatives, and screenees with the highest actual risk used medication more, perceived a greater risk and opted more often for future gene therapy.

Risk perception of having FH was influenced by cholesterol level, while MI risk perception was affected by age, education, cholesterol level, and cardiovascular disease (CVD) in the family. We conclude that FH-positive screenees correctly perceive a higher risk of getting a heart attack than do FH-negative screenees. Screenees did not believe that MI was inevitable and risk perception was associated with both medication use and the intention to opt for gene therapy, but not with other preventive measures. Thus, genetic risk notification seems to be acceptable and does not lead to aversion to preventive behavior.
Introduction

Genetic information is currently used for risk estimation of common diseases and this use will probably increase in the near future.[Bell, 1998] Consequently, genetic family and population screening has gradually become part of regular patient care. The main goal of genetic screening is to make people aware of their genetic risk, which in turn should stimulate specific preventive health behaviors.[Breslow et al., 1997; Womeodu and Bailey, 1996] However, while genetic risk notification should raise risk awareness, it should not distort the perception of actual and future risk.[Marteau, 1999] Despite extensive risk perception research (see e.g. Tversky and Kahneman [1974] and Van der Pligt [1998]), it is not clear whether providing genetic risk information will motivate people to engage in preventive health behavior or will even have the opposite effect. It could motivate to change behavior by strengthening the belief that current behavior combined with the genetic risk is putting oneself at increased risk of the disease; additionally, it could strengthen the belief that treatment will be more effective when it is recommended on basis of genetic information.[Marteau and Lerman, 2001] However, it has been observed that people who have a (non-genetic) family history of heart disease are not more or less likely to engage in risk reducing behavior.[Becker and Levine, 1987] Moreover, other studies showed that heritability and genetic risks could be viewed as being uncontrollable and inevitably leading to disease, thus making treatment useless.[Troen et al., 1997; Senior et al., 1999] Overall, there is currently no evidence that providing genetic risk information increases people’s motivation to change health behavior more than would be achieved with non-genetic information and for some people, genetic information may even reduce the motivation to change behavior.[Marteau and Lerman, 2001]

Familial hypercholesterolemia (FH) is a genetic risk factor for coronary artery disease (CAD), with an estimated frequency of 1 in 500 persons (in Western countries).[Goldstein et al., 1973; Goldstein and Brown, 2001; Motulsky, 1989] It results from a mutation that affects the function of the receptor that normally removes low-density-lipoprotein from the plasma, and thus can result in an accumulation of plasma-cholesterol and consequently in an excess CAD mortality.[Scientific Steering Committee 1991; Goldstein et al., 1973; Goldstein and Brown, 2001; Motulsky, 1989] Currently, over 700 different mutations are identified.[Anonymous, 2002] When either the plasma total cholesterol or LDL cholesterol level is used as a genetic marker, the FH gene is highly penetrant at all ages.[Goldstein et al., 2001] However, some recent studies show different LDL cholesterol levels for different mutations in the LDL gene.[Bertolini et al. 2000; Chaves et al. 2001; Slimane et al. 2001; Jansen et al. 2002] In FH a delay between –asymptomatic– hypercholesterolemia and overt CAD exists. Preventive measures are effective in this asymptomatic stage.[Anonymous, 1994 and 1998; Scientific Steering Committee, 1999; Downs et al., 1998; Hoogerbrugge, 1998; Shepherd et al., 1995] The availability of DNA diagnosis at an asymptomatic stage and effective lipid-lowering therapy make genetic screening on FH feasible.

In 1994, an FH-screening program started in the Netherlands in a provisional setting with a parallel, independent evaluation study. The evaluation study comprised, among other things, an evaluation of risk perception of screenees in terms of the perceived probability of getting a heart attack later in life, depending on risk status (FH-positive or negative) and personal characteristics. Furthermore, to determine whether risk perception was associated with preventive behavior.
The evaluation focussed on the perception and representation of information by FH-screenees, the change of risk perception over time, as influenced by test result and other information/experience, and the consequential influence of risk perception on actual risk reduction (cholesterol-lowering medication use, stated attitude towards gene therapy, smoking cessation and losing weight). The main aims of our study were to establish whether: 1) disease experience, e.g. cholesterol-lowering therapy and deceased family members would increase risk perception in general; 2) screenees would incorrectly ignore the risk difference between having FH and getting FH-related CAD; and 3) increased awareness of risk would lead to more risk reducing measures.

By carefully measuring risk perceptions in a large, relevant cohort, we hoped to contribute to quality-improvement of family-based screening programs.

**Material and Methods**

**Screening program**
The Dutch screening program actively approaches first- and second-degree relatives of index patients (i.e. clinically diagnosed FH patients with a known mutation). The 'Foundation for tracing hereditary hypercholesterolemia' (Dutch acronym: StOEH) is responsible for this pedigree investigation ('cascade screening'). [Umans-Eckenhause et al. 1999; Umans-Eckenhause et al. 2001] If relatives test positive, their first- and second-degree relatives are approached and offered testing, etc. Relatives are not tested for all known mutations, but only for the mutation found in the index-patient. Cholesterol is not measured within this screening program. All test results are communicated to the screenee by mail. Screen-positives get two additional letters: one directed to him/herself with the advice to consult the general practitioner (GP), and one to the GP, inviting the GP to refer the patient to a lipid clinic. This procedure requires the screen-positives to take the initiative to seek medical follow-up.

**Written information supplied in the screening program**
Before screening, relatives of FH-patients are approached by mail. This letter also comprises a leaflet, which gives more information about FH. As no exact figures are known about the penetrance estimates and consequent CHD risk, only a general description of FH is given. The leaflet explains that FH causes hypercholesterolemia, subsequently causes damage of the blood vessels, atherosclerosis, and eventually myocardial infarction (MI). Also, information about the chances of inheriting the gene defect is given: somebody with FH has a 50% chance to pass the gene defect to his or her child. Additional to this leaflet a specific booklet is included with the test result in the case the screenee tests positive. This booklet provides a detailed description of the biochemical mechanism of FH, information about inheritance and the risk of MI. It is stated that FH-positive screenees have a high risk to get an MI. Furthermore, the leaflet reassures the reader that hypercholesterolemia is treatable and that most FH-patients can normalize cholesterol levels with medication and diet, thus lowering the chance of getting an MI.

**Subjects**
Inclusion of the subjects in the study was between March and September 1998. The inclusion criteria were: informed consent to genetic testing and to our survey, and age 18 years or over. With consent of the participants, their FH-status was disclosed to the researchers. The study was approved by the medical ethical board of the hospital.
Data collection
For the study reported here, data were collected by means of three self-administered questionnaires (T0: at screening, before knowing the test result; T1 and T2: 3 days and 7 months after the test result, respectively). Risk perceptions were evaluated in all 3 questionnaires. The first questionnaire covered socio-demographic data, last year's prevalence of cardiovascular disease (CVD) manifestations and familial prevalence of CVD (a/o CVD death before the age of 50). In the third questionnaire body weight, height and smoking status were recorded, for both at the time of screening and 7 months after screening. Cholesterol level was asked in the first and third questionnaire. In the first questionnaire it was only asked whether people had hypercholesterolemia (yes, no, or I don't know), in the third questionnaire cholesterol level was asked in words (high, normal, low), and in numbers (mmol/l). Cholesterol-lowering medication use was asked in the first and third questionnaire and attitude towards gene therapy, should this become available, in the third.

Three prior risk strata were defined. High risk was defined by clinical hypercholesterolemia and/or cholesterol-lowering medication use; intermediate risk by an unknown cholesterol level and no cholesterol-lowering medication; and low risk by a normal cholesterol level while no cholesterol-lowering medication.

The risk perception of the screenees was studied, distinguishing between the probability of having FH and that of getting a heart attack later in life. The presentation of risk perception was pre-categorized and given both as numerical (1 in x) and verbal probability (see figure 2). Perceived risk of getting a heart attack later in life was subdivided into the perceived risk with and without treatment. Risk perception was studied before and after knowing one's FH status.

Data Analysis
Descriptive analyses were conducted and differences of the tested variables between groups were assessed by Pearson's Chi-square statistics and Student's t-test. For within-subject changes over time we used the Friedman test for categorical data. The relation at the time of screening between the set of clinical and socio-demographic independents on the one hand, and risk perception on the other was established. Risk perception was defined here as the perceived chance of having FH (at T0, hence before knowing the test result), and the perceived probability of getting a heart attack later in life when having FH and not being treated (both in numerical and verbal probability). Selected variables from the univariate analysis (p<0.1) were further offered to a standard multivariate multinominal logistic model (multinominal rather than standard logistic model as the dependents were polytomous). The Nagelkerke's R2 of the used models showed the explained variance.

Focussing only on FH-positive screenees, the association between medication use 7 months after screening and socio-demographic, clinical and risk perception variables was established. The variables were offered to a logistic regression model, using backward elimination method (pin=0.05; pout=0.1). Furthermore, the association between considering gene therapy and the above-mentioned set of variables was tested in a similar way.

The analyses are based on N=647 when only variables from the first questionnaires are used (basic characteristics and screenees' expected FH-status), and based on N=556 in all other analyses.

This statistical evaluation was performed using the SPSS version 10.0.07 for Windows.
Results

Response
In the evaluation study period, 720 people of the cohort met the inclusion criteria for our survey and were asked to participate (see Figure 1). Of those, 43 people did participate in the screening program but decided not to participate in our survey. This leaves 677 participants in the survey, of whom 647 sent back the first questionnaire and 556 (82%) sent back all three questionnaires. The risk perception questions were filled out nearly complete, with only 2-4% missings or uninterpretable responses per question.

Figure 1 Participation in survey

![Flowchart showing participation process]

Lost to follow-up
There was no significant difference in age, sex, marital status, FH-status and educational level between the screenees lost to follow up (N=91) and the screenees who returned all three questionnaires (N=556). Of the 30 people who agreed to participate but did not send the first questionnaire back, no further information was available; these screenees were considered as non-respondents rather than as lost to follow-up.

Basic characteristics of the screenees
Table 1 presents the basic characteristics of the screenees. Overall, 46% were men and the mean age was 47 years. Furthermore, 56% had not previously heard of FH either in general or as occurring in their family, still 45% of these screenees reported first-degree family members with CVD, and 15% reported family members (total family) who died of premature CVD. Of all screenees, 3% reported to have CVD, 36% reported being hypercholesterolemic, 26% reported a normal cholesterol level, and the remaining screenees did not know their cholesterol level. After testing, 32% of our study population proved to be FH-positive.
Table 1 Basic Characteristics of the screenees (N=647)

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<td><strong>Cholesterol (self-reported)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td><strong>Heard of FH before screening (% yes)</strong></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td><strong>Information about FH before screening (through):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family members</td>
<td>63</td>
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</tr>
<tr>
<td>Doctor</td>
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<tr>
<td>Media</td>
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<td></td>
</tr>
<tr>
<td>Friends/acquaintances</td>
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<tr>
<td>Work/studies</td>
<td>3</td>
<td></td>
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<tr>
<td>Other</td>
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<td></td>
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<tr>
<td><strong>Cardiovascular and related diseases</strong></td>
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<td>Diabetes</td>
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<tr>
<td><strong>1st degree relatives with CVD (% yes)</strong></td>
<td></td>
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<tr>
<td><strong>Premature CVD deaths in family (% yes)</strong></td>
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<td>19</td>
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<td><strong>Genetic test</strong></td>
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<td>FH positive</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>FH negative</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

*Missings excluded in percentages

In the first questionnaire the participants was asked whether they had a high cholesterol level. This level was not further specified.

Now or in the last 12 months

CVD death at the age of 50 or younger.
Risk perception at screening and change over time

Screenees’ expected FH-status
At the time of screening (T0; N=647) almost 50% of the screenees rated their verbal chance of having FH as high or very high and 44% rated their numerical chance of having FH 1 in 3 and higher. In retrospect the FH-positive screenees appeared to have rated their chance of having FH significantly higher than the FH-negative screenees (p<0.001). This remained true if we excluded screenees with prior knowledge of their cholesterol level. Screenees in the highest prior risk stratum perceived a significantly higher risk than screenees in an intermediate or low prior risk stratum (p<0.001; figure 2).

Figure 2 Risk perception of having FH and actual risk

Risk perception
The chance of getting a heart attack later in life (untreated)

Risk of getting a heart attack later in life
In figure 3 the verbal and the numerical risk perception for getting a heart attack are shown (N=556). At T0 both the expected risk in case of a being FH-positive and being FH-negative were asked; from T1, the risk perception refers to one’s actual FH-status. Both in verbal and numerical risk terms, and at all three points in time, the FH-positive screenees perceived a significantly higher risk of getting a heart attack later in life than FH-negative screenees (p<0.05). Generally, this difference was also observed in the situation with treatment. The risk perception of the FH-positive screenees was significantly lower in the condition with treatment than without treatment, at both T1 and T2 (p<0.001). On average, both FH-positive and FH-negative screenees perceived a decreasing risk (verbal and numerical) over time (p<.05), although in verbal risk perception 16% of the FH-negative and 19% of the FH-positive screenees perceived a higher risk at T2 than at T0. In numerical risk perception these figures were 16% and 13%, respectively.
Factors associated with risk perception

Screenees’ expected FH-status
In verbal risk perception the younger screenees rated their chance of having FH higher than older screenees. Furthermore, screenees with hypercholesterolemia, higher education and/or CVD in the family (having first-degree family members with CVD and premature CVD deaths in the family) rated their verbal chance of having FH higher than screenees without these characteristics (N=556; all: p<0.05, except having first-degree family members with CVD: p = 0.08). These factors explained 41% of the variance. Results in numerical risk perception were much alike: with the exception of having heard of FH (added) and educational level (removed), the explanatory variables were the same, as was the explained variance.

Risk perception of getting a heart attack later in life
In verbal risk perception the older screenees rated their risk lower than the younger screenees. Furthermore, screenees with hypercholesterolemia, higher education and/or first-degree relatives with CVD perceived a higher verbal risk than screenees without those characteristics. Screenees who did not know their cholesterol level perceived the lowest verbal risk (N=556; p<0.05; explained variance: 22%). In numerical risk perception the associated variables were the same, except for age, but the explained variance was only 14%.
Association of risk perception and preventive behavior

Medication utilization
The medication utilization in the FH-positives rose from 58% at T0 to 77% T2 (p<0.001). In the FH-positive screenees age, sex, cholesterol level in words and numbers, and numerical risk perception of getting a heart attack later in life with or without treatment were associated with medication utilization at T2 (p<0.05; explained variance: 56%). Screenees using cholesterol-lowering medication were significantly older, more often male, perceived a higher risk of getting a heart attack later in life (with and without treatment), had a higher cholesterol level and more often family members with CVD than screenees without these characteristics. Screenees with a substantial difference in risk perception between the situation with and without treatment (three or more categories difference and a lower risk perception in the situation with medication) are significantly more often using cholesterol-lowering medication (p<0.05).

Considering gene therapy
Of all FH-positive screenees, 69% would consider gene therapy when this would become available. Men, screenees who were living together or married, the higher educated, screenees who were not religious, screenees perceiving a higher risk of getting a heart attack later in life (with and without treatment) and screenees with hypercholesterolemia were more inclined to opt for gene therapy (p<0.05; explained variance: 43%).

Other preventive behavior
There was no significant change in smoking status and BMI, both in FH-positive and FH-negative screenees. At the time of screening 28% of the FH-positive and 26% of the FH-negative screenees smoked, compared to 23% and 26% at T2, respectively. The mean BMI at T0 was 24 and 25 kg/m2 in FH-positive and FH-negative screenees, respectively. This did not change at T2. There was no difference in risk perception in screenees who quitte d smoking or lost weight versus those who did not.

Discussion
The main goal of genetic risk notification is to facilitate a free, well-informed choice for the client, reflected by an accurate risk perception, perceived effectiveness of preventive measures, and compliance with these measures.[Beck and Frankel, 1981; Rogers and Mewborn, 1976; Weinstein and Klein, 1995] Less than 20% of the screenees rated their chance of having FH 1 in 2 (50%), the objective probability of first-degree family members of an FH-patient. Future FH-positive screenees rated their chance of having FH higher than the FH-negatives, only partly explained by the prior knowledge of cholesterol level. FH-positive screenees perceived a higher future heart attack rate than FH-negative screenees, but risk levels expressed numerically were again substantially lower than epidemiological risks in these patients. Screenees with a relative high risk perception more often used medication or opted for gene therapy. Also, medication utilization was the highest in screenees with the largest difference in risk perception between the situation with and without treatment. About 25% of the screenees smoked 7 months after screening, and, maybe even more disturbing, smoking status and BMI did not change over time nor differed between FH-positive and FH-negative screenees.
Some study features require consideration. A possible limitation of the study could be the sample size. Although our study included a large part of all Dutch screenees, it may not be large enough
to conduct a detailed causal analysis in subgroups (defined according their initial attitude behavior or behavioral change). This research could be conducted in the future. However, the power of this study was large enough to show whether in FH-positive screenees the average changes aimed for were met and whether in FH-negative screenees adverse changes on average were absent. Another possible limitation is that all persons tested for FH were of Caucasian background, which could impair the generalizability of the findings of this study for other genetic screening programs. From a clinical point of view, validity seems unimpaired in our case, as FH-mutations in the Netherlands are primarily restricted to Caucasians. However, our results may not fully apply to screening programs involving all ethnicities, or with altered risk conditions in ethnic minorities.

The Dutch program did not include (co)payment of the screenees, either for the test or for subsequent treatment. To some extent this enables to investigate personal health beliefs without interference of financial motives, on the other hand generalizability may be limited for countries with another financial arrangement.

We had to decide on relevant time anchors for measurement: distant enough from the risk notification to study stable, deliberate, views on personal health risk and preventive behavior, and approximate enough to be able to study causal reasoning of the screenee. From clinical experts and additional data we collected we know that the clinical management of FH-positive screenees often take some months to stabilize.[van Maarle et al. 2002]

A theoretical study feature, which needs consideration, is the risk perception concept used. We deliberately chose the concept of ‘conditional own risk’, that is the risk as perceived by the screenee given a certain condition. This concept has the advantage above unconditional measures in that it is more closely linked to preventive behavior.[van der Velde et al., 1996] Perceived risk predicts behavior as well as comparative risk appraisal.[van der Pligt, 1998] We included both numerical and verbal risk ratings, because numerical measures of risk perception are claimed to be best for checking the accuracy of screenees’ risk perception as influenced by risk notification, while verbal measures are found to be better predictors of people’s behavior intentions.[Windschitl and Wells, 1996] The latter was not confirmed in our study, rather we observed similar relations of both risk appraisals to preventive measurements. There is no indication that selective lost to follow-up was present and the respondents were well able to answer the risk perception survey-questions.

Risk notification is generally directed at facilitating risk-reducing behavior. Rogers [1975] suggested that three main stimuli could influence risk-reducing behavior: perceived severity of the disease, perceived vulnerability and the efficacy of the recommended response. Others have recognized that perceived vulnerability in the sense of an accurate risk perception is probably a necessary prerequisite for behavior change.[Breslow et al., 1997; Womeodu and Bailey, 1996] In this study we concentrated on perceived vulnerability after risk notification. This study showed that the screenees had an inaccurate low numeric risk perception on having FH and on getting a heart attack, although apparently differentiated between the two. The rather low numerical risk perception of the heart attack rate with FH, is consistent with the literature: large risks on events are in general underestimated[Liachtenstein et al., 1978; Sjöberg, 2000], and risk judgements frequently show moderate correspondence to epidemiological findings.[Legato et al., 97; Leventhal et al., 1999; van der Pligt, 1998; Wilcox and Stefanick, 1999] One explanation of this low risk perception is inadequate patient education. However, other factors have to be taken into account. Firstly, unrealistic optimism of one’s own health and health risks is a well-known phenomenon.[Weinstein, 1984; Weinstein, 1987; Weinstein and Klein, 1995] Secondly, this study shows, as other studies, that screenees without a direct or indirect risk-experience have a less
accurate risk perception than screenees with risk-experience.[Sjöberg, 2000; Weinstein, 1987; Wilcox and Stefanick, 1999] Apart from risk-experience, the age of the screenee compared to the affected family members could be of importance; the closer in age, the more likely a person might see him or her self at risk.[Hunt et al., 2001] Lastly, in this study we did not study the screenees’ prior expectations of and knowledge about the genetic test and diagnosis. These expectations and this knowledge could influence the way people handle the risk notification. However, unbiased measurement of the pretest status usually is impossible in practice due to (understandable) ethical requirements, which impose the candidate screenee to be informed on purpose of the screening offer and on preceding measurements.

Overall, the results show that the current information provision on vulnerability (having FH and getting a heart attack) fails to achieve a medical correct risk perception in the screenees.

Most models of preventive health behavior include the recognition of one's own risk status as an important condition to make a rational decision on adopting risk-reducing behavior.[van der Pligt, 1998] This study shows that screenees with the highest objective risk and risk perception also have the highest medication utilization and more often opt for gene therapy when this will become available. The conclusion that risk-information suffices to enhance rational behavior must be tempered if we take smoking habits and body weight into account. The screenees seem to make a rational choice concerning medical treatment, but not concerning life style adjustments. This could indicate that FH is seen as a ‘medical’ problem, without a direct link to ‘non-medical’ life style factors. In general, people seem to be quite aware of the relative health risks of specific behaviors, but the interpretation of these risks changes when this knowledge is applied to own risk behavior.[Ayanian and Cleary, 1999; Lee, 1989; McKenna et al., 1993; van der Pligt, 1998] Also, screenees might only focus on what they feel is the most risky factor (in this case FH), and using the information about other ‘less relevant’ risk factors much less.[French et al., 2000] As smoking cessation might have the same or even larger health impact than reducing everyone’s cholesterol levels to normal[Bonneux, 2000; Tsevat et al., 1991], this casts doubts on the utility of FH-screening in the present form. It may be that too little attention is given to other risk factors than the genetic risk factor. However, risk-modification of the old risks presumably requires more investments than that of the new one. Furthermore, using medication or opting for something ‘futuristic’ like gene therapy demands less of the patients (or is perceived to be less demanding) than quitting smoking or changing one's diet.

We conclude that the FH-positive screenees correctly perceive a higher risk of getting a heart attack later in life than do FH-negative screenees. Also, FH-positive screenees do not exaggerate their risks or feel that CVD are inevitable. Finally, risk perception was associated with medication use and the intention to opt for gene therapy, but not with other preventive measures, in particular smoking cessation. Thus, genetic risk notification seems acceptable and does not lead to aversion to preventive behavior. Also, correct representation of numerical risks is not a prerequisite for correct risk perception used for deciding on preventive behavior.
Acknowledgements

We thank the respondents of this study for their enthusiasm, Marina Umans-EckenhAUSEN and the Genetic Field Workers from the 'Foundation for tracing hereditary hypercholesterolemia' (StOEH) for their support and help with inclusion of the study population. The study was funded by The Health Research and Development Council of the Netherlands (grant number: 28-2751).

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Follow-up after a family-based genetic screening programme on Familial Hypercholesterolemia: Screening alone is not enough

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¹Department of Social Medicine, Academic Medical Centre, Amsterdam

BMJ. 2002 Jun 8;324(7350):1367-8
Familial Hypercholesterolemia (FH) is an autosomal dominant disorder of lipoprotein metabolism with an estimated frequency of 1 in 500 persons (in Western countries) and results in excess mortality from coronary artery disease (CAD).\cite{1} Once the genetic defects could be diagnosed and effective lipid-lowering therapy with statins was available, genetic screening has been considered.\cite{2}\cite{3} In 1994 a family-based genetic screening programme on FH started in the Netherlands. The programme's effectiveness primarily rests on the health gain due to evidence-based treatment of newly identified patients. We therefore assessed in FH-positive screenees the level of subsequent preventive care and short-term clinical outcome (as defined by current guidelines) as a proxy for the expected level of CAD in the long run.\cite{4}

**Participants, methods, and results**

The 'Foundation for tracing hereditary hypercholesterolemia' (Dutch acronym: StOEH) performs cascade screening in families of clinically diagnosed FH-patients with a known mutation, and actively approaches first- and second-degree relatives.\cite{5} Screenees are tested for the known mutation; their cholesterol level is not measured. The test result is communicated to the screenee only (by mail). The StOEH is not involved in the treatment of detected cases, nor in the monitoring of the follow-up process.

The evaluation study was conducted from March to September 1998 among all 215 screen-positives of a consecutive cohort of 677 screenees in the FH-screening programme. The inclusion criteria were: consent to genetic testing and the current study, a positive test result, and age 18 years or over. With consent of the participants, the FH-status was disclosed to the researchers.

Data were collected through three self-administered questionnaires: at screening, 7 and 18 months after the communicated test result. The main outcome measures were treatment and clinical outcome quality in FH-positive screenees. Treatment quality was defined according to the key recommendations of the Dutch guidelines on hypercholesterolemia; clinical outcome quality was measured by achieved cholesterol level, body mass index and smoking status (see table 1).\cite{4}

Two categories of FH-positive screenees were contrasted depending on the degree of awareness: screen-positives with an unknown cholesterol level or with a normal cholesterol level without treatment at the time of screening ('newly identified cases'), versus screen-positives known to be hypercholesterolemic – cholesterol level of 6.5 mmol/l or higher – or treated for this condition ('confirmed cases').

166 (77%) Screen-positives filled out all three questionnaires. Respondents and people lost to follow-up did not differ with respect to all but one characteristic (statin use; respondents versus people lost to follow-up: 57% versus 39%; p<0.05).

Overall, 45% of the screen-positives were men. Of the screen-positives, 25% were newly identified and 75% confirmed cases, latter being older (means: 48.2 versus 38.9 years), showing higher cholesterol level if known (10.7 versus 6.0 mmol/l), and having more often at least one first-degree family member with cardiovascular disease (CVD) (50% versus 32%) or premature CVD death (21% versus 5%) (all comparisons: p<0.05).

Although quality of treatment and clinical outcome improved substantially over time in both awareness groups (see table 1), screen-positives as a group ultimately did not attain an optimal care level. Treatment quality was still unsatisfactory in 21% (newly identified: 40% versus

\[87\]
confirmed patients: 14%) and clinical outcome quality was still insufficient in 47% (newly identified: 48% versus confirmed patients: 46%) of the cases. Of all FH-positive screenees, 36% was hypercholesterolemic at follow-up, 15% did not use statins while hypercholesterolemic, and 24% smoked.

Table 1 Treatment and clinical outcome quality in FH-positive screenees

<table>
<thead>
<tr>
<th></th>
<th>Newly identified cases (N=41)</th>
<th>Confirmed cases (N=125)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>At screening</td>
<td>At follow-up</td>
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<tr>
<td>Follow-up</td>
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<td>Cholesterol checked</td>
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</tr>
<tr>
<td>Medication use</td>
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<td>34%*</td>
</tr>
<tr>
<td>Statin use</td>
<td>0%*</td>
<td>34%*</td>
</tr>
<tr>
<td>Diet</td>
<td>12%*</td>
<td>46%*</td>
</tr>
<tr>
<td>Lifestyle advice</td>
<td>0%*</td>
<td>83%*</td>
</tr>
<tr>
<td>Treatment Quality&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Unsatisfactory</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0%</td>
</tr>
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<td>24%*</td>
</tr>
<tr>
<td>Cholesterol unknown</td>
<td>76%*</td>
<td>22%*</td>
</tr>
<tr>
<td>Smoking</td>
<td>34%</td>
<td>29%</td>
</tr>
<tr>
<td>BMI &gt; 27 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>7%</td>
<td>10%</td>
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<tr>
<td>Clinical Outcome Quality&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Good</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Unsatisfactory</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Significant difference in time (p<0.05).

<sup>a</sup> Treatment Quality:

'Good': 
statin use (depending on cholesterol level), diet adherence and advice to quit smoking and lose weight if necessary.

'Moderate':
statin use, without diet and/or no appropriate lifestyle advice

'Unsatisfactory':
no medication while being hypercholesterolemic, or using cholesterol lowering medication other than statins

<sup>b</sup> Clinical Outcome Quality:

'Good':
cholesterol < 6.5 mmol/l, BMI <= 27 kg/m2 and non-smoking status

'Moderate':
cholesterol < 6.5 mmol/l, BMI > 27 kg/m2 and/or positive smoking status

'Unsatisfactory':
cholesterol >= 6.5 mmol/l or unknown, regardless BMI/smoking status
Comment

Both confirmed and newly identified patients benefit from FH-screening as their risk status improves and cholesterol-lowering therapy is instituted. However, in almost half of the cases the achieved level of care does not keep up with current guidelines. Opportunities for improvement towards current guidelines are physician education, better guideline implementation and, foremost, an intensification of the link between diagnosis and follow-up care in the screen process.

Acknowledgements

We thank the respondents of this study for their enthusiasm, Marina Umans-EckenhAUSEN and the Genetic Field Workers from the ‘Foundation for tracing hereditary hypercholesterolemia’ (StOEH) for their support and help with inclusion of the study population.

Contributors: All authors conceived the study, for which the data were then collected by MvM and MS; MvM, MS and GJ contributed to the analysis and interpretation of the data, and all authors contributed to the preparation of the article.

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Competing interests: None declared

Reference List

Chapter 7

Getting insurance after genetic screening on familial hypercholesterolemia; the need to educate both insurers and the public to increase adherence to national guidelines in The Netherlands

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Keypoints

• In the Netherlands guidelines and legislation exist on the use of genetic test information.
• The present study shows that individuals still encounter insurance problems as a result of participating in a genetic screening program.
• It is not clear why these problems occur: whether insurance companies ask questions regarding genetic testing or questions that can be read as such, or that individuals themselves give more information than asked for.
• We conclude that guidelines and legislation on genetic information are but a prerequisite and that education of all involved is equally important.
Familial Hypercholesterolemia

Heterozygous Familial Hypercholesterolemia (FH) is a common autosomal dominant inherited metabolic disease with a prevalence of 1 in 500 in most Western countries. [1] [2] [3] Individuals with FH experience an increased risk for coronary artery disease (CAD) and excess mortality especially at a young age. [4] [5] Until recently the diagnosis of FH was based on clinical signs and symptoms alone. These included elevated cholesterol levels, in particular of LDL-cholesterol, in combination with the presence of tendon xanthoma, corneal arcus, xanthelasmata and a history of early (CAD). Frequently FH was diagnosed after a first cardiac event.

Genetic screening

The discovery of LDL receptor gene mutations in clinically diagnosed FH patients and the consequent development of DNA tests for these mutations, enabled the diagnosis of FH in pre-symptomatic patients. In principle, the availability of effective treatment for FH made screening of relatives of identified FH patients an attractive strategy to reduce the risk of CAD.

In 1994, such a family-based genetic screening program for FH was implemented in the Netherlands. [6] [7] This program is targeted at at-risk relatives (over 16 years of age) of clinically diagnosed FH patients with a known mutation in the LDL-receptor gene, also called index patients. First degree relatives of index patients are offered genetic testing for the mutation found in the index patient. If these relatives carry the mutation, their first degree relatives are screened. Mutation carriers are back-referred to their general practitioner with the advice to have a further specialist examination at a lipid clinic.

Social consequences of genetic screening

Participating in such a genetic screening program may induce other effects than the aimed health benefit due to reduction of CAD risk. As a result of screening there may be negative social consequences, such as problems with regard to the access to insurance. In the Netherlands, as in most other countries, health insurance is compulsory. The health system in the Netherlands can be classified as a Sickness Insurance model. The Netherlands has developed a mixed health care system in which approximately 70% of the population is covered for their medical costs (except chronic residential care) through an income related social health insurance, and the remaining 30% through private health insurance. [8] Insurance companies do not always accept people who apply for insurance, but a special insurance arrangement is available for persons difficult to insure. If, however, a person has to leave the social health insurance plan as a result of a higher income, national rules enforce acceptance by a private insurer. The last decade has shown a rapid fusion from many sick funds and private health insurers into fewer large insurance-bank companies. These companies offer a wide array of work disability and life insurance packages, often in combination with mortgages.

Individuals who apply for insurance have to fill in a health questionnaire. Coverage of claims depends on true response to this assessment of prior risks. However, the information asked for is restricted with regard to information from genetic tests. In the Netherlands, a moratorium has been declared on the use of genetic test results. In this moratorium, insurance companies state that below an amount of 300.000 Dutch guilders (approximately 85.000 British pounds) for life
insurance and below an amount of 60.000 Dutch guilders for the first year and 40.000 Dutch guilders for the second and following years in work disability insurance, the results of genetic tests do not have to be supplied (including information with regard to the suffering or death of family members due to serious untreatable familiar disorders). The Act on Medical Examinations, which has come into force in 1998, contains the same conditions. Many European countries have no legislation or guidelines on insurance and medical examinations with respect to genetic testing. [9] Other countries (e.g. France) have guidelines and have imposed a moratorium on the use of genetic tests. In the UK, guidelines on genetic testing are proposed by the insurance industry, rather than by the government. The issue of this paper is whether such a moratorium on the use of genetic tests or legislation protects participants of a genetic screening program from experiencing problems in the access to insurance.

Empirical study

We conducted an empirical study among individuals screened for FH in the Netherlands by the program mentioned above, in a period in which the moratorium and/or the Act on Medical Examinations were into force. The following questions were addressed:

• to which extent do individuals screened for FH, run into problems when applying for insurance (dependent on the test result);
• which problems were the most prevalent, if any;
• how did problems relate to the medical condition: were they due to having a mutation for FH or to an elevated cholesterol level alone.

From about 1000 persons screened between 1st of January 1994 and 31st of December 1997, 350 individuals aged 20 to 60 years with known test results were selected from the registration. We aimed for an equal distribution of age and gender in the group with (n=175) and without (n=175) a mutation for FH. The age range was chosen for two reasons. Life insurance and mortgages are predominantly relevant for this age range, and cholesterol levels for those aged over 60 often exceed cut-off points used by insurance companies. Administrative data were made available by the organisation responsible for the screening programme (the StOEH-foundation). To protect privacy, the StOEH, rather than the investigators, invited selected persons to participate by means of a postal questionnaire. Questionnaires could be returned to the StOEH. One reminder was sent two weeks after the first questionnaire. The study was approved by the Medical Ethical committee of the Academic Medical Center.

Of the 350 addresses, 327 apparently were valid. Of the 327 individuals who received the questionnaire, 202 returned the questionnaire (61% response). More women than men returned the questionnaire (116 versus 86). Of the 202 respondents, 46 individuals applied for insurance in the period between being screened and the present study (23%). Of those 46 individuals who tried to get insurance, 17 encountered problems (37%; see table 1).

The type of problem most often encountered was the requirement to pay a higher premium, the requirement to undergo additional medical tests, the requirement to let the insurance company scrutinise medical records, and complete rejection of the application for insurance. If stated, the argument of the insurance companies to support their policy was the fact that the applicant had FH. Surprisingly, most (13 out of 17) individuals who encountered problems applied for a life insurance well below the cut-off points stated in the moratorium and the Act on Medical
Examinations, which implies that the applicants were not obliged to provide the insurance company with information on genetic testing.

The question remains whether the problems individuals encountered were due to having a genetic mutation for FH or to the elevated cholesterol level. The table shows the relation of the clinical risk data among the 46 respondents who applied for insurance.

<table>
<thead>
<tr>
<th>Clinical Risk</th>
<th>Problems</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mutation</td>
<td>Cholesterol level</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>≤ 6.5 mmol/l</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.5 mmol/l</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.5 mmol/l</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>17</td>
</tr>
</tbody>
</table>

We apply a 6.5 mmol/l cut-off in cholesterol level since insurance companies consider individuals with a cholesterol level above this cut-off point to be at increased risk of death. We used loglinear analysis with having problems as the dependent variable and the mutation and cholesterol level as independents. Correlation between the independent variables was assumed. We looked for the most economic model that would fit the data, meaning the model with the fewest interactions. The model in which only the mutation is associated with having problems fitted the data (Likelihood Ratio Chi Square = 2.32, df=2, p=0.31), while the model in which only the cholesterol level is associated with having problems did not. Therefore, from this analysis it seems that encountered problems primarily relate to the FH mutation. This policy is at discrepancy with the current scientific state of the art which acknowledges the cholesterol (level) to be the transmitter or carrier of the higher mortality risk associated with FH. However, given the small sample sizes of the different subgroups, a definite conclusion regarding this issue cannot be drawn.

Discussion

This empirical study has shown that in the Netherlands, which combines relevant guidelines and legal arrangements on the use of genetic testing in insurance affairs, individuals encounter unanticipated insurance problems as a result of participating in a genetic screening program. Although the number of individuals exposed to an insurance procedure is small (46) due to the limited follow-up time of tested persons, the proportion of those encountering problems (a third) is worrisome, even if one accounts for some selective response. Moreover, others reported similar data [10].

Even more disturbing was the presence of problems in cases where the Act on Medical Examinations explicitly rules out a role for genetic test information. From our study it is not clear why these problems occur, i.e. whether insurance companies ask questions regarding genetic testing or questions that can be read as such, or that individuals themselves give this information without being asked for it. The latter may be particularly true for the relatively uneducated. If asked for, only 14% of the individuals knew about the Act on Medical Examinations or the moratorium. The line of questioning or the repeated statement in questionnaires that insurance coverage is lost if the information supplied is incorrect may induce over-response by the
applicant. Furthermore, compared to questionnaires designed for scientific purposes (e.g. health risk measurement in surveys), the existing insurance questionnaires frequently appear ambiguous, providing the applicant no clues as how to interpret questions. Our main conclusion is that implementation of the Act on Medical Examinations requires more control on its procedural execution. Moreover, the participants of a genetic screening programme, the public in general, but also those engaged in the insurance acceptance process should be educated about the existing guidelines regarding genetic testing. At this stage responsibilities are ill-defined. Recently, the screening organisation included explicit information on the issue prior to the testing procedure. Our case study demonstrates that the presence of national guidelines and regulations on the (mis)use of genetic information is but a prerequisite for appropriate use of genetic information in the context of insurance. Education of all involved, including the screenee/patient is equally important.

References


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Conflicts: None
Chapter 8

Summary and Discussion
With the emerging knowledge of genetics, predictive testing for an increasing number of genetically mediated risk factors will be likely to be more broadly available, the testing often being organised within screening programmes [1]. Before implementing such a screening programme, one has to consider the pros (e.g. health benefits) and cons. Even if the empirical evidence of beneficial health effects of the screening is convincing, the broader psychological and societal consequences may require a limited or at least carefully guided implementation [2,3].

Familial hypercholesterolemia (FH) is a genetic disorder, predisposing for coronary artery disease, with an estimated frequency of 1 in 500 persons in Western countries [4]. In 1994 the ‘Foundation for tracing hereditary hypercholesterolemia’ (Dutch acronym: StOEH) was founded in the Netherlands to perform genetic cascade-screening for FH. Within this screening programme, relatives of genetically confirmed FH patients are tested for FH [5,6].

The aim of this thesis was to evaluate the acceptability and feasibility of the implementation of this preliminary FH screening programme to support national decision-making on a future screening programme.

To evaluate the individual consequences of the screening programme a longitudinal study design was used following a large unselected cohort of screenees, screened between March and September 1998. Data for this evaluation of psychological consequences were collected by means of four self-administered questionnaires (T0: at screening, before knowing the test result; T1: 3 days after receiving the test result; T2: 7 months after the test result; T3: 1.5 years after the test result). The first questionnaire was handed out at screening and filled out at home. The other questionnaires were sent by mail. All participants of the evaluation study were 18 years or older. Non-participants of the screening programme were interviewed by phone.

To evaluate the possible social consequences of the screening, 350 individuals aged 20 to 60 years with known test results, and who were screened between 1st of January 1994 and 31st of December 1997, were selected from the StOEH registry. We chose to select this second sample of screenees different from those participating in the evaluation of psychological consequences, because due to the longer time span after testing, more people would have acquired life insurance and/or a mortgage (technically spoken, exposure was insufficient in the first sample). Again data collection was by means of a self-administered postal questionnaire.

The overall response rate of the evaluation of psychological consequences was 76% (see figure 1); 677 screenees agreed with participating in the evaluation study, 647 send back the first, 603 the second, 556 the third and 513 the fourth questionnaire. The response rate of the evaluation of the social consequences was 61%.

In chapter 2 the screenees’ views on, and the psychological impact of the family-based genetic screening programme for familial hypercholesterolemia (FH) were assessed and non-participation was evaluated. Less than 5% of the screenees were critical of the approach and of the information provided. Of all screenees, 20% expressed some degree of social pressure. Furthermore, effects on mood were minimal to absent, as were ‘quality of life’ (QoL) effects in general. In this chapter it was concluded that screening for FH is highly acceptable to screenees, although some degree of social pressure is prevalent. Only 2% of the people approached for screening declined the screening offer.
Figure 1 Response evaluation study

While chapter 2 described only short-term effects of the screening offer on QoL, chapter 3 focussed on the long-term QoL effects. The QoL in FH-screenees remained essentially unchanged during FH-screening. No differences between FH-positive and FH-negative screenees were found. Some known small effects of age and gender on QoL-levels were confirmed, as well as an initial effect on QoL in some of the screenees. Furthermore, the more one experienced a feeling of social pressure, and the higher one perceived the chance of having a heart attack later in life, the lower the QoL; all these significant effects, however, were small to negligible relative to the scale. Combining the results from chapter 2 and 3, no adverse effects both on short- and long-term QoL were shown and the set-up of the screening programme seemed adequate. Only a low percentage approached people declined the screening offer.

In chapter 4 the perceived control and preventive behaviour of the screeners was assessed by using the Multi-Dimensional Health Locus of Control scale, and by a question on ‘fatalism’ in FH-positive and ‘false reassurance’ in FH-negative screeners. Of the FH-positive screeners, 54% were labelled as ‘fatalistic’ and 23% of the FH-negative screeners as ‘falsely reassured’. Being ‘fatalistic’ or ‘falsely reassured’ was inversely related to clinical outcome quality. Almost all FH-positive screeners planned to have a cholesterol check in the future. However, the ‘falsely reassured’ FH-negative screeners planned this less often than other FH-negative screeners. Furthermore, both ‘fatalistic’ and ‘falsely reassured’ screeners externalise the locus of control of their cholesterol level more than those who were not. Overall, in people screened for FH, ‘fatalism’ and ‘false reassurance’ seem to be associated with worse clinical outcome quality and thus more effort should be put into preventing ‘fatalism’ and ‘false reassurance’ in the screening set-up.

In chapter 5 the accuracy and determinants of the screeners’ risk perception were described. Furthermore, it was tested whether a predicted influence of risk perception on subsequent preventive behaviour could be observed. On average, the screeners underestimated their numeric risk of having FH and getting a
myocardial infarction (MI). FH-positive screenees perceived being at higher risk of MI than FH-negative screenees, risk perception being measured prior to disclosure of FH status. Furthermore, screenees with the highest actual risk more often used medication, perceived a greater risk and opted more often for future gene therapy.

Risk perception of having FH was influenced by cholesterol level, while MI risk perception was affected by age, education, cholesterol level, and cardiovascular disease (CVD) in the family. The conclusion was that FH-positive screenees 'correctly' perceived a higher risk of getting a heart attack than FH-negative screenees. Screenees did not believe that MI was inevitable and risk perception was associated with both medication use and the intention to opt for gene therapy, but not with other preventive measures, like quitting smoking. Thus, genetic risk notification seemed to be acceptable and did not lead to aversion to preventive behaviour, despite inaccurate quantitative risk estimates.

To judge the performance of the screening programme, in chapter 6 the entire chain of detection, treatment process and clinical outcome quality in FH-positive screenees were assessed. Treatment process quality was measured by the number of people treated according to the key recommendations of the Dutch guidelines on hypercholesterolemia [7,8] at 7 months after screening; clinical outcome quality was measured by achieved cholesterol level, body mass index and smoking status at 18 months after screening. Although quality generally improved substantially, screen-positives as a group – 25% newly identified cases and 75% patients already known to be clinically hypercholesterolemic – ultimately did not receive optimal care. Treatment process quality was still unsatisfactory in 21% (new: 40% versus already known patients: 14%) and clinical outcome quality was insufficient in 47% (new: 48% versus already known patients: 46%) of the cases. Insufficiencies were observed for all predefined quality aspects and were unrelated to setting or patient. In conclusion, to justify screening, current treatment performance in screen-positives must be improved. This may be achieved by improved physician education, explicit treatment process monitoring and change of the programme's follow-up procedure for screen-positives.

In the last chapter (chapter 7) the presence of negative social consequences of the screening programme was evaluated, specifically the presence of unduly limited access to insurance. In spite of detailed guidelines and legislation on the use of genetic test information, screenees encountered unanticipated insurance problems. It is not clear why these problems occur: do insurance companies ask unjustified questions regarding genetic testing or questions that can be read as such, or do individuals themselves provide more information than strictly asked for. We concluded that guidelines and legislation on genetic information are but a prerequisite, that education of all involved is equally important, and that still actual risk and insurance behaviour are difficult to reconcile.

Having arrived at the end of the chapter by chapter summary of the results, we proceed with the ultimate goal of the evaluation study: the support of national decision-making on the future of the screening programme. As apparent from table 1, our research filled out the gaps in the table of key factors for screening evaluation (see also the introduction of this thesis).
Table 1 Known and unknown factors for the assessment of FH screening

1. Knowledge of population and FH
   a. Disease burden: In Western countries 1 in 500 persons has FH [4]
   b. Target population: Family members of clinically diagnosed and genetically confirmed patients
   c. Level of risk: Patients with a clinical diagnosis have an excess mortality from CVD, in particular at a young age [4,9-11]
   d. Pre-clinical phase: Present [4]
   e. Natural course of FH: Known [4], however in clinically diagnosed patients only, not in genetically identified patients without clinical signs of FH. The natural course of FH in genetically diagnosed patients was estimated in the evaluation study of the Dutch FH-screening programme using the Framingham function [12], assuming that the extra CVD risk in FH patients is caused completely by the raised serum cholesterol level [13]

2. Feasibility of screening procedures
   a. Test: Feasibility of the mutation analyses within the Dutch screening programme is evaluated within the evaluation study of the Dutch FH-screening programme [13]
   b. Acceptability of screening procedure to screened population: Screening procedure is well accepted by the screenees [Chapter 1 of this thesis]
   c. Screening process: Screening process is feasible [Chapter 2, 3 & 6 of this thesis]

3. Interventions and follow up
   a. Physical effects: the screening has a positive health effect [13]
   b. Psychological effects: no adverse effects both on short and long term QoL were shown; ‘fatalism’ and ‘false reassurance’ need more attention; genetic risk notification seemed to be acceptable and did not lead to aversion to preventive behaviour [Chapters 2 to 5 of this thesis]
   c. Social effects: no adverse effects on the social sub-scales of the QoL questionnaires was shown [Chapter 2 & 3 of this thesis]
   d. Follow-up: Quality of treatment generally improved substantially after screening, although 21% (treatment process) and 47% (clinical outcome quality) of the screenees ultimately did not receive optimal care. [Chapter 6 of this thesis]
   e. Consensus on management for those with FH: Present (cholesterol consensus) [7,8]

4. Societal and health system issues
   a. Economic and medical costs: the screening is ‘border-line’ cost-effective with costs per saved person year between €25.000,- and €32.000,- [13]
   b. Psychological costs: no adverse effects both on short and long term QoL were shown; ‘fatalism’ and ‘false reassurance’ need more attention; genetic risk notification seemed to be acceptable and did not lead to aversion to preventive behaviour [Chapters 2 to 5 of this thesis]
   c. Societal costs: Although guidelines and legislation on the use of genetic test information exist, screenees still may encounter unanticipated insurance problems [Chapter 7 of this thesis]
   d. Appropriate screening services accessible to entire population: Insufficiencies were observed for all predefined quality aspects and were unrelated to setting or patient [Chapter 6 of this thesis]
   e. Confidentiality procedures and anti-discrimination provisions: Although guidelines and legislation on the use of genetic test information exist, screenees still may encounter unanticipated insurance problems. Guidelines and legislation on genetic information are but a prerequisite and that education of all involved is equally important [Chapter 7 of this thesis]
The results described in this thesis, combined with the results from the overall report of the evaluation of the screening programme [13], including a cost-effectiveness analysis [14], allow for the following recommendations:

- Evidence so far warrants introduction of the screening for FH. However, follow up of this recommendation requires a political judgement whether the feasibility and cost-effectiveness is sufficient to cover expenses for screening for FH.
- Information provision has to be improved; this concerns information to clients (both screenees who test positive and negative), to general practitioners (on FH in general and on follow-up) and to insurance companies.
- Compliance with the Medical Examinations Act (MEA) concerning the interpretation of information on FH has to be ensured.
- Screening has to follow an explicit protocol, with concerning both the diagnostic and therapeutic pathway, especially after a positive test result. In the diagnostic pathway, a simultaneous DNA-test and cholesterol measurement should be considered. Regarding the clinical follow-up, the Dutch guidelines on hypercholesterolemia [7,8] should be more closely followed with extra attention to compliance.
- Once implemented, the screening programme should be (continuously) monitored, and its effectiveness and efficiency under practice circumstances should be re-estimated [15]. This evaluation should be conform a detailed description of the screenees, including their relation to the index patient, the presence of other CVD risk factors, and has to cover a relevant follow-up where on an individual basis process and outcome are observed. In general, a continuous evaluation of the screening process (including the DNA testing) should be implemented combining expertise of the executive organisation and relevant national organisations (e.g. the Dutch Heart Foundation, Foundation for Clinical Genetics in the Netherlands, National Health Board, Dutch Institute for Health Care, Health Care Insurance Board and academic research institutes).

Apart from the above direct recommendations, our investigations showed the utility and feasibility of systematic, quantitative research on the process effects of medical screening. As these process effects are relevant to all genetic screening programmes and their measurement is a returning challenge in screening evaluations, the methodological yields of this thesis are now summarised.

A general methodological achievement was the measurement of the quality of the first stage of the screening programme. With this first stage the invitation is meant, the background of participation and non-participation, the role of provided information and social processes, and the degree to which this vital part of any screening programme is in accordance with generally accepted ethical performance criteria. The successful operationalisation of the (adapted) Wilson and Jungner criteria, relevant to these issues, justifies in our view further application in the evaluation of future screening programmes.

A second general achievement of the study was the demonstration that a formal empirical analysis of insurance consequences was possible and showed facts crucial for societal decision making (see below). This analysis should be, in our view, a regular explicit part of any evaluation study.

It is regrettable that insurance companies and their representatives so far were inaccessible to provide information on the guidelines – if present – they use for decisions on acceptance and the
height of premiums. In a sense, our test is one-sided, as we have to rely on patient's experience only. However, our data suggested irrational behaviour of insurance companies. In the best case, insurance companies are not unwilling but ill-informed and base decisions on unreliable risk tables.

A third general achievement was the successful application of pre-specified models to describe and explain attitudes and behaviour of screenees in the various stages of the programme. We used standard QoL tools in a repeated measures design to describe QoL effects and adapted previously defined thresholds to define ‘abnormal’ or ‘adverse’, being aware that multi-item questionnaires need external reference to define a threshold of ‘relevance’. However, the wide experience with the measures chosen supported this application. The framework of ‘false reassurance’ and ‘fatalism’ was particularly successful to explain procedural adherence of the screenees. The addition of ‘locus of control’ as an explanatory concept has not only proved a valuable concept to explain variance in attitude, but also as a concept to individualise counselling. We intended to describe outcome in terms of preventive behaviour and medical follow-up undertaken to improve cardiovascular risk (rather than hypercholesterolemia alone), and in terms of more distal parameters of cardiovascular disease. Although follow-up was too short to be able to observe cardiovascular manifestations like myocardial infarction, still, the used outcome measures demonstrated an interesting discrepancy between actions undertaken and effects achieved. From a clinical point of view our results imply a warning to those process quality measures of screening and treatment alone: only distal measures can teach us the benefits of screening programmes. From a methodological point of view, this combination of effect measures may prove useful in any context with a long chain of events connecting primary events and final benefit.

Finally a remark should be made to the use of cost-effectiveness models, although the results are not a regular part of this thesis. From the cost-effectiveness analysis performed by Marang-van de Mheen et al. [14] it is clear that the cost of life long statin therapy, not the screening process itself, is the single most important determinant of the costs. These costs, combined with the life years gained, determine the cost-effectiveness ratio. Another study (performed by the STOEH in collaboration with the London School of Hygiene and Tropical Medicine) estimated considerably lower costs [16] (approximately 8.700 Euros compared to the 25.000 to 32.000 Euros per life year gained estimated in our evaluation study). In the analysis performed by Marang-van de Mheen et al., methods to avoid overestimation of the effectiveness of the FH screening programme were used. As the assumption was made that the increased CVD risk in FH patients is carried through the elevated cholesterol level [14], it is justifiable to use the Framingham risk function [12]. Although this may have underestimated the CVD risks in FH, the alternative _ using risks as found in the Simon Broome register [9] _ may not apply to this screening cohort, as many FH positive screenees in the Dutch screening programme did not comply with the clinical criteria of FH [4] (no overt CVD (this thesis) or hypercholesterolemia [17]). Moreover, the effectiveness as estimated in the analysis performed by Marang-van de Mheen et al. may even be lower because the compliance assumptions of 100% follow-up, treatment and treatment compliance were probably too generous [13, 18]. However, debate about the assumptions made for cost-effectiveness studies will always exist [19] and one can conclude that, at present, the cost-effectiveness as estimated by Wonderling et al. [16] will represent the lower limit and the estimate by Marang-van de Mheen et al. [14] the upper limit.

Another article on the evaluation of the implementation of the FH screening programme is
published recently [20]. In this study of Umans-Eckenhausen et al. less screenees were treated with statins before screening than in the current study (39% versus 57%). This difference might be due to a slight difference in study population, concerning age and inclusion period.

The implementation of the FH screening programme is both evaluated by the StOEH itself [16] and an external evaluation study (results partly reported in this thesis) [13]. We think that this external evaluation certainly has an additional value due to the conceptual approach using a systematic evaluation by the criteria of Wilson and Jungner.

Policy implications
After assessing the pros and cons of the screening as described in the independent evaluation study, the next logical step is to give a provisional analysis of what health policy actions actually were undertaken since our report appeared in September 2000 [13].

The policy judgement on the feasibility of the FH screening programme was positive and in July 2002 the Dutch minister of Health, Welfare and Sports endorsed the recommendations on the Dutch screening programme for FH as given in the evaluation study [21].

Furthermore, as the committee of the Health Council of the Netherlands concluded that FH is a treatable disease [17], the act does not limit the right of insurers to ask questions and carry out investigations in respect of FH, but asking questions about (the results of) genetic testing is not permitted below the 'question limit' (see chapter 7).

However, problems with access to important insurance policies for FH positive screenees were seen as a major obstacle to the implementation of the screening programme. The solution of these problems was put forward as a prerequisite and only if the insurers will have a suitable answer to the possible problems concerning the accessibility to insurance policies, the ministry will effectuate its decision to fund the genetic screening programme for FH.

The solution as seen by the committee of the Health Council of the Netherlands [22] were both more detailed rules on the permissibility of certain questions and the obligation for insurers to make clear to applicants what information he or she is required to give. Also improvements should be made in public publicity on this matter. Furthermore, insurers should base their assessment of risk on accepted medical understanding.

Attractive as this method of political pressure may seem, many involved in the screening programme fear discontinuation of the programme, given the long time involved in changing rules and perhaps even legislation. More effective on the short term would be better patient education, so patients can decide better both on whether they want to participate in the screening and, if they decided on participating and apply for an insurance, what to answer to the questions in the application.

Future genetic screening programmes
The genetic knowledge expands rapidly and it has been suggested that new technologies like DNA microarrays (or the so-called DNA chip) will be routinely used for disease diagnosis within the decade [23]. These new diagnostic tests will make large-scale genetic testing for various genetic risk factors feasible. Using these new techniques, more genetic screening programmes will become available in the future. When those programmes will become available, the cost-
effectiveness of those programmes should be assessed for every programme independently. Foreseeing this, what can we learn from the FH experience?

This thesis proves that a broad evaluation using a conceptual approach based on the criteria of Wilson and Jungner [2], independent of the screening set-up, is a good way to evaluate screening programmes, although it has to be seen whether this is applicable to other than Caucasian ethnic groups. An important part of this evaluation is a cost-effectiveness analysis, using fixed criteria [15]. Furthermore, persons who participate in a screening should not have unduly limited access to insurance. And lastly, the evaluation should support health policy decisions on the screening programme under evaluation.

Research implications

After this comprehensive evaluation study a few questions on FH and the screening for this condition remain to be unanswered. Most of these questions can only be answered by following a cohort of screenees over time. For justification of the screening programme in the future, it is e.g. important to know what the natural course of FH is when it is treated with statins from adolescence, and what the CVD risk is for FH-positive screenees without hypercholesterolemia. Thus a detailed description of the screenees, including relation to the index patient, other CVD risk factors, and during a follow-up period a description of therapy, hypercholesterolemia, and CVD events is needed. This should be done as a part of a continuous evaluation process of the screening programme.

Samenvatting

Met het groeien van de kennis over genetica zullen er steeds meer genetische risicofactoren ontdekt worden. De volgende stap is dat mensen, vóórdat ziekte is opgetreden, op deze genetische risicofactoren getest kunnen worden. Steeds meer van deze testen zullen beschikbaar komen en waarschijnlijk georganiseerd worden binnen screeningsprogramma's.

Voordat een screeningsprogramma op grote schaal ingevoerd kan worden, moeten een aantal factoren afgewogen worden. Het is belangrijk om te weten wat de positieve effecten van een screeningsprogramma zijn (bijvoorbeeld gezondheidswinst), maar het is net zo belangrijk om te weten of er niet te veel negatieve effecten zullen optreden. Dus, zelfs als er genoeg bewijs is voor de positieve effecten, verdienen de bredere psychosociale en maatschappelijke gevolgen aandacht voordat een screeningsprogramma kan worden ingevoerd.

Familiair Hypercholesterolemie (FH) is een genetische aandoening die hart- en vaatziekten kan veroorzaken. In Westerse landen wordt geschat dat 1 op de 500 mensen drager is van deze aandoening [4]. In Nederland worden familieleden van mensen met een genetische diagnose FH op deze aandoening getest binnen een genetisch screeningsprogramma.

Het doel van dit proefschrift was om de aanvaardbaarheid en de haalbaarheid van de invoering van het voorlopige screeningsprogramma op FH te onderzoeken. Dit ter ondersteuning van beleidsvorming op het gebied van toekomstige screening.

Wij evaluerden de mogelijke gevolgen van het screeningsprogramma door middel van een longitudinaal vragenlijstonderzoek. De deelnemers aan het onderzoek kregen vier vragenlijsten (bij screening, voordat het testresultaat bekend was (T0), en vervolgens 3 dagen (T1), 7 maanden (T2) en 1,5 jaar (T3) na het ontvangen van het testresultaat). De eerste vragenlijst kregen de deelnemers bij bloedafname, zij konden deze vervolgens thuis invullen. De overige drie vragenlijsten werden per post naar de deelnemers opgestuurd. De mensen die niet wilden deelnemen aan het screeningsprogramma werden per telefoon geïnterviewd.

Om te onderzoeken wat de mogelijke sociale gevolgen van de screening zouden kunnen zijn, werden 350 mensen benaderd. Deze mensen waren getest tussen 1 januari 1994 en 31 december 1997, waren tussen de 20 en 60 jaar, en hun testresultaat was bekend. We kozen ervoor om andere mensen te benaderen dan de deelnemers aan het psychologische deelonderzoek, omdat naar verwachting niet voldoende mensen een verzekering of hypotheek zouden hebben afgesloten in slechts anderhalf jaar na het krijgen van de testuitslag. Ook dit deelonderzoek werd verricht door middel van een vragenlijst.

De totale respons van de psychologische evaluatie was 76% (zie figuur 1); 677 gescreenden stemden in met deelname aan de studie, van wie 647 de eerste, 603 de tweede, 566 de derde vragenlijst en 513 alle vier de vragenlijsten terugstuurden. De respons van de evaluatie studie van de mogelijke sociale consequenties was 61%.
In hoofdstuk 2 hebben we zowel de mening van de gescreenden over het screeningsprogramma, de psychologische gevolgen van de benadering voor het screeningsprogramma, als de non-participatie van het screeningsonderzoek onderzocht.

Van de mensen die benaderd werden voor de screening, stemde 2% van de mensen niet in met deelname. Deze 2% was niet geïnteresseerd, al klinisch gediagnostiseerd met FH, of bang voor problemen met het afsluiten van verzekeringen.

Minder dan 5% van de gescreenden was niet tevreden over de benadering en de informatievoorziening. Van alle gescreenden, zei 20% sociale druk tot deelname gevoeld te hebben. Verder was er geen tot weinig invloed op stemming en algemene 'kwaliteit van leven' (KvL).

In dit hoofdstuk concludeerden we dat screening op FH zeer aanvaardbaar is voor de gescreenden, hoewel sociale druk aanwezig is. Verder besloot slechts een klein deel van de benaderde mensen om niet deel te nemen aan de screening.

Terwijl hoofdstuk 2 slechts de korte termijn effecten op de KvL beschrijft, gaat hoofdstuk 3 dieper in op de KvL effecten op langere termijn. De KvL van de op FH gescreende mensen veranderde vrijwel niet gedurende de screening en de periode daarna. Er werden geen verschillen in KvL aangetoond tussen mensen met en mensen zonder FH. Een aantal kleine bekende effecten van leeftijd en geslacht op de KvL werden in dit onderzoek bevestigd. Ook was er bij een aantal gescreenden een kortdurend effect op de KvL. Verder werd een slechtere KvL gerapporteerd door de mensen die een hogere sociale druk voelden en hun kans op een hartinfarct hoger inschatten. Al deze effecten waren wel statistisch significant, maar slechts klein of zelfs verwaarloosbaar. In dit hoofdstuk concludeerden we dat zowel op korte als op langere termijn geen effecten op de KvL van de gescreende mensen aantoonbaar was. De opzet van het screeningsprogramma lijkt op dit gebied dus adequaat.

In hoofdstuk 4 beschreven we de invloed die gescreenden denken te hebben op hun cholesterolgehalte en het preventieve gedrag dat gescreenden ondernemen na het horen van de


In hoofdstuk 5 beschreven wij de risicoinschatting van de gescreenden en de factoren die samenhangen met deze risicoinschatting. Ook testten wij of de voorspelde invloed van risicoinschatting op preventief gedrag kon worden aangetoond.

Over het algemeen onderschatten de gescreenden hun numerieke kans op het hebben van FH en het krijgen van een hartinfarct. Mensen met FH schatten hun kans op het krijgen van een hartinfarct hoger in dan mensen die geen FH hadden, ook voordat zij wisten of zij FH hadden of niet. Verder gebruikten de gescreenden die feitelijk het hoogste risico hadden ook vaker medicijnen, schatten zij hun kans op een hartinfarct hoger in en zeiden zij vaker dat zij gentherapie zouden overwegen wanneer dit in de toekomst beschikbaar zou zijn.

Hoe hoog de gescreenden hun kans inschatten op het hebben van FH werd beïnvloed door hun cholesterolgehalte, terwijl het inschatten van de kans op het krijgen van een hartinfarct werd beïnvloed door leeftijd, opleiding, cholesterolgehalte en hart- en vaatziekten in de familie.

Mensen met FH schatten hun kans op het krijgen van een hartaanval terecht hoger in dan mensen zonder FH. Verder dachten gescreenden niet dat een hartaanval onvermijdelijk was als men FH had en was de risicoinschatting geassocieerd met zowel medicijningen als het overwegen van het ondergaan van gentherapie. Risicoperceptie was niet geassocieerd met andere preventieve maatregelen, zoals het stoppen met roken.

We kunnen dus concluderen dat het geven van een genetische diagnose acceptabel leek voor de gescreenden en dat het niet leidde tot aversie tegen preventieve maatregelen, ondanks een inaccurate risicoinschatting.

Om in te kunnen schatten of het screeningsprogramma effectief was, analyseerden we in hoofdstuk 6 de gehele keten van het opsporen van FH, de behandeling en de kwaliteit van de klinische uitkomst in gescreenden met FH.

De kwaliteit van de behandeling werd afgemeten aan het aantal mensen dat behandeld werd volgens de Nederlandse consensus voor hypercholesterolemie, 7 maanden na het krijgen van de testuitslag. De klinische uitkomstkwaliteit werd 18 maanden na het krijgen van de testuitslag gemeten met behulp van het cholesterolgehalte, ‘body mass index’ en of de gescreende rookte of niet.
Hoewel de uitkomstkwaliteit over het algemeen substantieel verbeterde, kregen de mensen met FH als groep (25% nieuw gediagnostiseerden en 75% mensen die al klinisch gediagnostiseerd waren met een te hoog cholesterolgehalte) uiteindelijk geen optimale zorg. De kwaliteit van de zorg was onvoldoende in 21% (nieuw: 40% versus al bekende patiënten: 14%) en klinische uitkomstkwaliteit was onvoldoende in 47% (nieuw: 48% versus al bekende patiënten: 46%) van de gescreende met FH.

Tekortkomingen werden gesignaleerd in alle vooraf gedefinieerde kwaliteitsaspecten en waren niet gerelateerd aan setting of patiënt.

Geconcludeerd kan worden dat, om screening te rechtvaardigen, het huidige behandeltraject moet worden verbeterd. Dit kan worden bereikt door het beter voorlichten van de dokters, en door het aanpassen en vervolgens continu monitoren van het behandeltraject voor gescreenden met FH.

In hoofdstuk 7 beschrijven we het bestaan van eventuele negatieve maatschappelijke gevolgen. Een van de maatschappelijke gevolgen van genetische screening zouden problemen met het afsluiten van levensverzekeringen, ziektekostenverzekeringen of arbeidsongeschiktheidsverzekeringen kunnen zijn. In Nederland bestaat hierover sinds 1990 een moratorium tussen verzekeraars en overheid waarbij spelregels zijn afgesproken over het omgaan met informatie uit genetische screening. In de Wet Medische Keuringen, welke in 1998 van kracht is geworden, zijn hierover ook wettelijke regels vastgesteld. In het kader van een evaluatie van de genetische screening op Familiaire Hypercholesterolemie (FH) in Nederland is gebleken dat er ondanks afspraken in die periode toch problemen met het afsluiten van verzekeringen zijn voorgekomen. Het hebben van de aandoening FH lijkt hierbij eerder de aanleiding voor de problemen dan een te hoog cholesterolgehalte. Goede voorlichting aan zowel personen die zich willen laten screenen als aan verzekeraars, alsmede waakzaamheid bij het naleven van de gemaakte afspraken lijkt geboden.
Dankwoord

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De deelnemers aan het onderzoek
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De paranymfen

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Stellingen behorend bij het proefschrift:

**Familial Hypercholesterolemia Screening in the Netherlands:**
Psychological and Social Consequences

Merel van Maarle

1. Screening op FH is aanvaardbaar voor de deelnemers (dit proefschrift)
2. Screening op FH heeft geen korte en lange termijn effecten op de kwaliteit van leven van de deelnemers (dit proefschrift)
3. Het optreden van ‘fatalisme’ bij gescreenden met FH en ‘alse geruststelling’ bij gescreenden zonder FH verdient de aandacht (dit proefschrift)
4. Het stellen van de diagnose FH is noodzakelijk maar niet voldoende voor het bereiken van gezondheidswinst (dit proefschrift)
5. Normale mensen kunnen beter omgaan met kansen uitgedrukt in woorden dan in cijfers, bij onderzoekers is dit precies het tegenovergestelde (dit proefschrift)
6. Het wordt tijd dat verzekeraars gebruik gaan maken van ‘evidence-based medicine’ (dit proefschrift)
7. Het is altijd belangrijk de kleine lettertjes te lezen (zie dit proefschrift)
8. Dokters denken dat zij een patient een dienst bewijzen als zij een diagnose stellen (Immanuel Kant)
9. Je gaat het pas zien als je het doorhebt (Johan Cruijff)
10. Denken is zo buitengewoon vermoeiend dat velen de voorkeur geven aan oordelen (Otto Weiss)
11. Chaos is het woord dat we bedacht hebben voor een orde die we niet begrijpen (Henry Miller)
12. De ware reiziger heeft geen reden nodig om op reis te gaan (Goethe)