



**A POPULATION BASED STUDY ON
CORONARY HEART DISEASE IN FAMILIES**

The Finnmark Study 1974-1989

Tormod Brenn

Tromsø 2000



Institute of Community Medicine
University of Tromsø, Norway

*ISM skriftserie
blir utgitt av Institutt for samfunnsmedisin
Universitetet i Tromsø.*

*Forfatterne er selv ansvarlige for sine funn og
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“En skål førr Finnmark!”
(Boknakaran, 1999)

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I guess it all started about 20 years ago. As a student in statistics, I was introduced to a seminar with *Odd Aalen*, *Tore Schweder* (statisticians, the latter my supervisor at that time), *Knut Westlund*, *Egil Arnesen*, *Olav Helge Førde*, *Dag Thelle* and *Bjørn Straume* (from the Institute of Community Medicine (ISM)). Focus was on heritability of coronary heart disease, and one recurring theme was how to construct an optimal family risk score.

Being recruited by *Knut Westlund*, I started to work at ISM in 1981 at a time the first two health surveys in Finnmark and Tromsø had been conducted. Some family information also had been gathered and analysed. Due to *Egil Arnesen*, who over the years has been my supervisor, I became interested in the family data. This so-called family risk component seemed “intriguing”. Not only had no-one provided a definition, but *Knut Westlund*, who always has had a sharp tongue, said no more than “ye-es, you should select your parents with care”. I soon realised that family data required statistical treatment that was fascinating, and I also fancied the Fortran computer work necessary to assemble individuals into family units.

Over the years I have always enjoyed to work with the family data. They have required an interesting combination of computer programming and statistical analyses. Family data can to a large extent be analysed with simple and understandable statistical methods, but more sophisticated tools are also sometimes required. I have always felt at home among computer programmers and biostatisticians. They have formed their own subculture, and these men and women are the real driving forces behind so much of the research activity.

In some sense, I consider this thesis an extension of the work initiated at ISM by the pioneers named above. They collected more data than they were able to fully describe and analyse, and it is a privilege to continue their work and to take care of the current data before they disappear. *Knut Westlund*, *Egil Arnesen* and *Olav Helge Førde* still show keen interest in the family data. Another important person has been *Anders Forsdahl* with his detailed knowledge about Finnmark and his studies on health hazards due to bad living conditions. A final motivating factor to mention is the fact that I have always enjoyed to write.

Most of all, the 19,017 men and women in Finnmark who participated should be thanked. Then there is the staff at the National Health Screening Service and ISM who collected the data. *Inger Njølstad* provided essential follow-up data and has also been a partner for discussion. Community medicine has many exiting aspects, and ISM is an inspiring place to undertake research. Besides those men and women already named, *Tom Wilsgaard* also has provided valuable help. My wife *Elinor Ytterstad* should be thanked for many things. Financial support has been provided by ISM and the Norwegian Research Council.

LIST OF PAPERS

The thesis is based on the following papers:

- I. Brenn T. Adult family members and their resemblance of coronary heart disease risk factors: The Cardiovascular Disease Study in Finnmark. *Eur J Epidemiol* 1997; 13:623-30.
- II. Brenn T. Genetic and environmental effects on coronary heart disease risk factors in Northern Norway. The cardiovascular disease study in Finnmark. *Ann Hum Genet* 1994; 58:369-79.
- III. Brenn T, Njølstad I. Coronary heart disease risk factors in subjects whose brothers, sisters or husbands developed premature myocardial infarction during 12 years of follow-up. The Finnmark Study (1977-1989). *J Cardiovasc Risk* 1998;5:325-30.
- IV. Brenn T, Wilsgaard T, Njølstad I, Arnesen E. Predicting onset of coronary heart disease from risk factors measured once and repeatedly. The Finnmark Study 1974-89. Submitted.
- V. Brenn T, Njølstad I, Førde OH. Prospective study of an extensive family history of coronary heart disease: The Finnmark Study 1977-1989. Submitted.

1. INTRODUCTION

Coronary heart disease accounts for approximately one half of the total number of deaths, making it the number one killer of men and women in developed countries. Also in a world-wide perspective, cardiovascular disease is rapidly becoming the number one cause of death [Ballantyne, 1997]. Death rates from coronary heart disease vary by age and sex. For the age group 40 to 59 years, the disease is the cause of death for 33 percent of the men and 16 percent of the women in Norway. Although women are much older than men are when they die from the disease, coronary heart disease was the cause of death for a similar proportion of both sexes [Royal Norwegian Ministry of Health and Social Affairs, 1996].

In Norway, cardiovascular mortality increased during the 1930s, then was reduced during the war years, and increased again after the war. During the 1950s and most of the 1960s, mortality rates from myocardial infarction increased markedly before levelling off around 1970. Since then, Norwegian mortality rates have dropped, but still 44 percent of all deaths in 1995 were from cardiovascular diseases [Central Bureau of Statistics of Norway, 1977; Statistics Norway, 1998].

Data on cause specific mortality in various geographical areas of Norway are available from around 1960 [Bjartveit et al., 1979]. The regional differences are considerable, and among the 20 Norwegian counties, Finnmark at that time had

the highest mortality rates in both sexes for cardiovascular disease and ischaemic heart disease. During the 1980s the male rate showed a marked decline [Krüger and Ny-moen, 1990], but more recent data confirm Finnmark's position with the highest mortality of cardiovascular diseases [Statistics Norway, 1998].

Coronary heart disease has a complex aetiology, and the factors identified to be associated to its incidence are many. Firmly established and considered to be most important (apart from older age and male sex) are elevated serum (total) cholesterol, high blood pressure and cigarette smoking. The frequent use nowadays of the term "risk factor" may be unfortunate in instances where it refers to a collection of variables that stand in different levels in the chain of causation. With this reservation in mind, a host of other risk factors includes high fat diet, alcohol abuse, physical inactivity, obesity, diabetes, low high density lipoprotein (HDL) cholesterol and coffee drinking. However, the list of such risk factors is almost constantly changing as new factors are considered, evaluated, and eventually included. The so-called family factor is considered important by most researchers, but its exact role and impact appears to be described with much inconsistency.

Just like the incidence of coronary heart disease, also risk factor profiles have been found to be particularly adverse in the northern part of Norway, and especially in Finnmark [Hewitt et al., 1995]. It has been concluded that a large proportion of the

excess mortality in Finnmark can be accounted for by the general high level of total cholesterol [Tverdal, 1989]. Also, cardiovascular morbidity and mortality in young Finnmark women have been strongly associated with smoking [Njølstad et al., 1996]. Between 1974 and 1996 six population based health surveys have been accomplished in Finnmark. Levels of total cholesterol means have declined, blood pressure values have remained at the same level and the percentage of daily smokers has gone down among men and up among women. Notable is also a markedly body weight increase, especially in men [Statens helseundersøkelser, 1998].

The county of Finnmark lies situated well within the Arctic Circle and at the same latitude as Alaska's northern coastline. Seasonal variations of daylight and climate are considerable as illustrated by the yearly average of air temperature in Karasjok of -1.5 centigrade, ranging from a January mean of -14.8 to that of 13.9 in July [Central Bureau of Statistics of Norway, 1977]. Finnmark had a resident population of 79,351 in 1977 [Central Bureau of Statistics of Norway, 1977] and 75,575 in 1997 [Statistics Norway, 1997]. With a population density per square kilometre of 1.7, Finnmark is the most sparsely populated county in Norway. Many people have settled in small towns, primarily scattered along the coast. Traditional occupations are related to fishing, farming and reindeer breeding. The residents fall into the ethnic groups of Norse, Finnish and Sami.

The population sample eligible for the

current study was mainly born between 1925 and 1954, and the first years of this period was characterised by extensive poverty [Forsdahl, 1973]. During the war, most Finnmark residents were evacuated, and practically all houses were burnt down. The county was rebuilt after the war. Historically, most health and social welfare parameters have shown that Finnmark is the least favourable area in Norway. Adverse living conditions during early life has also been found to be a disease risk factor [Forsdahl, 1978]. Thus, Finnmark is a particular interesting place to undertake studies, also those that focus on families.

The family factor or component is an extraordinary type of risk factor. Not only is it not a simple personal attribute like high blood pressure or cigarette smoking, but it involves characteristics that have been inherited as well as influence from sharing a particular environment. For those with a background and interest in statistical methodology, family data have many interesting aspects. One example is how to compute correlation coefficients among the varying number of individuals found in families. Another issue concerns the sophisticated mathematical models involved in efforts to identify effects from genes and environment. Also, it is well known that individuals who have close relatives who have experienced disease themselves are under higher risk of obtaining the disease in the future [Goldbourt et al., 1994]. It is thus interesting to explore whether information on close relatives can be in-

corporated in an enumerated score, a family risk score, in a way that effectively identifies those few individuals under extreme risk of developing disease.

1.1 Coronary heart disease incidence in families

Pioneer works from the 1950s and 1960s reported a threefold increase in coronary heart disease among men with compared to men without a family history of disease [Thomas and Cohen, 1955; Rose, 1964; Slack and Evans, 1966]. More recent case-control data have shown a relative risk of myocardial infarction of 2.0 [Roncaglioni et al., 1992] and 2.7 [Silberberg et al., 1998] in those with myocardial infarction in a first-degree relative compared to subjects without a family disease history. Furthermore, for two or more relatives affected, ratios were 3.0 [Roncaglioni et al., 1992] and 5.4 [Silberberg et al., 1998], the latter ratio being based on relatives with coronary heart disease before age 55 years. Other researchers have also pointed out that incidence rates appeared to be higher in subjects whose relatives had had a heart attack at a relatively young age [Schildkraut et al., 1989]. Studying Framingham sibships, the incidence of myocardial infarction in the older brother was significantly related to myocardial infarction experience of the younger brother, even after the effects of total cholesterol, systolic blood pressure and cigarette smoking were controlled for [Snowden et al., 1982]. Most reported estimates have been derived from middle-aged or older men, but there

are findings of a dissimilar family trend in women [Goldbourt, 1994]. Female patients have more commonly than male patients been found to have first-degree relatives with coronary artery disease before the age of 65 [Pohjola-Sintonen et al., 1998]. Also, when two first-degree family members were assumed to have coronary artery disease, then the probability of the patient being a woman was as formidable as 11.3 times higher than being a man [Hofstad et al., 1998]. Thus, women may seem to inherit heart disease more often than men do.

At least a single question on heart disease onset among any first-degree relative has routinely been included in the studies in the Norwegian counties [Westlund, 1997] and most other population based health studies around the world. This information has been the foundation for prospective studies, and death due to coronary artery disease in parents was associated with a 30 percent increase in the risk of the disease in Framingham [Schildkraut et al., 1989]. In Finland, the risk ratio of acute myocardial infarction associated with positive family history of either parent was 1.6 in men and 1.9 in women [Jousilahti et al., 1996]. Reports from Norway have merely supported other research, but magnitudes have been of 1.6 in men [Tverdal, 1989], and of 1.5 in men and 1.3 in women [Njølstad, 1998]. The current score model of the National Health Screening Service has included a factor of 1.5 for a "Yes" or "Don't know" answer to the family question [Statens helseundersøkelser, 1987]. Thus, with some variations in magnitude

probably reflecting differences in coronary endpoints, study sample age and inclusion of confounding variables, myocardial infarction has been found to occur in around 50 percent more of the persons with than those persons without a family disease history.

Although the simple and binary outcome family history variable included in self-administered questionnaires has been regarded a practical measure of familial influence, its limitations are many. Not only have reports on disease developed in relatives proved to be inaccurate [Kee et al., 1993], but potential important elements concerning family structure and disease status are lacking. To obtain more detailed and extensive family disease histories, structured interviews were undertaken in the early screening rounds in the north of Norway [Førde and Thelle, 1977; Thelle and Førde, 1979]. Based on the interview information, a continuous family history score was constructed in Tromsø. It was thought that such an enumerated score rather than a dichotomous variable better would represent a polygenic mode of inheritance [Thelle et al., 1979]. However, no large-scaled prospective evaluation of this or other family history scores for coronary heart disease has yet been published.

1.2 Coronary heart disease risk factors in families

Relatives tend to be more alike than unrelated individuals, and not only coronary heart disease incidence but also the disease risk factors appear to aggregate in families.

For example, offspring of high blood pressure fathers or mothers are likely to have elevated readings themselves. There are some studies that have been aimed at the prediction of risk factor levels in the offspring on the basis of parental levels [Heuch et al., 1985]. More commonly seen, however, has been the correlation coefficient as a measure of risk factor resemblance among various types of family members. Values have been found to be positive for all major cardiovascular risk factors, thereby confirming the existence of substantial familial aggregation. As an illustration, blood pressure correlations for Nord-Trøndelag, Norway, made available from a large-scaled study of more than 70,000 participants, were around 0.16 for each of the four possible parent-offspring sex combinations and around 0.20 among siblings. For 79 identical twins, values were 0.52 and 0.43 for the systolic and diastolic pressure, respectively. For the more distant familial relationships such as second-degree relatives, correlations were lower [Tambs et al., 1992]. Several other studies originating from the US and elsewhere have demonstrated a similar pattern of family resemblance [Namboodiri et al., 1983; Namboodiri et al., 1984; Patterson et al., 1987].

Another common research strategy has been to divide ostensibly well individuals into subgroups with and without a family history of heart disease and compare their mean risk factor profiles. In a review of 18 such studies, not many were found to establish a strong relation between family

history of coronary heart disease and risk variables. The association was statistically significant for total cholesterol in 11 of 18 studies, for HDL cholesterol in six of 10 studies, for triglycerides in seven of 14, for blood pressure in none of 12, for smoking in five of 13, and for body weight in one of 12 [Jorde and Williams, 1988]. In Tromsø, age-adjusted mean of total cholesterol was 0.14 mmol/l higher and mean systolic blood pressure was 1.1 mmHg higher in men with as compared to men without family history of myocardial infarction. The authors concluded that the differences were surprisingly small, and that the slight elevations in serum cholesterol and blood pressure contribute only to a very small extent to the increased risk in subjects with a positive family history [Førde and Thelle, 1977].

Like many other contemporary studies [Deutscher et al., 1969; Aro, 1973; Welin, 1978], those initiated in Tromsø and Finnmark in the mid 1970s also put particular emphasis on the family component in coronary heart disease [Thelle et al., 1976; Førde and Thelle, 1977]. Early efforts included examination of probands and their wives' first-degree relatives [Mjøs et al., 1977]. Some years later, a family intervention study was undertaken [Knutsen and Knutsen, 1989], and it was concluded that members who shared household with a person with increased risk for coronary heart disease, also are at an increased risk [Knutsen and Knutsen, 1990; Knutsen and Knutsen, 1991].

1.3 Influence from heredity and environment

Death or disease may be caused by single genes, such as in familial hypercholesterolemia [Müller, 1938; Brown and Goldstein, 1986]. However, the generally observed family pattern of coronary heart disease is best explained by a polygenic mode of inheritance [Carter, 1974]. This means that a large and unspecified number of genes each have a small effect on the observed phenotype. In recent years, it has also become increasingly clear that a majority of coronary heart disease cases are caused by a combination of genetic and environmental factors [Nora et al., 1991]. For example, individuals exposed to the same environment may have variable susceptibility to disease due to genetic variation.

Inevitably, the existence of familial aggregation reflects both genetic and environmental influence. Once familial aggregation has been established, the second and more difficult step is to achieve discrimination between them. Their specific contribution cannot always be directly separated, but some information is provided by comparing genetically unrelated and related family members. As spouses are not usually blood-related, any risk factor relation probably does not reflect genetic influence, but rather the environmental factors to which the couple is exposed. The observed spousal blood pressure correlations in Nord-Trøndelag were only 0.08 and 0.09 for the systolic and diastolic pressure, respectively, hence being of less magni-

tude than values derived between genetically related individuals [Tambs et al., 1992]. Other studies have also shown that the similarity between husband and wife appears to be rather small, regardless of whether couples are newly wed or have shared same spousal environment for decades [Knuiman et al., 1996]. This finding indicates so-called assortative (selective) mating and only a modest effect of cohabitation over the years. Furthermore, parent-offspring correlations appear to be of similar size from childhood throughout early adult life [Morrison et al., 1982; Greenberg et al., 1984]. Findings from family correlation studies therefore have suggested strong influence from genes or early shared family environment and only a modest effect from later life environment.

The coefficient of heritability (h^2) measures how much of the total variation among individuals for a certain characteristic that can be attributed to genes [Khoury et al., 1993]. A high heritability means a large proportion of the variation among relatives follow patterns predicted by genetic factors. Such observed estimates have been from 0.57 to 0.62 for total cholesterol and somewhat smaller and more varying for systolic blood pressure (from 0.25 to 0.41). Effects attributable to the environment, sometimes called cultural heritability (c^2), on the other hand have been found to be only between 0.03 and 0.07 for total cholesterol and between 0.04 and 0.16 for systolic blood pressure [Glueck et al., 1985]. It is noteworthy that

estimates of environmental effects have been so modest as compared to their genetic counterparts.

Studies on adoptees, twins and pedigrees all offer excellent opportunities of resolving genetic and environmental effects. In men, the relative hazard of death from coronary heart disease when one's twin died of the disease before the age of 55 years, as compared with the hazard when one's twin did not die before 55, was 8.1 and 3.8 for monozygotic and dizygotic twins, respectively [Marenberg et al., 1994]. Results from other twin studies are similar [Berg, 1983], and since the proportion of monozygotic twins affected is significantly greater than that of dizygotic twins, a substantial genetic component in the aetiology of coronary heart disease is indicated. In a study of 42 extended families (including 1,236 first-, second-, and third-degree relatives), age, gender, and other environmental covariates accounted in general for less than 15 percent of the total phenotypic variation for lipids and lipoprotein, and 15 to 30 percent for glucose, hormones, adiposity and blood pressure. Correspondingly, genes accounted for 30 to 45 percent and 15 to 30 percent, respectively [Mitchell et al., 1996].

Thus, various family constellations have been the subject for many types of studies over the last three or four decades. Based on case-control and twin studies, a positive family history of heart disease easily can be regarded as a major risk factor together with serum cholesterol, blood pressure and smoking. Further supporting this view is

the formidable proportion of variation apparently related to genes. On the other hand, risk factor profiles have not been found to be very adverse in disease prone families, and the more well-controlled prospective investigations of positive family histories have not revealed so much excess risk as twin studies and early case-control efforts. To what extent the well-documented familial aggregation of risk factors can explain the observed aggregation of heart disease in families still remains unclear. Mathematical calculations have indicated that the statistical association of risk factors within a family does not in itself lead to any great familial aggregation of disease [Khoury et al., 1988; Aalen, 1991]. The pathogenesis of atherosclerosis is generally agreed to be complex. Involved are probably interactions among the vessel wall, circulating elements and disturbed flow, and a number of genetic factors could play a role [Marian, 1997]. The mechanisms behind the familial aggregation of coronary heart disease are thus yet far from completely understood.

2. AIMS OF THE THESIS

This is an epidemiological study of the familial risk component in coronary heart disease. Data on the general population of Finnmark were collected at health surveys undertaken from 1974 with follow-up throughout 1989.

The aims were:

- * to assess the degree of family resemblance in coronary heart disease risk factors and incidence in a relatively young population in the high risk area of Finnmark
- * to try to separate family influence into components attributable to heritability and environment
- * to evaluate the prognostic significance of a more comprehensive as compared to the more common abbreviated family histories of heart disease
- * to apply, adapt and empirically compare statistical methods applicable to study disease aggregation in families by data available from the cardiovascular screenings in the Norwegian counties.

3. SUBJECTS AND METHODS

The data sources of the current study were mainly the cardiovascular disease studies in the Norwegian counties where data from 1977-78 were extracted from four Finnmark municipalities including an additional interview of the examinees on family members, and follow-up data on death and disease endpoints. Data from the studies in Norwegian counties were also used from Finnmark as a whole and from other screening rounds.

Figure 1 shows the number of men and women involved in the current study and also in which papers they were included in the analyses. Information on experienced heart disease in family members was collected from the questionnaire as well as from the interview in four municipalities. The interview also served the distinct purpose of providing information to assemble individuals into family units. The figure also indicates the use of this family information in each paper.

3.1 Surveys

Apart from the marginal use of data from the sixth Finnmark screening round in 1996-97 given in the general discussion, the data for the current study were taken from the following surveys:

Finnmark 1974-75 (also referred as Finnmark 1974 or Finnmark I)

Invited were all county residents aged 35 to 49 years (born 1925 to 1939). A random 10 percent sample of subjects between 20

and 34 years of age (born 1940 to 1954) were invited, but in four municipalities (Kautokeino, Porsanger, Gamvik and Vadsø), all those men and women were included. Altogether, 17,517 men and women were invited, and 14,401 (82.2 percent) participated [National Mass Radiography Service et al., 1979; Bjartveit et al., 1979].

Each person was invited by mail with a cover letter and a one-page questionnaire on the reverse side (Appendix 1). The questionnaire was assumed answered at home and brought along to the survey where it was checked for inconsistencies by a trained nurse. Inquiries were also made regarding municipality of birth and time since last meal, and for women also menopausal status and pregnancy.

The questionnaire covered (A): History of cardiovascular disease, diabetes mellitus, and treatment for hypertension. (B): Symptoms that could be related to cardiovascular disease or lung disease. (C): Physical activity during leisure time. (D): Smoking habits. (E): Stress factors in social life and level of physical activity at work. (F): Family history of coronary heart disease and ethnic origin group.

Next was the physical examination which comprised measurements of body height, body weight and blood pressure. Height and weight were measured to the nearest centimeter and half-kilogram. For some participants, data on body height and weight were missing. The blood pressure was measured twice in a sitting position with a mercury sphygmomanometer. The

Use of:
 Questionnaire on family disease
 Interview to assemble families
 Interview on family disease
 Follow-up data

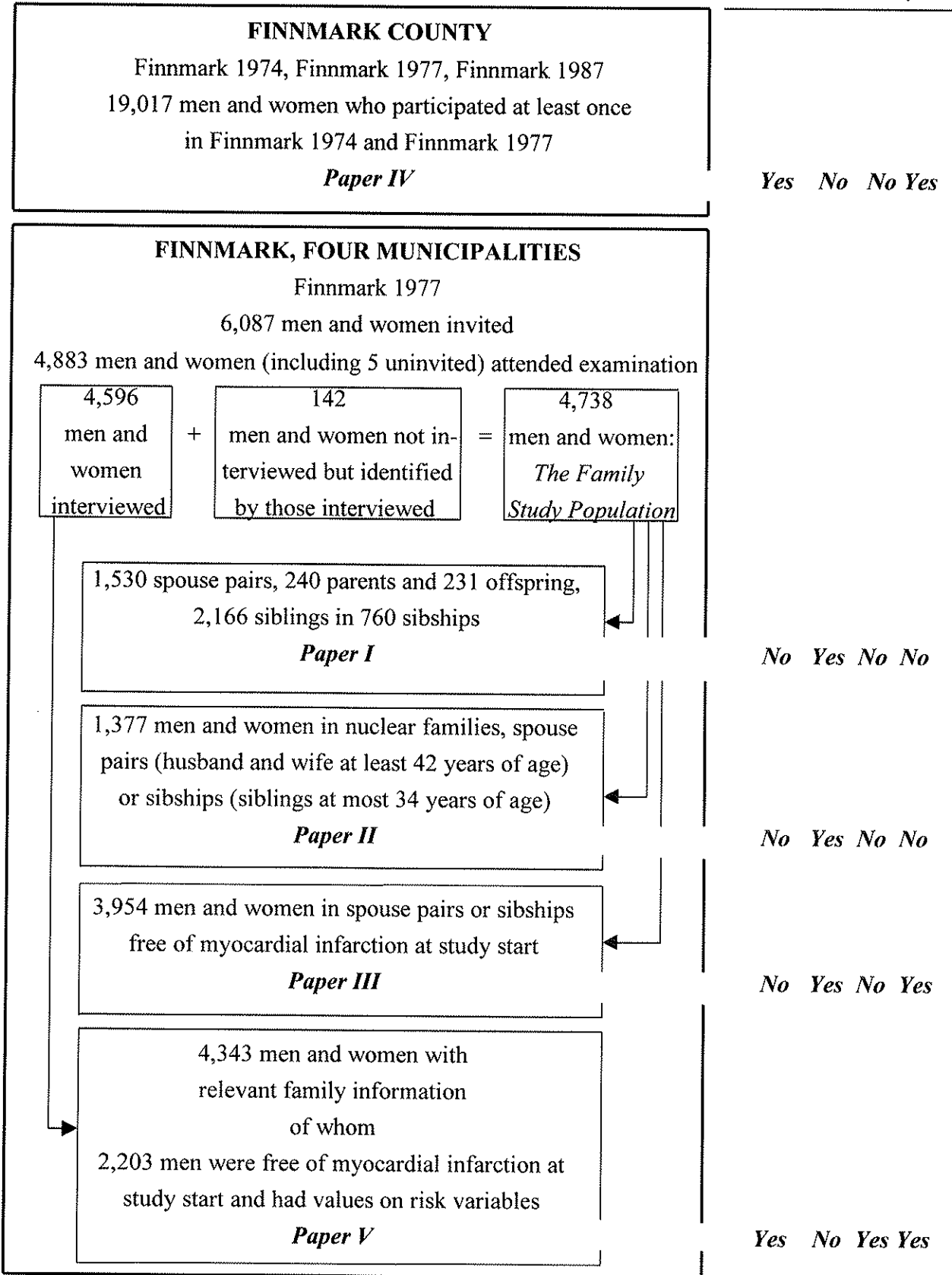


Figure 1. Outline of study population, use of family data and papers.

systolic pressure was defined as the nearest even number of mmHg when the first Korotkoff sound appeared (phase 1). The diastolic pressure was measured at the disappearance of the Korotkoff sounds (phase 5), or phase 4 when that phase was lacking [Bjartveit et al., 1979].

A non-fasting blood sample was also drawn. The serum was sent to the Central Laboratory, Ullevaal Hospital, Oslo for analyses of total cholesterol, triglycerides and glucose [Bjartveit et al., 1979].

Finnmark 1977-78 (also referred as Finnmark 1977 or Finnmark II)

Invited were all residents aged 35 to 52 years (born 1925 to 1942). For the ages 23 to 34 years (born 1943 to 1954), all subjects were invited who also had been invited to the survey in 1974-75 (and still were living in the county), in addition to a random sample of 11 percent. However, in the four municipalities, all men and women between 23 and 34 years of age were invited. For the ages 20 to 22 years (born 1955 to 1957), a random 10 percent sample was invited. Altogether 20,683 persons were invited and 17,181 met (83.1 percent). [The National Health Screening Service et al., 1988].

The procedures were virtually identical to those followed in the previous screening round. One discrepancy was an additional question G on visit to physician after the previous screening round (Appendix I).

HDL cholesterol was determined at the University of Tromsø (4,480 samples from four municipalities) or in Oslo. The Oslo

samples were frozen, and it was necessary to add 0.12 mmol/l to the values to compare with the unfrozen Tromsø samples [Thelle et al., 1982].

After this survey, there was a change in method of determining total cholesterol and triglycerides. The (original) old method values were found to be expressed by the new method values as [The National Health Screening Service et al., 1988]:

Serum cholesterol (mmol/l):

New method = $0.92 \cdot (\text{Old method}) + 0.03$

Serum triglycerides (mmol/l):

New method = $0.90 \cdot (\text{Old method}) - 0.11$.

The current analyses make use of both old and new method values. Old method values can be found in Papers I (Table I) and III (Tables 2 to 4 and Figure 2), and new method values in Paper IV (for the 1974 and the 1977 lipid data in Tables 1, 3 and 4). Other tables present correlation coefficients [Paper I] or heritability estimates [Paper II] which were invariant for the scale used. In instances where lipids were included as covariates, results for the analysis variable family history of heart disease also are invariant for the scale used for lipid variables [Paper V].

Finnmark 1987-88 (also referred as Finnmark 1987 or Finnmark III)

Invited were all residents aged 40 to 62 years (born 1925 to 1947). For the ages 20 to 39 years (born 1948 to 1967), all subjects were invited who also were invited to the 1977-78 survey round (and still living in the county), and in addition a random sample of 10 percent. A total of 22,941

men and women were invited, and the number of participants was 17,821 or 77.7 percent. The procedures were similar to the previous screenings, but this time blood pressure was measured automatically with Dinamap. Also, three questionnaires were used, and the first was almost identical to the one used previously [West-

lund and Sjøgaard, 1993].

3.2 Interview on family members

As a side project to the standard routines, an interview was undertaken in Finnmark 1977-78 (Figure 2). All screenees in four municipalities (family study area) were included, and the municipalities were delibe-

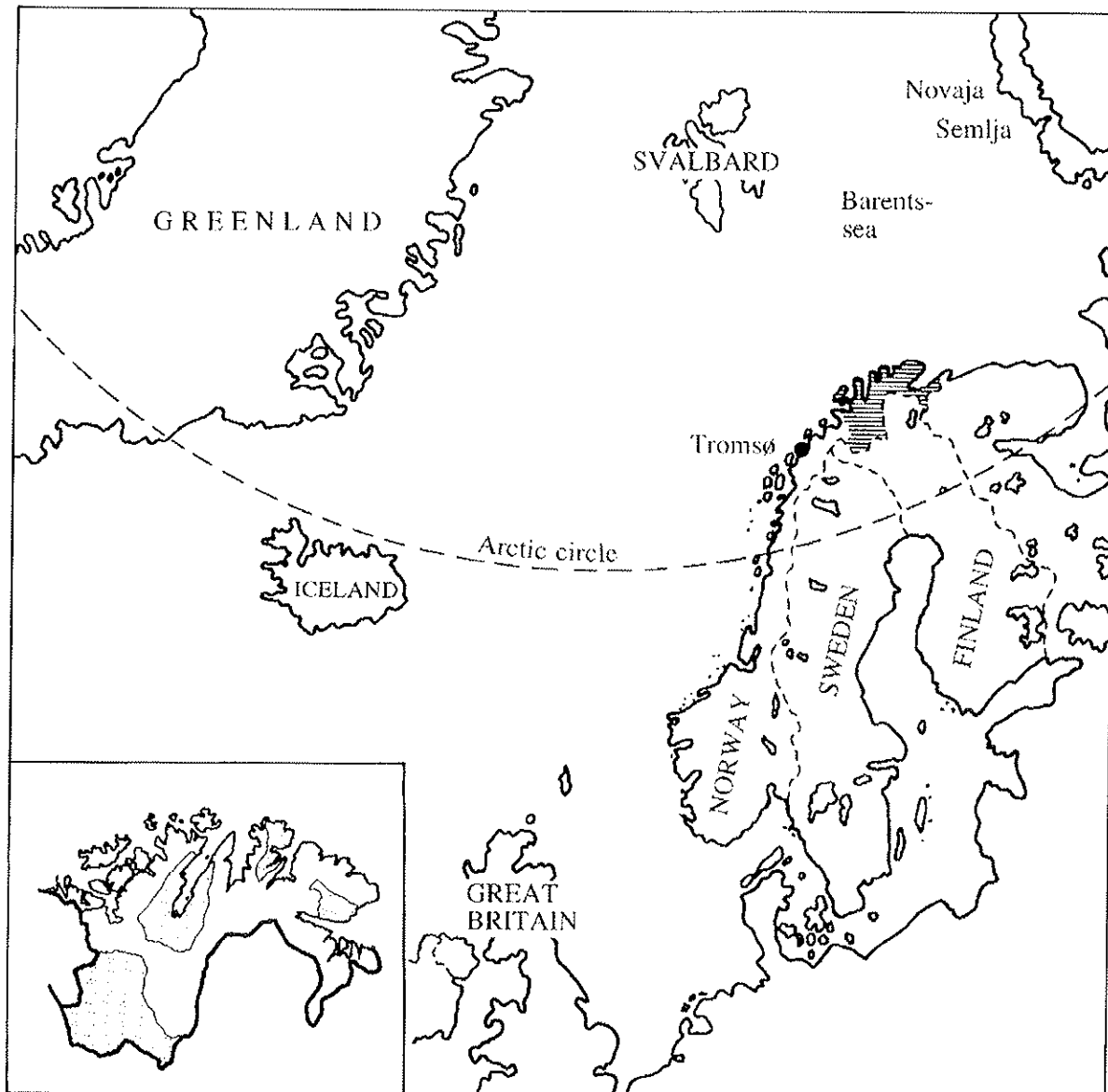


Figure 2. Map showing Finnmark (marked) with the four family study municipalities; from left to right (with resident population January 1, 1977 [Central Bureau of Statistics of Norway, 1977]) Kautokeino (2,817), Porsanger (4,485), Gamvik (1,767) and Vadsø (6,017).

rately selected to be different with regard to degree of urbanisation, employment type, geographical location (coast, inland) and composition of ethnic origin (Norwegian, Finnish, Sami).

The interview was carried out by eight specially trained assistants. They obtained histories using systematic interviews, and participants were first asked about personal diseases or disease symptoms and medication (Appendix 2). The last part of the interview concerned the first-degree family members (spouse, mother, father and each sibling). In instances where the interviewee did not know the exact date of birth or death, the assistant was instructed to approximate the date rather than let the question remain unanswered. The intention was to accept as family members only biologic parents and full siblings. On this point, lack of answer was accepted rather than pressing an interviewee that appeared to hesitate. After sex and year of birth were recorded, questions were asked on occurrence of myocardial infarction and ulcer. In instances with uncertainty due to lack of knowledge about the exact character of the disease, further questions were asked on whether or not the attack was acute and had led to hospitalisation or death. For the "Yes" responses, more details such as address, hospital and year of the attack were recorded (Appendix 2). Then, unless already filled in, the possible year of death was recorded. Finally, the assistants asked whether any first-degree relatives lived within the same municipality and were between 20 and 54 years of age. For positive

responses, the relatives' names were taken.

The interview was an extended version of the same type of interview used in Tromsø 1974 [Førde and Thelle, 1977] and Finnmark 1974-75 [Thelle and Førde, 1979]. The results from the current interview questions regarding use of antihypertensive drugs have been published previously [Arnesen et al., 1983].

Among the 6,087 men and women invited to the screening at a location inside the four municipalities, the number who attended the examination was 4,883 after five subjects from elsewhere in Finnmark also were included. The interview was completed by 4,596 of the examinees (Kautokeino ($n = 913$), Porsanger ($n = 1,276$), Gamvik ($n = 507$), Vadsø ($n = 1,895$) and the five subjects from elsewhere).

For the more recent purpose of the current study, information collected at the interview was used to link family members who attended the survey. The considered relationships were spouse pair, parent-offspring and sibship. In instances where relatives living within the four municipalities had participated in the examination but had not completed the interview, it was decided to include these subjects ($n = 142$) as well. The resulting 4,738 participants comprised the family study population (Figure 1), and some vital characteristics are shown in Table 1. Each reported relative was identified in the consensus file that also supported the 11 digit official national identification number. With this number as the key, a computer program was written to link the family members. Tests were

Table 1. Some characteristics* of family study population ($n = 4,738$). Finnmark 1977, four municipalities.

	Men		Women	
	20-34 years ($n = 1,142$)	35-52 years ($n = 1,305$)	20-34 years ($n = 1,151$)	35-52 years ($n = 1,140$)
Age (years)	29.0	43.0	28.7	42.9
Serum lipids (mmol/l)				
Total cholesterol**	6.28/5.81	7.21/6.66	6.02/5.57	7.05/6.52
HDL cholesterol	1.23	1.28	1.48	1.52
Triglycerides**	2.01/1.70	2.25/1.91	1.44/1.18	1.70/1.42
Blood pressure (mmHg)				
Systolic	133.4	136.8	120.0	130.7
Diastolic	78.7	85.1	76.3	82.8
Body mass index (kg/m ²)	24.2	25.5	22.9	25.4
Daily smokers (%)	58.2	54.9	48.0	41.3
Physically inactive† (%)	21.9	21.4	21.8	21.3
Family history of heart disease (%)	23.6	31.4	24.2	33.3
Ethnic origin (%)				
Finnish	19.4	25.8	15.9	23.5
Sami	19.3	19.2	20.9	21.7

* Values are means or percentages.

** Old/new (enzymatic) method of determining total cholesterol and triglycerides.

† Sedentary physical activity in leisure time.

performed both manually and by computer to verify the logic and correctness of the family grouping with respect to number of members, years of age and family names. Special care was taken for families with inconsistent information and for the 142 non-interviewees where cross-checking possibilities were limited. The numbers of determined combinations for the various relationships are given in Tables 2 to 4. The numbers of subjects linked into zero, one, two or three relationships depending on the participation of their family mem-

bers were 640, 2,615, 1,367 and 116, respectively (Table 4). Papers I to III present analyses of a subsample of various family units.

With the exception of 253 interviewees who were unable to provide relevant information about at least one of their parents, the remaining 4,343 men and women reported on a total of 12,834 fathers and brothers and 12,855 mothers and sisters (Paper V concentrates on those aged 30 years more). The numbers of reported male and female relatives were maximum

Table 2. Number of determined relationships between family study parents and their offspring. Finnmark 1977, four municipalities.

Parent	Number of offspring ($n = 231$)										Total	
	Sons			Daughters			Sons and daughters					
	1	2	3	1	2	3	1	2	3	4		5
Father ($n = 75$)	27	4	2	45	4	0	59	13	3	0	0	94
Mother ($n = 165$)	80	13	3	87	9	1	117	40	7	0	1	223

Table 3. Number of determined family study sibships. Finnmark 1977, four municipalities.

Sibling	Sibship size									All sizes
	2	3	4	5	6	7	8	9		
Brothers ($n = 872$)	235	83	32	5	0	0	0	0	0	355
Sisters ($n = 688$)	213	46	23	4	2	0	0	0	0	288
Brothers and sisters ($n = 2,166$)	404	192	79	58	17	8	0	2		760

Table 4. Distribution of family study participants in various familial relationships. Yes or No indicates whether or not the relationship was determined. Finnmark 1977, four municipalities.

Relationship			Number of relationships determined	Number of subjects ($n = 4,738$)
Spouse pair*	Parent-offspring**	Sibship†		
No	No	No	0	640
Yes	No	No	1	1694
No	Yes	No	1	121
No	No	Yes	1	800
Yes	Yes	No	2	117
Yes	No	Yes	2	1133
No	Yes	Yes	2	117
Yes	Yes	Yes	3	116

* 1,530 pairs (3,060 subjects).

** 240 parents and 231 offspring.

† 2,166 subjects in 760 sibships.

11 and 12, respectively, with identical averages of 2.96. There was some family size variation across ethnicity with an average number of reported parents and siblings of 5.12 for the Norse ($n = 1,835$), 6.15 for the Finnish ($n = 923$) and 6.96 for the Sami ($n = 865$).

Altogether 1,002 interviewees reported heart disease in 1,142 parents or siblings (Table 5). The positive reports, but not the negative ones, were compared with information from the national bureau of statistics and the records of doctors and hospitals. The diagnoses entered in these records were always accepted. For most case events, verification procedures had already been completed during a previous interview (Finnmark 1974-75) of a majority of the participants [Thelle and Førde, 1979]. Altogether 115 cases could not be verified due to incomplete or inconsistent information provided by the interviewee or lack of

record files on early deaths.

The interview on heart disease in the relatives was also used to compute a family history score (FHS). A previously defined score was applied [Reed et al., 1986], and for each individual the value was computed as:

$$FHS = \sum_j \frac{O_j - E_j}{\sqrt{E_j}},$$

where O_j is the observed heart disease status (0 or 1) for the j th member in family and E_j is the sex and five-year age group specific expected risk for heart disease in that individual. Classified as myocardial infarction were the verified diagnoses of myocardial infarction, imminent infarction and sudden death.

In men ($n = 2,234$), FHS values ranged from -3.0 to 39.8 with an average of 0.18. Corresponding female ($n = 2,109$) values were from -3.0 to 40.2 with an average of

Table 5. Results of the verification of the positive interview reports on heart disease developed in a parent or sibling. Finnmark 1977, four municipalities.

Verified diagnoses	Men and women with information ($n = 4,343$)		Men who were followed up ($n = 2,203$)	
	No. of interviewees	No. of reports	No. of interviewees	No. of reports
Myocardial infarction	625	672	299	321
Imminent infarction	26	26	20	20
Sudden death	79	79	42	42
Angina pectoris	85	89	34	37
Other diagnoses	156	161	82	85
Not traced for verification	109	115	51	52
Total	1002*	1142	505*	557

* Less than sum in categories due to multiple reporting.

0.33. There was no systematic change of values with age in either sex.

Among the 4,343 men and women (Figure 1) who had relevant information on their family members, the number of men was 2,234. After excluding 17 men who had developed myocardial infarction at the time of examination and 14 other men who lacked information on risk factor variables, the remaining 2,203 men were included in the FHS analysis (Paper V). For these men also, the number of heart disease events among first-degree relatives has been given in Table 5.

3.3 Follow-up

The prospective part of the current investigation made use of follow-up data on cause specific deaths and diseases from Finnmark. These data were collected for the Finnmark Study and have been described in detail [Njølstad 1996 et al., Njølstad 1998].

In short, the screenees were followed from screening until death or through December 31, 1989 by the means of official health data and medical records ((A): Causes of Death Registry at Statistics Norway. (B): Discharge diagnosis lists from the Finnmark hospitals, and from the Regional Hospital in Tromsø. (C): Medical record files in hospitals and community health care centres in Finnmark) and a postal questionnaire. Considered were first event of myocardial infarction, first event of stroke, onset of diabetes, and death. The current investigation used the endpoint myocardial infarction, and classification

criteria included (I): Definite myocardial infarction. (II): Probable myocardial infarction. (III): Sudden death. (IV): Uncertain myocardial infarction. Altogether 97 percent of the participants were followed up, including the 11 percent who had moved from Finnmark [Njølstad et al., 1996].

Among the 4,738 individuals of the family study population, a total of 17 individuals had developed verified myocardial infarction before the time of the survey. During the period of follow-up, altogether 97 men and 17 female events of first myocardial infarction were observed.

3.4 Handling the family data

Epidemiological studies commonly analyse the individual as the unit of observation. In family studies, however, the analysis may be of a particular relationship or the nuclear family. This change of analytic unit requires some additional procedures for handling, organisation and analyses of the data. First, the information from the interview on family members was stored in separate variables and organised in computer files together with the usual survey information on the individual participant. One additional variable per considered relationship was added with identical values for individuals who were so related. For individuals who had no relative of a particular type in the survey file, the value for this relationship was set to missing.

With the help of the family relationship variables, the relevant individuals were easily selected in the next step. For exam-

ple, this could be to compute the correlation coefficient for total cholesterol for the father-daughter relationship. It was then necessary to make pairs of their observed values, and a family with the father and two daughters, were organised into two pairs of data (father-daughter 1 and father-daughter 2). Once the tedious data programming required to organise the data values was completed, the computation of the correlation was easily handled by a program package.

Developments in computer hard- and software over the two decades elapsing since the data first were collected are difficult to summarise. In the first years, there were the University Computing Centre in the town's centre and an unstable telephone line to Bergen. Also, there were punching cards and noisy machines. Then came the Nord computers, processing data with Cobol and Fortran programs at a speed at that time considered to be almost unbelievable. Today, all data described herein are easily stored on a single PC, and with the SAS programware data are organised and analysed in fractions of a second [SAS Institute Inc., 1990].

More recently, program packages specifically developed to handle and analyse family data have been made available [Fischer et al., 1996]. The programs have, however, been directed more towards the need of human geneticists than for our purposes, and we have deliberately decided to continue writing our own programs in the SAS language. To process family data with their inherent variations on the num-

ber of family members and other peculiarities, adequate programming tools are arrays and do-loops. The required facilities for handling as well as statistical analyses of such data are provided by SAS [DiIori and Hardy, 1996]. The particular path analytic model that was currently applied [Paper II], however, was run on a special non-commercial program developed in St. Louis, USA [Rao et al., 1984]. Although SAS has been the primary program software, SPSS [SPSS Inc., 1990], S-Plus [Venables and Ripley, 1996] and Excel [Dretzke and Heilman, 1998] have also been used marginally.

4. MAIN RESULTS

Paper I: Adult family members and their resemblance of coronary heart disease risk factors: The Cardiovascular Disease Study in Finnmark.

Altogether 4,738 men and women aged 20 to 52 years who in 1977 attended the health survey in four municipalities of Finnmark were included. The subjects were assembled into the familial relationships of spouse pairs (1,530 pairs), parent-offspring (240 parents and 231 offspring) and sibships (760 sibships with 2,166 siblings). Similarity of the major coronary heart disease risk factors was investigated among the various types of family members. Lipid and blood pressure correlations among parents and their offspring ranged from 0.13 to 0.27 and among siblings from 0.11 to 0.22; all statistically significant. Between the genetically unrelated husbands and wives correlations were small (0.02 to 0.06) except for a larger value (0.11) for total cholesterol. The degree of resemblance was generally stronger for total cholesterol than for HDL cholesterol and triglycerides, and also stronger for systolic than diastolic blood pressure. Across age groups, sibling correlations were consistent. Smoking concordance was demonstrated (p value < 0.01) among spouses (similar habits in 63.5 percent of all marriages as compared with the expected 49.4 percent) and also among siblings (42.9 percent observed and 34.9 percent expected).

Paper II: Genetic and environmental effects on coronary heart disease risk factors in Northern Norway. The cardiovascular disease study in Finnmark.

Among 4,738 men and women aged 20 to 52 years in four Finnmark municipalities, included were all those individuals who were assembled into nuclear families (at least one parent and one offspring), spouse pairs (husband and wife both at least 42 years of age) or sibships (all siblings at most 34 years of age). For the resulting 575 families with 1,377 men and women, the path analysis model with the environmental index was applied to estimate influence from genes and environment. Genetic and cultural heritabilities were 0.46 and 0.05 for total cholesterol, 0.42 and 0.10 for HDL cholesterol, 0.21 and 0.07 for triglycerides, 0.48 and 0.04 for systolic blood pressure and 0.35 and 0.05 for the diastolic pressure. Thus, genetic sources contributed much more than the environment. In general, the Finnmark heritabilities agreed fairly well with those observed elsewhere. Several estimates were among the highest reported, but the genetic component for total cholesterol and triglycerides was somewhat lower.

Paper III: Coronary heart disease risk factors in subjects whose brothers, sisters or husbands developed premature myocardial infarction during 12 years of follow-up. The Finnmark Study (1977-1989).

Among 4,738 men and women aged 20 to

52 years in four Finnmark municipalities, the individuals who were linked together in heart disease free sibships or spouse pairs were considered. The 3,954 distinct individuals in 753 sibships and 1,518 married couples were followed for 12 years, and 53 men and 50 women had a brother or sister and 64 women had a husband who developed a first myocardial infarction during the period. Multiple adjusted means of total cholesterol were 7.17 mmol/l in the 53 men with and 6.84 mmol/l in the remaining 932 men without a brother or sister who became affected (p value 0.07). In the same two groups, systolic blood pressure readings were 140.8 mmHg versus 135.6 mmHg (p value 0.02) and for the diastolic pressure 85.7 mmHg versus 82.5 mmHg (p value 0.04). Total cholesterol readings were higher the younger the sibling who became affected. In women, elevations were less pronounced, but daily smoking was reported among 58.3 percent of wives whose husband became affected as compared to 41.2 percent of wives whose husbands remained unaffected (p value 0.007). For HDL cholesterol, triglycerides and the body mass index, means differed only marginally in men as well as women.

Paper IV: Predicting onset of coronary heart disease from risk factors measured once and repeatedly. The Finnmark Study 1974-89.

Data analysed were from the entire Finnmark County on 19,017 men and women

from one, two or three screening rounds. After a maximum 15-year follow-up of first myocardial infarction, the numbers of male and female events were 669 and 130, respectively. With the use of Cox's proportional hazards regression method, risk ratios were derived for all major coronary heart disease risk factors, including the questionnaire answer on family history of heart disease in any parent or sibling. Each of the three screening rounds was analysed separately and with two distinct applications of the Cox method that allowed risk factor values to be measured (updated) repeatedly. Except for subject age, the results did not differ much across the various analyses of risk factors measured once, twice or three times. Thus, only a modest impact was observed by upgrading risk factor information. For the question "Have one or more of your parents or sisters or brothers had a heart attack (heart wound) or angina pectoris (heart cramp)?" (yes, no, don't know: the latter response alternative was considered as no), the adjusted risk ratios in men were 1.63 (for the 1974 survey data), 1.55 (for the 1977 survey data), 1.59 (for the 1987 survey data) and 1.66 and 1.63 using two different techniques of updating family histories over time. Corresponding female risk ratios were 1.26, 1.37, 0.68 (the number of events was only 20), 1.51 and 1.49. As other major risk factors also went into the model and thus were adjusted for, the family heart disease history acted as a consistent risk factor.

Paper V: Prospective study of an extensive family history of coronary heart disease: The Finnmark Study 1977-1989.

Altogether 4,596 men and women aged 20 to 52 years participated in the examination and an additional interview of the survey in four Finnmark municipalities in 1977, and 4,343 subjects had relevant interview information on family members. Family histories of heart disease were obtained from a questionnaire (whether or not heart attack or angina pectoris had been developed in an unspecified parent or sibling) and from a detailed interview on age, sex and possible heart disease onset in each parent and sibling. The positive interview answers were verified, and accepted were reports identified as myocardial infarction, imminent infarction or sudden death. A total of 2,203 men were followed up, and after 12 years, altogether 87 men had experienced a first myocardial infarction. Due to the limited number of 16 observed female events, women were not included in the further analyses. A numerical family history score was computed summarising information from the interview. The score showed only a modest ability to predict disease, and the risk ratio (per 10 units) was 1.14 (95 percent confidence interval 0.6-2.2 and $R^2 = 0.0462$). For simple dichotomised definitions of family disease history taking into account age at disease onset (maximum 50 or 60 years) and male or female sex of the affected relative, risk ratios were also small and insignificant. However, in many instances the number of

cases was limited. Many more men answered "Yes" on the questionnaire than on the interview, and the risk ratio for the simple questionnaire definition of a family heart disease history was 1.55 (95 percent confidence interval 1.0-2.4, $R^2 = 0.0478$). Extensive interviews thus appeared to hold no potential to be more useful for defining disease risk in the general population than the information obtained from questionnaire.

5. GENERAL DISCUSSION

The current unit of analysis was either the individual subject or familiar relationships (such as spouse pairs or sibships). Consequently, bias due to systematic errors in inclusion has to be considered not only on the common individual level, but also for each particular relationship.

Confounding variables play a particular important role in family data. Not only should they be adjusted for when computing family correlations, but estimates of environmental factors depend heavily upon which information is available. Also, all potential risk factors should be included to identify the independent contribution of a positive family history of disease.

A family history of heart disease has not only been considered an important part of the medical record, but it has also provided the foundation for analyses of the familial and hereditary nature of the disease. It is possible that risk is particularly increased in individuals who have relatives who developed the disease at young ages or where the relatives were of female rather than male sex. Yet another study aim was to explore the statistical methods required to analyse typical data from the population based studies undertaken in the Norwegian counties.

5.1 Selection bias

The participation rates of 82.2 percent and 83.1 percent for the 1974-75 and the 1977-78 Finnmark survey rounds have been previously discussed and considered high

enough to avoid systematic inclusion errors [Thune, 1997; Njølstad, 1998]. This view would also apply for the current individual participation rate of 80.1 percent (4,878 out of 6,087).

Not all family members were included in many instances. Some relationships were incomplete either because one or more family member fell outside the age range considered or because they lived outside the study area at the time of examination. It should be kept in mind that the individual man or woman was the primary survey target, and that the family aspect merely was considered for a subsample as an additional side project. There were thus no routines employed that secured that all relatives of the participants were also invited, and those who met as a result of the individual invitation were linked to other participants after the survey was completed.

Married men or women were linked due to information provided at the interview on current spouse, and data were not collected on marriage length or previous divorces and separations. The marital status as recorded in official registers was available at the time the person file for the study invitation was produced, and was also included with categories unmarried, married, widow or widower, divorced, and separated. The number of married men was 1,641 (67.1 percent of all 2,447 men) and married women 1,837 (80.2 percent of all 2,291 women). Hence, these numbers, which referred to an unknown number of invited and uninvited spouses, as expected

to some extent exceeded the 1,530 spouse pairs currently established from the interview.

For the two generation relationship (parent-offspring), combinations were possible only for the rather few families where parents were among the older part of the invited subjects and children were in the younger age range. Also, only children born before parents were a maximum of 32 (52 minus 20) years of age were included. Thus, only 471 subjects were found, and the fact that mothers outnumbered fathers (165 vs. 75) illustrates that they usually are younger than fathers.

For the sibships, every living and deceased brother and sister regardless of age and place of living were reported, although not all were named, by the individuals who completed the interview ($n = 4,596$). The

siblings who were actually assembled had to have attended the examination, and Table 6 compares the numbers reported and assembled according to the numbers assembled. For the interviewees who were linked into a sibship of size two, the mean number of reported brothers or sisters (including the interviewee himself or herself) was 2.26, illustrating that for some sibships with two participating siblings, there existed a third and possibly in a few instances a fourth sibling who did not participate. For the larger sibship sizes, chances as expected were higher that one or two siblings were not included. Regardless of size, altogether 75 percent of the interviewees reported an identical number of siblings with that included in the study.

For Finnmark at large, data from 1974 exist on the number of children in families.

Table 6. Number of siblings reported and assembled by sibship size. Finnmark 1977, four municipalities.

Assembled sibship size	Number of subjects*	Reported sibship size Mean**	Reported and assembled sibship size	
			Mean difference	Agreement (%)
2	780	2.26	0.26	81.0
3	547	3.35	0.35	74.8
4	306	4.45	0.45	70.6
5	277	5.36	0.36	70.0
6	100	6.57	0.57	60.0
7	53	7.25	0.25	75.5
9	18	9.50	0.50	50.0
All sizes	2081	3.68	0.34	75.0

* Number of interviewees (among $n = 4,596$) with other siblings in the family study population ($n = 4,738$).

** Including the interviewee.

The percentage of families with one, two, three or at least four offspring were 35.1, 31.0, 18.2 and 15.7, respectively [Bjartveit et al., 1979]. Among families with two or more offspring (i.e. sibships of size two or larger), these numbers recalculate into the percentages of 47.8, 28.0 and 24.2 for the sizes two, three and at least four, respectively. The current percentages (Table 3) were 53.2 (404 of 760), 25.3 (192 of 760) and 21.6 (79, 58, 17, 8 and 2 of 760), further illustrating that at least one sibling did not participate in some families.

One reason why 287 (4,883 minus 4,596) men and women skipped the interview was probably that it was the last station and at times crowded. That one half (145 of 287) of these men and women were not later linked in any familial relationship, also suggested that a considerable number of subjects did not know their real "genetic" status or was without a family, at least within the study area.

An unknown number of families was probably put together with at least one individual misplaced. The personnel responsible for the interview was specially trained, but there were inherent difficulties regarding adoptees and half-siblings. The exact number of such interviewees was unknown, but the number of men and women with incomplete family information was 253. In most instances, it was the biologic father that was unknown or believed to be someone else. Even although adoptees and half-siblings were accepted as interviewees, they were disregarded as relatives. Because of this fact and also because

of the tedious cross-checking procedures applied in the linkage of the family members, it is unlikely that the number of misclassified individuals was substantial.

That all families were not included or were incomplete probably had some effect on the analysis results. It is hard to see how for instance a correlation or a heritability coefficient [Papers I, II] systematically would be larger or smaller due to this fact of selection. On the other hand, no parent-offspring pair could possibly have been included in the study in instances where the parent was more than 32 years of age when the child was born. This systematic inclusion could have led to biased correlations. In the analyses of ostensibly well individuals in heart disease affected and unaffected families, some more families would have been classified as affected had follow-up information on disease endpoints been available for the non-participating siblings [Paper III]. Compared to the rather high number of subjects in unaffected families ($n = 932$, $n = 845$ or $n = 1,324$), however, the unknown number of subjects involved was not substantial. Thus, this misclassification might have led to only a marginal underestimation.

5.2 Confounder adjustments

Adequate adjustments for confounder information are essential in family studies. For instance, spouse correlations, which almost always are modest in value, would undergo a substantial relative change even in instances where the absolute change ap-

peared to be small. Consequently, the present spouse correlations were manifold increased without adequate control for the subjects' attained age [Paper I]. This was due to the simple fact that those who marry each other usually are of relative similar age, and that lipid and blood pressure values tend to increase with age. For similar reasons and to derive a plausible estimate of the true correlation, it may also be necessary to control for other lipid or blood pressure correlates (such as smoking, physical activity, time since last meal and seasonality). Some variables, like for instance body weight, have probably a heritable component of their own and therefore perhaps should be omitted in confounder adjustments. A good practice may be to derive correlations both with and without body weight adjustments to see whether they are any different [Paper I].

In the analysis of genetic and environmental effects [Paper II], the path model with the environmental index was used. Some variables usually considered confounders were here used to provide an estimate for the environment. These variables included information on smoking, physical activity at leisure and the body mass index. Other traditional confounders (age, sex, time since last meal, ethnic origin, seasonality, current pregnancy and menopause started) were adjusted for in the usual manner. In the analyses of the prospective data [Papers III-V], means and risk estimates were obtained for the classic risk factors total cholesterol, blood pressure, body mass, physical activity, smo-

king and various definitions of family history of heart disease, each adjusted for the others.

Confounder adjustments inevitably rely upon what information has been collected. The present investigation included no analyses on diet and drinking habits. This was a weakness, and it is likely that the analysis results would have been somewhat influenced by for instance coffee consumption. Indeed, information on food intake, but not alcohol consumption, was obtained at the Finnmark survey 1977-78 through a questionnaire. However, this information was collected by the Section for Dietary Research, University of Oslo, Norway and not considered available for our purposes at the relevant time. These data have been linked and analysed later [Gaard et al., 1994]. Although the response rate was as high as 83 percent (for women in Oppland, Sogn og Fjordane, and Finnmark), including these data would have further reduced the already limited number of some family constellations. However, the exact impact of diet and drinking in family data remains unclear because analyses of such variables are scarce in most other similar studies also.

Epidemiologists are seldom able to explain a lot of the inter-individual variation of continuous variables, but the variation attributable to genes by h^2 appears to be much higher. The contribution from the environment has been modest in other studies and also was small here [Paper II]. Environmental exposure may go unmeasured or inaccurately measured where-

as genetic variation can be well specified from the known degrees of relatedness among individuals [Susser, 1985]. The contribution of environment relative to genes hence may be underestimated. Diet and drinking variables would have been relevant candidates for inclusion in the path model environmental index, and the suspected environment underestimation could thereby have been lessened [Paper II].

5.3 Family history variables

Family history variables are the most common measure of familial predisposition of diseases. A history of disease in the family relies on the questioned individual's knowledge about the family members and the diseases they have experienced. Altogether 81.2 percent of the men and 84.0 percent of the women repeated a "Yes" answer from Finnmark 1974-75 at Finnmark 1977-78 [The National Health Screening Service et al., 1988]. To assess the accuracy and validity of such family history information, one strategy is to compare the accuracy of reports provided by different members of the same family. A recent large-scaled study of a proband's report of their relatives' history was compared to their relatives' self-report [Bensen et al., 1999]. Utilising the relatives' self-report as the "gold standard", sensitivity of the proband report on their spouse, parent and sibling for coronary heart disease was 87, 85 and 81 percent, respectively. Correspondingly, specificity values were 99, 93 and 98 percent, and older probands were less accurate reporters of disease than

younger probands. It was concluded that family history of coronary heart disease could be captured effectively based on proband reports. Another approach is to compare the family history reports to medical records. Verifying all positive reports of myocardial infarction, the agreement between the reports and the diagnoses obtained from doctors' records, hospital records and death certificates was 78 percent in Tromsø [Førde and Thelle, 1977] and 70.5 percent in Finnmark 1974-75 [Thelle and Førde 1979]. The current agreement was 76 percent (672, 26 and 79 of 1,027 (1,142 minus 115), see Table 5). In addition, there were many more men and women who responded "Yes" on the questionnaire to the simple question on attained heart disease or angina pectoris in parents or siblings [Paper V].

A family history of disease depends on many factors, such as the number and type of relatives and their age distribution. Hence, two individuals under the same genetic influence may have different family histories because one does have an affected brother or sister and the other being an only child cannot possibly have so. Also, family disease histories once turning positive never can change back to negative, and the negative histories most individuals are born with, will in many instances eventually turn positive with attained age. For those subjects who met to the Finnmark surveys in 1974, 1977 and 1987 and were 20 to 49 years of age in 1974, we observed that 17 percent and 21 percent of the men and women, respectively, had changed

from negative to positive family histories of heart disease between 1974 and 1987 [Paper IV]. Because young individuals, even in disease prone families, often will have negative family disease histories simply because parents are too young to yet have developed the disease, grandparents' disease histories perhaps should have been considered. It has, however, been experienced that interviewees had more than enough difficulties in giving reliable information on morbidity in first-degree relatives [Førde and Thelle, 1979].

Risk factor values are known to change in individuals over time [Mulder et al, 1998], but the traditional fixed covariate analysis of prospective data does not take such change into account. Information from the many Norwegian health surveys by now has been collected repeatedly over many years, and we thought it was time to analyse the family history variable together with the other classic risk factors allowing values to change whenever new information became available from rescreenings. This inclusion of updated information was however not found to change risk estimates much [Paper IV]. Indeed, in men a small risk ratio increase was observed from 1.63, 1.55 and 1.59 for the 1974, 1977 and 1987 surveys, respectively, to 1.66 and 1.63 for two different methods for incorporating risk variable change. In women, corresponding changes were from 1.26, 1.37 and 0.68 (the latter ratio was based on 20 incident cases only) to 1.51 and 1.49. It is likely, therefore, that the standard baseline screening analysis tends

to slightly underestimate the family history risk. The magnitude we observed, however, was too small to warrant revisions of the established impact of this variable.

The simple family history variable relating to disease in any first-degree relative omits potential important factors such as number, type, sex and age of each specific relative. Over the past three decades, several efforts have been made to include such information into a quantitative family history score (also called index) [Silberberg et al., 1999]. In Tromsø, one family score based on the male and another based on the female first-degree relatives were constructed from the years free of myocardial infarction that were "gained" or "lost" [Thelle et al., 1979]. With the exception of a single paper with another focus [Brenn and Arnesen, 1985], the score has not yet been evaluated prospectively due to lack of follow-up data. More recent efforts have all been formulated according to the expected and observed heart incidence rates, and it was decided in the current study to apply this definition now common. We found that the family history score did not predict heart disease any better than the common simple family history variable [Paper V].

A positive family history by itself provides little indication of the mechanisms by which the risk of disease increases. It has been argued that once all potential risk factors have been discovered, measured adequately and included in predictive models, much of the risk would go through these variables and the remaining contribu-

tion of a family history variable would decrease considerably [Conroy et al., 1985; Perkins, 1986]. Had much of the risk been attributable to the classic risk factors themselves, we would have expected the risk ratio of the family history variable in our data to show a marked decline in value after lipid and blood pressure variables also were taken into the model. However, the age adjusted only risk ratios of family history of heart disease were 1.74 and 1.63 for men and women, respectively, and the values became 1.63 and 1.49 [Table 4 of Paper IV] after inclusion of the other variables (total cholesterol, systolic blood pressure, body mass index, physical activity at leisure, and daily smoking). Consequently, the family history variable appeared to be a consistent predictor of myocardial infarction in addition to major risk factors.

5.4 Role of subject age at diagnosis

In instances where coronary heart disease develops before the age of 40 or 50 years, genes may play a particularly important role. The risk of having coronary heart disease by age 55 was, respectively, 6.7, 3.6 and 1.8 times greater in the east of Finland for the brothers of patients than for brothers of reference subjects depending on whether the diagnosis of myocardial infarction in the patient had first been established before the age of 46 years, at age 46 to 50 years, or at age 51 to 55 years [Rissanen, 1979]. In the Nurses' Health Study, the age-adjusted relative risk of non-fatal myocardial infarction for women

with a parental history of myocardial infarction at a maximum of 60 years of age compared with no family history was 2.8, and above 60 years 1.0 [Colditz et al., 1986]. For US male health professionals there was a markedly increase of myocardial infarction risk with decreasing age at parental disease [Colditz et al., 1991]. Among men, when one's twin died of coronary heart disease before the age of 55 years, the relative hazard was 8.1 for monozygotic twins. With age, the hazard went gradually down to 0.9 for the age 86 years or more, and similar trends were also seen for dizygotic twins and women [Marenberg et al., 1994].

In the present investigation, total cholesterol values were found to be more increased among the men who had a brother or sister who received the diagnosis at a young age [Paper III]. However, sibling correlations by subject age revealed no systematic pattern [Paper I]. During follow-up, altogether 87 of the 2,203 men developed a first myocardial infarction [Paper V]. Few of the cases had a relative that developed heart disease at a young age, and the risk ratios were only 0.95 and 0.57 for having a parent or sibling with verified myocardial infarction diagnosed at a maximum of 50 and 60 years of age, respectively. However, the seemingly protective impact indicated by the risk ratios being less than unity was far from statistical significant. Based on the results from previous studies indicating excess risk for early family disease, our findings came as a surprise. The result can also explain the

lack of predictive ability of the family history score because it attached extra weight to myocardial infarction developed at a young age. Admittedly, the number of incident cases was no larger than 87, but this number should still be sufficiently large to reveal some sort of a tendency had much excess risk been involved with having an early family attack. The reason why no such excess risk was present remains unclear. It is possible that an unknown secular trend is in work, or that individuals

who had a particular severe family history were notified and in time improved their risk factor profile.

When yet another screening round was undertaken in Finnmark in 1996-97, it was decided to collect further questionnaire data on relatives' age at disease diagnoses and also on the type of relative that had become affected. Results have not been published so far, but values for total cholesterol are presented in Table 7. The values based on relatives who had become af-

Table 7. Age-adjusted values of total cholesterol (mmol/l) by type of relative and age at onset* of myocardial infarction. The Finnmark Survey 1996-97.

Age of relative when affected	Type of relative who developed myocardial infarction				
	Father	Mother	Brother	Sister	Any**
	n Mean	n Mean	n Mean	n Mean	n Mean
MEN (<i>n</i> = 3,842; 26-71 years of age)					
< 40 years	48 6.19	25 6.33	74 6.22	21 5.81	135 6.28
40-49 years	117 6.38	28 6.29	129 6.37	28 6.18	277 6.37
50-59 years	319 6.41	122 6.44	189 6.30	53 6.38	527 6.40
60-69 years	417 6.52	240 6.45	97 6.16	38 6.15	524 6.39
≥ 70 years	227 6.24	169 6.31	25 6.30	14 6.49	282 6.31
Unanswered†	2714 6.25	3258 6.28	3328 6.30	3688 6.30	2097 6.23
WOMEN (<i>n</i> = 4,055; 26-71 years of age)					
< 40 years	59 6.60	31 6.60	81 6.24	22 6.61	162 6.33
40-49 years	129 6.52	43 6.74	141 6.39	37 6.55	303 6.48
50-59 years	321 6.45	139 6.38	202 6.44	69 6.26	565 6.43
60-69 years	425 6.41	251 6.38	109 6.42	54 6.27	563 6.38
≥ 70 years	256 6.26	223 6.43	13 6.80	16 6.89	306 6.43
Unanswered†	2865 6.31	3368 6.32	3509 6.33	3857 6.33	2156 6.27

* In instances where more than one relative had been affected in different age groups, the youngest age group was used.

** Any of father, mother, brother or sister had developed myocardial infarction.

† Not crossed for developed disease in any age group.

ected before the age of 40 years should probably be interpreted with caution because either some events of hyperlipidemia may be involved or because the (unverified) myocardial infarction diagnoses dating several decades back in time now may be uncertain. The diagnoses may also be questioned in the oldest age group. As seen, the men who had a family history of early-onset heart disease had only slightly higher values than the men without affected relatives. In women, results were not consistent either. These cross-sectional results therefore do not point towards a strong association between cholesterol level and age at disease onset.

The potential excess risk involved with early-onset heart disease was not impressive in the present study. However, with the massive body of consistent risk increase as described above and from other studies, the inevitable conclusion on this point is that an attack in a young relative is indeed associated with increased risk. Also, an European task force has listed lifestyles and other characteristics associated with increased risk of future heart disease. Included was family history of coronary heart disease or other atherosclerotic vascular disease at early age (in men less than 55 years and in women less than 65 years) [Pyörälä et al., 1994].

5.5 Role of sex

The two sexes differ with respect to the incidence of and risk factors for coronary heart disease. Less women than men die from the disease during young or middle

age, and risk factors also have been found to play a somewhat different role in the two sexes [Lerner and Kannel, 1986]. The possibility therefore exists that the family risk component as well may show some sex specificity.

Some family correlations were observed to be higher for one sex than the other [Paper I]. However, it was concluded that no consistent sex specific pattern could be found currently or by reviewing the literature. Moreover, the 53 well men whose brother or sister developed myocardial infarction during a 12 year follow-up had somewhat more increased levels of total cholesterol than did the corresponding 50 women [Paper III]. This sex pattern did however not appear in the cross-sectional data in Table 7.

In the prospective and time-dependent covariate analysis of a large number of individuals and incident events, adjusted risk ratios for a positive family history of heart disease were 1.63 in men and 1.49 in women [Paper IV]. In other large-scaled prospective studies including both sexes, risk ratios for men and women respectively were 1.5 and 0.8 in Rancho Bernardo [Barrett-Connor and Khaw, 1984], 1.3 and 1.2 in Framingham [Schildkraut et al., 1989] and 1.6 and 1.9 in eastern Finland [Jousilahti et al., 1996]. Although some case-control studies provides no difference between men and women [Roncaglioni et al., 1992; Silberberg et al., 1998], estimates from some such approaches have been larger in magnitudes and also shown higher risk in women than men. Family concen-

trations of ischaemic heart disease were noted especially in the families of the female patients [Slack and Evans, 1966], and female patients also more often had first-degree relatives with coronary artery disease [Pohjola-Sintonen et al., 1998]. A recent Norwegian study of heart disease patients found that women who had developed the disease had a positive history in two first-degree relatives as much as 11.3 times more often than had the men who developed the disease. However, the number of male cases with such positive history was only four and the confidence interval ranged from 3.5 to 40.3 [Hofstad et al., 1998]. Case-control studies are less well-controlled than their prospective counterparts, and positive family histories have also been shown to overestimate relative risk measures in that particular approach [Khoury and Flanders, 1995].

It is also possible that having a family member of male sex who developed the disease may be associated with more or less risk than had the disease been onset in a female relative. Little difference was observed between the relative risks of myocardial infarction among health professionals with either a maternal or paternal history of the disease [Colditz et al., 1986; Colditz et al., 1991]. For British men, the risk of heart attack was higher had the father rather than the mother died of heart trouble (2.11 vs. 1.32) [Phillips et al., 1988]. Framingham adjusted relative risks of coronary artery disease were 1.2 when the father and 1.3 when the mother had died of the disease [Schildkraut et al.,

1989]. Risk of acute myocardial infarction was higher for heart disease history in father than mother for Finnish men, and higher for mother than father in Finnish women [Jousilahti et al. 1996]. In case-control studies, the risk associated with histories of heart disease in the father and the mother were identical [Roncaglioni et al. 1992; Silberberg et al., 1998].

Currently and in men, verified myocardial infarction in a father or brother were associated with a risk ratio of 1.04 as compared with that of 1.20 in instances where the relative was a mother or sister [Paper V]. However, the latter risk ratio was based on only four incident cases. The total cholesterol means according to the type of relative who developed disease did not reveal any systematic sex pattern (Table 7). In Tromsø, total cholesterol means were elevated with a magnitude of 0.11 mmol/l both for the men with male and the men with female first-degree relatives with myocardial infarction [Førde and Thelle, 1977].

Thus, some sex differences were seen currently and also have been reported elsewhere. However, the conclusion on this point is that persistent sex specific trends are non-existent or of marginal importance in the observed family clustering of risk factors and incidence of coronary heart disease.

5.6 Ethnicity

The Finnmark population is known to consist of people with Norse, Finnish or Sami origin, or a mixture thereof. As seen from

Table 1 and based on the questions on grandparents' origin (Appendix 1), approximately 20 percent answered Finnish and another 20 percent Sami. However, the ethnic origin definitions have been discussed [Kvernmo and Heyerdahl, 1996], and the current study provided a unique opportunity to assess sibling agreement. Because full siblings inevitably have the same grandparents, answers on grandparents' ethnic origin should be identical within each sibship. Response alternatives were several (two questions each with three categories) [Thelle et al., 1982], and answers were identical in 350 (or 46.1 percent) of the 760 sibships (results not presented in table). As expected, concordance was highest in the smaller sized sibships, ranging from 54.7 percent (size two) to 29.4 percent (size five or larger). It is therefore hard to avoid concluding that considerable disagreement on ethnic origin was observed.

Although the above considered lack of agreement in itself provided a good argument against any attempt to classify sibships, or other family relations for that matter, into specific ethnic groups, some analyses were undertaken based on the majority of ethnic answers. Results to some extent were found to vary across the ethnic identity groups, probably due to the relative small number of families involved. No consistent pattern emerged, and results have not been presented. The percentages of men and women who reported to have parents or sibling with myocardial infarction or angina pectoris were 28.1, 34.5 and

19.5 among those of Norse, Finnish or Sami origin, respectively [National Mass Radiography Service et al., 1979]. Other research on risk factors [Thelle and Førde, 1979] and cardiovascular disease [Tverdal, 1997; Njølstad et al., 1998] across the ethnic groups has not established a strong gradient. Furthermore, heritability estimates have been published for population samples spread all over the world. Results have been remarkably equal [Paper II], and the Finnmark heritabilities did not differ much.

5.7 Data opportunities and limitations

The family component in coronary heart disease over the years has been regarded as substantial and well worth further exploration. The health surveys in the Norwegian counties have also always included a question on the occurrence of serious disease in any family members. By asking participants whether or not heart disease had been experienced in a close relative, the opportunity was provided to compare risk profiles between individuals with positive and negative family disease histories. These histories also provided the foundation for later prospective analyses after follow-up for disease onset.

Currently, the data taken from the additional interview opened up for further analyses. For one, familial correlations could be computed, allowing us to quantify the degree of resemblance among family members, at least for spouse pairs and siblings. Due to the limitations on subject age of those invited, rather few combi-

nations on the two-generation relationship (parent-offspring) were available. The interview also included extensive family disease histories providing information to construct a continuous family history score.

Epidemiological studies, like the current, can only to some extent address the underlying causes of familial aggregation. For instance, parent-offspring and sibling correlations by themselves do not directly permit separation of genetic and environmental contributions. The relative impact, however, is indirectly suggested in studies where correlations can be derived from various types of relatives. When traits or diseases are shared in the same or greater degree both by genetically unrelated and by related members, the interplay of shared family experience and degrees of genetic relatedness points to the role of the environment, a cohabitational effect. The current data were scarce on two or more generation familial relationships, lacked information on which family members were living together and apart, and also were limited on the common family environment. Consequently, the data were less efficient or informative for the study of genetic and environmental effects than twin or pedigree data. It was, however, possible to undertake some path analyses with the environmental index [Paper II].

In other and similar studies, entire family units have often been invited and investigated [Dawber, 1980; Family Study Committee for the Lipid Research Clinics Program, 1984]. More than the current stu-

dy, these approaches have put a special emphasis on families, aiming at all family members to meet. Such routines have probably lead to a high participation rate within families. Furthermore, these investigations would be less restrictive on subject age, resulting in more data on the parent-offspring constellation. However, a potential source of bias may be inherent in the data collected. For instance, measured values such as blood pressure which tend to vary with time of day and investigator, would be more similar within than between spouse pairs in instances where both spouses were investigated together. Such a procedure may therefore have led to spurious spouse correlations. In Framingham, spouse resemblance for blood pressure was reduced when survey procedures were changed from seeing spouses on similar to different days [Havlik et al., 1979]. A strength of the present study was that families as a rule were not investigated together, for instance men and women were invited on separate days.

The parent-offspring concordance currently found for daily smoking was surprisingly small [Paper I]. Many other studies have asked school children or students about smoking habits of their own as well as their parents. Relying on children's perceptions of the behaviour of their relatives may contribute to an overestimation of family influence on smoking initiation [Øygaard et al., 1995]. Current estimates were not subject to this source of bias as offspring were adults and the offspring and parents answered for themselves, indepen-

dent of each other. Consequently, the current family data were collected in a way that reduced or eliminated some potential sources of bias.

5.8 Statistical methods

In family studies the analytic unit may be a particular relationship or the nuclear family, and this fact may compel modifications of prevailing approaches or even constructions of novel statistical methods. One independent study aim thus was to investigate, apply and adapt statistical methods relevant for epidemiological and population based studies in families. One type of family data is that of risk factor measures taken in each member of a family. Spouse, parent-offspring or sibship resemblance of continuous variables can then be assessed by computing correlation coefficients. With the exception of spouse pairs, some method modifications are needed due to the varying family sizes. For the parent-offspring constellation, one option is to pair each offspring with the father or mother and then compute the Pearson correlation coefficient. The statistical significance can then be obtained using so-called effective degrees of freedom to compensate for the fact that values from some parents have been duplicated [Donner, 1979]. For the present investigation [Paper I], this pairwise method was considered preferable over other approaches as the family-weighted pairwise, the single-sib, the maximum likelihood or that of regression [Donner and Eliasziw, 1991]. For the siblings, and rather than making all possible

pairs out of the sibships or applying any other method, it was decided to compute the intraclass correlation coefficient [Paper I], easily derived from a standard one-way analysis of variance [Donner, 1979]. In the epidemiological literature, it has become more and more common to present results together with an interval indicating the precision of the estimate [Donner and Eliasziw, 1991; Savitz et al., 1994]. Procedures for computing such confidence intervals are now readily available [Gardner and Altman, 1989], and it is possible that they would have accompanied the correlations in Paper I had the presentation been given today.

To separate effects from gene and environment, the statistical techniques of variance component analysis [Lange et al., 1976] and path analysis [Morton and MacLean, 1974] have become the analytic cornerstone. Both have their specific data requirements, and information in addition to the mere nuclear family data must be available. Variance component analysis also requires information on either second-degree relationships or particular family members living together or apart. Analyses by this model have been reported for serum cholesterol and blood pressure from the study in Tecumseh, Michigan, [Sing and Orr, 1978; Longini et al., 1984]. Path analysis has the same requirements as variance component analysis, and for the Nord-Trøndelag data which included second-degree relationships, a path analytic model was applied [Tambs et al., 1992]. However, path analysis can also be used in

instances where nuclear family data include variables that can be used to index the environment [Rao and Wette, 1990]. The current data had no information regarding second-degree relatives or family members living together or apart. However, siblings who were married or exceeded a certain age could have been expected to live apart. It was considered as the more appropriate to apply the path analysis with the environmental index, even although this method has been described as controversial [Rao and Wette, 1990]. Furthermore, it was not obvious how the particular data characterised by so few complete nuclear families and so many more spouse pairs and sibships should go into the path analytic model. It was decided to include only those spouses who were of similar ages as the parents, and correspondingly to include only those siblings who were of similar ages as the offspring.

Another type of family data to analyse statistically is those containing a family history of disease. This information is considered a personal attribute, and the individual rather than the family is the analytic unit. In the common analyses of such data with follow-up information, standard statistical methods for analysis of individuals apply, for instance that of Cox regression [Cox, 1972]. In its simplest form this method assumes that the covariates are fixed (do not change with time), but it is possible that covariate values can change at any point of time [Cox and Oakes, 1984]. We used the method with this extension,

and tedious data programming was required. Results were not very different from those obtained from the standard single screening analyses [Paper IV]. Predicting total deaths and coronary heart disease, the mean of total cholesterol and blood pressure from the first and second screening round in Norwegian counties was found to be better than the best of the single values, but only slightly so [National Health Screening Service, 1991].

Yet another methodological concern was the comparison of risk ratio estimates derived for various types of variables. Because such estimates are scale dependent, they cannot be directly compared. It is therefore not straightforward to assess whether a simple dichotomous form of a variable for the family history of disease predicts disease any better than a corresponding count variable or an enumerated family history score. One option is to include the candidate family history variables in the model one at a time and compute how well the data are explained each time. For Cox's method, one such convenient measure, which also we used [Paper V], is the generalised coefficient of determination (R^2) [Allison, 1995].

6. SUMMARY AND IMPLICATIONS

This population based study on coronary heart disease risk factors and endpoints in families included a large number of young adult men and women from a high risk area in the north of Norway. Family resemblance of the classic risk factors was observed for genetically related family members, but only to a modest degree between husbands and wives. Observed within-family aggregation inevitably reflects the conjoined contributions of environmental and genetic factors, and heritability estimates showed that the contribution from genes was much larger than that relating to the environment. However, this study provided little information about the importance of early life family environment.

Well individuals with a family member who developed a first myocardial infarction had a somewhat more adverse risk factor profile than well individuals without disease in the family. Furthermore, the increased risk of developing heart disease was found to approximate 60 percent in men and 50 percent in women who had a history of the disease in their close families. Finally, prediction of future disease was no better using a detailed family interview than by a sole and simple questionnaire response on whether any first-degree relative had developed the disease.

The data taken from the ongoing health studies in Norwegian counties with an additional interview and follow-up, to some

extent were found to provide information on the family risk component for coronary heart disease. The analyses of such data could be done with common statistical methods, often with some modifications. However, more rare methods or new applications of prevailing methods also were required.

The present population based study confirmed the findings of other studies that the family component plays a somewhat important role in the aetiology of coronary heart disease. Familial aggregation was observed for coronary heart disease endpoints as well as for the risk factors. Having a family member with developed heart disease was a consistent risk factor, but it did not predict disease as good as the major risk factors high total cholesterol, high blood pressure or cigarette smoking. Those results that could be directly compared with other studies corresponded very well, and the residents of Finnmark thus were not found to deviate much from population samples elsewhere.

The study findings may to some extent concern the population as a whole. Not much can currently be done with the genes, but the worse they are, the more important it probably is to reduce high levels of total cholesterol, blood pressure and numbers of cigarettes smoked. Individuals with a severe family history of heart disease thus should be particularly encouraged to improve their risk factor profile.

7. FURTHER RESEARCH

A variety of studies have been conducted world-wide that have shed considerable light on the familial aggregation of coronary heart disease endpoints and its risk factors. However, the results still must be considered incomplete and preliminary and will require confirmation from studies of future generations. The health surveys in Norwegian counties by now have continued for 25 years, and over the years, the young-aged part of the adult population has been recruited at each new screening round. This routine makes the data more and more useful for investigations in families because the data gradually accumulate over the generations. Moreover, so far most individuals have been rather young, and the number of incident events obviously will increase rapidly with the higher attained age of the pioneer screenees.

The epidemiological approach of the health surveys in Norway has not been explicitly designed to test particular genetic models that may underlie familial aggregation. This study demonstrated the limitations regarding the study of genetic and environmental effects. More efficient and informative designs should be implemented, including large varieties of familial constellations. Detailed family disease histories including who live together and who live apart should be attained. However, this type of information is sensitive, and future efforts may be prevented. Another problem is that marriages do not last as long as before. It is also important to col-

lect information on specific, observable environmental risk factors. Data on body weight and physical activity were currently available without making much impact [Paper IV]. Such characteristics may very well play a more prominent risk role in the future and hence should be more thoroughly analysed. Finally, the use of genetic markers to determine risk is still in its infancy [Pyörälä et al., 1994], and so far such information has not yet been obtained.

At the University of Tromsø, a large-scaled family database for long has been under construction. Based on a family interview undertaken at the Tromsø Study 1979-80, altogether 74,152 individuals have been included. The number of established spouse pairs, mother-offspring, father-offspring and sibling constellations each exceed 10,000. So far the family database has been used only marginally, but with the future linkage with disease endpoint data, opportunities may be many and diverse. It will, however, be necessary to develop new and more collaborative research routines involving a team of personnel with expertise in data handling, genetic epidemiology and statistics.

The family database should possess the potential to play an important role regardless of what the future will bring with respect to research on familial and genetic factors in the pathogenesis of coronary heart disease. The field of medical genetics is rapidly expanding beyond the boundaries of single gene disorders to the realm of almost all diseases of major public

health impact. The Human Genome Project [Hoffman, 1994], genetic markers, genetic tests, genetic tracing and recent advances in molecular genetics are all part of the future visions of public health. Despite the seemingly vast progress in genetics, there is still a future for epidemiological and population based studies on families. Epidemiology may very well assume a greater role in assessing disease risk and defining genotype-phenotype correlations [Khoury, 1997]. A major challenge confronting epidemiological research is to incorporate genetic concepts and remove artificial barriers between the disciplines of genetics and epidemiology in order to realise their tremendous joint potential [Ellsworth and Manolio, 1999]. An article in the National Geographic magazine recently summed up the combined role of genetics and epidemiology [Shreeve, 1999]: "Someday DNA tests may provide instant snapshots of future ailments and life expectancy, but not yet. Genes for more than 1,200 disorders have been identified, but most people probably can learn more from their parents' health history than they can from a DNA printout. Most of us carry a few defective genes with no signs of disease, and many genes only contribute to susceptibility. Lifestyle choices such as diet and smoking and environmental factors can raise or lower disease risk."

8. REFERENCES

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Appendix 1.

Questionnaire Finnmark Survey 1974 and 1977

The questionnaires were identical except
for the 1977 inclusion of question G

Norwegian and English version

A		JA	NEI
Har De, eller har De hatt:			
Hjerteinfarkt?	33		
Angina pectoris (hjertekrampe)?	34		
Annen hjertesykdom?	35		
Åreforkalkning i beina?	36		
Hjerneslag?	37		
Sukkersyke?	38		
Er De under behandling for:			
Høyt blodtrykk?	39		
Bruker De:			
Nitroglycerin?	40		

B		JA	NEI
Får De smerter eller ubehag i brystet når De:			
Går i bakker, trapper eller fort på flat mark? ..	41		
Går i vanlig takt på flat mark?	42		
Hvis De får smerter eller ubehag i brystet ved gange, pleier De da å:			
1 Stanse?	43		
2 Saktne farten?			
3 Fortsette i samme takt?			
Hvis De stanser eller saktner farten, forsvinner smertene da:			
1 Etter mindre enn 10 minutter?	44		
2 Etter mer enn 10 minutter?			
Får De smerter i tykkleggen når De:			
Går?	45		
Er i ro?	46		
Hvis De får leggsmarter, besvar da:			
Forverres smertene ved raskere tempo eller i bakker?	47		
Gir smertene seg når De stopper? ..	48		
Har De vanligvis:			
Hoste om morgenen?	49		
Oppspytt fra brystet om morgenen? ..	50		

C		JA	NEI
Bevegelse og kroppslig anstrengelse i Deres fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året. Sett kryss i den ruten hvor "JA" passer best.			
1 Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse?	51		
2 Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? .. (Heri medregnes også gang eller sykling til arbeidstedet, søndagsturer m.m.)			
3 Driver mosjonsidrett, tyngre hagearbeid e.l.? .. (Merk at virksomheten skal være minst 4 timer i uken.)			
4 Trener hardt eller driver konkurranseidrett, regelmessig og flere ganger i uken?			

G		JA	NEI
Har noen i Deres husstand (utenom Dem selv) vært innkalt til nærmere undersøkelse hos distriktslegen etter forrige hjerte-kar undersøkelse? ..	52		

D		JA	NEI
Røyker De daglig for tiden?	53		
Hvis svaret var "JA" på forrige spørsmål, besvar da:			
Røyker De sigaretter daglig? .. (håndrullede eller fabrikkframstilte)	54		
Hvis De ikke røyker sigaretter nå, besvar da:			
Har De røykt sigaretter daglig tidligere? ..	54		
Hvis De svarte "JA", hvor lenge er det siden De sluttet?			
1 Mindre enn 3 måneder?	55		
2 3 måneder - 1 år?			
3 1 - 5 år?			
4 Mer enn 5 år?			
Besvares av dem som røyker nå eller har røykt tidligere:			
Hvor mange år tilsammen har De røykt daglig? ..	56-57		
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag (håndrullede + fabrikkframstilte)	58-59		
Røyker De noe annet enn sigaretter daglig?			
Sigarer eller serutter/cigarillos? ..	62		
Pipe?	63		
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?			
Oppgi gjennomsnittlig antall pakker pr. uke.	64-66		

E		JA	NEI
Har De vanligvis skiftarbeid eller nattarbeid?	67		
Kan De vanligvis komme hjem fra arbeidet:			
Hver dag?	68		
Hver helg?	69		
Har De i perioder lengre arbeidsdager enn vanlig? .. (f.eks. under sesongfiske, onnearbeid)	70		
Har De i løpet av siste året hatt:			
Sett kryss i den ruten hvor "JA" passer best.			
1 Overveiende stillesittende arbeid? .. (f.eks. skrivebordsarb., urmakerarb., montering)	71		
2 Arbeid som krever at De går mye? .. (f.eks. ekspeditørarb., lett industriarb., undervisen.)			
3 Arbeid hvor De går og løfter mye? .. (f.eks. postbud, tyngre industriarb., bygningsarb.)			
4 Tungt kroppsarbeid? .. (f.eks. skogsarbeid, tungt jordbruksarb. tungt byggningsarb.)			
Har De i løpet av de siste 12 mnd måttet flytte fra hjemstedet på grunn av forandring i arbeidssituasjonen?	72		
Er husmorarbeid Deres hovedyrke?	73		
Har De i løpet av de siste 12 mnd fått arbeidsledighetstrygd?	74		
Er De for tiden sykmeldt, eller får De attføringspenger?	75		
Har De full eller delvis uførepensjon? ..	76		

F		JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? ..	77			
Er to eller flere av Deres besteforeldre av finsk ætt?	78			
Er to eller flere av Deres besteforeldre av samisk ætt?	79			

English translation of the questionnaire used in the cardiovascular disease study in Norwegian counties 1977-83 (Finnmark, Sogn og Fjordane, Oppland) and Tromsø 1979-80

English translation; Mrs. Anne Clancy and Mr. Kevin McCafferty

Tick "yes/no" or "yes", as appropriate.

Part A

Have you, or have you had:
a heart attack?
angina pectoris (heart cramp)?
any other heart disease?
arteriosclerosis of the legs?
a cerebral stroke?
diabetes?

Are you being treated for:
high blood pressure?

Do you use:
nitroglycerine?

Part B

Do you have pain or discomfort in the chest when:
- walking up hills or stairs, or walking fast on level ground?
- walking at normal pace on level ground?

If you get pain or discomfort in the chest when walking, do you usually:
(1) stop?
(2) slow down?
(3) carry on at the same pace?

If you stop or slow down, does the pain disappear:
(1) within 10 minutes?
(2) after more than 10 minutes?

Do you have pain in the calf while:
- walking?
- resting?

If you get pain in the calf, then:
- does the pain increase when you walk faster or uphill?
- does the pain disappear if you stop?

Do you usually have:
- cough in the morning?
- phlegm chest in the morning?

Part C

Exercise and physical exertion in *leisure time*. If your activity varies much, for example between summer and winter, then give an average. The questions refer only to the last twelve months.

Tick "YES" beside the description that fits best:

- (1) Reading, watching TV, or other sedentary activity?
- (2) Walking, cycling, or other forms of exercise at least 4 hours a week? (including walking or cycling to place of work, Sunday-walking, etc.)
- (3) Participation in recreational sports, heavy gardening, etc.? (note: duration of activity at least 4 hours a week).
- (4) Participation in hard training or sports competitions, regularly several times a week?

Part D

Do you smoke daily at present?
If "Yes":
Do you smoke cigarettes daily?
(handrolled or factory made)

If you do not smoke cigarettes at present:
Have you previously smoked cigarettes daily?

If "Yes", how long is it since you stopped?
(1) Less than 3 months?
(2) 3 months to 1 year?
(3) 1 to 5 years?
(4) More than 5 years?

For those who smoke or have smoked previously:
How many years altogether have you smoked daily? *Number of years*

How many cigarettes do you, or did you, smoke daily? Give number of cigarettes per day (handrolled + factory made)

Number of cigarettes

Do you smoke tobacco products other than cigarettes daily?

- cigars or cigarillos?
- a pipe?

If you smoke a pipe, how many packs of tobacco (50 grams) do you smoke per week?

Give average number of packs per week.

Number of tobacco packs

Part E

Do you usually work shifts or at night?

Can you usually come home from work:

- every day?
- every weekend?

Are there periods during which your working days are longer than usual? (e.g.: fishing season, harvest)

During the last year, have you had: (Tick "YES" beside description that fits best):

- (1) mostly sedentary work? (e.g., office work, watchmaker, light manual work)
- (2) work that requires a lot of walking? (e.g., shop assistant, light industrial work, teaching)
- (3) work that requires a lot of walking and lifting? (e.g., postman, heavy industrial work, construction)
- (4) heavy manual labour? (e.g., forestry, heavy farmwork, heavy construction)

During the last 12 months, have you had to move house for work reasons?

Is housekeeping your main occupation?

Have you within the last 12 months received unemployment benefit?

Are you at present on sick leave, or receiving rehabilitation allowance?

Do you receive a complete or partial disability pension?

Part F (alternatives: yes, no, don't know)

Have one or more of your parents or sisters or brothers had a heart attack (heart wound) or angina pectoris (heart cramp)?

In Finnmark and Tromsø only:

Are two or more of your grandparents of Finnish origin?

Are two or more of your grandparents of Lapp origin?

Part G

Has anyone in your household (other than yourself), been called in to a doctor for further medical examination after the previous cardiovascular disease survey?

Appendix 2.

Scheme for interview on family members - Finnmark Survey 1977

In Norwegian

Ja	Nei

Har du hatt hjerteinfarkt
 Bruker du blodtrykksmedisin
 Tidligere brukt blodtrykksmedisin
 Annen medisin for hjertet

Ja	Nei

Har du hatt/har du magesår
 Ofte/av og til sure oppstøt/brystbrann
 Sultsmertner
 Spiselindring
 Bruker du regelmessig avføringsmiddel
 Annen medisin for fordøyelsen

Medikament Seponert

Medikament.....

Har du brukt globoid el.1. siste året? Sjelden/aldri Nei
siste uke?

En el.fl.g.mnd. Fl.g. uka Dgl. Ant.
 1-2 tabl. 3-6 tabl. Dgl. Ant.

Slektskap Navn Person nr.

Ektefelle																				
Mor																				
Far																				
1. søsken																				
2. søsken																				
3. søsken																				
4. søsken																				
5. søsken																				
6. søsken																				
7. søsken																				
8. søsken																				
9. søsken																				
10. søsken																				

Kjønn	M/K																			

Fødselsår																				

Infarkt	Ja	Nei																		

Magesår	Ja	Nei																		

Dødsår																				

Utfyllt av:

HJERTEINFARKT

Slektning:

Navn:

Født:

Adresse:

Død:

Verifisering:

HJERTEINFARKT

Slektning:

Navn:

Født:

Adresse:

Død:

Verifisering:

MAGESÅR

Slektning:

Navn.....født

Lokalisasjon:

Magesekk

Tolvfingertarm

Vet ikke

Diagnosegrunnlag:

Operasjon

Innlagt sykehus

Rtg.undersøkelse

Primærlege

Kalenderår

Sykehus/institutt

Første g. påvist sår

Magesårsoperasjon

Siste sykehusopphold

Verifisering:

MAGESÅR

Slektning:

Navn.....født

Lokalisasjon:

Magesekk

Tolvfingertarm

Vet ikke

Diagnosegrunnlag:

Operasjon

Innlagt sykehus

Rtg.undersøkelse

Primærlege

Kalenderår

Sykehus/institutt

Første g. påvist sår

Magesårsoperasjon

Siste sykehusopphold

Verifisering:

Paper I



Paper IV

Paper V

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskattede i Sør-Varanger kommune.
Av Anders Forsdahl, 1976. (nytt opplag 1990)
2. Sunnhetstilstanden, hygieniske og sosiale forhold i Sør-Varanger kommune 1869-1975 belyst ved medisinalberetningene.
Av Anders Forsdahl, 1977.
3. Hjerte-karundersøkelsen i Finnmark - et eksempel på en populasjonsundersøkelse rettet mot cardiovasculære sykdommer. Beskrivelse og analyse av etterundersøkelsesgruppen.
Av Jan-Ivar Kvamme og Trond Haider, 1979.
4. The Tromsø Heart Study: Population studies of coronary risk factors with special emphasis on high density lipoprotein and the family occurrence of myocardial infarction.
Av Olav Helge Førde og Dag Steinar Thelle, 1979.
5. Reformen i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten.
Av Jan-Ivar Kvamme, 1980.
6. Til professor Knut Westlund på hans 60-års dag, 1983.
- 7.* Blodtrykksovervåkning og blodtrykksmåling.
Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.
- 8.* Merkesteiner i norsk medisin reist av allmennpraktikere - og enkelte utdrag av medisinalberetninger av kulturhistorisk verdi.
Av Anders Forsdahl, 1984.
9. "Balsfjordsystemet." EDB-basert journal, arkiv og statistikkssystem for primærhelsetjenesten.
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