THE TROMSØ HEART STUDY

POPULATION STUDIES OF CORONARY RISK FACTORS WITH SPECIAL EMPHASIS ON HIGH DENSITY LIPOPROTEIN AND THE FAMILY OCCURRENCE OF MYOCARDIAL INFARCTION

OLAV HELGE FØRDE

DAG STEINAR THELLE

Universitetet i Tromsø
Institutt for Samfunnsmedisin
ISN-skriftserie - før utgitt:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskjøttede i Sør-Varanger kommune.
   Av Anders Forsdahl, 1976.


Egil Arnesen

Egil H. Lehmann

ISBN 82 – 90262 – 03 – 5
THE TROMSØ HEART STUDY

POPULATION STUDIES OF CORONARY RISK FACTORS WITH SPECIAL EMPHASIS ON HIGH DENSITY LIPOPROTEIN AND THE FAMILY OCCURRENCE OF MYOCARDIAL INFARCTION

OLAV HELGE FØRDE    DAG STEINAR THELLE

INSTITUTE OF COMMUNITY MEDICINE AND INSTITUTE OF CLINICAL MEDICINE, UNIVERSITY OF TROMSØ, NORWAY

TROMSØ 1979
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFACE</td>
<td>4</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>5</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>7</td>
</tr>
<tr>
<td>- Population studies of coronary heart disease in Norway</td>
<td>9</td>
</tr>
<tr>
<td>- Recall frequency and intervention procedures after the Tromsø screening</td>
<td>12</td>
</tr>
<tr>
<td>SUMMARY AND MAIN CONCLUSIONS OF THE PAPERS</td>
<td>16</td>
</tr>
<tr>
<td>GENERAL DISCUSSION</td>
<td>19</td>
</tr>
<tr>
<td>- Causality and prediction</td>
<td>19</td>
</tr>
<tr>
<td>- The role of high density lipoprotein in lipid transport</td>
<td>21</td>
</tr>
<tr>
<td>- Methodological problems in assessing the family occurrence of coronary heart disease in populations studies</td>
<td>22</td>
</tr>
<tr>
<td>- The prevention controversy</td>
<td>26</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>31</td>
</tr>
</tbody>
</table>

THE PAPERS

I Methods and main results of the cross-sectional study

Thelle, D.S., Førde, O.H., Try, K. & Lehmann, E.H.

II A multiple regression analysis of the relationship between coronary risk factors and some physical and social variables
Førde, O.H. & Thelle, D.S.
Submitted for publication

III Risk factors for coronary heart disease related to the occurrence of myocardial infarction in first degree relatives
Førde, O.H. & Thelle, D.S.
Am J Epidemiol 105:192, 1977

IV Coronary risk factors and the occurrence of myocardial infarction in first degree relatives in subjects of different ethnic origin
Thelle, D.S. & Førde, O.H.
Am J Epidemiol In press

V A model for describing family-associated risk for coronary heart disease as a continuous variable
Thelle, D.S. & Førde, O.H.
Submitted for publication

VI Family study of high density lipoprotein cholesterol and the relation to age and sex
Mjøs, O.D., Thelle, D.S., Førde, O.H. & Vik-Mo, H.

VII High density lipoprotein and coronary heart disease: A prospective case-control study
Miller, N.E., Førde, O.H., Thelle, D.S. & Mjøs, O.D.
Lancet i:965, 1977

VIII Serum apolipoprotein AI concentration in relation to future coronary heart disease
Ishikawa, T., Fidge, N., Thelle, D.S., Førde, O.H. & Miller N.E.
Eur J Clin Invest 8:179, 1978

IX Distribution of serum cholesterol between high density and lower density lipoproteins in subjects of Norse, Finnish and Lappish ethnic origin
Førde, O.H., Thelle, D.S., Miller, N.E. & Mjøs, N.E.
The University of Tromsø was founded for regional political reasons. Research relevant to the problems in Northern Norway was given high priority in the early plans for the University. One of the first professors at the Medical School and Head of the Medical Department at the University Hospital, Professor Arne Nordøy was early aware of the high incidence of coronary heart disease and its impact as a health problem in this part of the country. He therefore initiated a population study in Tromsø, as an attempt to explore the problem of coronary heart disease, and, if possible, to offer interventive measures. This initiative was supported by the Municipal Health Officer, Dr. Hans Anstad.

The organization structure of the Medical School in Tromsø, with the close relationship between the institutes, made it natural to plan the study as a collaborative project between the Institutes of Clinical medicine, Community medicine and Medical Biology. The practical work was performed by a working-group formally connected to the Institute of Clinical Medicine,
ACKNOWLEDGEMENTS

Not being naturally honest, to reach a level of truthfulness
- above that afforded by chance - we have drawn on the stores of
Professor Knut Westlund.

We also wish to express our sincere thanks to:

- Professor Arne Nordøv, who initiated The Tromsø Heart Study,
  for his stimulating ideas and continuous encouragement.

- Professor Ole D. Mjøs who with an open mind and never failing
  cooperability, led us into the field of high density lipoprotein.

- Professor Kenneth Try for good cooperation and carefully
  handling of the laboratory analyses.

- Dr Kjell Bjartveit, Thore Gjervig and the rest of the staff of
  the State Mass Radiography Service for their cooperation and help
  with the data collection and data processing in connection with
  the family study in Finnmark.

- Inger Johanne Sellevold who during the first two years had the
  questionable pleasure of administering our untidy persons.

- Tove Eriksen and Helga Johannessen for their assistance in the
  primary examination.
- Elin Normann Fosse for patience and skill in preparation of manuscripts.

- Thale Henden for her endurance with the high density lipoprotein cholesterol analyses.

- Peter Kraft, Ulrich Raddatz and Ole Krog Thomsen for skilful data processing.

- Egil H. Lehmann, Egil Arnesen, Anders Forsdahl and the other colleagues at the Institute for helpful advice and positive criticism.

The project was financially supported by The Norwegian Research Council for Science and the Humanities, The Norwegian Council for Cardiovascular Diseases, The County of Troms, The Municipality of Tromsø, and Norsk Kollektiv Pensjonskasse.
INTRODUCTION

The epidemiological approach to coronary heart disease (CHD) is suggested by the sheer magnitude of the problem and the fact that this highly lethal disease frequently attacks without warning. Despite modern innovations in the management of the acute coronary attack, the coronary care unit to safeguard the myocardial infarction (MI) victim who reaches hospital alive, and the cardiac surgery to revascularize and repair the ischaemic heart, there is no evidence that coronary mortality has been substantially affected. Hope of controlling this disease can only come from preventive measures applicable to populations or population segments. Epidemiological investigations form the basis on which preventive medicine depends. They start with finding the facts about the population frequency of the disease - prevalence and incidence - and if proper methods and criteria are used they can reveal relationships between the disease frequency and other characteristics of the population. In other words, epidemiological studies should be able to provide information relevant to the etiology of CHD.

In order to assess whether statistical associations are etiologically important, the following criteria from the Report to the Surgeon General on Smoking and Health (1) should be fulfilled:

1. Strength of association
2. Graded nature of the association
3. Temporal sequence, i.e., does the presumed etiologic factor precede the disease?
4. Consistency of the finding, in study after study
5. Independence of each of the associations
6. Predictive capacity in other populations than the examined
7. Coherence of the findings — in two senses, i.e. consistency of the epidemiological findings with those from other research methods (animal experimental, clinical and pathological investigation), and coherence in that reasonable pathogenetic mechanisms are known, indicating the pathways whereby the etiologic agents act to produce the disease.

Most of these criteria are analogous to those necessary to declare causality in experimental biological settings. In contrast to these settings, where experimental conditions may be controlled, the epidemiological observations will inevitably be influenced by confounding variables. This characteristic of epidemiological studies requires emphasis on standardization, comparability and large numbers as well as repetition in different populations.

The epidemiological studies can rarely produce final proof of a causal sequence, particularly in CHD in which there is no single cause. The pathological mechanisms and the biological explanations are tasks for the basic medical sciences. This fact together with the demands in criterion 7 — coherence with reasonable pathogenetic mechanisms — implies close collaboration between epidemiological investigators and more biologically oriented research groups.

The major part of today's knowledge of the etiology and prevention of CHD stems from epidemiological studies which started in the USA in the 1950s and later spread throughout the industrialized world. The main finding from these studies was the establishment of serum
cholersterol, blood pressure, and cigarette smoking as major risk factors for CHD in middle-aged men. The criteria for the etiologically important association between these factors and CHD were fullfilled. Still, questions concerning both etiology and prevention of CHD remained unanswered. These questions to a great extent influenced the design of the epidemiological studies in Norway in the 1970s:

1. Which social and behavioural factors determine the variation of the coronary risk factors?

2. Do the risk factors of middle-aged men operate with similar impact in all populations or subgroups of the populations, i.e. sex, age, geographical, and social groups?

3. Can we find new factors which could increase our predictability of CHD?

4. Can intervention towards high-risk individuals reduce:
   a. The risk factor level?
   b. The subsequent incidence of CHD?

Population studies of CHD in Norway

It was shown in 1964 by Jervell et al (2) that there was a considerable difference in the incidence of CHD in different areas in Norway. This difference could to a large extent be explained by differences in the serum cholesterol level. A later prospective study comprising 6,886 men drawn from twenty industrial physicians in Oslo was carried out by Westlund and Nicolaysen (3). This study established serum cholesterol as a major risk factor for CHD in middle-aged urban men in Norway. The necessity of a further exploration of coronary risk factors in men aged 20-49 years and the demand for controlled
intervention trials initiated the Oslo Study in 1972 (4). The methods of the cross-sectional part of this study was later adapted by the Cardiovascular Disease Studies in Norwegian Counties and the Tromsø Heart Study, both started in 1974 (5). The similarities in the methods reflect to some extent the fact that the planning committees for the studies had some members in common. Future comparability was a main objective. This resulted in the use of an almost identical main postal questionnaire, the same methods for blood pressure measurements and the use of non-fasting blood samples for lipid analyses. The Oslo Study and the County Studies had their blood samples analysed in the same laboratory at the Ullevål Hospital, Oslo, whereas the blood samples from the Tromsø Heart Study were analysed in Tromsø. Parallel samples were analysed to insure comparability in the two laboratories. In the Oslo Study and the County Studies blood glucose was determined, whereas hemoglobin was measured in the Tromsø Heart Study. The re-examination of the Finnmark population took place in 1977-78, and at this time HDL-cholesterol was analysed in all subjects. The main differences in study populations and subprojects of the three studies are shown in table 1.
<table>
<thead>
<tr>
<th>Study (geographical area)</th>
<th>Age</th>
<th>% invited</th>
<th>Men</th>
<th>Women</th>
<th>Major subprojects</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Oslo Study (the municipality of Oslo)</td>
<td>20-39</td>
<td>7%</td>
<td>1,763</td>
<td>0</td>
<td>Randomized controlled trials of intervention on hypertension, serum cholesterol and smoking</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>100%</td>
<td>16,202</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>The Cardiovascular Disease Study in Norwegian Counties</td>
<td>20-34</td>
<td>10%</td>
<td>4,034</td>
<td>4,075</td>
<td>Investigation of impact of family occurrence of CHD *</td>
</tr>
<tr>
<td>(the counties of Pinmark, * Sogn og Fjordane and Oppland)</td>
<td>35-49</td>
<td>100%</td>
<td>25,163</td>
<td>24,556</td>
<td>Investigation of the prevalence of peptic ulcer and pepsinogen determination *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uncontrolled intervention on hypertension, hyperlipemia and smoking. Dietary investigation in subsamples</td>
</tr>
<tr>
<td>The Tromsø Heart Study (The municipality of Tromsø)</td>
<td>20-49</td>
<td>100%</td>
<td>6,595</td>
<td>0</td>
<td>Investigation of impact of family occurrence of CHD. Uncontrolled intervention on hyperlipemia and hypertension</td>
</tr>
</tbody>
</table>

* In four municipalities all subjects aged 20-49 years were invited.

The family history study, as well as the peptic ulcer study, were conducted in the same four municipalities.
Recall frequency and intervention procedures after the Tromsø screening

Subjects satisfying the recall criteria for more than one group were re-examined according to the priority given in the following table.

<table>
<thead>
<tr>
<th>Recall group</th>
<th>Recall criteria *</th>
<th>Age group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20-29</td>
<td>30-39</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>&lt;12.5 or &gt;17.5</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Chest pain</td>
<td>&quot;Rose formula&quot;</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>Leg pain</td>
<td>&quot;Rose formula&quot;</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>20-29 ≤ 300</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-39 ≤ 350</td>
<td></td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>40-49 ≤ 380</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>DBP 20-29 &gt;100 or &gt;160</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-39 &gt;105 or &gt;170</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>40-49 &gt;110 or &gt;180</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>&gt;4.5</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>405</td>
<td>383</td>
</tr>
</tbody>
</table>

* Not recalled:
Subjects who reported to have or have had diabetes mellitus, myocardial infarction, angina pectoris, treated hypertension, or other atherosclerotic disorder
Hemoglobin

Of the 74 men called for re-examination, 59 actually turned up. At the reexamination 46 proved to have hemoglobin values within the recall limits. Ten men had hemoglobin below 12.5 g/dl, but the majority of these were aware of their anaemic state.

Chest pain

207 men were re-examined. Of these 13 were found to have angina pectoris according to common clinical criteria.

Leg pain

101 men were re-examined. Of these two were found to have atherosclerotic obliterative disease. One was previously diagnosed (but not reported as a known disease by the subject at the primary examination).

Serum cholesterol

390 men out of 420 met at the first re-examination, which consisted of a single fasting blood sample for lipid analysis. The 152 men who at this examination had serum cholesterol below the recall limits were not further examined, only given a brochure with dietary advice. 238 men were invited to take part in a dietary intervention trial, including interview and instruction by a dietician. 175 of these men were followed for twelve weeks, with serum cholesterol determination every six weeks. The results
from this intervention will be described when the long-term
effect is available from the new study planned for 1979-80 in
Tromsø.

61 subjects who did not respond satisfactorily to the dietary
intervention were included in a randomized double blind cross-over
study with clofibrate and placebo. Only 34 of these men kept up
with the trial throughout the planned six months. This high
drop-out rate reflects to some extent side-effects, which young
asymptomatic men find intolerable, but also our own attitude to-
towards persuading these men to continue to take two pills of partly
unknown effect four times a day.

Figure 1 summarizes the results of the trial. In spite of the
small numbers the cholesterol lowering effect of clofibrate was
significant. None of the men continued with clofibrate medication
after the trial.

Serum triglycerides

23 men had fasting serum triglycerides above 2.5 mmol/l at the
first re-examination. They were recommended dietary changes like
reduction of carbohydrate and caloric intake.

Blood pressure

The procedure and results of the intervention on high blood pres-
sure are published elsewhere (10) and will only be summarized
here. Subjects who exceeded the blood pressure limits only were
directly referred to one of six general practitioners. Those who also satisfied other recall criteria were first examined at the out-patient clinic, and thereafter, if blood pressure medica-
tion was considered, referred to their general practitioner.
Of the 134 men who at the screening exceeded the recall limits, 95 men were referred*. The general practitioners found indication for medical treatment in twelve men, 34 were recommended further observation and eight were declared normotensive.

* In the published abstract it was erroneously stated that 61 men were referred for hypertension, this is however the number of available reports from the general practitioners.
SUMMARY AND MAIN CONCLUSIONS OF THE PAPERS

The present papers are, with the exception of paper IV, based on The Tromsø Heart Study. Paper IV describes a subproject of the Cardiovascular Disease Study in Finnmark.

The papers deal with three main topics:

A. The occurrence and the level of coronary risk factors and their relation to physical and social variables, (Papers I and II).

B. The relationship between the occurrence of myocardial infarction (MI) among first degree relatives and the subsequent risk for MI, (Papers III, IV, and V).

C. HDL-cholesterol as a risk factor for coronary heart disease, (Papers VI, VII, VIII, IX).

A. The occurrence and the level of coronary risk factors and their relation to physical and social variables

The first paper describes the methods and some of the cross-sectional results. The high level of serum cholesterol and its rapid increase with age were not unexpected considering the high mortality rate of CHD observed in Tromsø County. The cigarette consumption was a little higher than for the country as a whole. The blood pressure level in Tromsø was lower than in the Oslo Study. The observation in paper I that some social characteristics were related to coronary risk factors, was further explored by multiple regression technique presented in paper II.
Even if the impact of several variables was reduced to some extent by this technique, it was confirmed that characteristics related to lower social groups i.e. low height, heavy physical work, and residence in rural areas, were associated with a higher coronary risk factor level. Similar observations have also been made in The Oslo Study (6). In the future CHD will therefore probably occur predominantly in the lower social classes.

B. The relationship between the occurrence of myocardial infarction (MI) among first degree relatives and the subsequent risk for MI

First degree relatives of MI cases have been reported to have a significantly higher MI risk compared to subjects without MI relatives (7). In paper III and IV this risk elevation could only to a small extent be explained by higher levels of blood pressure, blood lipids, and cigarette consumption. On this basis we therefore concluded that the occurrence of MI among first degree relatives must be considered an independent risk factor for later MI. The methodological problems in assessing the occurrence of MI among relatives in population studies, and in the use of this variable in the risk analysis, are large. These problems are discussed in paper V and enlarged upon in the general discussion. A model is suggested for estimating a continuous variable containing the family-associated risk. Our intention with this variable is to use it in addition to other coronary risk factors in order to improve the predictability of MI. The real value of this variable can first be evaluated in a prospective material.
C. HDL cholesterol as a risk factor for CHD

In 1975 Miller and Miller (8) put forward the hypothesis that lower HDL cholesterol was associated with an increased risk for CHD. Already six months earlier contact between O. Mjøs and N. Miller lead to the inclusion of HDL cholesterol analysis in a family study which was part of the Tromsø Heart Study (paper VI). This family study did not reveal any difference in the HDL cholesterol level in subjects with and without MI among their relatives. However, in this comparison the family histories were not verified. The HDL cholesterol level in males aged 30-49 years was lower than in females. Stored serum samples from the 1974 survey permitted testing of the HDL hypothesis in a small prospective case-control study, (Paper VII). This analysis established HDL cholesterol as a strong discriminant variable between cases and controls, an observation which has been confirmed in a larger prospective study from Framingham (9). In paper VIII it was examined if the observed difference in HDL cholesterol between cases and controls in this material reflected a corresponding difference in apoprotein AI level. A difference was observed but less than for HDL cholesterol, and as the material was accidentally reduced, the conclusions are only tentative. The promising findings from the prospective studies encouraged us to try to clear up differences in CHD incidence which could not be explained by conventional risk factors. The differences in CHD incidence between the three ethnic groups in Tromsø, however, could not be explained by differences in HDL cholesterol (Paper IX).
GENERAL DISCUSSION

Causality and prediction

Assuming that preventive measures are effective, the incidence of CHD can be reduced by changing detrimental living habits in the population. But even in an improved environment there will remain in the foreseeable future high risk individuals who may benefit from personally adapted intervention. Such intervention must be based on the ability to identify the high risk subjects through predictive tests. Much knowledge has been gained on predisposing factors for CHD, and our ability to predict future CHD victims is higher than for any other chronic lethal disease. Still, a combined risk function of serum cholesterol, blood pressure and cigarette smoking can only place 50 per cent of the future MI cases in the upper quintile of risk (11, 12, 13). This finding is consistent in most population studies, disregarding differences in incidence of CHD in the populations. The MI cases found in the lower four quintiles of risk, the so-called "unexplained" cases, are a recurrent source of controversy. Their existence has been used as an argument against the causal role of the major risk factors. Such inference is based on the misconception of a one to one relationship between pathogenic agent and disease, relationships which are extremely rare in medicine. The fact that a majority of cases occurs at risk levels below the upper 10 or 20 per cent is of course irrelevant for the assessment of causation. As the risk is continuously increasing without any threshold which distinguishes between those with and without risk,
a certain number of cases has to occur below the upper quintile. Such cases might therefore more properly be called unpredicted than "unexplained". This lack of predictive power to some extent reflects the methodological difficulties in assessing the true level of the risk factors. The assessment of individual risk in most longitudinal studies is based on a single measurement, which to a great extent is influenced by intra-individual variation and analytical errors, and which leads to misclassification of subjects. The errors involved are well-documented for serum cholesterol and blood pressure (14, 15, 16, 17), and are of such magnitude that they have to confound prediction of risk in individuals (3). The assessment of smoking habits is also encumbered by considerable methodological difficulties. If we therefore want to avoid the extra, and mostly non-applicable effort of multiple measurements in the same individual, we have to develop methods which to a large extent measure the true level of the risk factors. The methods for measurements of the major risk factors and the errors involved are in fact principally the same today as they were thirty years ago. Thus more promising alternatives would probably be to examine subfractions of the risk factors - possibly closer to the biological mechanism - and assessed with greater accuracy, or to include other factors in the risk function to increase the predictive power.

Improvement of prediction is an important objective - and may also improve our insight into the web of causation. Future research will probably reveal specific agents which will increase our knowledge of the pathological mechanisms of CHD, but they are unlikely to be sufficient causes of CHD anymore than the bacillus.
is for tuberculosis. Retrospectively, it is admissable to say that the drastic reduction of tuberculosis as cause of death in the industrialized world did not depend on the recognition of the bacillus.

The role of high density lipoprotein in lipid transport

The high predictive power of HDL cholesterol compared to total cholesterol (paper VIII, 9, 18) may depend on either a higher reliability of the HDL cholesterol measurements, or that HDL cholesterol plays an independent part in the atherogenesis. Recent data indicates that within-subject variation and the analytical error do not differ considerably in HDL cholesterol and total cholesterol measurements (19). Thus the higher predictive power of HDL cholesterol if it proves to be a general phenomenon - is probably explained by this variable being closer to the atherogenic process. The advantage of the HDL hypothesis is that it fits into an already existing theory of lipid transport without conflicting with the consistent epidemiological observations of the association between total serum cholesterol and CHD. A large fraction of the low density lipoproteins (LDL) which carries most of the lipids accumulating in atherosclerotic lesions, is degraded in peripheral cells. The cholesterol moiety, however, can only be degraded in the liver. Thus cholesterol brought into the cell by the LDL or synthetised intracellularly must be transported back to the liver for degradation. The LDL uptake in the cell, and thereby the cholesterol uptake, is primarily determined by receptors on the cell membrane (20). Any interference with the LDL
uptake will slow atherogenesis by reducing the rate of cholesterol delivered to the cell. HDL may interfere with this process either by inhibition of the LDL uptake in the cells or through facilitating cholesterol transport back to the liver. The inhibition of the LDL uptake may be effected through competition for the receptor sites. Recent studies have shown that subfractions of HDL, apoprotein E, compete more effectively than unfractioned HDL with LDL for the receptor sites (21). This finding may be indirectly supported by the lack of increased predictive power of apoprotein AI compared to HDL cholesterol reported in paper VIII. However, the need for a larger body of quantitative data from epidemiological studies, as well as further research on the control of the lipid transport across the cell membrane are evident before the true role of HDL as a risk factor for CHD can be defined.

Methodological problems in assessing the family occurrence of CHD in population studies

Despite early recognition of the family history as a risk factor, this variable has not been included in the risk function based on the major risk factors. There are mainly two reasons for this: firstly the widespread view that the family-associated risk operates through the major risk factors, a view which is not supported by our data, and secondly the fact that "measurement" of the family history also is associated with considerable methodological difficulties.

A thirty-eight year old man who participated in one of our screenings was interviewed on the family occurrence of MI. He reported to have had MI one year earlier, but to the question
concerning MI among his first degree relatives, he was obviously in doubt. During the interview the following history was revealed. His father was healthy and aged sixty years. His mother, who was fifty-eight years old, had had angina pectoris for the last five years. Two of his mother's brothers had died from MI before the age of fifty, and his mother's youngest brother had a MI at the age of forty-four. His two sisters were healthy at the age of thirty-three and thirty-six respectively. This young man, who according to common clinical judgement had a heavy family predisposition for CHD, was recorded with a negative family history according to our criteria. The history illustrates the following methodological problems.

1. Choice of endpoints, which to a large extent determines the reliability of the family history. (Generally the softer the end-points, the less reliable the data.) Angina pectoris, with its often imperceptible and undramatic natural history, is too soft an end-point in mass-interviews. Nevertheless, also angina pectoris may well confer risk on first degree relatives, especially when it occurs in young women. A harder end-point is age of death of the relatives. This end-point, however, requires - to be discriminating - a high age of relatives, which again implies high age of the survey population, or data on grand-parents. If the last alternative is chosen, the family history is extended to include:

2. Data on second degree relatives, which inevitably would be less reliable than data on first degree relatives.

To our experience interviewees have more than enough difficulties in giving reliable information on morbidity in first degree relatives. But we are well aware of the possible loss of information due to the exclusion of the second degree relatives from the family
histories. This loss of information may lead to:

3. **Misclassification due to few and young first degree relatives.** This is a persisting problem when data is collected in young subjects. Often the number of first degree relatives is small and their age so low that the chance of finding a MI case among them is very low. Thus, a negative family history in these subjects has a low predictive value. A practical compromise for the family history of CHD which would fulfil both the demands for reliability and for high predictive power might perhaps be to collect information both on the occurrence of MI among first degree relatives and longevity in grand-parents. It then remains to find a practical and reliable method for collection of the family data;

4. **Interview or self-administered questionnaire.** Our choice of interview together with a verification procedure was made with the intention of optimizing reliability. The procedures, especially the verification, are, however, too laborious to be applicable in routine screenings. The main questionnaire included a question on the occurrence of MI or angina pectoris among first degree relatives. This enables comparison of the two methods, the interviews and the self-administered questionnaire. The answers from the interviews and the questionnaires are cross-tabulated in table 2. The higher number of positive responses to the questionnaire to some extent reflects the inclusion of angina pectoris, but the two methods apparently yield different results also for MI. The questionnaire picks out 79 per cent of the verified MI positive family histories. It also gives a considerable number of false positives, but it is a far more practical method, and we have to search for more precise questions to improve the reliability of the questionnaires in the future. Our basis for suggesting the
Table 2

QUESTIONNAIRE ANSWERS TO THE QUESTION: "HAS ONE OR MORE OF YOUR PARENTS OR SIBLINGS HAD MYOCARDIAL INFARCTION OR ANGINA PECTORIS?" DISTRIBUTED ACCORDING TO RESULTS OF VERIFIED INTERVIEW. THE CARDIOVASCULAR DISEASE STUDY IN FINNMARK, FOUR MUNICIPALITIES, 4,450 HEALTHY MEN AND WOMEN AGED 20-49 YEARS

RESULT OF VERIFIED INTERVIEW

<table>
<thead>
<tr>
<th>QUESTIONNAIRE ANSWERS</th>
<th>Total</th>
<th>No MI among first degree relatives</th>
<th>Myocardial infarction</th>
<th>Sudden death</th>
<th>Uncertain MI</th>
<th>Angina pectoris</th>
<th>Not traced for verification</th>
<th>Lack of information about relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1034</td>
<td>385</td>
<td>417</td>
<td>30</td>
<td>8</td>
<td>79</td>
<td>96</td>
<td>27</td>
</tr>
<tr>
<td>No</td>
<td>2918</td>
<td>2741</td>
<td>53</td>
<td>17</td>
<td>1</td>
<td>7</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>Don't know</td>
<td>498</td>
<td>407</td>
<td>40</td>
<td>9</td>
<td>2</td>
<td>8</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>4450</td>
<td>3533</td>
<td>510</td>
<td>56</td>
<td>11</td>
<td>85</td>
<td>143</td>
<td>111</td>
</tr>
</tbody>
</table>
family history included in the risk function was that the family-associated risk could have an independent contribution to the prediction. Even if it were not so, i.e. the family risk was conferred through the major risk factors already included in the risk function, the family history would be another way of measuring the risk, which together with the other measurements could bring us closer to the true risk level.

The prevention controversy

Even if some controversy still exists concerning the causal role of the major risk factors, the main controversy is related to the benefit of intervention measures in individuals or society at large. This controversy is partly caused by conceptional differences within the medical profession, but the principal cause is inadequate data. Unequivocal evidence of a worth-while benefit of intervention still does not exist.

If we look at the diet-heart controversy, most diet trials to date have been encumbered by methodological problems or inconsistency in results (22, 23). Some studies, however, have been encouraging, especially with regard to the feasibility of cholesterol reduction in men by dietary means (24). With regard to antihypertensive treatment most studies have shown indisputable effects on the incidence of cerebrovascular strokes, whereas the effect on the incidence of CHD has been less equivocal striking (25, 26). In order to further investigate the effectiveness of antihypertensive treatment on moderately elevated blood pressure the British Medical Research
Council has recommended a controlled trial including 18,000 subjects, a number which requires screening of 380,000 - 450,000 subjects (27). The effect of quitting smoking has been examined in several studies. A gradual decrease in relative risk for CHD has been observed during the first two years after having stopped smoking (28). Such results however, may be biased by other changes in behaviour taken by those who stop smoking cigarettes. These changes cannot be adjusted for without controlled trials. Only one controlled trial of smoking intervention is known, with participants drawn from the Whitehall study of male civil servants in London (29). In that study approximately one half of the cigarette smokers did stop smoking, but also a rather large group of the controls stopped smoking in the same period, and the CHD incidence did not differ between the groups, the results remain inconclusive. The present status of intervention is, in summary, that the evidence of a beneficial effect of quitting smoking and the benefit from dietary changes are encouraging, whereas the effect of medical treatment for hypertension, although overall clearly beneficial, is debatable with regard to CHD.

Both the risk factor concept with additive effect from each single factor, and the almost insuperable difficulties in changing one single factor at a time, have initiated multiple risk factor intervention trials. The future results from the large American Multiple Risk Factor Intervention Trial (MRPIT), started in 1973 and including approximately 12,000 men aged 35-57 years, will probably have considerable effect on the policy of intervention (30). Inconclusive results also from this study must, however, be anticipated in the light of the recent reports on decreasing CHD mortality rates in USA,
corresponding to changes in life style habits (31). Both this fact, the use of drug intervention (32) and the relatively late onset of intervention may reduce the chances for conclusive results.

It has been argued that the total body of "indirect" evidence - epidemiologic, clinical, animal experiments - only permits formulation of hypotheses, and that only experiments, i.e. randomized controlled trials, permit decisive testing of a hypothesis. If this approach to the methodology of science should prevail, most of the knowledge acquired by modern medicine would have to be classified as hypotheses. It is of course justified to ask for a final proof for the beneficial effect of intervention, but the methodological difficulties of experiments within this field, and the ideal experiment i.e. to randomize and intervene upon newborn babies, are so unrealistic that we probably have to live with circumstantial evidence. Nevertheless, we feel that the time is ripe for more attempts at controlled mass scale preventive action.

The fact that the detrimental way of living is so ordinary, everyday and widespread in modern industrial societies, suggests measures towards society at large rather than the single individual. Measures towards the society must arise from political decisions, but examples of such decisions are rare. In Norway a three-year old parliamentary report suggesting well-founded changes in nutritional habits has still not resulted in any political action. Similar to the ban on tobacco advertisements, which was put into effect anyhow, the suggested changes are so entangled in circumstantial interests that political decisions are very complex. This political dilemma and our inability to provide effective health education, necessitate also individual intervention measures.
Ideally, individual intervention should be a task for the primary health service. In Norway, however, the resources allocated to the primary health service do not at present allow any substantial increase in work-load. A reinforcement both educationally and financially is needed before the primary health service can handle these tasks properly.

In the mean-time, the work-sharing exemplified by the County Studies, where the State Mass Radiography Service performed the screening and the general practitioners the intervention has proved to be a feasible model. Besides giving research opportunities such screening programmes have a health educational value both for the public and the health personnel.
REFERENCES


26. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213:1143-1152, 1970


