Quality of life in a family based genetic cascade screening programme for familial hypercholesterolaemia: a longitudinal study among participants

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

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. 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.

Familial hypercholesterolaemia (FH) is a genetic disorder, predisposing to coronary artery disease. The estimated frequency of the genetic factor in western countries is 1 in 500 persons. In about 90%, the associated metabolic defect results in an accumulation of plasma cholesterol and consequent excess CAD mortality. The availability of DNA diagnosis at an asymptomatic stage and of effective lipid lowering therapy have called for cascade screening.

In 1994, an FH screening programme was started in The Netherlands on a provisional basis, 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. In non-genetic screening programmes, participants showed a temporary decline in the psychological domain of QoL. For example, in breast cancer screening, anxiety and depression following screening were raised but to a subsclinical level, without lasting adverse psychological effects. The psychological disturbance of prostate cancer screening was even less.

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 of the disorder, although mood in general seems to be unaffected.

The current study considers the effects of FH screening, where evidence is scarce and inconclusive. Some anxiety has been reported, but other studies report normal QoL and unchanged psychosocial functioning. Adverse psychological effects of genetic screening may not only originate from the screening procedure, but also from the induced awareness of one's genetic status. 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 screening participants, which in turn may affect the QoL.

The principal objective of this paper is to establish in a large cohort of FH screening participants 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 (that is, clinically diagnosed FH patients with a known mutation). The “Foundation for tracing hereditary hypercholesterolaemia” (Dutch acronym: StOEH) is responsible for this pedigree investigation (“cascade screening”). Family members are informed about their possible risk by mail. A week after this notification a genetic field worker (GPW) telephones and, if the family member agrees to participate, makes an appointment for testing. The family members are tested at home by a geneticist.

Key points

- Familial hypercholesterolaemia (FH) predisposes to coronary artery disease and has a frequency of 1 in 500 persons in western countries.
- In The Netherlands, relatives of genetically confirmed FH patients are tested for FH in a genetic cascade screening programme.
- We investigated the transient and permanent effects on quality of life (QoL) of the screening programme with a focus on psychological effects.
- In four self-administered questionnaires (at screening and at three days, seven months, and 18 months after the test result), the QoL of a consecutive cohort of 677 participants was assessed (response 76%: 513 participants screened).
- QoL in FH screening participants remained essentially unchanged during FH screening. No differences between FH positive and FH negative subjects 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 participants. Furthermore, the more they experienced a feeling of social pressure, and the higher they 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.
- Overall, our longitudinal survey of an unselected cohort of FH screening participants showed on average no adverse effects either on short or long term QoL. Thus, the set up of the screening programme seems to be adequate.
GFW, who gives them more information about the procedure and about FH. Furthermore, before agreeing to give a sample for DNA analysis, the potential participant 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 participants by mail. Screening positive subjects get two additional letters, one directed to him/herself with advice to consult the general practitioner (GP), and one to the GP inviting the patient to a lipid clinic. This procedure requires the participants to test positive 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 programme

Before screening, relatives of FH patients are approached by mail. This letter also includes 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 hypercholesterolaemia, which subsequently causes damage to 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 participant tests positive. This booklet provides a detailed description of the biochemical mechanism of FH and information about inheritance and the risk of MI. It is stated that FH positive subjects have a high risk of MI. Furthermore, the leaflet reassures the reader that hypercholesterolaemia is treatable and that most FH patients can normalise cholesterol levels with medication and diet, thus lowering the chance of having an MI.

Subjects

The inclusion of the subjects was between March and September 1998. The inclusion criteria were being 18 years of age or older and giving informed consent to genetic testing and to our survey (98% of the invited family members consented to genetic testing). The subjects undergoing screening were asked to participate in the current study by the GFW and signed a separate informed consent for this study. With the 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 (T1, T2, T3: before knowing the test result; T4: after the test result). Four questionnaires were used, all with available Dutch reference data.

Quality of life questionnaires

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

The SF-36 questionnaire contains 36 items on eight 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. We standardised the PCS and MCS as described by Ware et al. with Dutch population data. 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 state of health) to 100 (best imaginable state of health). The SF-36 questionnaire sets (T0: at screening, before knowing the test result; T4: after the test result). We additionally distinguished between participants into three groups: (1) concordant, (2) discordant, and (3) participants who had an indifferent expectation of the test result. We additionally distinguished between subjects aware and unaware of a cholesterol problem at the time of screening. Unaware cases were defined as subjects with an unknown cholesterol level or with a normal cholesterol level (cholesterol level <6.5 mmol/l) without treatment, and aware cases as subjects with either known hypercholesterolaemia (with and without treatment) or a normal cholesterol level under treatment, all at the time of screening.

Risk perception

The risk perception of the screening participants was studied, the perceived probability of (1) having FH and (2) having a heart attack later in life without treatment. Risk response was precategorised 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 participants into three groups: (1) concordant, (2) discordant, and (3) participants who had an indifferent expectation of the test result (neither high nor low expectation, irrespective of the test result). We additionally distinguished between subjects aware and unaware of a cholesterol problem at the time of screening. Unaware cases were defined as subjects with an unknown cholesterol level or with a normal cholesterol level (cholesterol level <6.5 mmol/l) without treatment, and aware cases as subjects with either known hypercholesterolaemia (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 three 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. 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 chi-square statistic and 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 participant 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; 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 (fig 1). Of these, 43 people participated 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.

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

Basic characteristics of the screening participants
Table 1 presents the basic characteristics of the screening participants. Overall, 46% were men and the mean age was 47 years. Furthermore, 36% had not previously heard of FH either in general or as occurring in their family, 45% of them reported first degree family members with CVD, 13% reported family members (total family) who had died of premature CVD deaths at the age of 50 or younger, 19% were aware that they had a cholesterol problem. Of all screening participants, 26% reported a normal cholesterol level, and the remaining participants did not know their cholesterol level. Of all screening participants, 36% were aware that they had a cholesterol problem. After testing, 32% of our study population proved to be FH positive.

Quality of life
SF-36
The physical component score (PCS) of the SF-36 was within the normal range at screening compared to the general Dutch population and did not change significantly over time (fig 2, table 2). On average, older participants and those with 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, but deteriorated slightly but significantly over time (fig 2, table 2). Women, participants with hypertension, and those 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, participants with hypertension, diabetes, and/or any other chronic disease scored their health worse (table 2). Furthermore, those with a higher perceived chance of having a heart attack later in life evaluated their present health lower. Perceived social pressure was not associated with the VAS of the EuroQol.

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

Table 1 Basic characteristics of the screening participants (n=647)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>%*</th>
</tr>
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<td>Sex (% men)</td>
<td>46</td>
</tr>
<tr>
<td>Mean age (y)</td>
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</tr>
<tr>
<td>Total (range)</td>
<td>47 (18-87)</td>
</tr>
<tr>
<td>Men (range)</td>
<td>48 (18-79)</td>
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<tr>
<td>Women (range)</td>
<td>47 (18-87)</td>
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<td>Marital status</td>
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<td>Single</td>
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</tr>
<tr>
<td>Married/living together</td>
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<tr>
<td>Educational level</td>
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<td>Elementary school</td>
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<tr>
<td>Lower secondary school</td>
<td>42</td>
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<tr>
<td>Higher secondary school</td>
<td>28</td>
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<tr>
<td>Higher vocational level/university</td>
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<td>Religious (% yes)</td>
<td>63</td>
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<tr>
<td>Cholesterol (self-reported)</td>
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<tr>
<td>High</td>
<td>36</td>
</tr>
<tr>
<td>Normal</td>
<td>26</td>
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<tr>
<td>Don’t know</td>
<td>39</td>
</tr>
<tr>
<td>Aware of a cholesterol problem</td>
<td>36</td>
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<td>FH positive subjects</td>
<td>73</td>
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<tr>
<td>FH negative subjects</td>
<td>19</td>
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<td>Heard of FH before screening (% yes)</td>
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<tr>
<td>CVD</td>
<td>3</td>
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<tr>
<td>Hypertension</td>
<td>12</td>
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<tr>
<td>Stroke</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Other chronic diseases</td>
<td>55</td>
</tr>
<tr>
<td>1st degree relatives with CVD (% yes)</td>
<td>49</td>
</tr>
<tr>
<td>Premature CVD deaths in family (% yes)</td>
<td>19</td>
</tr>
<tr>
<td>Forced by circumstances to participate</td>
<td></td>
</tr>
<tr>
<td>Agree</td>
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</tr>
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<td>Neutral</td>
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<tr>
<td>Disagree</td>
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<tr>
<td>Freedom of choice to participate</td>
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<td>Agree</td>
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<td>Neutral</td>
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<tr>
<td>Disagree</td>
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<tr>
<td>Genetic test</td>
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<tr>
<td>FH positive</td>
<td>32</td>
</tr>
<tr>
<td>FH negative</td>
<td>68</td>
</tr>
</tbody>
</table>

* Missings excluded in percentages.
† Now or in the last 12 months
‡ CVD death at the age of 50 or younger

Electronic letter of the EuroQol.

The chance of having a heart attack later in life evaluated their physical condition. Risk perception did not influence the PCS. Neither risk perception nor perceived social pressure was associated with the PCS.

The mental component score (MCS) was within the normal range at onset, but deteriorated slightly but significantly over time (fig 2, table 2). Women, participants with hypertension, and those 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, participants with hypertension, diabetes, and/or any other chronic disease scored their health worse (table 2). Furthermore, those with a higher perceived chance of having a heart attack later in life evaluated their present health lower. Perceived social pressure was not associated with the VAS of the EuroQol.

None of the explanatory factors included was 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 (fig 2, table 2). Overall, women, participants with hypertension and/or any other chronic disease, and those with a higher risk perception showed more anxiety. Furthermore, subjects who did not feel free to choose whether to participate in the screening programme showed more anxiety. None of these variables was significantly associated with the change over time.

On the depression scale and the overall score of the HADS, the older participants and those with a chronic disease scored worse (fig 2, table 2). Furthermore, on the depression scale, the participants who felt more or less forced to take part in the screening programme scored worse, and on the overall HADS score participants with a higher risk perception. None of these

<table>
<thead>
<tr>
<th>Measure</th>
<th>SF-36</th>
<th>EuroQol Health valuation</th>
<th>HADS</th>
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<td></td>
<td>PCS</td>
<td>MCS</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Intercept</td>
<td>50.7 (0.77)**</td>
<td>51.8 (0.79)**</td>
<td>79.5 (1.6)**</td>
</tr>
<tr>
<td>Time</td>
<td>0.90 (0.60)</td>
<td>-0.42 (0.12)***</td>
<td>-0.53 (0.17)***</td>
</tr>
<tr>
<td>Time²</td>
<td>-0.02 (0.11)</td>
<td></td>
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<tr>
<td>Age</td>
<td>-0.10 (0.02)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (0=male, 1=female)</td>
<td>-0.86 (0.27)**</td>
<td></td>
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<tr>
<td>Hypertension (0=no, 1=yes)</td>
<td>-1.88 (0.50)**</td>
<td>-0.88 (0.43)***</td>
<td>-1.9 (0.81)*</td>
</tr>
<tr>
<td>Diabetes (0=no, 1=yes)</td>
<td>-3.5 (1.5)*</td>
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<tr>
<td>Chronic diseases (0=no, 1=yes)</td>
<td>-3.08 (0.32)***</td>
<td>-3.4 (0.51)***</td>
<td>0.31 (0.09)**</td>
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<td>Perceived chance of having a heart attack†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Negligible</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Very small</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small/large</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very large</td>
<td></td>
<td></td>
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<tr>
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<td>-0.04 (0.14)</td>
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<tr>
<td>Disagree</td>
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<tr>
<td>Freedom of choice to participate†</td>
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<td>-0.47 (0.49)</td>
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<td>0.20 (0.16)</td>
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<tr>
<td>Disagree</td>
<td>-1.56 (0.59)**</td>
<td></td>
<td>0.62 (0.20)**</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01; ***p<0.001.
†Category above as reference category.

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

Table 2  Regression estimates (SE) for effects of time and other explanatory variables on the Quality of Life Measures (n=513)
factors, however, was significantly associated with the change over time. In all analyses the test result was included as an independent variable, but appeared not to have any influence on the QoL.

**Individual changes**

On the individual level, 4% of the participants 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 did we observe 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 screening participants after screening for FH: however this change was not clinically relevant. No differences between FH positive and FH negative participants were found, either in the starting level of or 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, although again the absolute effects were small. Any interpretation of these measuring 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 an overall satisfactory quality of response and reliability (data not shown). Using a quantitative rather than a qualitative design may miss a very specific harmful effect, but owing to the deliberately overlapping QoL measurements with different response modes we think the chance of spurious findings was much higher than the missing of some negative screening effects. Furthermore, the sensitivity of these questionnaires in picking up many disorders (even of minor impact) has been established. Also, results from interviews with 15 FH screening participants (not published) confirm this finding.

As no selective non-response could be found on the personal level and non-response per questionnaire was low (6% or less per item), our findings seem representative of the current cohort of FH screening participants. Furthermore, only 2% of the people invited for FH screening refused the offer, so the findings seem generally applicable for all people eligible for FH screening.

Only a small percentage of the participants showed any substantial QoL change on FH positive status notification and changes were in both directions. Temporary QoL deterioration appears easy to explain, but an explanation for the paradoxic temporal improvement has also been reported. At the time of screening, the majority of the FH positive subjects were already aware of a cholesterol problem, and reliable information on their FH risk status may have resulted in relief from uncertainty. As a 35 year old female 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 of the FH status.

It is noteworthy that the test results within this screening programme were sent by mail and no follow up of the participants 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 could 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, either in the short or in the long term, so 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 participants is the time they had been aware that they did, or could have, a cholesterol problem. Unfortunately no exact data on this were available to the researchers.

Overall, our longitudinal survey of an unselected cohort of FH screening participants showed no important adverse QoL effects in the short or long term. Thus, the set up of the screening programme seems adequate and the implementation of FH screening may be advocated.

**ACKNOWLEDGEMENTS**

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