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ten Asbroek, A.H.A.

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Genetic screening for familial hypercholesterolaemia in 1992-1997: primarily younger patients in the care of general practitioners

A.H.A. ten Asbroek, S. van Lunsen, P.J. Marang-van de Mheen, L.J. Gunning-Schepers

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Translation by C. Higgins.
Abstract

Objective
To estimate the proportion of patients with familial hypercholesterolaemia (FH) who were identified with hypercholesterolaemia in general practice prior to screening by means of pedigree research and DNA analysis by the National Foundation for the Identification of Persons with Familial Hypercholesterolaemia (StOEH).

Design
Retrospective.

Method
General practice files of FH patients, diagnosed through genetic screening by the StOEH in 1992-1997 whose general practitioner’s (GP’s) practice in Amsterdam, Haarlem or Alkmaar, were studied for cholesterol and FH related information documented in the period prior to the screening.

Results
Out of the 121 persons selected 80 agreed to the study; one GP refused to co-operate. There was no difference between respondents and non respondents with regard to age, sex or domicile of the GP. In 48 of 79 (61%) general practice files studied, cholesterol measurements were reported prior to screening; 39 patients (49%) had hypercholesterolaemia and 29 (37%) were being treated with cholesterol lowering drugs. Mean age of the FH patients who had no record of their cholesterol levels was 25.1 years (SD: 17.0) at the time of screening, 22 years younger than the mean age of FH patients who did have cholesterol levels on record prior to screening (47.1 (SD: 18.4); p < 0.0001).

Conclusion.
Of the FH patients identified through family based genetic screening especially the younger FH patients are newly brought to the attention of their GP.
Introduction

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder characterized by extremely high cholesterol, which commonly leads to premature coronary heart disease (CHD) [1-4]. The prevalence of the heterozygous form is 1:400 [5]; the homozygous form is more rare (1:1,000,000) and is clinically more severe [1;3]. Here we will discuss data of patients with heterozygous FH.

The diagnosis of FH is usually made on clinical grounds after the appearance of CHD. FH is caused by a mutation in the low-density lipoprotein receptor gene. Using genetic diagnostics, a mutation can be detected before the first clinical symptoms appear [1]. Considering their sharply increased risk of FH and also CHD, this is particularly relevant for relatives of people with FH.

Treatment of FH is aimed at lowering cholesterol. Until the end of the 1980s, this meant lifestyle recommendations and medicinal therapy using fibrates and bile-acid-binding resins. With the introduction of cholesterol synthesis inhibitors – statins – the therapy became more effective and can achieve a significant decrease in the risk of CHD [6;7], also among FH patients [8-10]. The combination of genetic diagnostics with effective cholesterol-lowering therapy makes it advisable to screen populations with a sharply increased risk of FH. Relatives of patients with genetically confirmed FH form just such a high-risk group.

Since 1992, in the Netherlands, FH patients have been identified using a combination of family research and DNA analysis. In 1994, this led to the establishment of the ‘National Foundation for the Identification of Persons with Familial Hypercholesterolaemia’ (StOEH) [11;12]. FH patients who have been clinically diagnosed and genetically confirmed (referred to as ‘index patients’) and known to the StOEH through a lipid outpatient clinic form the starting point of the family research. Together with the index patient, the StOEH draws up a pedigree of his or her family. Relatives are then approached for DNA testing using the cascade principle: only when a first-degree relative has been shown to have FH are that person’s first-degree relatives approached. If first-degree relatives are dead (or do not want to participate), second-degree relatives are approached. As a result, although the FH patients identified are always first- or second-degree relatives of a genetically diagnosed FH patient, they are sometimes only ‘distant’ relatives of the index patient with whom the family study began. Those who have been screened receive the test results in writing, and people who test positive are referred to their general practitioners (GPs). The GP is advised to refer the patient to a lipid outpatient clinic for specialized care, which includes monitoring the lipid profile, followed by treatment if necessary.

Within the framework of a formal evaluation of the identification programme, it is important to estimate the health benefits that result from screening. In order to do this, it is important to know how many of the identified FH patients were already known to have hypercholesterolaemia. To answer this question, we examined the GP patient files of the FH patients for cholesterol and FH-related information. The main question was divided into four sub-questions:
• Using the information in the GP patient files, how many of the identified FH patients had ever had their cholesterol levels checked prior to the genetic screening?
• Of the FH patients identified, how many were already known to their GPs as having hypercholesterolaemia?
• How many of the identified FH patients were already being treated for hypercholesterolaemia?
• Of those identified as FH patients, for how many of these patients had their GPs recorded a positive family medical history or actually mentioned ‘familial hypercholesterolaemia’ in their patient files?

For the first sub-question, we studied whether the results were age-related.
The study was approved by the AMC’s Medical Ethics Commission.

Methods

Participants
Included in the study were all screened relatives of index patients who had been selected based on having a) a genetic mutation caused by FH, and b) a GP living in Amsterdam, Haarlem or Alkmaar. One-hundred twenty-one (121) people met these criteria, and all of them had been screened between 1992 and 1998. In this period, the StOEH drew up a total of 196 pedigrees and identified 1336 FH patients. The 121 people selected came from 48 pedigrees. Those selected were evenly distributed with regard to sex and age. Participants gave permission for access to their GP patient files; this permission was limited to information related to FH.

Analysis of patient records
The GP patient files were examined using an ‘item list’. All cholesterol-related information (including cholesterol measurements, cholesterol-lowering therapy, record of relevant family medical history or actual mention of ‘familial hypercholesterolaemia’) was included in the study, irrespective of the date the information was recorded. The data on consultations and what had been done were used to make it possible to select information prior to the genetic screening (and where necessary also prior to treatment with medicine). When analysing the cholesterol measurements, only those measurements taken prior to treatment were used. If there were multiple cholesterol measurements, an average of the cholesterol values during the untreated period was calculated for further analysis. ‘Treatment’ is understood to be treatment with statins. The information obtained came from handwritten information on the patient’s consultation card, in correspondence included in the GP patient files, and from automated GP patient files.

Because this study looks at information available from GPs, for defining hypercholesterolaemia we used cut-off points for total cholesterol of 6.5 mmol/l and 8.0 mmol/l from the 1991
standards of the Dutch College of General Practitioners. For comparison, the 95th percentile (P95) for total cholesterol was used, an internationally accepted cut-off point for clinical diagnosis of FH. This percentile is calculated from unpublished information gathered within the framework of the ‘Monitoring Project on Risk Factors and Health in the Netherlands’ (MORGEN project) in 1996 and 1997 [13]. Because there was no reference information for people younger than 20 and older than 59 years of age, for these age groups the 95th percentile was used for 20 to 25 year olds and 55 to 60 year olds respectively.

**Statistical analysis**

For analysis of the differences in average age we used Student’s t-test; for differences in percentage between sub-groups we used an $X^2$ test. Finally, we looked at whether the results of this study were influenced by the participation of patients screened before StOEH’s formal establishment in 1994.

**Results**

Eighty (80) of the 121 FH patients who were approached agreed to participate in the study. One patient’s GP was not willing to cooperate, which meant that in the end, 79 (65.3%) GP patient files were examined.

There was no statistically significant difference between respondents and non-respondents with regard to distribution according to sex ($X^2=0.02$, $p=0.88$), average age ($t=0.53$, $p=0.69$) (table 1), or GP address ($X^2=1.2$, $p=0.56$) (information not shown).

<table>
<thead>
<tr>
<th>Table 1. Age and sex of respondents and non-respondents.</th>
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<tbody>
<tr>
<td>Total</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Respondents</td>
</tr>
<tr>
<td>Non-respondents</td>
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<tr>
<td>Total</td>
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</table>

For 48 (60.8%) of the 79 patients, their patient files showed cholesterol had been measured prior to the genetic screening (table 2). The average age of these patients was 47.1 years (SD 18.4). The average age of the remaining patients was 25.1 years (SD 17.0). This 22.0-year difference is statistically significant ($t=5.32$, $p<<0.0001$).

Thirty-nine patients (39; 49.4%) patients had average cholesterol values higher than 6.5 mmol/l (untreated). Twenty-seven (27) of them had values higher than 8.0 mmol/l (table 3). Likewise, 39 of the 79 patients had cholesterol values higher than the P95. However, some of these were different patients, in particular patients younger than those diagnosed when using cut-off points of 6.5 mmol/l and 8.0 mmol/l.
Twenty-nine (29; 36.7%) of the 79 patients were already being treated for hypercholesterolaemia prior to the genetic screening. The difference in the percentage of men among treated and untreated patients was not statistically significant ($X^2=0.01$, $p=0.94$).

In 27 of the 79 GP patient files, we found a positive family medical history or actual mention of ‘familial hypercholesterolaemia’. In 9 of these 27 GP patient files, we found both.

The results found are no different than the results that would have been found if we had only used the information from those patients screened since the establishment of StOEH in 1994 (n=62) (separate information not shown here).

**Table 2.** Measurement of cholesterol prior to genetic screening.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Av. age ± SD</td>
<td>No.</td>
<td>%</td>
<td>Av. age ± SD</td>
<td>No.</td>
<td>%</td>
<td>Av. age ± SD</td>
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<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>measurement recorded</td>
<td>48</td>
<td>60.8</td>
<td>47.1 ± 18.4</td>
<td>21</td>
<td>60.0</td>
<td>45.7 ± 17.8</td>
<td>27</td>
<td>61.4</td>
<td>48.1 ± 19.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cholesterol</td>
<td>31</td>
<td>39.2</td>
<td>25.1 ± 17.0</td>
<td>14</td>
<td>40.0</td>
<td>22.5 ± 16.9</td>
<td>17</td>
<td>38.6</td>
<td>27.2 ± 17.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>measurement recorded</td>
<td>Total</td>
<td>79</td>
<td>100</td>
<td>35</td>
<td>100</td>
<td>36.5 ± 20.6</td>
<td>44</td>
<td>100</td>
<td>40.3 ± 21.0</td>
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</table>

**Table 3.** Hypercholesterolaemia defined by cut-off points of 6.5 and 8.0 mmol/l and 95th percentile (P95) for total cholesterol.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
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<tr>
<td>No cholesterol</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>measurement recorded</td>
<td>31</td>
<td>39.2</td>
<td>14</td>
<td>40.0</td>
<td>17</td>
<td>38.6</td>
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<td></td>
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<tr>
<td>&lt; 6.5 mmol/l</td>
<td>9</td>
<td>11.4</td>
<td>3</td>
<td>8.6</td>
<td>6</td>
<td>13.6</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>6.5-8.0 mmol/l</td>
<td>12</td>
<td>15.2</td>
<td>5</td>
<td>14.3</td>
<td>7</td>
<td>15.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 8.0 mmol/l</td>
<td>27</td>
<td>34.2</td>
<td>13</td>
<td>37.1</td>
<td>14</td>
<td>31.8</td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>79</td>
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<td>35</td>
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<td>44</td>
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|                      |       |     |     |     |     |     |     |     |     |     |     |     |
| No cholesterol       | 31    | 39.2| 14  | 40.0| 17  | 38.6|       |     |     |     |     |     |
| measurement recorded | < P95 | 9   | 11.4| 3   | 8.6 | 6   | 13.6  |     |     |     |     |     |
|                       | > P95 | 39  | 49.4| 18  | 51.4| 21  | 47.7  |     |     |     |     |     |
| Total                | 79    | 100 | 35  | 100 | 44  | 100 |       |     |     |     |     |     |

**Discussion**

This study investigated how many FH patients were already known to their GPs as having hypercholesterolaemia prior to the genetic screening. In 61% of the GP patient files examined, at least one cholesterol measurement was reported to have been done prior to screening. On average, these patients were 22 years older than the FH patients who had never had
their cholesterol measured. Forty-nine (49) percent were known to their GPs as having hypercholesterolaemia. Thirty-seven (37) percent were being treated with cholesterol-lowering medication prior to the genetic screening.

The GP patient files of 79 of the 121 selected FH patients were examined (65% response). The difference in average age and distribution according to sex between respondents and non-respondents was not statistically significant. There was also no difference in distribution according to GP address. Because of this, there is no reason to assume the respondents are not representative of all those selected.

Considering the prevalence of specific mutation types differs according to region [14] and that the level of total cholesterol depends on the mutation type [1,15], it is possible that the geographic concentration of the GPs (living in Amsterdam, Haarlem and Alkmaar) influenced the results. It is possible that in other regions, a different prevalence of previously diagnosed hypercholesterolaemia would be found among FH patients. There is as of yet no population information on the extent of the variation of cholesterol levels according to mutation type, nor is there a geographical description of the mutation types found in the Netherlands.

In the MORGEN project, the age- and sex-specific 95th percentile (P95) as cut-off point for hypercholesterolaemia is not available for those younger than 20 and older than 60 years of age. Because of this, for these groups the P95 for 20 to 25 year olds and for 55 to 60 year olds were used respectively. This could mean that the prevalence of hypercholesterolaemia is underestimated in the lowest age group and overestimated in the highest age group. However, when available percentiles for cholesterol are used from the Canadian population [16], for example – which strongly correspond to those in the Netherlands in the 20 to 60 year age group – it appears the method we chose scarcely influences the prevalence of hypercholesterolaemia: only one patient younger than 20 years of age was diagnosed with hypercholesterolaemia with the Canadian P95, but not with the MORGEN P95.

It is possible that not all cholesterol-related information was included in the GP patient files, for example, when cholesterol measurements were taken as part of a company physical examination or during a hospital stay. However, it is clear that markedly high cholesterol will be reported to the GP. Because of this, we expect this kind of underreporting to have had no effect on the estimate of the percentage of FH patients with hypercholesterolaemia.

This study shows that the FH patients with no record of cholesterol measurements in their GP patient files prior to the screening were on average 22 years younger than the other FH patients. This means that of the identified FH patients, it was particularly the young FH patients who were being brought to the attention of the GPs for the first time. As a result, they can be referred for specialized care at an early stage, including monitoring of the lipid profile followed by treatment if necessary. Nevertheless, the underlying assumption is that the cholesterol distribution among FH patients already known to their GPs is the same as among FH patients identified for the first time through screening. Data from another study among 215 untreated FH patients confirm this (data not shown). In this study, patient information was selected from the same database, in a period in which cholesterol was determined and a DNA test was also carried out.
Considering the increased risk of CHD (especially fatal CHD) for young FH patients [17], this study confirms the potential added value of genetic screening for individual FH patients over passive identification by GPs. Now, asymptomatic carriers of gene mutations can be closely followed, properly monitored and if necessary treated in order to minimize the risk of CHD.

Acknowledgements

We like to thank M.A.W. Umans-Eckenhausen and staff members of the StOEH for their cooperation during this study. We also thank P.J.E. Bindels, J.C. Defesche, J.J.P. Kastelein and E. Schadé for their comments on earlier drafts of this article. We are grateful for the opportunity to use unpublished data from the MORGEN-project. These were kindly made available to us by D. Kromhout, W.M.M. Verschuren en S. Houterman of the National Institute for Public Health and the Environment.

Reference List


Genetic screening for FH: primarily younger patients in the care of GPs