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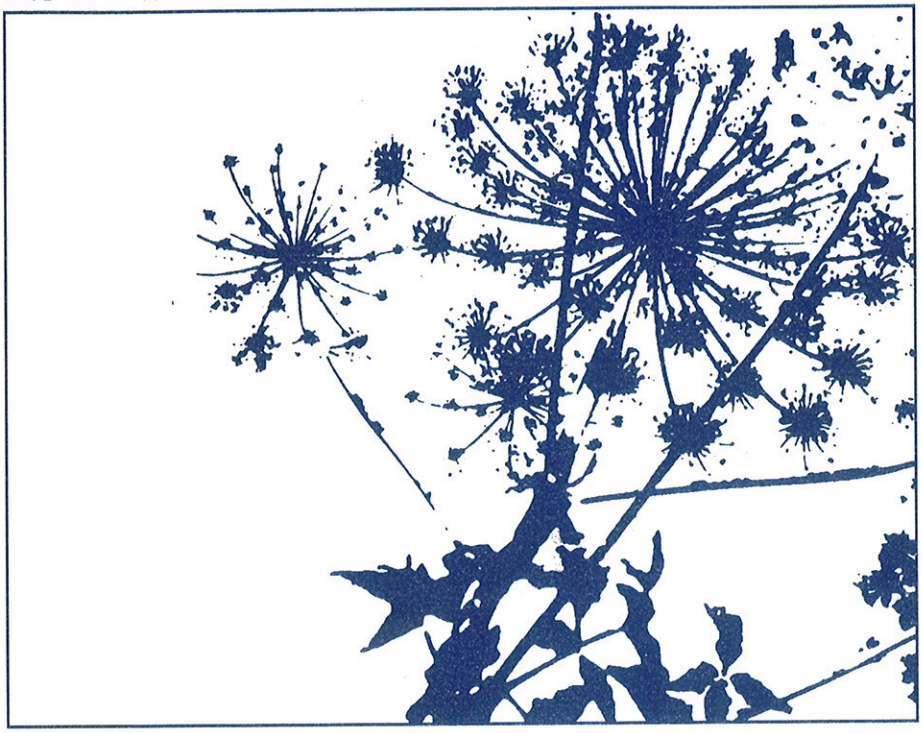

INCIDENCE OF AND RISK FACTORS FOR MYOCARDIAL INFARCTION, STROKE, AND DIABETES MELLITUS IN A GENERAL POPULATION

The Finnmark Study 1974 - 1989

Inger Njølstad

Tromsø 1998

Institute of Community Medicine
University of Tromsø, Norway

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by

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We are eleven siblings.
Ten have angina. Five have died from it.
I'm the second youngest.
Don't have angina yet.

Finnmark Study Participant

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First, I wish to thank Kaare Bønaa. He encouraged me to think twice at a time when I was making quite other plans for my further medical career than a thesis in cardiovascular epidemiology. I do not regret the choice!

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LIST OF PAPERS

This thesis is based on the following papers:

I Njølstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. *Circulation* 1996;93:450-456.

II Njølstad I, Arnesen E. Preinfarction blood pressure and smoking are determinants for a fatal outcome of myocardial infarction. A prospective analysis from the Finnmark Study. *Arch Intern Med.* In press.

III Njølstad I, Arnesen E, Lund-Larsen PG. Trends in incidence and case fatality in myocardial infarction: The Finnmark Study 1975 - 1989.

IV Njølstad I, Arnesen E, Lund-Larsen PG. Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women. A 14-year follow-up of the Finnmark Study. *Circulation* 1996;94:2877-2882.

V Njølstad I, Arnesen E, Lund-Larsen PG. Sex differences in risk factors for clinical diabetes mellitus in a general population: A 12- year follow-up of the Finnmark Study. *Am J Epidemiol* 1998;147:49-58.

VI Njølstad I, Arnesen E, Lund-Larsen PG. Cardiovascular diseases and diabetes mellitus in different ethnic groups. A prospective analysis from the Finnmark Study. *Epidemiology.* In press.

The papers will be referred to by their Roman numerals in the text.

1. GENERAL BACKGROUND

1.1 The scope of the problem

Cardiovascular diseases

Cardiovascular diseases account for approximately half of all deaths in western countries and have constituted a major cause of premature death in Norway for several decades. Large secular variations in cardiovascular mortality rates have been observed. A slight increase in cardiovascular mortality in both genders during the first part of the century was followed by a marked decline during World War II.[1] There was a dramatic increase in mortality rates that started immediately after the war[1] and continued through the 1960s.[2] The increase was largely confined to coronary heart disease, and was more pronounced in men than in women. After 1970, cardiovascular mortality in middle-aged subjects has declined and is now lower than in the early 1950s.[3] The decline has largely been attributed to dietary changes and the concurrent decline in average serum cholesterol.[4]

Regional mortality data became available around 1960 and revealed large countywise differences in coronary and cerebrovascular mortality. Finnmark County has had the highest cardiovascular mortality since then,[2,3] although secular trends have more or less paralleled the country as a whole.[5] The reasons for the geographical variations in cardiovascular disease are not completely understood. From repeated surveys in Norwegian counties, it is known that the distribution of some, but not all, classic coronary risk factors are more unfavourable in Finnmark.[6,7] According to Tverdal,[8] most of the countywise difference in cardiovascular mortality can be explained by serum total cholesterol, which is higher in Finnmark than in other counties.[6] Serum cholesterol is strongly associated with the total amount and composition of dietary fat.[9] However, in an ecological study, a correlation was observed between previous infant mortality and current average serum cholesterol among adult men,[10] and subjects who presumably did not reach their growth potential in late fetal life had higher serum cholesterol than others at the age of 50 years.[11] Thus, the key to understanding of the nature and the epidemiology of cardiovascular diseases may be found in a combination of the past and the present.

Diabetes mellitus

Diabetes mellitus is a heterogeneous group of disorders that share a tendency to chronic hyperglycemia and to vascular and renal complications.[12] The two major subtypes, insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), cannot be distinguished by therapy, since both may be treated with insulin. Diabetes is one of the most prevalent chronic diseases worldwide, and NIDDM is estimated to constitute 95% of the prevalent cases.[13] The prevalence and incidence of NIDDM is increasing and has reached epidemic proportions in some populations - currently, the prevalence exceeds 50% among middle-aged Pima Indians.[13] The prevalence of diabetes in Norway is estimated to be approximately 2%.[14] While the incidence of IDDM is lower in Finnmark than in other Norwegian counties,[15] the geographical distribution of NIDDM has been little investigated. The prevalence of self-reported diabetes among young and middle-aged adults

was lower in Finnmark than in counties in southern Norway in two population based surveys.[16]

1.2 Cardiovascular diseases and diabetes are multifactorial diseases

Both IDDM and NIDDM are associated with a twofold to fourfold increased risk of cardiovascular diseases, and coronary heart disease is the most common cause of death among diabetic subjects.[17] Coronary heart disease (CHD) and cerebrovascular disease share some risk factors, but despite intensive research, the necessary and contributing causes of cardiovascular diseases (CVD) and diabetes are still not completely understood. Rather than single causes, the relationships are characterised by complexity and a "web of causation".

Genetic factors

Environmental, modifiable factors are commonly held responsible for the post-war coronary disease epidemic, but genetic factors do play a role in coronary heart disease.[18] Mutations and defects in a single gene have been identified as the cause of a few conditions, such as Müller-Harbitz's disease (familial hypercholesterolemia),[19,20] but a number of genes are involved in lipoprotein metabolism,[21,22] blood pressure regulation,[23] and in thrombogenesis.[24] It is likely that certain genotypes or combinations of genotypes interact with environ-mental factors and result in an increased risk of disease.

Genes are involved in stroke disposition, and the contribution is polygenic.[25] Further, "stroke" represents several cerebrovascular disorders, with shared and separate[26] genetic traits.

Twin and family studies have provided strong evidence for genetic causes of NIDDM.[27, 28] While inheritance in rather uncommon NIDDM variants has been tracked to single genes,[29] most NIDDM is of polygenic heredity, but again, in an interplay with adverse environmental trigger factors.[30]

Early life factors. The Forsdahl/ Barker hypotheses

In 1973, Forsdahl presented the hypothesis that the high mortality rate in Finnmark is a consequence of previous poverty.[31] He showed that the considerable variations in cardiovascular mortality among 40 to 69-year old men in Norwegian counties in 1964-67 correlated with infant mortality rates from 1896 to 1925.[32] Forsdahl argued that differences in current mortality could not be explained by current differences in living conditions, and that poverty during childhood and adolescence, followed by affluence, is correlated with the risk of dying from atherosclerotic diseases. He also proposed that serum cholesterol is the main intermediate factor. In that study, no adjustment was made for countywise differences in smoking habits or other potential confounders, and caution is needed when drawing conclusions from ecological studies.[33] In another study, using data from the first Finnmark Survey, Forsdahl observed a positive correlation between infant mortality during 1921-1935 and average serum cholesterol among 35 to 49-year old men in the Finnmark municipalities.[10] These hypothesis-generating observations were supported by cross-sectional data from the Tromsø Study, where self-reported poverty in childhood was positively associated with age-adjusted serum cholesterol and negatively

associated with body height.[34] In a Finnish study specifically aimed at exploring the Forsdahl hypothesis, there was an association between childhood socioeconomic conditions and cardiovascular disease, but serum cholesterol was not distributed accordingly.[35]

Since 1986, Barker and colleagues have published numerous papers on fetal and infant origins of adult disease. Using ecological data from England and Wales, as well as birth record data and adult morbidity data in limited cohorts, they claim that adverse conditions in early life, measured as low birthweight (small for gestational date) or unproportional fetal growth, result in a higher risk for hypercholesterolemia,[11] hypertension,[36] insulin resistance,[37] glucose intolerance,[38] diabetes mellitus,[39] stroke,[40] and coronary heart disease[41] in adult life. The Barker hypothesis advocates that inadequate nutrition in a critical period of organ development will permanently affect structures and metabolism[42] through the process known as "programming".[43] For diabetes, this theory was labelled "the thrifty phenotype hypothesis",[44] as an alternative to the "thrifty genotype hypothesis" proposed by Neel.[45] Recent, larger cohort studies[46, 47] and twin studies [48] lend support to the Barker hypothesis.

Adult life style

Migrant studies of cardiovascular disease[49,50] and diabetes[51] have shown that when people move from low-risk to high-risk areas and change their lifestyle towards that of the resident population, their risk of disease may approach the risk of the resident population. Rapid changes in the incidence of cardiovascular disease[1] and diabetes[52] were observed in Norway during World War II, and in other populations undergoing large and rapid changes in diet and lifestyle.[54] Controlled intervention trials have provided convincing evidence that adverse risk factor levels in individuals at high risk may be reversed, and that risk factor reduction is followed by a reduction in disease risk.[54,55] Based upon the Norwegian ecological experiment[1,52] and clinical trials,[54,55] the time from risk factor exposure to risk reduction appears to be much shorter than the 10-year time lag proposed by Rose.[56] Important lifestyle factors that contribute to or protect against cardiovascular disease and diabetes include dietary habits, the use of stimulants, and physical activity and the balance between energy intake and energy expenditure. Diet may enhance atherosclerosis, but may simultaneously contain anti-atherosclerotic, thrombogenic and antithrombogenic components.[9] Boiled, unfiltered coffee raises serum cholesterol.[57,58] Alcohol increases,[59] while smoking decreases[60] serum high density lipoprotein (HDL) cholesterol. Physical activity influences blood pressure,[61] serum lipids,[62] and insulin and glucose metabolism[63] both directly, and through weight loss.[64]

Insulin resistance

The close relationship between diabetes and cardiovascular diseases seems to involve insulin resistance,[65] but causal pathways have not been established. Insulin resistance is a decreased sensitivity in skeletal muscles and other tissues to the action of insulin, and it is a characteristic of NIDDM.[65] The clustering of high triglycerides, low HDL cholesterol, high blood pressure, hyperinsulinemia, and insulin resistance was labelled "syndrome X" [65] or " the insulin-resistance syndrome."[66] It is

often accompanied by abdominal obesity.[67] A raised total (or LDL) cholesterol is not an inherent part of the insulin-resistance syndrome.[66] Although the tendency to insulin resistance is claimed to be mainly inherited,[28,65,68] twin studies have provided evidence that the cluster of components depend on both genetic and on environmental factors.[69]

2. AIMS OF THE STUDY

The present is a non-concurrent follow-up study of 35 - 52 year old men and women in Finnmark who participated in population based cardiovascular surveys in 1974 and/or 1977. The aims were to investigate

- incidence of and risk factors for myocardial infarction, stroke and diabetes
- whether there were sex differences in risk factors for cardiovascular diseases and diabetes
- whether there were ethnic differences in risk factors and in the incidence of cardiovascular diseases and diabetes

3. STUDY POPULATION AND METHODS

3.1 Study area and background population

Finnmark County is located well north of the Arctic Circle at 69-71° N, facing the Barents Sea, Russia and Finland. It is the largest and the most sparsely populated county in Norway, and is exposed to great seasonal variations in light and temperature. People live scattered in small townships and settlements; traditional occupations are the fisheries and fishing-related industries along the coast, small-scale farming and fishing in the fjords, reindeer breeding among indigenous Sami people in the highland regions, and mining. Finnish immigrants settled in the area since the 1700s, but the bulk of Finnish immigration occurred during the last part of the 19th century following severe crop failures in North Finland.[70] Until World War II, Finnmark experienced more poverty, a higher infant mortality, and a higher mortality from tuberculosis than other counties in Norway.[31] During the war, two-thirds of the population were forced to leave the county while one-third avoided evacuation by hiding when German troops used the "scorched earth tactics" during their withdrawal in 1944. Most people returned after the war and restored the county, which had been almost completely destroyed. Geographical socioeconomic inequalities in Norway are less today, but living conditions are still tougher and the educational level is lower in Finnmark than in other parts of the country.[71] Many of those who work in the white-collar sector as well as in the fishing industry, have immigrated from other counties.

3.2 Baseline data

3.2.1 The Cardiovascular Disease Study in Norwegian Counties

The background and organising of the CVD County Study has been extensively described.[71-73] Since 1943, the National Mass Radiography Service had carried out large population surveys for the detection of tuberculosis. As the incidence of tuberculosis declined and cardiovascular mortality increased, the organisation proposed in 1972 that

screenings aimed at detecting coronary heart disease should be initiated. At the same time, the County Medical Officer in Finnmark asked for actions against the high cardiovascular mortality in that county.

The first survey began in Finnmark in 1974 and was a collaboration between the National Mass Radiography Service (renamed the National Health Screening Service), health authorities and local health personnel in Finnmark, and the University of Tromsø. During the next two years, almost identical surveys were carried out in Oppland and Sogn og Fjordane, which represented counties with average and low cardiovascular mortality, respectively.

The CVD County Study had several aims. One was to analyse the distribution of cardiovascular risk factors in the three counties. Another was to serve as an intervention programme, combining general health education and a high-risk strategy. The study was thought to be an important epidemiologic tool, providing baseline data for follow-up studies on morbidity and mortality.

A second survey was undertaken three years after the first one in Finnmark (1977). A third survey was carried out in 1987. Data from the latter were only little used, and data from subsequent surveys among 40-42 year old subjects (1990 and 1993) were not used for the present study.

3.2.2 The Finnmark survey 1974/75 (Finnmark 1)

The first survey took place from March 1974 until February 1975. All Finnmark residents born from 1925 to 1939 were invited by means of a personal, mailed letter. An invitation was also sent to a 10 % random sample of subjects born between 1940 and 1954. In four municipalities, all residents born from 1925 to 1954 were invited. A total of 17,517 subjects were invited, and 14,401 (82.2%) participated.[16]

The screening included:

I: A questionnaire printed on the reverse side of the invitation letter (Appendix 1) which covered:

- A: History of cardiovascular disease, diabetes mellitus, and treatment for hypertension
- B: Symptoms that could be related to cardiovascular disease (translation of Rose questionnaire on angina pectoris) or lung disease
- C: Physical activity during leisure time
- D: Smoking habits
- E: Stress factors in social life and physical activity level at work
- E: Family history of coronary heart disease
- F: Ethnic origin (Norse, Sami (Lappish), Finnish or mixed)

II: A physical examination with measurements of height, weight and blood pressure

III: A non-fasting blood sample

In one municipality a questionnaire on food consumption was included.

The questionnaire was to be filled in at home and brought to the examination site where a nurse checked it for inconsistencies, and also inquired about municipality of birth and about time since last meal. Women were asked about menopausal status/-pregnancy. Height was measured to the nearest centimetre and weight to the nearest half kilogram. Blood pressure was measured with a mercury sphygmomanometer in sitting subjects and after 4 minutes' rest. Systolic and

diastolic pressures were measured twice with one minute's interval. Systolic pressure was read to the nearest even number of mmHg when the first Korotkoff sound appeared (phase I). Diastolic pressure was recorded at Korotkoff's phase V, or phase IV if phase V was absent. The examinations were performed by a small number of nurses who had been trained according to tapes produced by the London School of Hygiene and Tropical Medicine. After centrifugation of blood samples, the chilled serum was sent to the Central Laboratory, Ullevål Hospital, where it was analysed within 2 weeks for total cholesterol, triglycerides, and glucose. The laboratory methods and quality control of methods have been described.[16,71,73]

Subjects with suspected cardio-vascular disease or diabetes or with risk factor levels above pre-set limits, were offered a follow-up examination by the local public health unit (physician and nurse).[73]

3.2.3 The Finnmark survey 1977/78 (Finnmark 2)

Those invited were:
- All residents of Finnmark county 35 to 52 years old (born 1925 - 1942)
- All residents 23 to 34 years old (born 1943 - 1954) who were invited to the first screening
- An 11% random sample of residents aged from 23 to 34 years, who had not been invited to the first screening
- A 10 % random sample of residents 20 to 22 years old (born 1955 - 1957).

A total of 20,683 persons were invited and 17,181 (83.1%) participated.[16]

The municipalities were visited at the same time of the year as in the previous survey. Screening procedures and measurements were almost identical in the two surveys and were carried out by the same nurses. Analyses of serum total cholesterol, triglycerides and glucose were performed at the Central Laboratory at Ullevål Hospital using the same methods. Serum thiocyanate was determined as described by Foss et al.[74] Serum HDL cholesterol was determined at the Institute of Medical Biology, University of Tromsø.[75] Sera from 4 municipalities (n= 4,480) were stored at +4° C and analysed within two weeks. All other samples (n= 11,462) were stored at -20° C for 12 months before analysis. HDL cholesterol was determined by the cholesterol esterase cholesterol oxidase method after precipitation of LDL and VLDL with heparin and manganese. The average HDL cholesterol value was lower in the frozen batch. The differences varied between 0.11 and 0.13 mmol/L in various subgroups of sex and age.[75] As in previous reports,[75,76] we added 0.12 mmol/L to the HDL cholesterol values of frozen samples.

After the second survey, the Ullevål laboratory changed to an enzymatic method of determining total cholesterol and triglycerides with a Technicon AutoAnalyzer. In the papers for this thesis, the original values were transformed to be equivalent to the enzymatic methods that are commonly used today. The formulas used were based on an extensive test programme developed by the National Health Screening Service.[16]

3.2.4 Participation rate in Finnmark 1 and Finnmark 2

A non-missing value for systolic blood pressure or a non-missing value for serum total cholesterol was used by us to define participation, and the number of participants differs slightly from previous reports, which used other definitions.[16,71,75] The participation rate among those invited to the first and/or second screening varied by age and sex from 92% in men and 95% in women born from 1925 to 1929, to 45% in men and 58% in women born from 1955 to 1957.[16]

3.3 Follow-up data

3.3.1 Background

From the inception of the CVD County Study, a routine was established in which Finnmark hospitals informed investigators from the University of Tromsø and the National Health Screening Service of all patients with a cardiovascular discharge diagnosis. From 1975 until 1983, the investigators surveyed the record files in the Finnmark hospitals twice, and used discharge diagnosis lists to detect cases which then were validated by medical records. Linkage of the participant list of the Finnmark Study to the Causes of Death Registry at Central Bureau of Statistics (renamed Statistics Norway) was used to detect cases among the deceased. The registration came to a halt in 1983, and validated data from the early period have been sparsely used.[77]

3.3.2 Permissions and study approvals

No permanent registry of coronary heart disease, cerebrovascular disease or diabetes exists in Norway and must, therefore, be established for the present study. Permission was obtained from the Data Inspectorate. The Norwegian Directorate of Health permitted us to use data from the Causes of Death Registry, and gave us access to medical records in hospitals and in the primary health care. The Regional Committee for Medical Research Ethics approved the study.

3.3.3 Endpoints and classification criteria

The events under study were: first event of myocardial infarction (MI), first event of stroke, onset of diabetes, and, in paper VI, death. We recorded the date of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, carotis endarterectomy, and cerebral aneurysm surgery.

Myocardial infarction

Classification criteria were based upon WHO recommendations.[78,79] The criteria included symptoms, cardiac enzyme changes and ECG changes, where two out of the three were required for diagnosis. When performed, autopsy results were used. The classification criteria were published as an Appendix to Paper I.

Stroke

WHO criteria[78,79] were followed, where stroke was defined as rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until death, with no apparent non-vascular cause.

Diabetes

A physician-confirmed diagnosis was accepted without checking whether

recommended WHO criteria[12] had been followed. In case of discrepancies between self-reports and medical records regarding the date of diagnosis, medical record information was accepted. We registered the year that insulin or oral antidiabetic therapy was started, but a firm distinction between IDDM and NIDDM could not be made.

3.3.4 Data sources

Several data sources were used to obtain as complete registration as possible:

A: Official health data and medical records

1. Causes of Death Registry at Statistics Norway
2. Discharge diagnosis lists from the Finnmark hospitals, and from the Regional Hospital in Tromsø
3. Medical record files in hospitals and community health care centres in Finnmark

B: Postal questionnaire to participants

3.3.5 Register data

Causes of Death Registry

Statistics Norway provided information regarding name, 11-digit personal identification number, municipality of residence and county or municipality of death, and underlying and contributory diagnoses of death from the death certificate. The data were linked to the Finnmark Study at the National Health Screening Service.

Hospital data

The National Health Screening Service and the Institute of Community Medicine generously placed at my disposal the material that covered the years from 1974 to 1983. It included some 700 subjects with confirmed or suspected cardiovascular diseases. Not all cases had been validated.

For the period September 1983 - June 1990, discharge diagnoses lists were obtained from the hospitals in Hammerfest and Kirkenes. The lists included all hospitalised subjects born from 1925 onwards with a discharge diagnosis according to International Classification of Diseases, 8th Revision (ICD-8) or 9th Revision (ICD-9): 410-414 (ischemic heart disease), 430-436 (cerebrovascular diseases), 250 (diabetes mellitus), 795 (ICD-8) or 798.1 (ICD-9) (sudden, unexpected death). When one of the diagnoses appeared, the medical record was sought. The notes were read and data from the first event were recorded. If the first event had been treated in another hospital, information from the relevant hospital was sought.

Because some patients from Finnmark are admitted directly to the Regional Hospital in Tromsø (RiTø), corresponding discharge diagnosis lists for Finnmark residents were requested from RiTø and a similar validation procedure was performed. Such lists could be provided only for the period 1987 - 1990.

No diagnosis lists existed for patients treated in the out-patient departments.

Validity of discharge diagnosis lists/ survey of hospital record files

Because discharge diagnosis lists were suspected of being incomplete, a survey of the medical record files was undertaken. The files at Kirkenes Hospital comprised three parts: One file with those records that had been in use during the last three years (written notes, letters), a second file with "older" records, and a third file with records of

the deceased. In the first and the third file, records of all patients born from 1925 to 1954 were opened and the discharge diagnoses on the front page were read. If a diagnosis indicated any of the diseases in question, the notes were read. For the "old" file, all records of persons born in January were surveyed. This procedure gave no new information, and was thereafter dropped. The validation confirmed that the discharge diagnosis system was reliable. Among the 8,000 - 9,000 records that were surveyed, two undetected cases of acute MI were found. Among subjects treated in the out-patient department, 5 cases of probable or possible MI (examined after the event) and 25 cases of diabetes were previously undetected. In approximately 20 cases, the ICD code did not correspond to the written cardiovascular diagnosis, but such errors had not resulted in cases going unnoticed.

A similar validation procedure was carried out at Hammerfest Hospital. All records of patients born on the first and second day of each month were examined (approximately 1,200 records). No unnoticed cases were detected among those admitted. Two unnoticed cases of diabetes examined in the out-patient department were discovered. It was concluded that a full screening would be waste of time and effort.

Case validation procedures
Cases which had been registered previously were revalidated to ensure consistent classification criteria. Events prior to the surveys were validated and classified according to the same diagnostic criteria as those that occurred during follow-up.

Many deaths from the diseases under study had occurred outside of hospitals. If no medical record existed at the local hospital, a letter was sent to the medical officer in the municipality of residency or, in some cases, the municipality in which death occurred, requesting information about the event. I was given access to the record file at the community health care centre in the five largest municipalities. However, Norwegian law permits records in the primary health care to be destroyed 10 years after the death of the subject. The case validation was carried out in 1990/91, up to 17 years after the death, and some records were missing. When an autopsy had been performed, information was available from the relevant pathology department.

The greatest registration and validation problem occurred among those who had emigrated from the county. It was not feasible to obtain hospital discharge diagnosis lists from hospitals outside of Finnmark except for RiTø. From death certificate information about municipality of residency and municipality or county of death, it was possible to trace the attending physician or hospital.

3.3.6 Postal survey 1991

Survey procedures
In the autumn of 1991, a questionnaire (Appendix 2) was mailed to those who participated in Finnmark 1 or Finnmark 2 and who were alive as of June 1, 1991, according to the Central Person Register at Statistics Norway. Updated addresses were provided by Statistics Norway. The Data Inspectorate approved the postal survey, but did not allow letters to be sent to the next-of-kin

of deceased persons. One reminder was sent to non-responders.

The National Health Screening Service carried out the practical tasks of the survey and provided a data file. A total of 18,210 letters were mailed. The number included some subjects who had completed the baseline survey questionnaire, but had not been physically examined. A total of 376 letters were initially returned because of death or change of address; in 191 cases, no second letter could be sent. Using the attendance criteria of the present study, a maximum of 17,854 out of the 19,308 participants could have answered the postal survey, and 14,204 subjects (79.6%) did reply. A total of 3,475 (19.5%) questionnaire recipients had moved from Finnmark. The response rates were similar among those who had moved (80.4%) and among those who still lived in Finnmark (79.4%), and in men (79.8%) and women (79.3%), but varied by age from 80.8% in those born between 1925 and 1942 to 76.4% in those born between 1943 and 1957.

All 6,824 returned questionnaires (48.0%) where the respondent had been treated in a hospital for any reason were read to check for indications of cardiovascular disease or diabetes despite negative answers to the direct questions, and to learn from which hospital to seek information. The questionnaire did not ask for the address of attending physicians outside of hospitals, and medical information was sought from local health care centres for non-hospitalised patients.

Written consent for validation

A few subjects who reported one or several of the specified diseases did not give a written consent to collect data from medical records:

Table 1. Total number and percentage of self-reported cardiovascular diseases and diabetes, and number and percentage without consent for validation among 14,204 postal survey respondents

	Men (n= 7,247)				Women (n= 6,957)			
	Prevalence		No consent		Prevalence		No consent	
Self-reported medical condition	n	%	n	%	n	%	n	%
Myocardial infarction	422	5.8	12	2.8	84	1.2	2	2.4
Stroke	141	2.0	2	1.4	102	1.5	3	2.9
Diabetes mellitus	169	2.3	6	3.6	158	2.3	16	10.1

Out of 19 respondents with self-reported MI and stroke who did not give a consent for validation, 3 were assigned a probable MI or stroke. The remaining reported an event after end of follow-up, or had been detected through registers. Similarly, 12 out of 22 respondents were assigned probable diabetes.

Concordance between self reports and register data

Table 1 includes events before and after follow-up. Out of the 392 MIs that occurred during follow-up, 343 were verified. Reasons for non-concordance were (n):

Validated cases: Silent MI (5) , possible MI (11), angina pectoris/ coronary bypass grafting (7), other heart disease (2), not MI (13).

Validation impossible: No consent (2), too little information (9).

Thus, 93% of self-reported cases were confirmed coronary heart disease, although not all satisfied our classification criteria of MI.

Out of 174 strokes reported to occur during follow-up, 114 were verified. The phrasing of the questionnaire was the main reason for apparent low concordance, because the question included transient ischemic attacks (Appendix 2).

Validation of diabetes was more difficult, since several non-hospitalised subjects did not write the name of their physician. The Data Inspectorate did not allow us to re-contact respondents. Out of 222 cases of diabetes with reported onset during follow-up, 178 were confirmed. Twelve subjects did not give consent for validation. In 20 cases we did not have enough information to proceed with validation or did not get a reply from the physician/hospital. Five cases had been diagnosed after end of follow-up, 1 had glucose intolerance, and 2 had secondary diabetes. In 4 cases the diagnosis was disconfirmed.

Completeness of case detection through registers

The linkage to the Causes of Death Registry ensured a complete follow-up on vital status. The postal survey served first and foremost to detect out-of-county and ambulant events. Second, it served as a check of the efficiency of case finding through registers and medical records. As an example, among those followed for Paper I, only 17 unnoticed cases of MI were reported by questionnaire respondents in Finnmark. Three had been treated in the Finnmark hospitals, seven in cottage hospitals and primary health care, and seven events occurred during temporary leaves from the county. Similar percentages of events were registered among respondents (261 cases, 3.3%) and non-respondents (49 cases, 2.8%). Among all questionnaire recipients who had left Finnmark, 41 out of 51 cases were detected through the postal survey.

Thus, case finding through registers was nearly complete for those who stayed in Finnmark. The postal survey was needed to detect nonfatal cases among emigrants.

A total of 281 cases of verified or assigned diabetes were diagnosed during follow-up. Many diabetic subjects are not referred to a hospital, and the postal survey was an important source of diabetes detection, within and out of Finnmark (Table 2).

Table 2. Detection of diabetes mellitus diagnosed during follow-up

Primary source of detection	Residency at postal survey or at time of death (n) Finnmark (n=15,742)	Not Finnmark (n=3,566)
Diagnosis registers/hospital records		
Died before postal survey	30	4
Postal survey respondents	113	2
Postal survey non-respondents	38	1
Postal survey	69	24
Total	250	31

3.4 Morbidity register

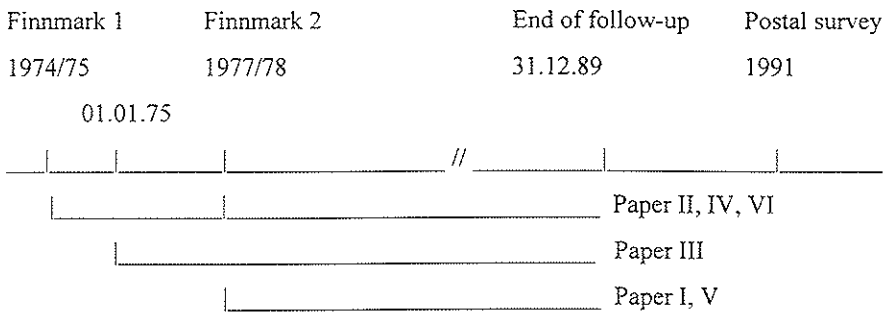
Morbidity data were registered in 2,082 (10.8%) of the participants. Most cases were validated by inspection of medical records in the Finnmark hospitals, RiTø, and in five community health care centres. Letters were sent to approximately 120 physicians and institutions, requesting information about some 400 subjects. Less than 10 addressees did not respond. Examples of letters are enclosed (Appendix 3). The type of data included in the data base are summarised in Appendix 4.

3.5 Outline of present study

Limitation of age groups included in the follow-up analyses

Data on endpoints were collected for participants in all age groups. However, the papers in this thesis comprise only those who were ≥ 35 years at the first baseline examination attended, i.e. subjects born 1925 to 1939 (III), or 1925 to 1942 (I-II, IV-VI). The reasons not to include younger subjects were the limited sample invited, the lower attendance rate, the lower postal survey response rate, and the low number of incident cases in the younger age group.

Outline of present study



Invitation and participation, age ≥ 35 years

Finnmark 1		
	Invited (n)	12,156
	Participated (n)	10,650 (87.6%)
Finnmark 2		
	Invited (n)	14,558
	Participated (n)	12,785 (87.8%)
Finnmark 1 and Finnmark 2 combined		
	Invited (n)	14,819
	Participated (n)	13,412 (90.5%)
Follow-up (first screening - 31.12.89)		
	Emigrated from Norway (n)	73
	Deceased (n)	974
Postal survey 1991		
	Questionnaire recipients (n)	12,151
	Non-respondents (n)	2,329 (19.2%)

4. MAIN RESULTS

Incidence and risk factors for myocardial infarction (Paper I)

The incidence rate was 7.1 per 1,000 personyears in men and 1.5 per 1,000 personyears in women, resulting in an overall male-to-female ratio of 4.6. Daily smoking was a stronger risk factor for MI in women (relative risk 3.3; 95% CI, 2.1-5.1) than in men (relative risk 1.9; 95% CI, 1.6-3.2), and carried a particularly high relative risk for younger women. Women who smoked at least 20 cigarettes per day had a six-fold increased risk of MI compared with never-smoking women, while the corresponding relative risk in men was less than three. The absolute risk of MI was higher in heavy smoking women than in men who had never smoked. Thus, the "female advantage" may literally be dissolved in smoke. Serum total cholesterol, HDL cholesterol and systolic blood pressure were significant risk factors, and the relative risk estimates were similar in the sexes.

Determinants of case fatality in myocardial infarction (Paper II)

We examined whether exposure variables measured at the baseline examination predicted a fatal outcome of the first MI. The 28-days' case fatality rate in MI was similar in the sexes. In men (women), case fatality increased with systolic blood pressure (SBP) from 24.5% (22.6%) at SBP < 140 mmHg, to 48.2% (41.7%) at SBP ≥ 160 mmHg. An apparent threshold effect was seen for diastolic blood pressure. A total of 348 of the 760 subjects with a first MI died during follow-up. In proportional hazards analysis, SBP was strongly related to death (relative risk per 15 mmHg, 1.2; 95% CI, 1.1-1.3). Daily smoking at baseline and age at time of event were also significant risk factors, while total cholesterol and HDL cholesterol were unrelated to death after MI.

Trends in incidence and case fatality in myocardial infarction (Paper III)

Sex specific MI incidence and 28-days' case fatality rates were determined for three 5-year birth cohorts and three 5-year time periods. Despite an ageing cohort, the overall case fatality did not increase, and was non-significantly lower among men in the last (30.7%) compared to the preceding (34.4%) period. Based upon data from the surveys in 1974, 1977 and 1987, antihypertensive treatment increased greatly, while smoking frequency and mean serum cholesterol changed heterogeneously in the various sex- and age-groups. The MI incidence rate in 46-50 year old men was stable (7.1, 6.4, and 7.1 per 1,000 personyears), while corresponding case fatality was 27.1%, 41.0% and 19.1% in the three 5-year periods. The unchanged MI incidence coincided with a stable level in major cardiovascular risk factors in this age-group. Thrombolytic therapy and coronary artery bypass grafting became more common towards the end of follow-up, but did not have any impact on incidence and case fatality.

Incidence and risk factors for cerebrovascular disease (Paper IV)

The incidence rate of stroke was 1.5 per 1,000 personyear in men and 1.1 per 1,000 personyears in women. Systolic blood pressure and smoking were positively associated, while serum total cholesterol was not associated with

stroke. An inverse relation was seen between body height and stroke in both sexes, and the stroke incidence was more than halved in the tallest as compared with the shortest height quartile in both sexes. Height seemed inversely related to all stroke subtypes; the strongest relation was with intracerebral hemorrhage. No significant relation was observed between total cholesterol and any stroke subtype, but the data suggested a positive association with cerebral infarction and a negative association with subarachnoid and intracerebral hemorrhage. Daily smoking was associated with a two-fold increased risk for all stroke subtypes except intracerebral hemorrhage.

Incidence and risk factors for diabetes mellitus (Paper V)

A total of 87 cases of physician confirmed diabetes among men and 75 cases among women were registered, resulting in an incidence rate of 1.2 per 1,000 personyears in men and 1.1 per 1,000 personyears in women. Several sex related differences in risk factors were noted: Serum HDL cholesterol was inversely associated with diabetes in women, but not in men. A dose-response relation between body mass index and diabetes was observed in both sexes, but the association was more confounded in women than in men. Body height was inversely associated with diabetes only in women, while serum glucose was a highly significant risk factor in both sexes.

Ethnic differences in cardiovascular diseases and diabetes (Paper VI)

Four mutually exclusive groups were defined: Norse born in Norwegian counties except Finnmark, and Norse, Finnish, and Sami subjects born in Finnmark. Norse men and women born out of Finnmark were taller and had the most favourable risk factor profiles. Sami men and Norse men born out of Finnmark had similar and slightly lower incidence rates of MI than Norse men born in Finnmark, while men of Finnish origin had a (nonsignificant) 20% higher rate of MI. After adjustment for major risk factors and height, there were virtually no differences in relative risks associated with ethnicity. Similar tendencies were seen for the other end points. Sami men had the lowest incidence rate of diabetes.

Few cases in each subgroup limit the statistical power of the analysis for women. Norse women born out of Finnmark had a lower incidence of MI and diabetes than other women. The incidence of diabetes in Sami women was similar to Finnish and Norse women born in Finnmark, despite a higher mean body mass index.

No data were collected on occupations, but observed between-group differences in height and in sedentary work may reflect differences in social class. It is not possible from this study to discern to what extent the more favourable risk factor levels and the lower risk of disease among Norse immigrants to Finnmark reflect genetic advantages, more favourable conditions during early life and childhood, or rather social class and lifestyle in adulthood.

5. GENERAL DISCUSSION

5.1 Methodological considerations

5.1.1 Misclassification of exposure variables

Misclassification of exposure variables is generally not considered a large problem in prospective studies, since they will be non-differential with regard to the outcome variable, and will underestimate the true association.[80] Standardised examinations in the whole cohort and quality controlled laboratory methods lessened the possibility of random errors and bias in data collection. However, blood pressure and serum triglycerides and glucose are subject to day-to-day variability as well as to true biological changes over time. As in other studies,[81,82] measurement of blood pressure at one occasion predicted cardiovascular events years later (I,II,IV). It has been estimated that a single measurement will underestimate the blood pressure - coronary heart disease association by 60%.[82] Similarly, observed relative risks for serum cholesterol are assumed to underestimate the true risk.[83] Correction for regression dilution bias may resolve the problem,[82] but the techniques rely upon accurate knowledge of the degree of misclassification, and if there is confounding, such adjustment can be misleading.[84] No attempt was made in the present study to correct for regression dilution.

Broad and imprecise categories of the exposure variable may dilute the relationship with the outcome. The relative proportion of muscle mass and adipose tissue, as well as fat distribution, differ between the sexes.[85] Body mass index (weight (kg)/height $(m)^2$) may, therefore, possibly blur rather than illuminate sex differences in relationships under study (V).

An inherent problem in cohort studies with a long follow-up is the lack of ability to take into account real changes in exposure status, unless data on exposure variables are upgraded, as in the Framingham[86] and other studies.[47] This problem was mainly discussed for smoking (I,II) and antihypertensive treatment (II,III), and the problem was partially resolved by using data from the third Finnmark survey towards the end of follow-up to assess population changes in risk factors (I,III). Restriction of the analysis to those who participate in several surveys, may, on the other hand, result in internal selection bias.[86]

The Finnmark Surveys 1-3 with repeated measurements over 10 years in a large number of individuals allowed us to compare different approaches to take into account changes in risk factors. In one study,[87] we compared three applications of Cox's proportional hazards method for prediction of myocardial infarction with explanatory variables included as single baseline measurements, with repeated measurements included as time-dependent covariates, and with pooling of repeated observations. In general, relative risk estimates were quite similar in the three models.

5.1.2 Diagnostic criteria

Definition of myocardial infarction

We followed international criteria,[78,79] but were hampered by limitations created by data collection in retrospect from medical records written for clinical purposes (I). Consistent criteria were used to avoid detection bias introduced by new and more sensitive diagnostic

tools (I,III), but new therapy regimens, such as aspirin or streptokinase used in imminent infarction, will abort a "sure" infarct and may underestimate the true incidence of coronary heart disease when this is determined from hard endpoints. Coronary artery bypass grafting may postpone MI and death and thus prevent high-risk subjects from becoming cases within the time frame studied. Those interventions were not important for the number of incident cases in this study.

The discrepancy between self-reported MI and the record-based registration, could in part be ascribed to silent MI. As in several,[47] but not all[88] epidemiologic studies, silent MI was not included in the coronary endpoint. Inclusion of silent MI would affect the case fatality rates. The proportion of silent MI [88] and the prevalence of silent ischemia[89] is higher in women, and their inclusion could dilute sex differentials in MI incidence. The MI sex ratios in this study correspond well to sex ratios in coronary mortality.[90]

Definition of stroke

The distinction between transient ischemic attacks (TIA) and stroke is one of hours of symptom duration[78] and explains some of the discrepancy between self-reported and registered events. New diagnostic tools, such as magnetic resonance imaging, may reveal brain infarction or hemorrhage in atypical cases. Such events were not classified as stroke to avoid bias by time and geographical residency.

We included subarachnoid hemorrhage in the endpoint, as is usual in epidemiologic studies.[47,49,81] Collapsing various stroke subtypes into a single endpoint may be questioned, given the different risk factor patterns for stroke subtypes (IV). Combining coronary and cerebrovascular endpoints[86] in epidemiologic studies may be even more questionable, since risk factor patterns differ between endpoints (I,IV), and case category distributions vary over time and between the sexes (I,IV), and may blur the associations of interest.

Definition of diabetes mellitus

The criteria usually followed in clinical settings are based on international consensus, but the diagnostic cut-off limits for serum glucose have been subject to changes.[12] The criteria will have consequences both for the number of subjects excluded, and for the number of cases detected during follow-up.[14] In Paper V, we excluded those with a verified clinical diagnosis prior to screening or with a baseline random glucose concentration satisfying WHO criteria of diabetes,[12] but we did not try to evaluate whether WHO criteria had been fulfilled for a diagnosis during follow-up. Ideally, all cohort members should have undergone a new examination by the end of follow-up, since diabetes may go undetected for years; however, this was not feasible. Inclusion of cases which that were unvalidated because of non-consent from the subject or non-response from the physician would increase the number of cases in Paper V from 87 to 93 among men, and from 75 to 86 among women. Judged by risk factor distributions in unvalidated as compared to validated cases, and from Cox's analyses with and without them, we have no reason to believe that the unvalidated cases represent false positive diabetes. Therefore the rates may be taken as under-estimations of the true incidence. Judged by available

data on age at onset of diabetes and from data on drug therapy, the admixture of IDDM cases is probably very small.

Validity of questionnaire responses
The number of false positive reports of MI and diabetes was very low (page 15). A validation has been made of questionnaire information about disease prevalence in Finnmark 1.[77] In that study, a total of 81% of MIs, 65% of strokes and 66% of diabetes cases were verified. In Nord-Trøndelag County ten years later, medical records verified 96% of self-reported diabetes, but the respondents tended to overestimate diabetes duration.[91]

5.1.3 Bias considerations

"Bias" is a systematic deviation from the truth that distorts the results of research. Biases may be grouped as systematic errors in inclusion (selection bias) or collection of data on exposure variables or end-points (information bias), and confounding.[80] Bias may lead to under- or overestimation of the association under study.

Selection bias
Selection bias is usually not a large problem in population based studies with a high participation rate. The participation rate was 90% in the current study. Those who already suffered from cardiovascular disease or were aware of their blood cholesterol and blood pressure could be less likely to participate in a survey aimed at detection of cardiovascular risk factors, but such a "healthy worker effect"[80] does not seem very likely because the oldest age groups with the highest disease prevalence had also the highest attendance rate. In an analysis comprising the CVD County Study and the Oslo Study, men in the highest and in the lowest socioeconomic groups had lower attendance rates than other men.[92] Present study subjects were also included in a mortality study of 40 to 49-year old men in five areas in Norway.[8] The total mortality rate ratio for non-attendees versus attendees was 1.4 in Finnmark, while the ratio was 2.1 -3.1 in the other areas.

Missing data on HDL cholesterol and height led to restrictions in the number of subjects included in Papers I and V, but we have no reason to believe that those selections represented bias. We excluded those who had suffered from the disease(s) under study before screening, but included high-risk subjects with angina pectoris, subjects with symptoms that could be attributed to angina, lung disease and claudicatio intermittens, and subjects on blood pressure treatment. In contrast, Tverdal[93] excluded all those subjects in a recent mortality follow-up study of ethnic groups in Finnmark. The differences in internal exclusion criteria led to discrepancies in conclusions and will be discussed further in Section 5.4.

Information bias and loss to follow-up
A possible bias should be considered if the degree of follow-up is less than 95%.[94] The Causes of Death Registry is virtually 100% complete,[95] and the vital status was known for all participants. Only 73 participants emigrated from Norway, while 1,863 subjects moved from Finnmark to other counties. The detection bias for non-fatal cases introduced by different follow-up procedures among those who moved and those who stayed was discussed (I,V). Such biases are believed to be of

minor importance due to the high response rate to the postal survey. Only 354 questionnaire recipients who had moved from Finnmark did not respond. Those subjects, and those who had moved and died between January 1, 1990 and the postal survey, comprised 4% of the entire cohort and were the only ones not followed for nonfatal events through hospital registers and/or postal survey. Possible detection bias by ethnic group was discussed (VI).

Confounding

"Confounding" exists if meaningfully different interpretations of the relationship of interest result when another variable is ignored or included in the data analyses.[96] This implies that the observed relation is partially or totally due to a variable (confounder) which is associated both with the exposure and the outcome. Confounding may under- or overestimate the association under study, and may even change the direction of the observed effect. A factor on the causal pathway between exposure and outcome is not a confounder.[80] Confounding may be handled statistically, but residual confounding may still occur due to imprecise categorisation of the explanatory variables or lack of data. One way to limit residual confounding may be to restrict the analysis to a homogeneous population, but that approach may reduce the external validity of the study.

Confounding was controlled through stratification by sex (I-VI) and ethnicity (IV,VI) and through age-adjusted and multivariably-adjusted models with potential confounders included. (I-II, IV-VI). Data on several potential confounders were not available, and issues such as the lack of data on alcohol (I,V), use of hormone replacement therapy (I,V), and data on exposure to poverty (IV, VI) were discussed. Information on social class was not requested, but social class is a proxy which, in part, acts through variables that were included (smoking, cholesterol, physical activity). Information on diet was not available, but serum cholesterol is the primary intermediate factor in the diet-heart hypothesis,[9] and this variable was included. Controlling for time since the last meal did not influcence the estimates and was omitted from the final analyses.

Seasonal variation in exposure variables could possibly confound associations between ethnicity and disease, since municipalities were visited at different times of the year. Seasonal variation was observed for total cholesterol, but not for HDL cholesterol, triglycerides or systolic blood pressure,[97] and is not, therefore, a confounder of the relations between ethnicity and diabetes and between ethnicity and stroke. Ethnicity-related estimates of MI risk did not change materially whether total cholesterol was included or excluded from the statistical models (VI).

5.1.4 Definitions of ethnicity

Ethnic groups in Finnmark

The Sami and the Finnish populations are recognised ethnic groups in Norway, with the majority residing in Finnmark.[98] Many Finnmark inhabitants lived in ethnic settlements with little intermingling well into this century.[99-101] Out of 33,000 residents in the year 1900, 55% were Norse, 29% were Sami, and 16% were Finnish.[98] Definitions of Sami ethnicity have

varied. The 1930 census registered almost 19,000 Sami subjects in the three northernmost counties, but less than 9,000 Samis were registered in the same area in 1950. Several questions were used to define Sami ethnicity in the 1970 census. In Finnmark, some 7,500 subjects reported to be Samis, but almost 8,600 reported the Sami language as their mother tongue, and 14,000 reported that Sami was the first language of at least one grandparent.[98] From the 1970 census, it was estimated that there may be 40,000 subjects with a Sami family history in Norway.[102] In 1997, the Sami Act criteria for being a Sami were changed from requiring one-quarter to one-eighth Sami background, defined as having at least one Sami-speaking great grandparent.[103] A subjective group ascription was required before and after the revision. The new definition has led to an estimation of 70,000 Sami subjects in Norway.[104]

According to the criteria used in the Finnmark surveys (Appendix 1), a person must be of at least one-half Sami origin to be defined as such. No subjective report of group belonging was needed for inclusion in a specific ethnic group.

But what does ethnicity imply? The concept is derived from the Greek "ethnos", meaning "peoples". According to social-anthropological literature,[105] an ethnic group "is largely biologically self-perpetuating, it shares fundamental cultural values, it makes up a field of communication and interaction, and has a membership which identifies itself, and is identified by others, as constituting a category distinguishable from other categories of the same order." The Sami group is defined by social relations through family history, geographical belonging to an area, traditional occupations, cultural and religious values, and formal and informal organisations.[98] However, the overt Norwegian assimilation policy exerted for a long period during this and the preceding century, has influenced ethnic self-identification among the Samis,[106] and may have influenced self-reported ethnic origin in this study.

In addition to social-anthropological aspects, the concept of ethnicity will inevitably comprise genetic elements. Importantly, neither a definition based on grandparents' origin, mother tongue, nor on group ascription will pick up genetics or cultural aspects solely, and a very wide definition may hide sub-group characteristics. Further, in an observational study such as this one, there will be no inherent assumption regarding genetic or environmental factors as the cause of ethnic differences. If ethnic differences are observed, then the next step will be to explain them.

Ethnic differences in body height

The current criteria of ethnicity resulted in distinct inter-ethnic differences in average body height (IV,VI). Further, height differed between Norse subjects born within and out of Finnmark (VI), consistent with previous reports.[107-109] Tverdal[93] included only those who had participated and answered consistently on ethnicity in two surveys, and reported a slightly higher proportion of Sami and Finnish subjects than we did. However, the inter-ethnic variations in height and risk factors in that study were close to those in Paper VI, where ethnicity was defined from answers at one survey. Judged by height, the current questions on ethnicity are precise enough to statistically

discriminate between groups; on the other hand, height cannot be used to categorise people into ethnic groups, because of large within-group variations with overlapping values.

5.2 Incidence and case fatality

It is debated whether the ongoing decrease in coronary mortality in industrialised countries is a result of decreasing incidence, a lower case fatality, or both. A decrease in coronary heart disease incidence is thought to reflect the effect of primary prevention, while a decrease in case fatality is mainly attributed to improved medical care. The declining coronary mortality in Scandinavian countries has been attributed to a combination of those factors.[110-112] Our data allowed a very limited assessment of age specific incidence trends in MI (III). There was no decline in the incidence rate among 46 to 50-year old men, and apparently no decrease in major coronary risk factors in that age group. No conclusion about incidence trends could be drawn for women. The MI incidence rates among men were, not unexpectedly, higher than in Oslo[113] and Kristiansund[114] in the 1960s. In both sexes the rates were higher than in South Sweden throughout the present follow-up.[112] The case fatality in first MI has apparently decreased compared to that reported from Oslo in the 1960s.[113]

The 40% higher incidence of stroke in men than in women compares to reports from several countries.[115] The incidence rates in Finnmark were higher than among 40 to 49-year old men in Oslo (0.95 per 1,000 personyears) who were followed from 1972 through 1984.[116] Trends in stroke were compared in the international MONICA study, which covers the ages from 25 to 64 years. In most of the 17 countries, stroke mortality declined in the 1980s, while incidence trends were less clear.[117] The 28-days' case fatality rate was lower in Denmark (20%), Sweden (18%) and Finland (21%) than in most MONICA populations in an anlysis of first and recurrent strokes.[117] The case fatality rate in our study was 24%. Our study included too few cases for an analysis of stroke incidence trends.

The incidence rates of diabetes were higher in Finnmark than previously observed in Oslo from 1925 to 1955,[52] and from 1956 to 1965,[118] but were apparently lower than currently in the US[119] and in several populations of similar age in western countries.[120] The Samis in our study did not have a higher incidence rate than Norse subjects. In contrast to other ethnic minorities in the US, Alaska Eskimos and Indians apparently do not have an increased prevalence of diabetes as compared to the general population.[121,122]

5.3 Risk factors and causal factors

Any exposure or characteristic showing a statistical association with the outcome of interest may be labelled a risk factor, and the term should not be confused with the concept of cause. The term "risk marker" may be chosen to emphasise that a causal relationship is not assumed, or to underscore that the variable is a proxy (II). Scientific criteria have been listed[123] to guide judgment whether associations may express causality.

Both possible causes and intermediate factors may be included in multivariable analyses to assess their

role as disease predictors (I-II,IV-VI). Angina pectoris may be regarded as a stage on the pathway leading to MI. However, it does not always precede MI and does not always result in MI. Self-reported angina pectoris showed a different relation with MI in the two sexes (interaction) (I), in agreement with other studies.[88] Serum glucose is the diagnostic criterion of diabetes and of glucose intolerance,[12] and is not a cause of diabetes. However, consistent with other studies (discussed in V), one random measurement of glucose with values within the "normal " range, predicted future diabetes. This finding points to a graded relation, and to the possibility of detecting the disease process earlier than by using today's diagnostic tools.

Major cardiovascular risk factors

The strong role of smoking as a coronary risk factor was confirmed (I). Not only was there a strong dose-response relationship, especially in women, but as a consequence of the high smoking prevalence, the population impact was very large. The population attributable risk of smoking was close to 50% in both sexes and translates into some 300 "saved" cases of MI, if all participants had incidence rates similar to never-smokers. Controlled for confounders, smoking increased the risk of a fatal outcome of the heart attack by 40% (II), and smoking was a risk factor for stroke and stroke subtypes except intracerebral hemorrhage (IV). Smoking did not predict diabetes (V). Intermediate MI incidence rates in ex-smokers point to a reversibility of smoking induced risk, and to a large potential for the prevention of MI in this population. Smoking was prevalent in subjects at high risk. One-third of those who had suffered from MI by 1987, reported to be current smokers (I), and smoking was common among subjects on antihypertensive treatment. In some hypertension treatment trials, coronary mortality was not reduced among smokers,[124] raising the possibility of adverse interactions between anti-hypertensive drugs and cigarette smoking.

Serum total cholesterol was a significant risk factor for MI (I), but did not predict a fatal outcome of the heart attack (II). A question is whether the high serum cholesterol levels in this population could have masked an effect of cholesterol on case fatality, but our results were similar to two other studies, where average cholesterol levels were lower (see paper II). Serum total cholesterol was unrelated to diabetes. The lack of association between cholesterol and stroke is not surprising, given the heterogeneity of disorders included in the endpoint. The subtype analysis suggested that cholesterol was positively related to ischemic stroke, and inversely related to hemorrhagic stroke, a finding in accordance with other studies (see Paper IV).

Blood pressure was a risk factor for MI and stroke (I,IV), in accordance with numerous studies.[80,81] However, although risk factors for MI and stroke apparantly overlap, they do not necessarily exert their action through the same pathophysiological mechanisms. The effect may be mediated both through a "direct" effect on small vessels due to the increased pressure, and through atherosclerosis, involving kinetics of a disturbed blood flow.[125] Such different mechanisms could be involved in the different outcomes of blood pressure treatment in

stroke and CHD prevention. In a large overview of randomised drug trials,[126] the risk of stroke was reduced as expected, but the risk of CHD was reduced much less than expected from observational studies.[82]

We observed a strong relation between blood pressure and case fatality in MI (II), which has been little reported in epidemiologic literature. Our finding is at variance with the British Regional Heart Study,[127] which had an analytic design more closely resembling ours than any other epidemiologic study examining blood pressure and case fatality. However, that study observed an increased risk of dying associated with antihypertensive treatment, while we observed the opposite. The difference in results remains unexplained.

Subjects on blood pressure treatment were at an increased risk of cardiovascular diseases and diabetes. In the analysis presented in Paper I, Table 6, the adjusted relative risk (RR) associated with antihypertensive treatment was 1.6 (95% CI, 1.2 - 2.3) in men, and 1.8 (95% CI, 1.1-3.1) in women.[128] Antihypertensive treatment was positively associated with stroke in men (RR 3.2), but not in women (RR 1.1) (IV), and was positively related to diabetes in both sexes (V). On the other hand, antihypertensive treatment was associated with a nonsignificantly improved survival after MI. The use of antihypertensive treatment increased greatly during follow-up, and we discussed (II, III) whether primary and secondary prevention of hypertension may have contributed to a reduced coronary mortality. An increased risk of coronary heart disease and stroke in subjects on antihypertensive treatment has been reported from observational studies.[129-131] Adverse drug effects have been suggested as one cause of the increased risk,[131] and it has been discussed whether treatment may do more harm than good in some subgroups.[131] On the other hand, randomised clinical trials[124,126,132] and clinical studies among hypertensive subjects[133,134] have demonstrated a beneficial effect of treatment on cardiovascular mortality. It seems reasonable to conclude that antihypertensive treatment reduces, but does not fully reverse, the increased risk associated with hypertension.

Protective factors

Epidemiologic studies have provided strong evidence that a sedentary life style is associated with an increased risk of coronary heart disease.[135] Physical fitness was an independent predictor of cardiovascular mortality in middle-aged, healthy Norwegian men.[136] The "westernization" of many societies including a decline in physical activity is considered important for the increasing prevalence of NIDDM.[15, 53] In the present study, an inverse, non-significant, relation was seen between physical activity and MI and stroke, but no association remained after multivariable adjustment (not shown), possibly because the effect is mediated through variables that were included.[62] Physical activity was inversely associated with diabetes. The association was weakened in multivariable analyses, but a protective effect of borderline significance was observed among obese men. This may signify that physical activity is particularly beneficial for subjects who are at high risk of disease. Insulin sensitivity increases in working muscles,[137] and the benefits of physical

activity is not dependent on weight loss. Moderate physical activity equivalent to very brisk walking or light effort in bicycling, skiing or ball games for at least 40 min/week was associated with lower risk of NIDDM, and less intensive activity was sufficient for risk reduction among obese and hypertensive men.[138]

A high HDL cholesterol concentration was associated with a decreased risk of MI in our study, and a similar dose-response relationship was observed in the sexes. A graded relation between HDL cholesterol and CHD was also observed in several populations, including Japanese men with far lower total cholesterol levels than in our study.[139] Physical activity increases HDL cholesterol, but only a modest association was observed between HDL cholesterol and self-reported habitual leisure physical activity in the Finnmark Study.[76]

Heredity and early environment

No data on genetic markers were included, but a family history of premature coronary heart disease may be a marker of an inherited predisposition.[18-20,140] However, an aggregation of cases within families may represent both genetics and a shared environment. The question on family history of coronary heart disease was unspecified with regard to age and to parental or sibling relations (Appendix 1). When included in an analysis as in Paper I, Table 6, family history (yes/no) was positively associated with MI in men (RR 1.5; 95% CI, 1.2-1.8) and in women (RR 1.3; 95% CI, 0.9-2.0), but did not confound the associations between other variables and MI (unpublished).

No direct data were available on exposure to poverty or unfavourable prenatal and infant living conditions. We argued that a reduced body height is a marker of unfavourable factors in early life or childhood. Such an assumption is based upon ecological associations (Section 3.1), and we could not assess whether a low height represented a non-fulfilled growth potential in individuals. Used in epidemiologic studies without individual information, the assumption may be valid only in populations that are relatively homogeneous with regard to age and racial composition, since height is also determined by genetic factors,[141] and since average height is a very sensitive indicator of a nation's public health status,[142] changing living conditions[143,144] and of social class.[145] A reduced final height and increased levels of serum glucose and indices of insulin resistance were observed among young adults who were born small for gestational age.[146]

An inverse dose-response relationship was observed between height and stroke (IV). The risk of stroke was halved in the tallest as compared to the shortest quartile in both sexes, and the relation was observed within ethnic groups (VI). For the other endpoints, the associations with height differed by sex. Height was inversely related to diabetes in women, but not in men (V). Height was inversely associated with MI in women (RR per 5 cm, 0.8; 95% CI, 0.7-0.9), but not in men (RR 0.99, 95% CI,0.9-1.1) (unpublished). The evidence of an association between height and cardiovascular disease and diabetes is inconsistent in epidemiologic literature, as discussed in Papers IV and V.

Improved nutrition, mainly with regard to a reduced salt intake and an increased animal fat and protein content in the diet, is believed to explain much of the large decline in stroke mortality in Japan after World War II.[23,147] Poor nutrition was widespread in Finnmark during the first part of this century.[31] All subjects in this cohort were born before the extremely difficult period in Finnmark in 1944, but they were children and youngsters during the war. Height was apparently more strongly related to intracerebral hemorrhage than to other stroke subtypes (IV). Height and total cholesterol were inversely related to fatal stroke, probably reflecting the high proportion of intracerebral hemorrhage in this endpoint. Thus, this study provides indirect evidence that nutritional factors early in life may be involved in the relatively high stroke mortality in this county,[3,4] in addition to the role of high blood pressure and smoking. On the other hand, the diverging associations in the sexes between height and MI, and height and diabetes, call for cautious interpretations.

5.4 Ethnic differences in risk factors and disease

Genetically and environmentally determined ethnic differences

Several genetically determined ethnic differences have been reported from North Scandinavian populations.[148-150] On the other hand, ethnic differences in a disease such as scurvy have been attributed to corresponding differences in diet.[151,152] It is an old clinical observation that scurvy did not occur among highland Samis[151] despite the lack of fresh fruits, vegetables, and potatoes. Reindeer meat is the traditional staple food among nomadic Samis, and it is lean and relatively rich in ascorbic acid,[151] α-tocopherol, and other anti-oxidants.[153] Berries and herbs were additional sources of vitamin C.[151] As recently reviewed,[154] observational studies have found inverse associations between antioxidant vitamin intake and coronary heart disease, while intervention trials found either no benefit (of beta carotene) or a possible benefit (of vitamin E). The low coronary mortality among Greenland Eskimos is attributed to an antithrombogenic diet,[155] possibly combined with genetic protective factors.[156]

Average serum cholesterol was higher in Samis and Finns than among Norse in this study. There is a difference between Sami and non-Sami populations in the distribution of genetic types involved in LDL polymorphism.[157] Apolipoprotein E phenotype E4/4 , which is associated with high serum cholesterol,[158] is relatively frequent in Finland,[159] and was more common among Samis than among Finns in a Finnish study.[160] The high consumption of boiled, unfiltered coffee in Norway,[4, 161] and in Finnmark in particular,[161] is probably of importance for the high serum cholesterol levels in this population. Lacking fresh cow's milk, the consumption of coffee may have been even higher among nomadic Samis than in the general population.[151] Reindeer herders living in a Sami area in Finland had high serum cholesterol levels, but more favourable serum concentrations of antioxidants, which varied with the weekly intake of reindeer meat.[160] The authors attributed the observed lower coronary mortality among the Samis to diet rather than to genetics. Thus the

cross-sectional observations in Finnmark of less coronary heart disease among Samis,[72] could indicate a more favourable life style or a genetic advantage. In a mortality follow-up study, Tverdal concluded that middle-aged Sami men seem protected against coronary heart disease, and suggested that genetic factors may be responsible.[93] His conclusion contrasts that of Paper VI, which also used the two first Finnmark surveys as the base line. In our analysis, ethnic differences in MI incidence were largely explained by differences in well known risk factors and height. The differences in results will be discussed.

Two studies of ethnic differences in coronary heart disease in Finnmark

A reanalysis of our material was done to explore possible reasons for the different results between Tverdal's study[93] and Paper VI. There were some methodological differences between the studies, and the follow-up periods were not identical. From Table 3 (Appendix 5), which includes men without a self-reported history or symptoms of CHD, it is apparent that the different definitions of ethnicity, with concomitant differences in sample sizes, did not explain the different conclusions. In Paper VI, subjects with a previous infarction, stroke and diabetes were excluded, while those with symptoms or diagnosed angina pectoris, and subjects on antihypertensive treatment were included. Tverdal, on the other hand, excluded all those subjects from one set of analyses (subjects without a history), or included all who had met (all subjects). For comparison, results for all men, and for men without a self-reported history in our study population (VI) and in the study by Tverdal, are presented in Table 4 (Appendix 5). Tverdal's exclusion of sudden deaths from the coronary mortality endpoint did not account for the low coronary mortality among Sami men. We could not adjust for income or education, but those variables did not confound the association between ethnicity and mortality (Tverdal, personal communication). Table 5 (Appendix 5) comprises those men who actually were included in Paper VI, and elucidates how different inclusion criteria within that cohort would provide different results. Sami "low risk" men had a lower case fatality rate and a lower CHD mortality rate compared with Norse men born in Finnmark, while Sami "high risk" men had higher rates. On the other hand, the MI incidence rates in the ethnic groups were more similar within each risk-group. The nature of the interaction between risk-group and ethnicity with respect to CHD mortality is not obvious. Adverse interactions between drugs and risk factors, an ethnic bias in treatment policy or in cause-of-death classification, selective mortality, and ethnic differences in drug metabolism or other genetic traits, should all be considered possible explanations which need investigations beyond the scope of this thesis.

5.5 Sex differences in risk factors and disease

Coronary heart disease and stroke

Coronary heart disease is often labelled a men's disease because of the large sex ratios in incidence and mortality observed among young and middle-aged subjects. The male-to-female ratios in the incidence of MI (4.6) and stroke

(1.4) in this study correspond well to sex ratios in coronary and cerebrovascular mortality in many countries.[90] Our observation that smoking is a stronger risk factor in women, is consistent with previous, but little-focused findings (see Paper I). The strong association between smoking and MI in women may be related to the anti-estrogenic effect of cigarette smoking. Serum lipids, including HDL cholesterol, are favourably influenced by estrogen,[162] and serum lipids in women increase shortly after menopause.[163,164] Many attribute the sex difference in coronary heart disease to favourable effects of female sex hormones,[165] and claim support from the great increase in coronary mortality in women past the age of menopause.[165,166] However, coronary mortality in women is very close to that in men throughout life, with a time lag of approximately 10 years,[3,88] making the role of endogenous sex hormones less obvious.

Among women included in Paper V, 1169 (21%) reported having undergone menopause at base line. No information was collected on age at menopause, and time of transition from pre- to post-menopause during follow-up was not known. When included in a multivariable analysis, menopause (yes/no) was not a significant predictor (RR 0.99) and did not confound the relations between other risk factors and MI. Postmenopausal hormone replacement therapy (HRT) is widely claimed to have a beneficial effect on cardiovascular risk,[166,167] but data on adverse events, pooled from short term clinical trials of postmenopausal HRT, cast some doubt on that belief.[168] No data on such therapy was collected for this study, but HRT was very little used by Finnmark women in the 1980s, as discussed (I).

Our data (II) showed a similar one-year survival curve after MI in men and women, consistent with a recent review.[169] If treatment policies after MI differed in the sexes, which has been claimed by some authors,[170,171] that difference had apparently no impact on survival up to one year. It is not clear why more women than men were treated for hypertension at base line, given their lower blood pressure distributions.

Total cholesterol was positively associated with MI in both sexes, but only at serum cholesterol ≥ 7.40 mmol/L did the risk increase in women. The dose-response relationship was similar in smoking and non-smoking women. Given the simultaneous strong association between smoking and MI, coronary heart disease prevention among middle-aged women should first and foremost focus on the avoidance of smoking.

Focusing on sex-related differences in risk factors for stroke is less relevant, because the stroke subtype distribution differed by sex (Table 2 in Paper II).

Sex differences in diabetes mellitus

Women with diabetes are at a relatively much higher risk of developing MI than are diabetic men, compared to non-diabetics of the same sex,[172,173] Thus, diabetes tends to eliminate the sex differences in MI, and 55-64-year old women with diabetes had the same incidence rate of MI as did nondiabetic men in the northern Swedish MONICA population.[173] Future diabetic women, in contrast to non-diabetic women, had baseline risk factor levels similar to those of men (V), and this difference was not dependent upon age or

menopausal status. Similarly, future diabetic women had a relatively more adverse risk factor profile than did men in the San Antonio Heart Study.[174] This may lend support to the view that NIDDM is an android condition.[175,176] Women with severe hyperandrogenicity are at increased risk of cardiovascular disease and NIDDM, but women in unselected populations, who have low levels of sex hormone binding globulin and serum testosterone in the upper part of the "normal" distribution, are also at increased risk.[176] Body mass index was a strong predictor of diabetes, but the dose-response relationship was weakened in women by multivariable adjustment, with HDL cholesterol being the main confounder (V). It was not possible to examine whether a "male" fat distribution in some women could explain the sex difference in the relationship between body mass index and diabetes. Among Mexican Americans, central adiposity was more strongly associated with diabetes incidence in women than in men,[177] and measures of central adiposity provided additional prediction of NIDDM beyond that of body mass index in female, mainly white, American nurses.[178] The diabetes incidence among Sami women was lower than expected from their mean body mass index (VI), but our data were insufficient to examine whether there were corresponding inter-ethnic differences in obesity pattern.

It is not completely understood why some women develop a male fat distribution when they gain weight, and with few exceptions,[176] possible sex differences in insulin resistance have been little discussed.[65-67,179] A low HDL cholesterol is one of the major features of the insulin-resistance syndrome,[65-66] and the dyslipidemia may account for the excess cardiovascular risk among diabetic subjects.[180] HDL cholesterol is an equally important protective factor for MI in both sexes (I), and the strong dose-response relation between HDL cholesterol and future diabetes among women which was observed in this study, may be relevant for the apparently accelerated atherosclerosis in diabetic women.[172] Further studies are needed to fully disclose the differences in the relations between cardiovascular disease and diabetes in the sexes. Such studies should include measures of insulin resistance.

6. SUMMARY

Results from the Finnmark Study are consistent with findings from numerous cardiovascular studies worldwide, that smoking, serum cholesterol and blood pressure are the most important risk factors for myocardial infarction. By contrast, blood pressure was a strong determinant, while total and HDL cholesterol were unrelated to a fatal outcome of MI. The study confirmed that blood pressure is the most important determinant for stroke, and that body mass index is a major determinant for diabetes mellitus. Body height was a strong predictor of stroke in both sexes and predicted diabetes in women. The results are consistent with the view that both early living conditions and modifiable lifestyle factors are determinants of cardiovascular diseases and diabetes in adult age. In addition, the Finnmark Study has provided evidence for sex differences in risk factors, that at present are little known or poorly understood, and which, therefore, should be investigated further.

7. CONCLUDING REMARKS

Focusing on those who do not get sick, and not only on those who do get sick, was a fruitful advantage of epidemiology over clinical medicine to enhance the understanding of risk factors and causes of major chronic diseases.[181] Within epidemiology, studying men and women within the same population, who share some, but not all exposures, and who have different rates of disease, may offer important clues for uncovering causal relationships. Population-based studies such as the Finnmark Study, are well suited for the purpose. However, although the present follow-up covered 15 years, the low numbers of incident cases limited the analytic possibilities. A prolongation of the follow-up period would greatly increase the scientific value of the analyses, and should be performed in the future.

Cardiovascular diseases and diabetes are multifactorial diseases, and genes, early environment and lifestyle interact in complex webs where causes, mere associations and consequences are not yet fully clarified. At this stage of knowledge it should be stressed, first, that "bad" genes, or an adverse fetal or childhood environment, do not determine future cardiovascular disease, only disease susceptibility; and second, that disease susceptibility may be modified by self-determined behaviour.

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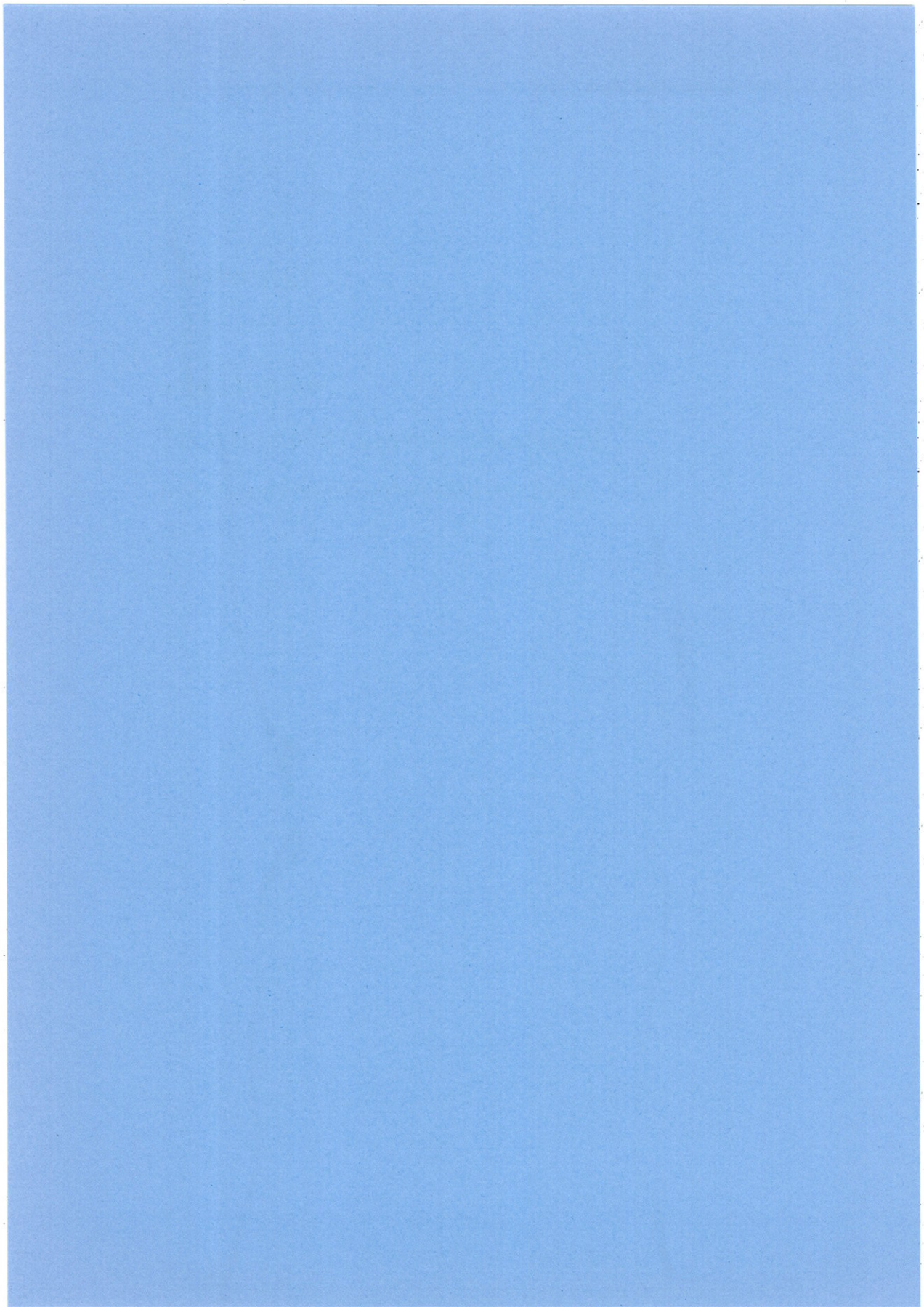
Appendix 1

Questionnaire

Finnmark surveys 1974 and 1977

(identical questionnaires, except for section G)



MELDING OM SKJERMBILDEFOTOGRAFERING OG HJERTE-KARUNDERSØKELSE

(Gjelder bare den person brevet er adressert til)

Skjermbildefotograferingen kommer nå til Deres distrikt.

Tid og sted for Deres frammøte vil De finne nedenfor.

Også denne gangen vil en del av befolkningen få tilbud om hjerte-karundersøkelse. De tilhører denne gruppe. En orientering om undersøkelsen er gitt i vedlagte brosjyre.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med tuberkulinkort eller helsebok, om De har.

Fravær bes eventuelt meldt på vedlagte seddel.

Med hilsen

HELSERÅDET FYLKESLEGEN
STATENS SKJERMBILDEFOTOGRAFERING

Født dato | Personnr. | Kommune | Kretsnr.

Møtested | Kjønn | Første bokstav etternavn | Dag og dato | Klokkeslett

SKRIV IKKE HER!

T. S. M.: (17) M: (18) (19) / (24) (25) / (30) (31) (32)

A

	JA	NEI
Har De, eller har De hatt:		
Hjerteinfarkt? 33		
Angina pectoris (hjertekrampe)? 34		
Annen hjertesykdom? 35		
Åreforkalkning i bena? 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 leggsmerter, 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
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 arbeidsstedet, søndagsturer m.m.)	
3 Driver mosjonsidrett, tyngre hagearbeid e.l.? (Merk at yrksomheten skal vare 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? 52		
Hvis svaret var „JA" på forrige spørsmål, besvar da:		
Røyker De sigaretter daglig? 53 (håndrullede eller fabrikkframstilte)		
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 — Antall år:		
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag 58-60 (håndrullede + fabrikkframstilte) — Ant. sigaretter:		
Røyker De noe annet enn sigaretter daglig?		
Sigarer eller serutter/cigarillos? 61		
Pipe? 62		
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?		
Oppgi gjennomsnittlig antall pakker pr. uke. 63-64 — Ant. tobakkpk:		

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? 70 (f.eks. under sesongfiske, onnearbeid)		
Har De i løpet av siste året hatt:		
Sett kryss i den ruten hvor „JA" passer best.		
1 Overveiende stillesittende arbeid? 71 (f.eks skrivebordsarb., urmakerarb., montering)		
2 Arbeid som krever at De går mye? (f.eks. ekspeditørarb, lett industriarb., undervisn.)		
3 Arbeid hvor De går og løfter mye? (f.eks. postbud, tyngre industriarb, bygningsarb.)		
4 Tungt kroppsarbeid? (f.eks skogsarbeid, tungt jordbruksarb. tungt bygningsarb.)		
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 Oslo* 1972-73, Norwegian counties 1974-78 (Finnmark, Oppland and Sogn og Fjordane) and Tromsø 1974.

English translation; 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?
- hardened arteries in 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)

*In Oslo preset groups of cigarettes smoked per day and packs of pipe tobacco smoked per day (see original questionnaire)

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 at 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:

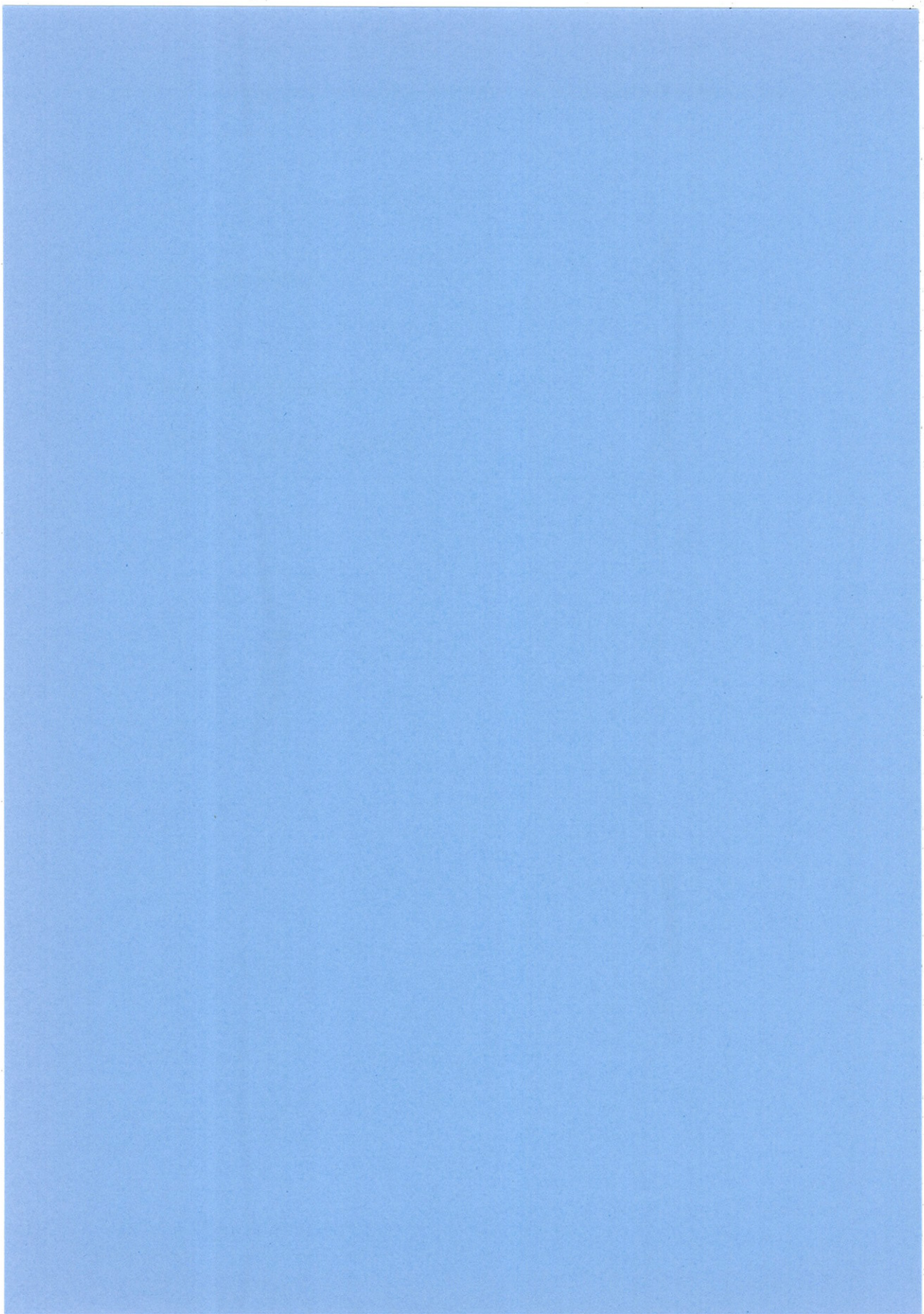
Are two or more of your grandparents of Finnish origin?

Are two or more of your grandparents of Lapp origin?

Appendix 2

Questionnaire

Postal survey 1991



Statens
helseundersøkelser
(tidl. Statens skjermbildefotografering)

UNIVERSITETET I TROMSØ

INSTITUTT FOR
SAMFUNNSMEDISIN

Brevet er laget på både samisk og norsk. Bruk det språk som passer deg! På baksiden står det noen spørsmål vi ber deg svare på.

Reive lea sihke sámegillii ja dárogillii. Geavat dan giela mii dutnje buorebut heive! Duogábealde leat moadde gažaldaga maid ávžžuhit du vástidit.

Kjære mottager!
Den høye forekomst av hjerte/karsykdommer er et stort helseproblem i Finnmark og i Norge. Derfor ønsker vi å finne ut mer om hvordan sykdommene kan forhindres. For å finne ut hvorfor noen blir syke må vi vite hvem som blir syke og hvem som holder seg friske.

Du er en av dem som i 1970-årene deltok i hjerte-karundersøkelsene i Finnmark. Undersøkelsene ble gjort av Statens skjermbildefotografering (nå Statens helseundersøkelser) i samarbeid med Universitetet i Tromsø og Helsetjenesten i Finnmark. Et av hovedformålene var å finne ut mer om årsakene til hjerte/karsykdom og andre kroniske sykdommer.

Statens helseundersøkelser og Universitetet i Tromsø ved Institutt for samfunnsmedisin sender ut dette brevet for å få vite hvem som har fått hjerte/karsykdom og andre kroniske sykdommer siden undersøkelsene fant sted. Brevet blir sendt til alle som deltok i hjerte/karundersøkelsene, og vi håper at du vil svare på spørsmålene (se baksiden) så fullstendig som mulig.

Det er selvsagt frivillig å svare på brevet.
Opplysningene vil bare bli brukt i forskning og blir behandlet strengt fortrolig. Vi ber også om at du gir oss tillatelse (ved å undertegne tillatelsen på baksiden) til å få opplysninger fra lege/sykehus der du eventuelt har vært behandlet. Slike opplysninger er viktig for å avgjøre nøyaktig sykdommens art og alvorlighetsgrad. Dersom du ikke ønsker å besvare brevet, vil dette ikke få noen konsekvenser for deg.

Vi har til hensikt å fortsette å følge alle som ble undersøkt ved hjerte/karundersøkelsene over lang tid (20–30 år). Opplysningene vi nå får blir derfor arkivert, slik at vi kan benytte dem i senere analyser av sykelighet.

Vennligst send det utfylte skjemaet tilbake i vedlagte konvolutt. Portoen er betalt.

På forhånd takk!

Med vennlig hilsen

Fylkeslegen i Finnmark Universitetet i Tromsø

Statens helseundersøkelser

Buorre vuostáiváldi!
Váibmo/varrasuotnadávddat leat stuorra dearvvašvuođalaš vuorjjan Finnmárkkus ja Norggas. Danne dáhtošeimmet gávnnahit vugiid mo dáid dávddaid hehttet. Gávnnahan dihtii manne muhtumat buohccájit, mii fertet vuos diehtit geat dat buohccájit ja geat dat bissot dearvvasin.

Don leat okta dain olbmuin guđet 1970-jagiid ledje mielde váibmo/varrasuotnaiskkadeamis Finnmárkkus. Iskkademiid čađahedje ovttas Stáhta suonjargovat (dáláš Stáhta dearvvašvuođaiskkadeamit), Romssa Universitehta ja Dearvvašvuođabálvalus Finnmárkkus. Váldoulbmil lei gávnnahit eambbo das manne váibmo/varrasuotnadávddat ja earáge bistevaš dávddat čuožžilit.

Stáhtá dearvvašvuođaiskkadeamit ja Romssa Universitehta servodatmedisiinna ossodaga bokte sáddejit dán reivve olbmuide diđoštan dihtii geat leat buohccán váibmo/varrasuotnadávddaid ja earáge bistevaš dávddaid maŋŋá iskkademiid. Reivve sáddejuvvo sidjiide guđet serve váibmo/varrasuotnaiskkademiide, ja mii doaivut don vástidat gažaldagaide (geahča duogábeallai) nu dárkilit go juo sáhtežat.

Dieđusge lea friddja ášši vástidatgo vai it. Dieđut geavahuvvojit ávkin dutkamis ja daid eai oačče sahteolbmot. Mii jearrat maid lobi dus viežžat dieđuid doaktáris/buohcciviesus gos leat leamaš divššus (ja dan lobi attát midjiide go čálát iežat nama dan báhpirii nuppe beallai). Dat dieđut leat dehálaččat go galgat dárkilit mearredit dávdda luonddu ja vearráivuođa. Jos it dáhto vástidit dán reivve, de ii leat dus geatnegasvuohta dan dahkat.

Min ulbmil lea joatkevaččat čuovvut sin buohkaid guđet ledje váibmo/varrasuotnaiskkademiin (20–30 jagi). Dieđut maid dál attát, mii danne vurkkodat, vai sáhttit daid geavhit boahttevaš buohcuvuođa dárkkástallamiin.

Leage nu buorre ahte deavddát dán báhpira ja sáddet dan mieldečuovvu reivegokčasis ruovttoluotta.

Giitit du ovddalgihtii!

Ustitlaš dearvvuođaiguin

Finnmárkku fylkkadoavttir Romssa Universitehta

Stáhta dearvvašvuođaiskkeamit

Har du noen gang vært behandlet av lege for en eller flere av de følgende sykdommer?
Kryss av for hver sykdom (og angi eventuelt hvilket år sykdommen ble oppdaget):

	Ja	Nei	Årstall
Hjerteinfarkt (sår på hjertet)	☐	☐	19..
Hjertekrampe (angina pectoris)	☐	☐	19..
Høyt blodtrykk (tablettbehandlet)	☐	☐	19..
Sukkersyke (diabetes)	☐	☐	19..
Hjerneslag (hjerneblødning, drypp)	☐	☐	19..
Magesår	☐	☐	19..
Lårhalsbrudd	☐	☐	19..

	Ja	Nei
Har du vært innlagt på sykehus etter 1970?	☐	☐

Hvis du har vært innlagt på sykehus etter 1970, skriv da i det åpne feltet under hvor (hvilket sykehus og avdeling) og når (hvilken måned og år) du var innlagt. Dersom du har hatt flere sykehusopphold, ber vi om opplysninger om alle.

Hvis du har vært innlagt eller har hatt noen av de ovennevnte sykdommer, ber vi om å få innhente opplysninger fra sykejournal. Vi ber deg derfor å undertegne følgende erklæring:

Jeg samtykker i at opplysninger kan hentes fra min journal om de sykdommer som er nevnt. Opplysningene må bare brukes slik det framgår i orienteringen om denne undersøkelse.

Sted: ..... Dato: 1991

.....
Underskrift

Leatgo goassege šaddan doaktára lusa dás namahuvvon dávdda geažil? Sárgulastte juohke dávdda nammii mas leačča buohcan (ja dieđit guđe jagi dávda fuomášuvvui):

	Juo	Ii	Jahki
Váibmoinfárkta (váibmohávvi)	☐	☐	19..
Váibmogeassáhat (angina pectoris)	☐	☐	19..
Alla varradeaddu (tableahttadikšu)	☐	☐	19..
Sohkardávda (diabetes)	☐	☐	19..
Vuoiŋŋaščaskkástat (vuoiŋŋasvardin)	☐	☐	19..
Čoavjehávvi	☐	☐	19..
Doddjojun čoarbealnoras	☐	☐	19..

	Juo	Ii
Leatgo šaddan buohccivissui maŋŋá 1970?	☐	☐

Jos leačča leamaš buohcciviesus maŋŋá 1970, de čális dán siiddu vuolit ruktái man buohcciviesus ja ossodagas ja guđe mánus ja jagis don ledjet doppe. Jos eambbo gerddiid leat leamaš buohcciviesus, de čális buot gerddiid birra.

Jos dus lea leamaš oktage dás bajábealde namuhuvvon dávda, de jearrat dus lobi viežžat doavttergirjjiin dieđuid du dávdda birra. Don galggat de lobi attedettiin čállit namat dán cealkámuša vuollai:

Mun mieđihan addit lobi viežžat dieđuid mu dávdda birra doavttergirjjiin. Dieđut galget geavahuvvot nu mo dán báhpiris čilgejuvvo.

Báiki: ..... Beaivi: 1991

.....
Vuollaičálli namma

Om sykehusopphold.
(Sykehus/avdeling og tidspunkt.)

Buohcciviesu birra dieđut.
(Buohcciviessu/ossodat ja áigi.)

This letter is written in Sami and in Norwegian. Use the language which you prefer. On the reverse side are some questions which you are requested to answer.

Dear recipient!

The high frequency of cardiovascular diseases is a major health problem in Finnmark and in Norway. Therefore, we are trying to find out how the diseases can be prevented. In order to understand why some people become ill, we must determine who becomes ill and who remains healthy. You are one of those who participated in the cardiovascular surveys in Finnmark in the 1970s. The National Health Screening Service, in co-operation with the University of Tromsø and the health care providers in Finnmark, performed the surveys. One of the main purposes was to find out more about causes of cardiovascular diseases and other chronic diseases.

The National Health Screening Service and the University of Tromsø, represented by the Institute of Community Medicine, are distributing this letter to find out who has had cardiovascular diseases and other chronic diseases since the surveys took place. The letter is being mailed to all who participated in the surveys, and we hope that you will answer the questions (see reverse side) as completely as possible.

Answering the letter is, of course, voluntary.

The information will only be used for research purposes and will be treated with strict confidentiality. We also ask for your consent (by signing the consent form on the reverse side) to collect information from the physician/hospital where you were treated. Such information is important to determine the exact nature and severity of the disease. If you decide not to answer this letter, there will be no consequences for you.

We intend to continue to follow up everyone who participated in the cardiovascular surveys for a long time (20-30 years). The information that we receive now will be stored, so that we can use it in later analyses of morbidity.

Please return the completed questionnaire in the enclosed envelope. The postage has been prepaid.

Thank you very much!

With kind regards,

The County Medical Officer in Finnmark

The National Health Screening Service

The University of Tromsø

Has a doctor ever treated you for one or more of the following diseases?
Tick the appropriate box for each disease (and write in what year the disease was discovered):

	Yes	No	Year
Myocardial infarction (heart attack)	☐	☐	19____
Angina pectoris (heart pain)	☐	☐	19____
High blood pressure (drug treated)	☐	☐	19____
Diabetes	☐	☐	19____
Stroke (brain haemorrhage, minor stroke)	☐	☐	19____
Stomach ulcer	☐	☐	19____
Hip fracture	☐	☐	19____

	Yes	No
Have you been admitted to a hospital since 1970?	☐	☐

If you have been admitted to a hospital since 1970, write in the space below where (which hospital and department) and when (which month and year) you were hospitalised. If you have had several hospital stays, please provide information concerning all of them.

If you have been hospitalised or have had any of the above-mentioned diseases, we ask for your permission to obtain information from medical records. We therefore ask you to sign the following statement of consent:

I consent that information concerning the diseases mentioned above may be retrieved from my medical records. The information shall only be used as stated in this letter.

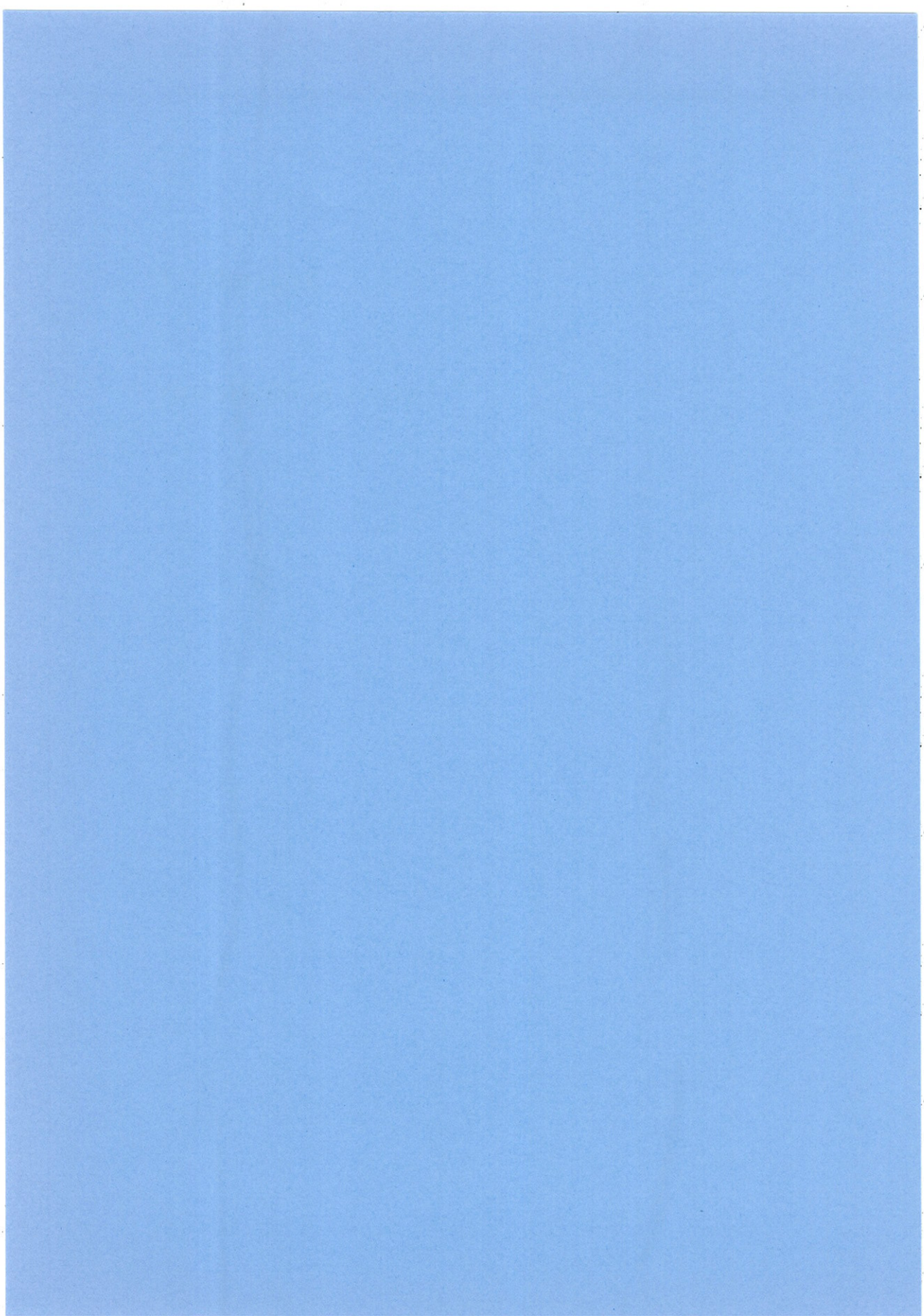
Place:_____ Date:_____1991

_____
Signature

Information regarding hospital stays.

Appendix 3

Letters to physicians



UNIVERSITETET I TROMSØ

INSTITUTT FOR
SAMFUNNSMEDISIN

Tromsø.....1992

Forespørsel om opplysninger til forskningsformål:

INSIDENSUTVIKLING AV HJERTE-/KARSYKDOM OG DIABETES BLANT MENN OG KVINNER 20-49 ÅR I FINNMARK.

Prosjektet er en oppfølging av hjerte-/karundersøkelsene som Statens Helseundersøkelser gjennomførte i 1974 og 1977 i samarbeid med helsetjenesten i Finnmark og Universitetet i Tromsø. Hensikten er å kartlegge forekomst av hjerteinfarkt, slag og diabetes i tidsrommet 1974-90 blant dem som ble undersøkt. Sykdomsforekomst vil bli sammenholdt med registrerte risikofaktorer. Ingen personidentifiserbare opplysninger vil bli publisert. Sykdomstilfelle registreres via journalarkiv ved sykehus, dødsårsaksstatistikk, SSB, og spørreskjema til deltakerne.

Prosjektet er godkjent av Datatilsynet (ref 90/954-5 TSÅ) og Helsedirektoratet (ref 90/03145 4 GHe) og av Regional komite for medisinsk forskningsetikk (sak 6/91).

.....

har opplyst at han/hun har vært innlagt ved

sykehus/avd:.....tidsrom:.....

p.g.a. .....

og har gitt skriftlig samtykke til innhenting av journalopplysninger om sykdommen.

Vi ber om å få tilsendt relevante epikriser.

Med vennlig hilsen

Inger Njølstad
prosjektleder

Postadresse:
Inger Njølstad
Universitetet i Tromsø
Institutt for samfunnsmedisin
Breivika
9000 Tromsø

Tromsø, ... 1992

Request for information for research purposes:

INCIDENCE TRENDS IN CARDIOVASCULAR DISEASES AND DIABETES AMONG MEN AND WOMEN 20 - 49 YEARS OLD IN FINNMARK

This project is a follow-up of the cardiovascular surveys which the National Health Screening Service carried out in 1974 and 1977 in a collaboration with the Health Services of Finnmark and the University of Tromsø. The aim is to determine the incidence of myocardial infarction, stroke, and diabetes during 1974-90 among those who participated. The incident cases will be linked to the risk factors registered. No information will be published that can be traced back to individuals. Incident cases are being detected from medical record files in hospitals, cause-of-death statistics at Central bureau of Statistics of Norway, and by a postal questionnaire to the participants.

The project has been approved by the Data Inspectorate (ref 90/954-5 TSÅ), by the Directorate of Health (ref 90/03145 4 GHe), and by the Regional Committe for Research Ethics (case 6/91).

.....

has informed us that he/she was admitted to

hospital/ward:..... period:.....

because of: .....

and has given written consent to collect medical information about the disease.

We will kindly ask you to send us the relevant letters of discharge.

With kind regards

Inger Njølstad
head of the project

Mail address:

UNIVERSITETET I TROMSØ

INSTITUTT FOR
SAMFUNNSMEDISIN

Tromsø, 5. nov. 1991

Forespørsel om opplysninger til forskningsformål:

INSIDENSUTVIKLING AV HJERTE-/KARSYKDOM OG DIABETES BLANT MENN OG KVINNER 20-49 ÅR I FINNMARK.

Prosjektet er en oppfølging av hjerte-/karundersøkelsene som Statens helseundersøkelser gjennomførte i 1974 og 1977 i samarbeid med helsetjenesten i Finnmark og Universitetet i tromsø.

Hensikten er å kartlegge forekomst av hjerteinfarkt , slag og diabetes blant dem som deltok. Sykdomsforekomst vil bli sammenholdt med registrerte risikofaktorer. Sykdomstilfelle registreres via journalarkiv ved sykehus, Dødsårsaksregisteret, SSB, og spørreskjema til deltakerne. Ingen personidentifiserbare opplysninger vil bli publisert.

Prosjektet er godkjent av Datatilsynet, helsedirektoratet og av regional etisk komite. Fylkeslegen i Finnmark støtter undersøkelsen.

En del av de innsamlede opplysninger er ufullstendige mht diagnosegrunnlag og tidspunkt for 1. gangs sykdomstilfelle. De er oppgitt som behandlende lege for

.....

.....

Jeg håper at De vil være behjelpelig med supplerende opplysninger, jfr vedlagte skjema.

På forhånd takk for hjelpen!

Med vennlig hilsen

Inger Njølstad
prosjektleder/stipendiat

Tromsø, Nov 5 1991

Request for information for research purposes:

INCIDENCE TRENDS IN CARDIOVASCULAR DISEASES AND DIABETES AMONG MEN AND WOMEN 20 - 52 YEARS OLD IN FINNMARK

This is a follow-up of the cardiovascular surveys which the National Health Screening Service carried out in 1974 and 1977 in a collaboration with the Health Services of Finnmark and the University of Tromsø. The aim is to determine the incidence of myocardial infarction, stroke, and diabetes among those who participated. The incident cases will be linked to the risk factors registered. Incident cases are being detected from medical record files in hospitals, the Cause of Death Registry at Central Bureau of Statistics of Norway, and from a questionnaire to the participants. No information will be published that can be traced back to individuals.

The procject has been approved by the Data Inspectorate, the Directorate of Health, and by the Regional Committee of Reseach Ethics. The County Medical Officer in Finnmark is supporting the study.

Some of the medical information collected is not complete with respect to diagnostic criteria and the time of first event.

You have been named as the attending physician of

.....

.....

I hope that you will provide additional medical information, cf. the enclosed form.

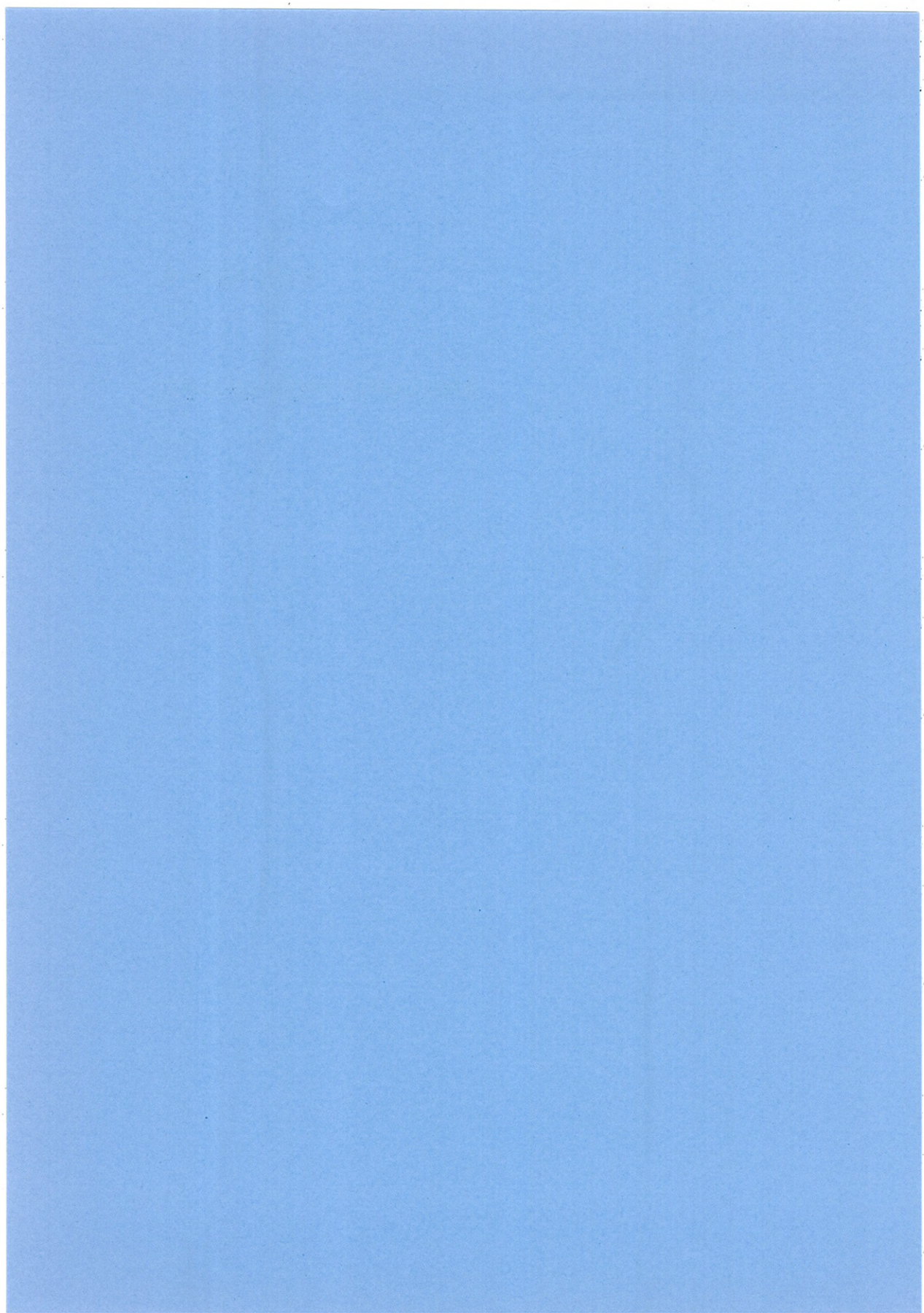
Thank you for your help!

With kind regards

Inger Njølstad
head of the project/research fellow

Appendix 4

Morbidity register data



MORBIDITY REGISTER DATA

Myocardial infarction

Date of :

first clinical MI, first silent MI, bypass surgery

Diagnostic criteria:

Symptoms

Cardiac enzymes; including maximum value of ASAT, CK, LDH

ECG changes; including type of MI (Q/non-Q wave, location of infarct)

Autopsy results

Risk conditions:

Antihypertensive treatment, angina pectoris by time of event.

Therapy:

Streptokinase (yes/no) at hospital admission

Cerebrovascular disease

Date of:

first stroke, carotis endarterectomy, cerebral aneurysm surgery

Diagnostic criteria:

Lumbar punction

Angiography

Cerebral tomography

Autopsy results

Risk conditions: Antihypertensive treatment, transient ischemic attack (TIA)

Diabetes mellitus

Date of diagnosis :

(midpoint estimation in cases where a time interval was reported)

Therapy:

Oral antidiabetic agents (year started)

Insulin (year started)

Risk condition: Antihypertensive therapy by time of diagnosis

Appendix 5

Tables 3 - 5

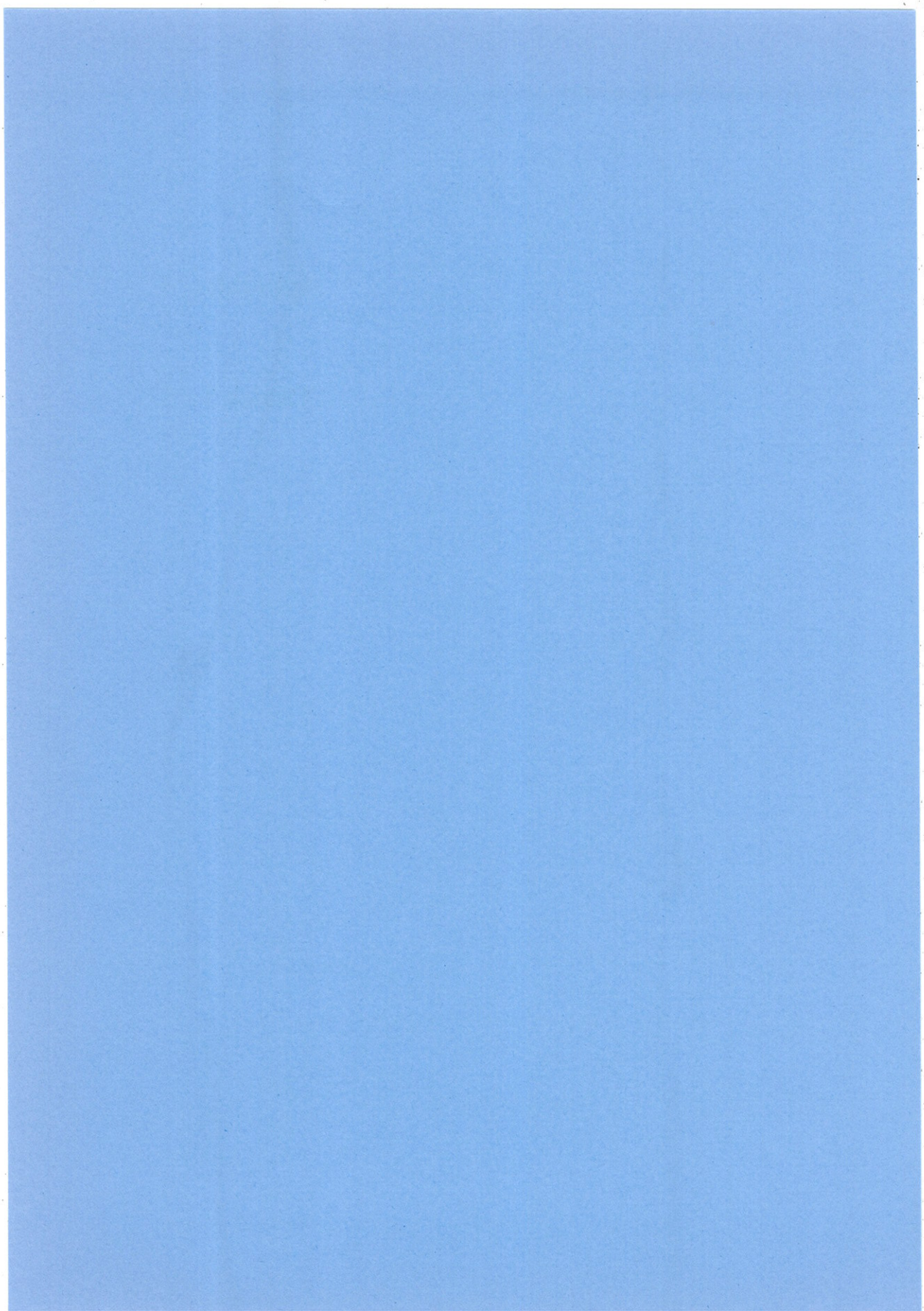


Table 3. Age-adjusted rates per 1,000 personyears of MI incidence, mortality from CHD and sudden death (CHD+ SD) (ICD-9 410-414, 798.1), and all cause mortality in two cohorts of men[§] without history or symptoms of CHD[§§] , followed from Finnmark 2 through 1989.

Ethnic group (person-years for death)	MI incidence			CHD+SD mortality			All cause mortality		
	Cases n	Rate/ 1,000*	Rate ratio*	Cases n	Rate/ 1,000*	Rate ratio*	Cases n	Rate/ 1,000*	Rate ratio*
Tverdal's definition									
Norse (21,407)	131	5.8	ref	41	1.8	ref	124	5.4	ref
Finnish (7,176)	53	7.3	1.26	14	2.0	1.11	51	7.0	1.29
Sami (5,835)	27	5.0	0.86	5	0.9	0.50	30	5.7	1.06
Paper VI's definition									
Norse I (11,412)	48	4.7	0.70	11	1.1	0.58	55	5.2	0.80
Norse II (21,931)	139	6.7	ref	41	1.9	ref	139	6.5	ref
Finnish (11,491)	83	7.5	1.12	22	2.0	1.05	83	7.4	1.14
Sami (11,903)	58	5.2	0.78	11	1.0	0.53	72	6.3	0.97

[§] age 35 years or more at Finnmark 2 [§§] self-reported at Finnmark 2

*age-adjusted by 5-years age groups; standard-population: participants in Finnmark 2

Table 4. Mortality from coronary heart disease (CHD) (ICD-9 410-414), coronary heart disease and sudden death (CHD + SD) (ICD-9 410 - 414 and 798.1) and all cause mortality in all men and men without a CHD history or symptoms. Comparison between the study population for Paper VI and a study by Tverdal.

Group of men (person years)	CHD mortality Cases n	Rate/ 1,000*	Adj RR**	CHD + SD mortality Cases n	Rate/ 1,000*	Adj RR**	All cause mortality Cases n	Rate/ 1,000*	Adj RR**
Tverdal's study									
All men									
Norse (30,228)	107	3.5	ref	-	-		248	8.2	ref
Finnish (10,299)	41	4.0	0.91	-	-		103	10.0	1.01
Sami (8,201)	14	1.7	0.38	-	-		57	7.0	0.65
Men without history									
Norse (27,242)	67	2.5	ref	-	-		183	6.7	ref
Finnish (9,067)	23	2.5	0.88	-	-		86	8.4	1.07
Sami (7,503)	6	0.8	0.24	-	-		42	5.6	0.63
Paper VI									
All men									
Norse I (16,553)	32	2.0	1.17	40	2.5	1.13	97	6.0	0.97
Norse II (30,950)	64	2.0	ref	83	2.6	ref	218	7.0	ref
Finnish (15,982)	43	2.6	1.10	46	2.8	0.88	137	8.4	1.07
Sami (16,271)	27	1.7	0.76	34	2.1	0.73	122	7.5	0.97
Men without history									
Norse I (15,058)	18	1.3	0.85	24	1.7	0.84	72	5.0	0.91
Norse II (28,175)	49	1.8	ref	66	2.4	ref	170	6.1	ref
Finnish (14,088)	32	2.3	1.14	34	2.4	0.87	104	7.3	1.11
Sami (14,637)	15	1.1	0.55	18	1.3	0.48	89	6.2	0.92

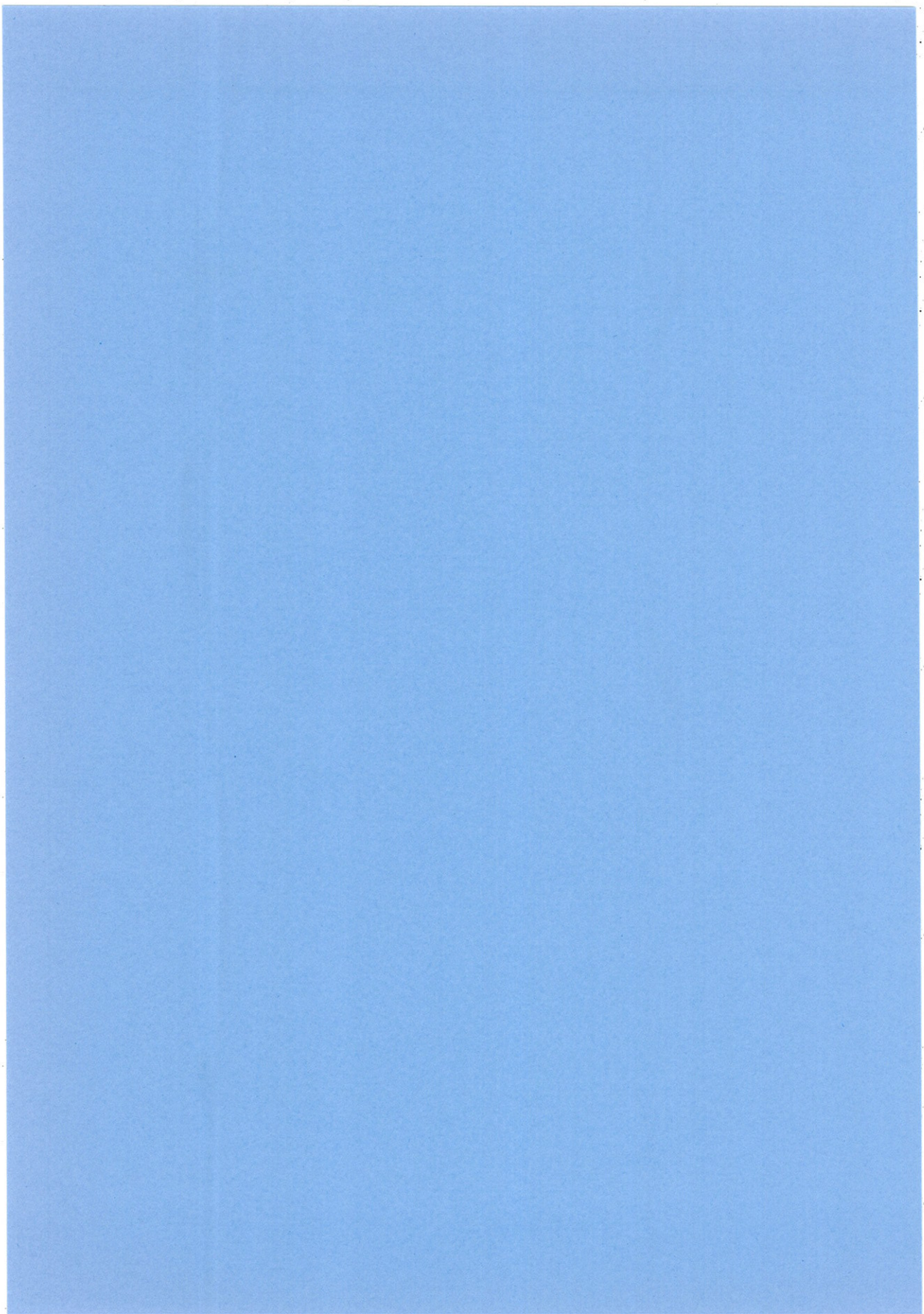
* Rates per 1,000 personyears adjusted for age ** Relative risk adjusted for age, total chol, triglycerides, systolic blood pressure, smoking (y/n)leisure physical activity, body mass index, height, family history of chd, and, in Tverdal's study: education, income

Table 5. Age-adjusted rates per 1,000 personyears of MI incidence, mortality from coronary heart disease and sudden death (CHD + SD) (ICD-9 410-414, 798.1), and all cause mortality, in subgroups of men included in Paper VI.

Group of men (p-yrs for MI incidence)	MI incidence Cases n	Rate/ 1,000	Adj RR*	Case fatality in first MI Cases of MI Total n	Fatal n	CFR§ %	CHD + SD mortality Cases n	Rate/ 1,000	Adj RR*	All cause mortality Cases n	Rate/ 1,000	Adj RR*
Total cohort												
Norse I (16,016)	89	5.8	0.98	89	27	30.3	32	2.0	0.95	85	5.3	0.91
Norse II (29,817)	199	6.7	ref	199	64	32.2	78	2.5	ref	201	6.6	ref
Finnish (15,342)	125	8.0	1.10	125	36	28.8	43	2.7	0.92	129	8.0	1.14
Sami (15,876)	96	6.1	0.85	96	29	30.2	33	2.1	0.75	118	7.2	1.06
Low risk men												
Norse I (14,796)	76	5.4	1.02	76	24	31.6	24	1.7	0.84	72	5.0	0.89
Norse II (27,608)	164	6.0	ref	164	56	34.1	65	2.3	ref	169	6.1	ref
Finnish (13,702)	96	7.0	1.10	96	26	27.1	34	2.4	0.93	104	7.4	1.14
Sami (14,360)	73	5.2	0.79	73	15	20.6	18	1.3	0.50	89	6.2	0.97
High risk men												
Norse I (1,220)	13	10.3	0.77	13	3	23.1	8	5.8	1.57	13	9.2	0.99
Norse II (2,209)	35	13.6	ref	35	8	22.9	13	4.4	ref	32	10.1	ref
Finnish (1,639)	29	17.6	1.00	29	10	34.5	9	4.1	0.82	25	12.8	0.97
Sami (1,516)	23	12.1	0.96	23	14	60.9	15	7.7	1.83	29	17.5	1.42

High risk men: men with angina pectoris, on antihypertensive treatment, or with symptoms of cardiovascular disease or lung disease
Low risk men: all other men.
* Relative risk adjusted for systolic blood pressure, total cholesterol, and smoking (yes/no); § CFR, 28-days' case fatality rate

Paper I



Smoking, Serum Lipids, Blood Pressure, and Sex Differences in Myocardial Infarction

A 12-Year Follow-up of the Finnmark Study

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Background Few epidemiological studies have investigated the relative importance of major coronary risk factors in the two sexes within the same study population. In particular, it is not clear whether smoking carries a similar risk of coronary heart disease in men and women.

Methods and Results The associations between smoking, serum lipids, blood pressure, and myocardial infarction were examined in a population-based prospective study of 11 843 men and women aged 35 to 52 years at entry. During 12 years, 495 cases of first myocardial infarction among men and 103 cases among women were identified. Myocardial infarction incidence was 4.6 times higher among men. The incidence was increased sixfold in women and threefold in men who smoked at least 20 cigarettes per day compared with never-smokers, and the rate in female heavy smokers exceeded that of never-smoking men. Multivariate analysis identified current smoking as a stronger risk factor in women (relative risk, 3.3; 95% confidence interval [CI], 2.1 to 5.1) than in men (relative risk, 1.9; 95% CI, 1.6 to 2.3). Among those under 45 years old at entry, the smoking-related sex difference was more pronounced (in women: relative risk, 7.1; 95% CI, 2.6 to 19.1) (in men: relative risk, 2.3; 95% CI, 1.6 to 3.2). Serum total cholesterol, HDL cholesterol, and systolic blood pressure were also highly significant predictors in both sexes.

Conclusions Smoking was a stronger risk factor for myocardial infarction in middle-aged women than in men. Relative risks associated with serum lipids and blood pressure were similar despite large sex differences in myocardial infarction incidence rates. (*Circulation*. 1996;93:450-456.)

Key Words • coronary disease • smoking • blood pressure • epidemiology • lipids

Serum total cholesterol, HDL cholesterol, smoking, and blood pressure are established major risk factors for coronary heart disease. They are often presumed to apply similarly to both sexes[1] despite the current threefold to fivefold higher coronary heart disease mortality among men in industrialized countries[2] and despite the scarcity of prospective studies published on risk factors in women. Among the few studies that actually had the potential to explore sex differences in risk factors within the same population, several had a limited number of coronary heart disease cases among women[3-6] or the inclusion of various "soft" disease manifestations in the coronary heart disease end point.[7]

The present study is the third prospective study[8,9] to examine relationships between smoking, other major risk factors, and myocardial infarction incidence in the two sexes. Furthermore, it is the only study restricted to a middle-aged population. Other large studies of smoking and coronary heart disease that included both sexes used mortality as an end point and lacked baseline information on other major risk factors.[10-15] Although thoroughly investigated in men, current knowledge of the relation between smoking and myocardial infarction in women stems mainly from case-control studies[14-16] and the prospective Nurses' Health Study.[17]

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We examined the relations between smoking, serum lipids, and blood pressure and the incidence of myocardial infarction in a population-based, 12-year follow-up of nearly 12 000 men and women aged 35 to 52 years at study entry. Sex-stratified analyses with validated and identical end points allowed comparisons of risk factor patterns in the two sexes. The dose-response relation between smoking and myocardial infarction and possible risk modifying effects of serum lipids and blood pressure was assessed.

Methods

Study Population

In 1977, all residents aged 35 to 52 years and a sample of those aged 20 to 34 years in Finnmark County in Northern Norway were invited to a cardiovascular screening. In all, 20 683 subjects were invited through a personal, mailed letter. The survey was organized by the National Health Screening Service, and details of study design and procedures have been published.[18,19] The present analysis is limited to age group 35 to 52 years, in which 12 785 subjects (87.8%) attended the screening. Eighty-eight men and 11 women were excluded from the follow-up because of verified myocardial infarction or hospitalization as a result of a severe attack of angina pectoris before screening. Persons with self-reported angina pectoris but no previous infarction-suspect attack (93 men and 71 women) were included, as were 33 male and 23 female diabetics. Baseline values of HDL cholesterol were missing in some subjects, leaving 11 843 subjects available for analysis. Almost 20% of these were of Finnish origin, 13% were Sami, and the rest were Norse (50%) or of mixed ethnicity.

Screening Data and Procedures

Enclosed with the letter of invitation was a questionnaire that covered history and symptoms of cardiovascular disease,

ethnicity, and smoking habits. Current and previous smokers were asked about the number of cigarettes smoked per day, number of years smoked, and, in case, time since smoking cessation. The questionnaire was to be completed at home and brought to the examination, where it was checked for consistency.

The examination included measurements of weight, height, and blood pressure and a nonfasting blood sample. Systolic and diastolic blood pressures were measured twice with the patient in the sitting position after 4 minutes' rest. The lower values were used in this analysis.

Details of the laboratory methods have been published.[19,20] Briefly, the serum was analyzed for total cholesterol and triglycerides within 2 weeks at Ullevål Hospital in Oslo. Total cholesterol was measured by the Liebermann-Burchard method[21] and triglycerides by a fluorimetric method.[21] HDL cholesterol was determined in frozen sera at the Institute of Medical Biology, University of Tromsø, after precipitation of LDL and VLDL with the heparin-manganese method.[20] Data on cross-sectional relations between HDL cholesterol and other variables in the Finnmark Study have been published previously.[20,22]

Pearson correlation coefficients between baseline serum lipids were generally similar in the two sexes. Strong intercorrelations were observed between serum triglycerides and total cholesterol (r=.4) and between serum triglycerides and HDL cholesterol (r=−.4). In women, there was no association between total cholesterol and HDL cholesterol (r=−.0), whereas a weak, positive correlation (r=.1, P<.001) was seen in men.

Follow-up and Case Identification

The subjects were followed from screening through December 31, 1989. The national 11-digit identification number enabled a linkage to the Causes of Death Registry at Norway Statistics and ensured a 100% follow-up on vital status. For persons with a death certificate diagnosis according to ICD ninth revision codes 410-414 and 798.1, additional information from the relevant hospital or physician was collected for case validation. Possible cases were also detected through hospital discharge diagnosis lists and a systematic screening of the medical record files in the only two hospitals in Finnmark. For persons with any mention of coronary heart disease, the medical record was reviewed by one of the authors (I.N.) to determine if and when a first event of myocardial infarction had occurred according to preset diagnostic criteria.

To detect ambulant and out-of-county nonfatal events, a questionnaire was sent to all 10 923 participants who were alive by June 1991. The Data Inspectorate did not allow questionnaires to be sent to relatives of deceased persons. Eleven percent of the study population had moved from Finnmark, but linkage to the Central Population Registry of Norway provided updated addresses regardless of area of residency. When a questionnaire reply indicated cardiovascular disease, medical record information from the relevant hospital or attending physician was obtained, with the respondent's written consent. The postal survey response rate was 82% among those who stayed and those who had moved from Finnmark. In all, 97% of the participants were followed up by means of the postal survey and/or official diagnosis registers and hospital record surveys.

Each case was classified as definite or probable myocardial infarction or as sudden death on the basis of the available data. Diagnostic criteria of myocardial infarction were based on symptoms, on ECG changes and changes in cardiac enzymes, and on autopsy results in fatal events, when performed (see "Appendix"). Not included as cases were 49 men and 34 women with uncertain myocardial infarction.

In 1987, 76% of the cohort members attended another county- and population-based cardiovascular screening in Finnmark. This allowed an assessment of changes in smoking habits during follow-up to be made.

TABLE 1. Baseline Characteristics in Men and Women: The Finnmark Study, 1977-1989

Variable	Men (n=6142)	Women (n=5701)
Age, y	43.4 (5.3)	43.4 (5.3)
Serum lipids, mmol/L		
Total cholesterol	6.69 (1.23)	6.52 (1.31)
HDL cholesterol	1.29 (0.35)	1.52 (0.36)
Triglycerides	1.82 (1.00)	1.36 (0.74)
BMI, kg/m^2	25.3 (3.1)	25.1 (4.4)
Blood pressure, mm Hg		
Systolic	134.3 (16.3)	129.5 (17.6)
Diastolic	86.1 (11.2)	81.9 (10.9)
Smoking habits		
Never-smokers, %	15.8	39.4
Former smokers, %	27.3	16.7
Current smokers, %	56.9	43.9
Cigarettes per day*	15.4 (7.6)	11.0 (5.7)
Prevalent conditions		
Angina pectoris, %	1.5	1.3
Diabetes, %	0.5	0.4
Treated hypertension, %	3.5	5.8

BMI indicates body mass index. Values are mean (standard deviations in parentheses) or percentages.
*In current cigarette smokers.
To convert cholesterol values to milligrams per deciliter, multiply by 38.76. To convert triglycerides to milligrams per deciliter, multiply by 88.57.

Data Analysis

Incidence rates were based on the number of person-years calculated from date of examination until first event of myocardial infarction or sudden death, with date of death from other reasons or December 31, 1989, as the censoring date. Age adjustment of incidence rates was performed directly on 5-year age groups with all attending men and women as the standard population. Sex differentials and other rate ratios of myocardial infarction incidence were assessed with the use of age-adjusted rates.

Some persons combined cigarettes with other smoking habits, leaving 108 men as exclusive pipe or cigar smokers. They were included as current smokers but were left out of analyses of quantity smoked.

Cox proportional hazards analysis was used for multivariate modeling. In models stratified by sex, the following continuous variables were considered: serum total cholesterol, HDL cholesterol and triglycerides, systolic blood pressure, and body mass index (weight/height^2). Daily smoking was included as a binary variable. Self-reported angina pectoris, diabetes, and medically treated hypertension were included as covariates, along with ethnic group. Relative risk estimates were determined for units of increase arbitrarily chosen to approximate the standard deviation for both sexes. Probability values less than .05 were regarded as statistically significant. All significance tests were two-tailed. The SAS statistical package version 6.07 was used.

Results

Baseline mean values and frequencies are presented in Table 1. Noteworthy are the high means of serum total cholesterol and the rather high prevalence of daily smoking in both sexes. Men had a more unfavorable risk profile, with higher mean total cholesterol, triglycerides, and blood pressure and lower HDL cholesterol. Fewer women than men were daily smokers, and female smokers consumed fewer cigarettes per day than their male counterparts. Among current nonsmokers, a larger proportion of men than of women were ex-smokers (63.1% versus 29.8%). Smokers had lower mean serum HDL

TABLE 2. Case Categories of Myocardial Infarction by Sex: The Finnmark Study, 1977-1989

	Men		Women	
Case Category	N	%	N	%
Definite myocardial infarction	290	58.6	55	53.4
Probable myocardial infarction	135	27.3	37	35.9
Sudden death	70	14.1	11	10.7
Total	495	100.0	103	100.0

$\chi_2^2 = 3.41$, $P > .05$.

cholesterol than nonsmokers, and the difference was larger in women (0.10 mmol/L [3.87 mg/dL], 6%) than in men (0.03 mmol/L [1.16 mg/dL], 2%) (data not shown).

During 12 years of follow-up (139 836 person-years), 495 first events of myocardial infarction and sudden death among men and 103 first events among women were identified (Table 2). There was no significant sex difference in case category distribution.

The relation between smoking and myocardial infarction incidence is shown in Table 3. In both sexes, markedly higher incidence rates were seen among the current smokers. Intermediate rates were observed among ex-smokers yet were significantly higher compared with never-smokers only in men (relative risk, 1.5; 95% confidence interval [CI], 1.1 to 2.4). In each smoking category, men had a higher rate of infarction than did women. However, the risk associated with increasing numbers of cigarettes was greater in women. Women who smoked 20 cigarettes per day or more had a nearly sixfold increased risk of myocardial infarction compared with never-smoking women, while the corresponding ratio in men was less than 3. This reduced the male-to-female ratio from 5.2 in never-smokers to 2.5 in heavy smokers, and the incidence rate among female heavy smokers exceeded that of never-smoking men. The population attributable risk of smoking was close to 50% in both sexes. If incidence rates in the total study population were the same as for never-smokers, 55 events among women and 236 events among men would not have occurred.

Table 4 presents the age-adjusted myocardial infarction incidence by sex according to smoking and serum total cholesterol. The cutoff points were chosen to divide the total study population into approximate quartiles. Among men, relative risks were similar in smokers and nonsmokers, and the smoker-to-nonsmoker ratios were 1.4 to 2.1 across all total cholesterol strata. Only one case of infarction occurred among nonsmoking women with baseline serum total cholesterol less than 5.7 mmol/L (220 mg/dL), and the lowest cutoff point was chosen at 6.5 mmol/L (250 mg/dL). Only at serum total cholesterol levels of 7.4 mmol/L (285 mg/dL) or more did the incidence rise in women, significantly in smokers only. The ratios between smoking and nonsmoking women were greater than for men at all levels of total cholesterol and ranged from 2.9 to 4.5.

When examining myocardial infarction incidence in relation to smoking and serum HDL cholesterol (Table 5), identical cutoff points were chosen in the two sexes. In all subgroups, the relative risk decreased significantly with increasing HDL cholesterol. The ratio between smokers and nonsmokers was less in men (1.6 to 1.9) compared with women (2.4 to 6.3) in all HDL cholesterol strata.

Table 6 presents relative risks adjusted for age first and then for several risk factors and confounders. Adjusted for age, all variables considered were highly significant predictors in both sexes except body mass index, which was significant in men (relative risk, 1.19; $P < .0001$) but not in women (relative risk, 1.12; $P = .0626$). In both sexes, serum triglycerides and body mass index became nonsignificant when adjusted for the other risk factors and were not included in the final model. The relative risk estimates of serum cholesterol, HDL cholesterol, and blood pressure were similar in the two sexes and were virtually unchanged after multivariate adjustment. Daily smoking made a striking exception to the rule. The relative risk associated with current smoking and adjusted for other risk factors was 3.3 (95% CI, 2.1 to 5.1) in women and 1.9 (95% CI, 1.6 to 2.3) in men. A further age-stratified analysis revealed apparent large age-related differences in relative risk estimates. Among women aged 35 to 44 years at study entry (median age at diagnosis, 49 years), the multivariate adjusted relative risk of smoking was 7.1 (95% CI, 2.6 to 19.1). This estimate was based on 31 cases, and the confidence interval was wide. The corresponding relative risk was 2.6 (95% CI, 1.6 to 4.3) in women 45 to 52 years old at entry (median age at diagnosis, 57 years). A much smaller age effect was observed among men. The relative risk estimate was 2.3 (95% CI, 1.6 to 3.2) in the younger

TABLE 3. Age-Adjusted Incidence Rates of Myocardial Infarction per 1000 Person-Years by Smoking Habits and Sex: The Finnmark Study, 1977-1989

	Men					Women					
Smoking Status	Person-Years	Cases, n	Rate per 1000	Rate Ratio	95% CI	Person-Years	Cases, n	Rate per 1000	Rate Ratio	95% CI	Male-to-Female Ratio
Never-smokers	11 698	33	3.63	1.0	ref	27 242	20	0.70	1.0	ref	5.2
Ex-smokers	19 601	107	5.40	1.6	1.1-2.4	11 527	10	0.96	1.4	0.6-2.9	5.6
Current smokers	39 913	355	8.62	2.4	1.7-3.4	29 855	73	2.55	3.6	2.2-6.0	3.5
Cigarettes per day											
1-9	6148	56	8.20	2.3	1.5-3.5	10 944	19	1.58	2.3	1.2-4.2	5.2
10-19	20 010	160	7.98	2.2	1.5-3.2	15 159	40	2.90	4.1	2.4-7.1	2.8
20+	12 427	125	10.30	2.8	1.9-4.2	3627	13	4.11	5.9	2.9-11.8	2.5
Unknown	80	1	...	...		125	1	...	...		
Pipe/cigar only	1248	13	10.34	2.8	1.5-5.4	...	...	...			
Total	71 212	495	7.05			68 624	103	1.52			4.6

CI indicates confidence interval.

TABLE 4. Age-Adjusted Incidence Rates of Myocardial Infarction per 1000 Person-Years, Relative Risk, and 95% Confidence Interval According to Serum Total Cholesterol and Smoking Status by Sex: The Finnmark Study, 1977-1989

	Daily Smoking							
	Yes				No			
Total Cholesterol, mmol/L	Cases, n	Rate per 1000	Relative Risk*	95% CI	Cases, n	Rate per 1000	Relative Risk*	95% CI
Men								
<5.70	29	3.68	1.00	ref	12	2.57	1.00	ref
5.70-6.49	59	6.14	1.58	1.01-2.47	25	3.26	1.48	0.74-2.94
6.50-7.39	104	9.08	2.30	1.52-3.47	39	4.80	1.97	1.02-3.80
7.40+	163	14.43	3.37	2.26-5.03	64	8.07	3.45	1.84-6.45
P, test for trend			.0001				.0001	
Women								
<6.50	22	1.79	1.00	ref	9	0.46	1.00	ref
6.50-7.39	13	1.75	0.87	0.43-1.76	7	0.61	1.07	0.38-3.01
7.40+	38	4.14	2.03	1.16-3.57	14	1.31	2.02	0.82-4.98
P, test for trend			.0092				.1153	

CI indicates confidence interval.
*Relative risk adjusted for age, systolic blood pressure, serum HDL cholesterol, ethnic group, treated hypertension, angina pectoris, and diabetes.

age group (median age at diagnosis, 48 years) and 1.7 (95% CI, 1.3 to 2.2) in the older age group (median age at diagnosis, 56 years). The relative risk estimates for serum lipids and blood pressure did not vary substantially between sex and age groups.

Discussion

This study confirms that smoking, serum lipids, and blood pressure are major risk factors for myocardial infarction in both sexes. The relative risks associated with serum lipids and blood pressure were generally similar, although men were overall 4.6 times more likely to have a myocardial infarction. However, one important sex-related difference was observed. Smoking had a much larger relative detrimental impact in women, and the risk gradient associated with increasing number of daily cigarettes was larger. Women smoking 20 cigarettes or more per day totally eliminated any "female advantage" relative to men who had never smoked. Smoking carried a particularly high risk in younger women.

This study used several sources to detect all incident cases of clinical myocardial infarction in the study population. However, an underregistration of nonfatal events must be expected, mainly among those who had moved from Finnmark and who did not respond to the postal survey in 1991. We estimated the total number of missed events to be less than 15. No attempt was made to register silent myocardial infarctions. Only fatal and nonfatal "hard" coronary heart disease manifestations were included in the end point, thus avoiding a potential source of misleading sex differentials. Long-term outcome of angina pectoris[23,24] and survival rate after a myocardial infarction[25] appear to be different in the two sexes. Mortality time trends and sex ratio patterns are very different for coronary and cerebrovascular disease.[26] This may result in diluted sex differentials if all cardiovascular disease is included in a single end point.

A sex-biased misclassification of smoking status due to sex differences in smoking cessation[2] during follow-up

TABLE 5. Age-Adjusted Incidence Rates of Myocardial Infarction per 1000 Person-Years, Relative Risk, and 95% Confidence Interval According to Serum HDL Cholesterol and Smoking Status by Sex: The Finnmark Study, 1977-1989

	Daily Smoking							
	Yes				No			
HDL Cholesterol, mmol/L	Cases, n	Rate per 1000	Relative Risk*	95% CI	Cases, n	Rate per 1000	Relative Risk*	95% CI
Men								
<1.00	104	13.00	1.00	ref	36	7.73	1.00	ref
1.00-1.49	208	8.91	0.77	0.60-0.97	79	4.69	0.70	0.47-1.05
1.50+	43	4.74	0.43	0.30-0.61	25	3.20	0.46	0.27-0.77
P, test for trend			.0001				.0029	
Women								
<1.00	8	4.75	1.00	ref	2	1.57	1.00	ref
1.00-1.49	42	2.93	0.72	0.33-1.56	20	1.22	1.13	0.25-5.07
1.50+	23	1.83	0.46	0.20-1.06	8	0.38	0.37	0.07-1.84
P, test for trend			.0337				.0171	

CI indicates confidence interval.
*Relative risk adjusted for age, systolic blood pressure, serum total cholesterol, ethnic group, treated hypertension, angina pectoris, and diabetes.

TABLE 6. Risk Factors for Myocardial Infarction, Adjusted Relative Risk, and 95% Confidence Interval by Sex: The Finnmark Study, 1977-1989

	Men			Women		
	Relative Risk			Relative Risk		
Risk Factor	Adj*	Adj†	95% CI	Adj*	Adj†	95% CI
Total C, 1 mmol/L	1.44	1.36	1.27-1.45	1.44	1.38	1.25-1.52
HDL-C, 0.4 mmol/L	0.67	0.74	0.66-0.83	0.59	0.70	0.56-0.89
Triglycerides, 0.8 mmol/L	1.20	...		1.39	...	
BMI, 3 kg/m^2	1.19	...		1.12	...	
Systolic BP, 15 mm Hg	1.24	1.20	1.11-1.29	1.39	1.35	1.18-1.55
Daily smoking (yes/no)	1.90	1.89	1.55-2.30	3.38	3.30	2.13-5.11

Adj indicates adjusted; CI, confidence interval; total C, total cholesterol; HDL-C, HDL cholesterol; BMI, body mass index; and BP, blood pressure.

*Relative risk adjusted for age.

†Relative risk adjusted for age, the other variables, and for ethnic group, treated hypertension, angina pectoris, and diabetes.

possibly could explain some of the observed differences between men and women. We were able to explore this hypothesis indirectly, because 76% of the present cohort attended another cardiovascular screening 10 years after study entry. More men than women reported to have quit smoking since the baseline examination (19.5% versus 16.0%; $P<.001$). No sex differential in smoking cessation was observed among those with angina pectoris or a myocardial infarction during the 10 years (32.0% in men versus 34.5% in women; NS). Thus, misclassification bias of the exposure variable is unlikely to explain the sex differentials.

Our finding of larger relative risks with increasing amounts smoked among women compared with men is in accordance with the Copenhagen City Heart Study,[9] which reported that the relative risk of first myocardial infarction was 9.4 in women and 2.9 in men who smoked at least 30 g tobacco per day compared with nonsmokers. According to Tverdal et al,[13] the relative risk of coronary death per 10 cigarettes per day was 1.8 in women and 1.2 in men. Data from case-control studies among young women of fatal[14] and nonfatal[15] myocardial infarction and from prospective studies confined to one sex also indicate that increasing amounts of smoking may have a more detrimental effect for women than for men. In the Nurses' Health Study, the risk of myocardial infarction increased with number of cigarettes, and a relative risk of 6.0 was observed among women smoking at least 25 cigarettes per day compared with never-smokers.[17] Among the men screened for the MRFIT study, cigarette smoking was a significant predictor for coronary death.[27] The risk increased with smoking amount but leveled off at 25 cigarettes per day, and the relative risk compared with nonsmokers did not exceed 2.5. On the other hand, in a number of publications, the Framingham Study reported no significant relation between smoking and coronary heart disease among women.[28] In the classic American[10] and British[11,12] studies of coronary mortality, the relative risks associated with daily smoking were similar in the two sexes. Different smoking frequencies, possible sex-specific smoking habits, different age distributions in the study samples, and different end points may all be related to the various study results. Our finding of a higher relative risk associated with smoking in younger rather than older women may contribute to an explanation of previous apparently conflicting study results.

Oral contraceptive use[15,29] could have contributed to the strong relation between smoking and myocardial infarction among women but is unlikely to have had any impact in this particular study population. Only three women were below the age of 45 at the time of the event. Median age at diagnosis in the younger age group was 49 years. Oral contraceptives appear to carry no residual risk for myocardial infarction after quitting.[29,30] Also, 55% of the women had their first myocardial infarction after 1984, when low-dose estrogen pills totally dominated the market in Norway.[31] It is uncertain whether oral contraceptives with <50 μg estrogen are associated with any elevated risk of coronary heart disease.[32]

Cigarette smoking probably increases myocardial infarction risk through long-term effects on atherosclerosis[33] and through readily reversible effects on hemostasis[34] and the hemodynamic system.[35] Intermediate incidence rates in ex-smokers relative to never-smokers in this and other studies[15,17] may be taken in support of a reversibility of smoking-induced risk effects. This may also partly explain why smoking appears to be strongly related to myocardial infarction in case-control studies,[14-16] while several prospective studies of coronary heart morbidity and mortality found weaker associations.[10-13] In longitudinal studies, smoking status at the time of the event is more prone to be misclassified than in case-control studies. This bias will be more pronounced as length of follow-up increases.

In this study, the role of systolic blood pressure as a major coronary risk factor[36] was confirmed. Serum total cholesterol was a strong independent predictor in both sexes. This is accordant with a number of coronary disease studies in men[37] and women,[38] but the importance of total cholesterol as a coronary risk factor has been questioned.[39-41] The multivariate model showed a risk increase in both sexes by almost 40% per mmol/L serum cholesterol. The relative risk increased similarly in smokers and nonsmokers across the total cholesterol strata, each sex considered separately. However, in women, an apparent threshold level was observed. The smoker-to-nonsmoker ratios were greater in women than in men at all levels of total cholesterol, again pointing to the hazardous effect of cigarette smoking for women. Few studies among younger women offer data on the combined effect of smoking and serum lipoproteins or history of hypercholesterolemia, and results were inconsistent.[15,17]

HDL cholesterol has been claimed as a more important risk factor for coronary heart disease than total cholesterol, especially in women,[38] while epidemiological studies disagree regarding the role of triglycerides.[42] In the present study, HDL cholesterol was a strong predictor for myocardial infarction in both sexes, and relative risks were similar. Serum triglycerides and HDL cholesterol were strongly inversely intercorrelated. Triglycerides were a significant predictor univariately and in models that included total cholesterol but became nonsignificant in both sexes as soon as HDL cholesterol was included in the model. Similar results were reported from several of the few prospective studies (mostly among men) in which both HDL cholesterol and triglycerides were accounted for,[6,43,44] but there are exceptions.[45]

In our study population, baseline serum HDL cholesterol was absolutely and relatively more reduced in female than in male smokers compared with nonsmokers of the same sex. This is in accordance with previous findings.[46-48] A reduced HDL cholesterol concentration in smokers may be related to sex hormone metabolism,[49-51] but to our knowledge, the apparently greater reduction in women has been only little explored.[48] Stratified by serum HDL cholesterol, the smoker-to-nonsmoker ratios of myocardial infarction were consistently greater in women than in men, and the largest ratio (6.3) was observed among women with serum HDL cholesterol above 1.50 mmol/L. Our data suggest that women who smoke heavily lose relatively more of the protection against myocardial infarction that is associated with HDL cholesterol than their male counterparts do. However, few cases in the female population reduce the power of subgroup analyses. Our data are consistent with a case-control study by Rosenberg et al,[15] which estimated the risk of infarction in women who smoked at least 25 cigarettes per day relative to nonsmoking women. In the low HDL cholesterol group (cutoff point at 40 mg/dL [1.03 mmol/L]), Rosenberg et al observed a relative risk of 4.7 compared with 14 in the high HDL cholesterol group.

Exogenous estrogen[1] and alcohol[52] are potential confounders that could not be assessed in this study, since no baseline data were collected. However, by 1987, only 2% of Finnmark women aged 45 to 62 years used exogenous estrogen.[53] More women (40%) than men (13%) were alcohol abstainers.[53] Among users, alcohol intake was more frequent in men. Alcohol raises HDL cholesterol,[48,52] and moderate alcohol intake appears to be associated with decreased risk of myocardial infarction.[52] Sex differences in drinking habits may therefore have influenced our findings.

Possible mechanisms behind the apparently greater hazard of smoking for women were not elucidated by this study. The antiestrogenic effect of cigarette smoking[50,51,54] could be the mediator that increases the risk of coronary heart disease in young female smokers relatively more than in men. Added to this is the greater reduction in HDL cholesterol in female smokers than in male smokers. The recent increase in smoking among young women in some countries[55] should be of great concern because it may have a serious effect on future coronary heart disease mortality.

Appendix

Myocardial Infarction Classification Criteria

One of the following must have occurred: (I) Definite myocardial infarction (MI) (290 men, 55 women): (1) dynamic ECG changes typical of MI and lasting more than 24 hours, with or without symptoms and/or cardiac enzyme changes, (2) typical (prolonged chest pain) or atypical symptoms (acute congestive heart failure, syncope) and serial cardiac enzyme elevation exceeding twice the upper limit of reference range, (3) in fatal event: autopsy proved recent MI or fresh coronary artery thrombus. (II) Probable MI (135 men, 37 women): (1) symptoms and a clinical development typical of MI, but death before a definite diagnosis could be given, and no autopsy performed (23 men, 4 women), (2) typical or atypical symptoms and equivocal ECG and/or serial cardiac enzyme elevation between upper and twice the upper limit of reference range (59 men, 18 women), (3) clinical episode with prolonged chest pain and persisting ECG changes typical of MI, but patient examined too late to record dynamic ECG changes and/or enzyme elevation (16 men, 3 women), (4) death certificate or other medical record diagnosis of coronary heart disease (CHD) (ICD-8 and ICD-9 410-414) or sudden death (ICD-8 795, ICD-9 798.1), with no indication of competing cause of death, but confirmative medical information unaccessible (37 men, 12 women). (Case validation was performed in 1990 to 1991, up until 17 years after death of study participants. Norwegian laws permit physician medical records to be destroyed 10 years after the death of the patient.). (III) Sudden death (70 men, 11 women): (1) death within 1 hour after acute collapse or chest pain or since last time seen without symptoms. No indication of competing cause of death (40 men, 5 women), (2) death more than 1 hour or unspecified time after last time seen alive, with no indication that other disease or condition may have caused death (30 men, 6 women); (IV) uncertain MI (49 men, 34 women): symptoms, ECG, and/or enzyme changes indicate MI but criteria of definite or probable MI not fulfilled. (Most cases were hospitalized persons with prolonged chest pain but whose initial ECG changes resolved within 24 hours.)

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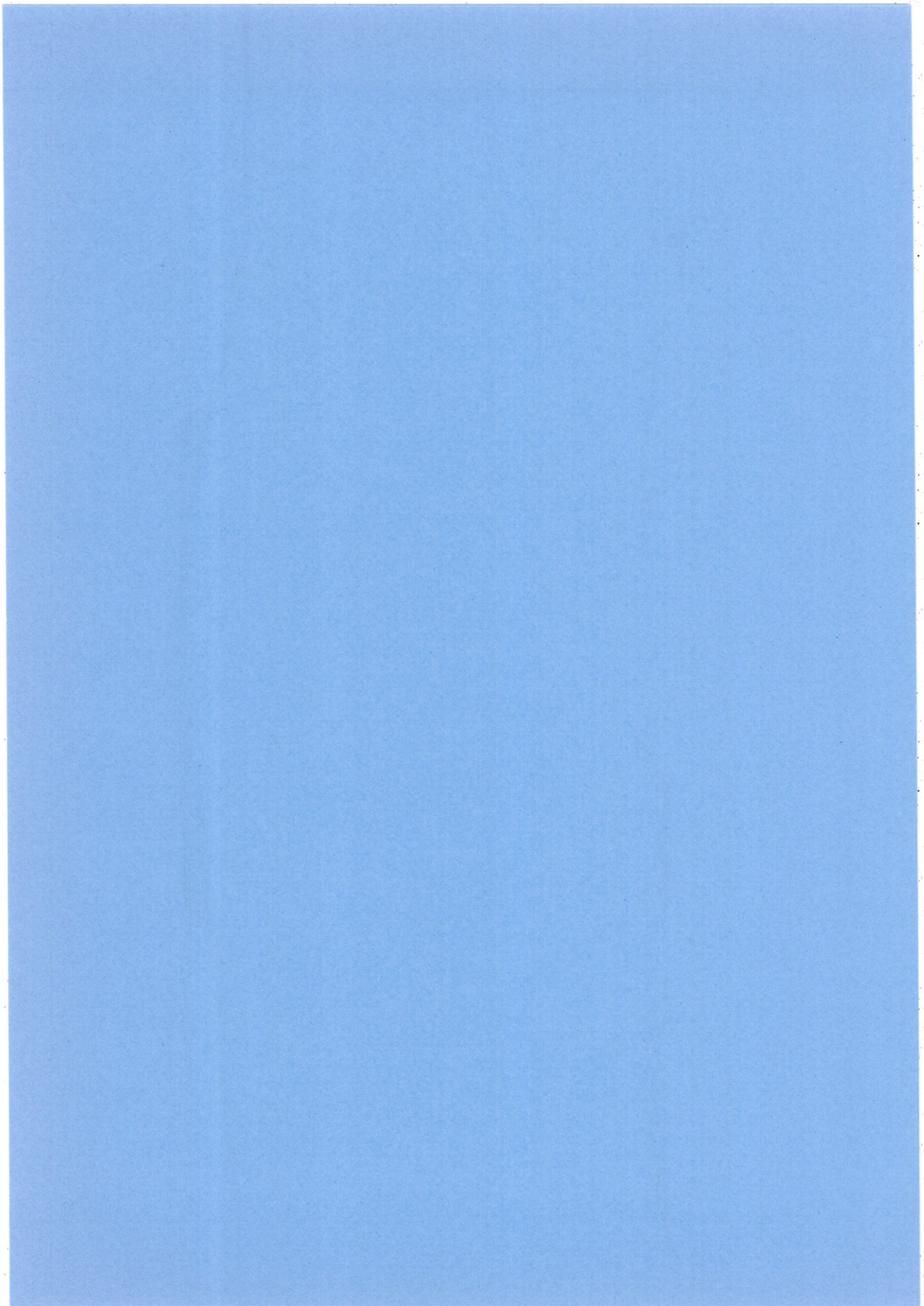
Paper II



PREINFARCTION BLOOD PRESSURE AND SMOKING ARE DETERMINANTS FOR A FATAL OUTCOME OF MYOCARDIAL INFARCTION

A prospective analysis from the Finnmark Study.

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ABSTRACT

Background: Serum cholesterol, blood pressure and smoking are the classic coronary risk factors, but what determines whether a myocardial infarction will be fatal or not?

Methods.- All inhabitants 35 to 52 years old in Finnmark county, Norway, were invited to a cardiovascular survey in 1974-75 and/or 1977-78. Attendance rate was 90.5%. A total of 6995 men and 6320 women were followed for 14 years with regard to incident myocardial infarction and sudden death. Predictors for 28-days' case fatality in first myocardial infarction were analysed.

Results.- During 186 643 person years, 635 events among men and 125 events among women were registered. Case fatality was 31.6% in men and 28.0% in women (P=.50). Among men (women), 28-days' case fatality was 24.5% (22.6%) at baseline systolic blood pressure (SBP) < 140 mmHg , 35.6% (28.2%) at SBP 140 - 159 mmHg , and 48.2% (41.7%) at SBP ≥ 160 mmHg.

Out of the 760 subjects with myocardial infarction, 348 died during follow-up. In Cox' regression analysis, SBP at baseline was strongly related to death (relative risk (RR) per 15 mmHg, 1.22; 95% confidence interval [CI],1.13-1.31). Daily smoking at baseline (RR, 1.40; 95% CI, 1.07-1.85), and age at time of event (RR per 5 years, 1.12; 95% CI, 1.01-1.24) were additional significant risk factors, while serum total and HDL cholesterol were unrelated to survival. Similar results were obtained with diastolic blood pressure in the model.

Conclusions.- Preinfarction blood pressure was an important predictor of case fatality in myocardial infarction. Daily smoking and age were additional significant predictors.

Great efforts have been made to reduce in-hospital fatality of myocardial infarction (MI), but more than 50% of coronary deaths occur suddenly and out of hospitals.[1-7] Therefore one should identify those factors which influence the risk of dying in a heart attack and - if possible - intervene on such factors before the event occurs. Smoking, serum cholesterol and blood pressure are the classic coronary risk factors, but so far no firm conclusion could been drawn as to their role for a fatal outcome in MI.[1,8-12] Factors that are known to influence case fatality are an advanced age,[1,3,12-15] a previous infarct,[1,10,12,14] and diabetes mellitus.[10,16-18] Some studies claimed women to fare better[11,14,17,18] or worse[19,20] than men after a major heart attack, while others found no independent effect of gender.[21-25] The size and location of an infarct are important immediate predictors for subsequent death.[9,26]

However, several studies on predictors for case fatality and survival in MI were hospital based.[9,15,16,18-21,25] Some studies included only subjects who initially survived a heart attack,[11,14,19,21] measured risk factors after the first event,[9,11,19] or included first and re-current attacks,[3,18,20] although a study among survivors may not reveal the most important causes of a fatal out-come in MI. Community based studies on risk factors for case fatality and survival after heart attacks are few. To our knowledge, only the Framingham Study[4,8] and the British Regional Heart Study[12] published data on predictors of case fatality in MI in a general population with standardized pre-event measurements of potential risk factors in the whole cohort. In the latter study, which comprised 7,735 middle aged men, physical inactivity and increased heart rate, arrhythmias, and antihyper-tensive treatment emerged as significant predictors, while blood pressure and smoking were not related to case fatality. In contrast, pre-event blood pressure was related to survival after first MI among men in Framingham.[8] Neither of the two reports included women.

The aim of this population based prospective study was to investigate cardiovascular risk factors which may influence survival in coronary heart disease (myocardial infarction and sudden death). Included were 13,315 middle aged men and women free from previous MI and stroke. The subjects were followed for 14 years with regard to MI incidence and mortality. Potential risk factors for a fatal outcome of MI were examined.

STUDY POPULATION AND METHODS

Study population

In Finnmark county, northern Norway, all residents 35 to 49 years old and a sample of those aged 20 to 34 years were invited to a cardiovascular survey in 1974. The survey was conducted by the National Health Screening Service, in cooperation with the University of Tromsø and local health authorities. Three years later the survey was replicated. Details of study design and procedures have been published.[27,28] A total of 22,612 persons were invited to the first and/or second survey through a personal, mailed letter, and 19,308 attended. The present analysis is limited to age-group 35 to 52 years, in which all residents were invited and 13, 412 men and women attended either or both surveys. Attendance rate was 90.5% in

this age group. Subjects with a previous MI (62 men, 6 women) or stroke (16 men, 13 women) were excluded, leaving 6,995 men and 6,320 women for the present analysis. Fifty percent were of Norse, 17% of Finnish, and 14% of Sami origin, while the remaining subjects were of mixed or unknown ethnicity.

Screening Data and Procedures

On the reverse of the invitation letter was a questionnaire which covered history and symptoms of cardiovascular disease, ethnicity, physical activity, and smoking habits. The questionnaire was to be completed at home and brought to the examination site, where it was checked for inconsistencies.

The examination included measurement of weight, height, and blood pressure, and a nonfasting blood sample. Systolic and diastolic blood pressure were measured twice after 4 minutes' rest and with the patient sitting, and were read to the nearest even mmHg. The lower values were used in this analysis.

Details of the laboratory methods have been published. [27,28] Briefly, the serum was analyzed for total cholesterol, triglycerides and glucose within 2 weeks at Ullevål Hospital in Oslo. Serum thiocyanate was measured in the second survey, and mean concentrations varied by self reported smoking status. The method has been described.[29] Serum HDL cholesterol was determined only at the second screening, at the Institute of Medical Biology, University of Tromsø. [30]

Follow-up and Case Identification

The subjects were followed from the first survey attended through December 31, 1989. The national 11-digit identification number enabled a linkage to the Causes of Death Registry at Statistics Norway, and date and causes of death are known for all deceased subjects. For persons with an underlying or contributory death certificate diagnosis which accorded to ICD ninth revision codes 410-414 or 798.1, additional information from the relevant hospital or physician was collected for case validation. Fatal and non-fatal cases were also detected through hospital discharge diagnosis lists and through a manual survey of the medical record files in the only two hospitals in Finnmark. For persons with any mention of ischemic heart disease, the medical record was reviewed by one of the authors (I.N.) to determine if and when a first MI had occurred. Diagnostic criteria were based on symptoms, on ECG changes and changes in cardiac enzymes, and on autopsy results in fatal event, if performed. Fatal events with a death certificate diagnosis of MI, but where additional confirmative information was inaccessible, were classified as probable MI. The classification criteria have been published.[31]

To detect ambulant and out-of-county nonfatal events, a questionnaire was sent to all 12,112 participants who were alive by June 1, 1991. Fifteen percent of the study population had moved from Finnmark, but the Central Population Registry of Norway provided updated addresses regardless of present area of residency. The response rate was 81% in those who stayed and those who had moved from Finnmark. When a questionnaire reply indicated cardiovascular disease, medical information was obtained from the relevant hospital or attending physician, with the respondent's written consent. A

total of 97% of the participants were followed up by means of the postal survey and/or diagnosis registers and hospital record surveys. The linkage to the Causes of Death Registry ensured a 100% follow-up on vital status.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The Norwegian Directorate of Health permitted access to medical record files.

Data Analysis

Incidence rates were based on the number of person-years from date of first examination until first event of MI or sudden death, with date of death from other reasons, emigration, or December 31, 1989 as the censoring date. Case fatality was calculated as death from any cause within 28 days after date of first MI (including sudden death). All 232 subjects who died within 28 days, died from cardiovascular disease. Among the 116 subjects who died later during follow-up, 89% had a been assigned a cardiovascular diagnosis (ICD-8 or ICD-9 390-438) as the underlying cause of death, and only 3 had no such diagnosis mentioned on the death certificate.

In 26 cases there was a discrepancy between date of onset of symptoms and hospital admission, with the latter registered by us as time of event. All those subjects survived for more than 28 days after symptom onset. One subject died on the 28th day after hospital admission and was assigned a nonfatal myocardial infarction in the present analysis.

Analysis of covariance was used for age-adjusted between-group comparisons of baseline variables. Cox's proportional hazards analysis was used for multivariable analysis of predictors of survival after a first MI. Of the 88 subjects who experienced a first MI during the last year and survived until the end of follow-up, all but 3 were alive by June 1, 1991, 1 ½ year after end of follow-up. One year survival curves were estimated by the Kaplan-Meier method.

Due to a high intercorrelation (Pearson's $r = .6$), either systolic or diastolic blood pressure was used in the multivariable modeling. Blood pressure, serum lipids and body mass index were entered as continuous variables, while smoking and diabetes, angina pectoris and antihypertensive treatment were entered as binary variables in the regression analysis. Leisure physical activity was self reported into one of four categories which best described the usual activity level: L1 - reading, watching TV or other sedentary activities, L2 - walking, bicycling or light physical activity for at least 4 hours per week, L3 - exercise to keep fit, heavy gardening etc for at least four hours per week, L4 - regular hard training. For this study, leisure activity was dichotomized into low (L1 and L2) and high activity (L3 and L4). Probability values less than .05 were regarded as statistically significant, and two-tailed significance tests were used. All statistical modeling was performed with the SAS statistical package version 6.09 (SAS Institute Inc, Cary, NC).

In two analyses, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were categorized according to the fifth report of Joint National Committee (JNC V) criteria[32] of normal pressure (SBP< 140 mmHg / DBP< 90 mmHg), mild hypertension (SBP 140-159 mmHg / DBP 90-99 mmHg) and moderate/severe hyper-

tension (SBP ≥160 mmHg / DBP≥ 100 mmHg).

RESULTS

During 186,643 person years of follow-up, 635 events of first MI and sudden death among men and 125 events among women were registered. Mean follow-up was 14 years. The age-adjusted incidence rate of MI was 6.6 and 1.4 per 1,000 person year in men and women, respectively. The distribution of case categories did not differ between the sexes (Table 1) although men had a 4.7 fold higher incidence of MI.

Subjects who suffered from MI during follow-up were significantly older at study entry than those who did not. Mean age at time of event was similar in the sexes (fatal MI: 53.5 years in men, 54.9 years in women; non-fatal MI: 52.6 years in men, 53.7 years in women). In Table 2, age- adjusted base line variables are shown for subjects without MI, and for those who suffered either a nonfatal or a fatal MI during follow-up. Systolic and diastolic blood pressure was significantly higher in those who died than in those who survived a heart attack. Angina pectoris was more common in women who died after an MI. No significant difference was observed in the age adjusted frequency of smoking between survivors and succumbers.

In Fig. 1, one year survival curves are shown for the 760 men and women who suffered from a first MI or sudden death. Overall, there was no gender difference in case fatality. In both sexes, 28-days' case fatality increased with age at time of event (Table 3) and with SBP (Table 4). Among the 163 men and 234 women who were treated for hypertension at study entry, 27.0% of the men and 7.3% of the women experienced a MI, as opposed to 8.7% and 1.8% respectively, among those not treated. However, in both sexes and in all blood pressure categories, case fatality was apparently lower in those on antihypertensive treatment. There were few cases, and the differences were not statistically significant (not shown in table). In an analysis similar to Table 4, DBP < 90 mmHg was associated with a case fatality rate of 24.4% in men and 20.8 % in women. At DBP 90-99 mmHg and DBP ≥100 mmHg, the case fatality rates in men (women) were 39.3% (37.5%) and 40.0% (38.1%), respectively. Exclusion of those on antihypertensive treatment did not alter the results (data not shown).

Those who experienced a first MI during follow-up were included in a Cox regression analysis of death /survival (Table 5). Because of few fatal cases among women, both sexes were included in the same model. Data on all covariates were available for 754 subjects, of whom 346 died before the end of follow-up. Blood pressure measured at screening was the most important predictor of death. For each 15 mmHg increase in SBP, the risk of dying increased by 22%. Daily smoking at study entry (relative risk [RR]1.40; 95% confidence interval [CI], 1.07 - 1.85) and age at time of event (RR per 5 years, 1.12; 95% CI, 1.01 - 1.24) were also significant predictors in the multivariable model. The risks associated with angina pectoris and diabetes mellitus were increased but statistical significance was not reached; there were few subjects with these conditions at base line and confidence intervals were wide. Leisure time

physical activity, body mass index, serum triglycerides and total cholesterol did not predict a fatal outcome of MI. Ethnic origin was unrelated to case fatality (risk estimates not shown). Similar results were obtained when DBP replaced SBP in the model. The relative risk of dying associated with a 10 mmHg increase in DBP was 1.20 (95% CI, 1.10-1.32). To examine the role of HDL cholesterol, a separate analysis was performed with the 1977 survey as base line and with 686 cases (255 fatal) included in the Cox' model. Adjusted for the variables as in Table 5 except triglycerides, the relative risk per mmol/L increase in HDL cholesterol was 1.03 (95% CI, 0.71 to 1.47).

COMMENT

A previous analysis showed that smoking, serum total and HDL cholesterol, and blood pressure were significant risk factors for MI incidence in both sexes in the Finnmark Study.[31] The present analysis demonstrates that blood pressure was a highly significant predictor of a fatal outcome of MI. In the multivariable model, daily smoking and age were also significant determinants, while serum total and HDL cholesterol were unrelated to 28-days' case fatality.

Case fatality in first events of MI was close to 30% in both sexes. Case fatality varies greatly between populations[33] and in different studies,[2,7,12,34] depending heavily on diagnostic criteria, whether nonfatal and fatal cases were detected to the same degree, and notably on whether the study was community or hospital based. Since age[1,3,12-15] and a previous MI or stroke[1,10,12,14] are major predictors, case fatality will depend on the study population composition. The case fatality of 31% among men in the present study was somewhat lower than the 36% case fatality in first events in the British Regional Heart Study.[12] However, that study included men who were up till 7 years older at study entry. Case fatality in the present study was lower than in a community based study among subjects aged 30-64 years in Oslo 1967-69,[2] which included first MIs and sudden, out-of-hospital deaths. Case fatality was also lower than in other community based studies comprising similar age groups, but those studies included first and recurrent attacks.[33,34] A great effort was made to detect non-fatal events among the participants in the present study. From the responses to the postal survey we estimated less than 20 non-fatal cases to be missed, while the linkage to the official Causes of Death Registry ensured that all deaths in the cohort were registered

Blood pressure, measured according to standardized procedures in a population survey setting, was the most important predictor of a fatal outcome of MI. Our finding supports the early study by Weinblatt et al,[1] in which men with pre-event SBP > 140 mmHg had a 1 month case fatality rate of 43%, while normotensive men had a case fatality rate of 21% after a first MI. Our finding contrasts that of the British Regional Heart Study, where no relation was seen between blood pressure and case fatality.[12] The case fatality rose steadily with systolic blood pressure categories in all age strata. Case fatality increased with increasing diastolic pressure, but an apparent threshold was observed with no further increase in case fatality between DBP 90-99 mmHg and DBP ≥ 100 mmHg. Blood pressure

treatment in clinical settings has mainly been directed at diastolic pressure. In the current study, subjects with untreated high blood pressure were referred back to general practitioners, who generally used DBP 100 mmHg as a cut-off point for treatment in the 1970s.[35] This raises the possibility that the apparent threshold effect may be due to treatment started after the screening. Interestingly, antihypertensive treatment was associated with an increased risk of MI in the Finnmark study, especially among men,[31] while the present analysis shows that antihypertensive treatment was associated with a non-significantly lower risk of death during follow-up after MI (RR 0.76; 95% CI, 0.50-1.14), adjusted for several risk factors including blood pressure. In analyses stratified by blood pressure level, the case fatality rate was non-significantly lower in those treated for hypertension in all systolic and diastolic blood pressure categories. In contrast, the British Regional Heart Study reported that antihypertensive treatment carried an increased risk of dying within 28 days after a heart attack (odds ratio [OR] 1.97; 95% CI, 1.06-3.67).[12] Arrhythmias and heart rate could have been confounders, but were probably not the reason for the discrepant findings given the lack of association between age adjusted blood pressure and case fatality in the British study. The difference in statistical methods (proportional hazards vs. logistic regression) had little influence since the majority (67%) in our study died within 28 days, and our results did not change materially when we used the logistic regression method.

The mechanisms which link an increased blood pressure to MI and sudden death are incompletely understood, but may involve endothelial damage, atherosclerosis, insulin resistance and left ventricular hypertrophy (LVH),[36] and ventricular arrythmias.[37] Blood pressure is the most important risk factor for LVH,[38] which in turn increases the risk for and worsens the prognosis after MI.[39,40] An inconsistent effect on LVH reversal may possibly explain why common antihypertensives have not reduced coronary heart disease as expected.[41] In the MRFIT trial, an excess coronary mortality, mainly sudden deaths which occurred during the first 2-3 years on drug therapy, was observed among hypertensive men in the special intervention group treated with diuretics,[42] while diuretic treatment apparently reduced case fatality in the EWPHE trial.[43] β-blockers protect against sudden death[44] and reinfarctions after an initial MI,[45] but their ability to reduce first MI and sudden death in hypertensives is unsettled and may possibly depend on whether the subject smokes or not.[46] In the Framingham study, antihypertensive treatment contributed independently to the risk of sudden death in men and women with or without prior coronary heart disease and with or without ECG abnormalities.[47] Our data were insufficient to examine whether exposure for antihypertensive treatment at time of the event may have influenced survival. No data on drug types used at study entry were available, but diuretics and β-blocking agents were the most common antihypertensives in a Finnmark subsample in 1977.[48] One may speculate, but cannot conclude whether differences in drug therapy may be a reason for discrepant findings between the population studies.

In this study, the risk of dying after a MI was significantly 40% higher in daily smokers after adjustment for other variables. In the British Regional Heart Study, the odds ratio was 1.64 (P=0.09) in current versus never-smokers.[12] The frequency of daily smoking differed between the studies (41% in Britain, 57% in Finnmark). Our finding apparently contradicts a pooled analysis of six recent MI trials (of thrombolytic treatment),[49] which demonstrated a more favorable prognosis after MI among smokers. The authors ascribed the improved survival among smokers to younger age and less severe coronary vessel disease. A cohort selection bias may be added: those who smoke may be more likely to die suddenly [4] and never make it into the trials, while inclusion of out-of-hospital coronary deaths will allow detection of the impact of smoking in the general population. On the other hand, changes in exposure (smoking cessation) during follow-up but before the event, may blur the associations between risk factor and outcome in a prospective cohort analysis.

Serum cholesterol did not influence case fatality in our study, consistent with studies in the general population[12] and among hypertensive subjects.[50] Leisure physical activity level did not influence survival, in contrast to the British Regional Heart Study where high physical activity was associated with lower case fatality (OR 0.53, $P < 0.05$).[12] A broader range of activity categories in the latter study may better have detected real contrasts between groups.

Thrombolytic therapy has become common in hospital treatment of MI since the late 1980s. Seven percent of the present cohort may have received streptokinase, but some of those subjects were included in the ISIS-2 trial,[51] and the actual treatment given is not known to us.

In conclusion, pre-event blood pressure measured up till 14 years before the event was strongly associated with case fatality in MI, while age and daily smoking were additional significant predictors in this population based study. The results emphasize the role of the classic coronary risk factors and point to the possibility of preventing coronary deaths by avoiding cigarette smoking. A better understanding of the pathophysiological links between blood pressure, coronary heart disease and drug effects is needed before one can conclude whether antihypertensive treatment improves or worsens the outcome of myocardial infarction.

ACKNOWLEDGMENTS

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Fig 1. One-year survival curves after first myocardial infarction in men and women: The Finnmark Study

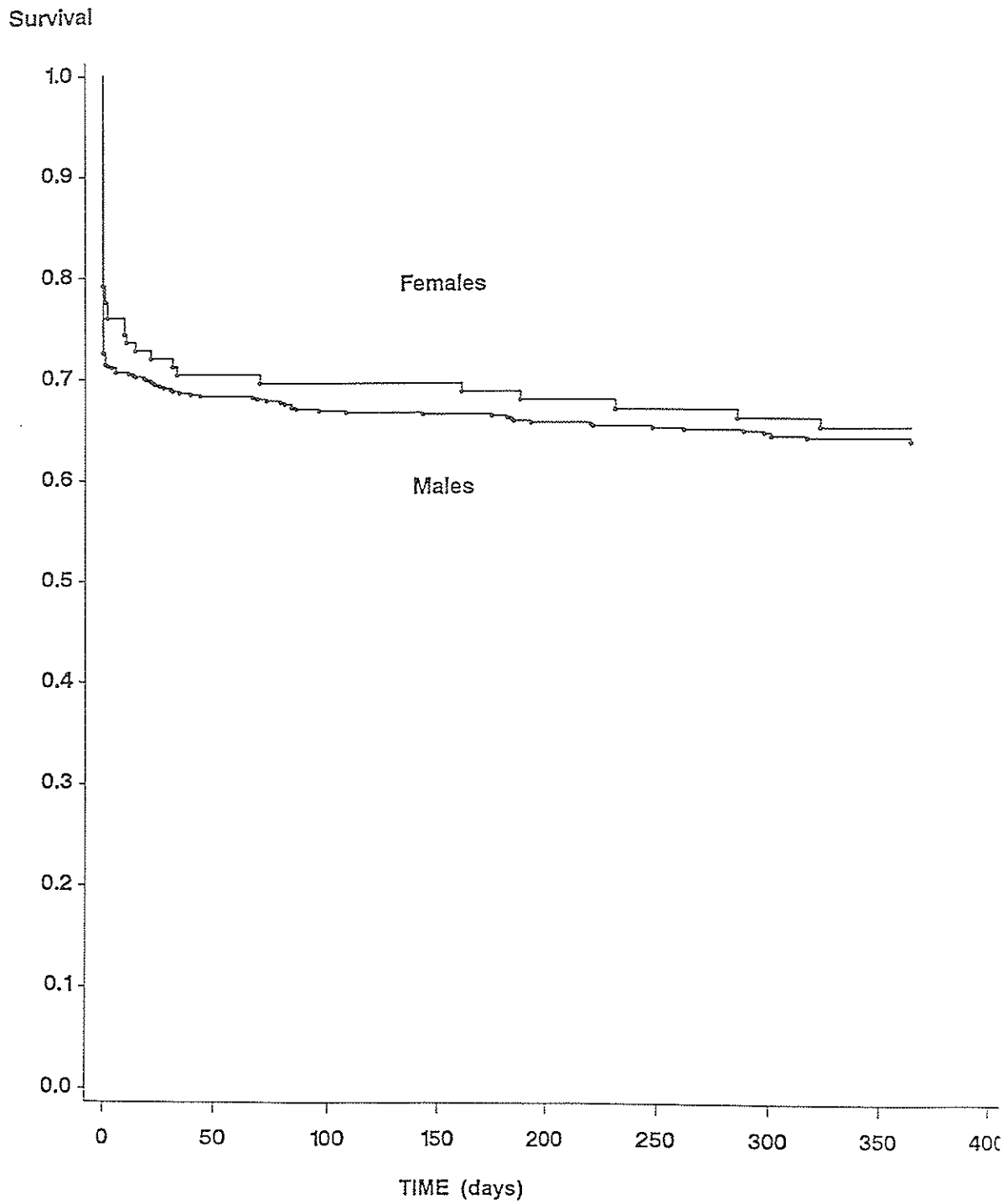


Table 1. 28-days' case fatality in first myocardial infarction (MI) in men and women by case category: The Finnmark Study 1974-1989

	Men			Women		
	All cases	Died within 28 days		All cases	Died within 28 days	
Case category	n	n	%	n	n	%
Definite MI	362	32	8.8	67	7	10.5
Probable MI	189	81	42.9	46	16	34.8
Sudden death	84	84	100.0	12	12	100.0
Total	635	197	31.0	125	35	28.0

MI indicates myocardial infarction

Table 2. Age-adjusted baseline variables in men and women 35 to 52 years who did and did not develop a fatal* or nonfatal myocardial infarction (MI): The Finnmark Study 1974-1989

	No MI	Nonfatal MI	Fatal MI	*P* for fatal vs nonfatal MI
MEN	*n=6360*	*n=438*	*n=197*	
Age at entry (years)**	41.2	43.4	44.3	0.020
Blood pressure (mmHg)				
Systolic	133.6	136.6	144.3	0.000
Diastolic	83.5	86.8	89.7	0.002
Serum (mmol/L) [mg/dL]				
Total cholesterol	6.80 [263.0]	7.40 [286.2]	7.25 [280.4]	0.185
HDL cholesterol***	1.30 [50.3]	1.17 [45.2]	1.22 [47.2]	0.096
Triglycerides	1.88 [166.5]	2.19 [194.0]	2.24 [198.4]	0.629
Body mass index (kg/m^2)	25.1	25.9	25.5	0.235
Daily smoking (%)	62.1	74.6	79.8	0.206
Antihypertensive treatment (%)	1.9	7.2	5.0	0.093
Angina pectoris (%)	1.0	3.1	4.1	0.302
Diabetes (%)	0.4	0.8	1.4	0.301
WOMEN	*n=6195*	*n=90*	*n=35*	
Age at entry (years)**	41.3	44.1	45.0	0.293
Blood pressure (mmHg)				
Systolic	128.8	138.1	145.4	0.023
Diastolic	79.7	83.6	89.6	0.003
Serum (mmol/L) [mg/dL]				
Total cholesterol	6.58 [254.4]	7.63 [295.1]	7.61 [294.3]	0.961
HDL cholesterol***	1.53 [59.2]	1.33 [51.4]	1.40 [54.1]	0.391
Triglycerides	1.37 [1213]	1.95 [172.7]	1.67 [147.9]	0.058
Body mass index (kg/m^2)	25.0	26.4	25.8	0.531
Daily smoking (%)	46.6	74.0	75.1	0.905
Antihypertensive treatment (%)	3.5	14.4	6.9	0.047
Angina pectoris (%)	0.8	4.0	8.0	0.034
Diabetes (%)	0.2	1.0	-	-

* Died within 28 days after MI * *not adjusted for age ** * in 5878 men and 5452 women in 1977 survey

Table 3. 28-days' case fatality rate (CFR) in men and women by age at first myocardial infarction (MI): The Finnmark Study 1974-1989

	Men			Women		
Age at first MI (years)	MI n	CFR n	%	MI n	CFR n	%
35-39	14	3	21.4	1	0	-
40-44	54	17	31.5	4	0	-
45-49	130	44	33.8	25	7	28.0
50-54	186	45	24.2	41	12	29.3
55-59	184	58	31.5	34	8	23.5
60-64	67	30	44.8	20	8	40.0
35-64	635	197	31.0	125	35	28.0

MI indicates myocardial infarction; CFR, 28-days' case fatality rate

Table 4. 28 days' case fatality rate (CFR) in first myocardial infarction (MI) by systolic blood pressure and age in men and women: The Finnmark Study 1974-1989

	Systolic blood pressure (mmHg)								
	- 139			140-159			160 -		
Age at first MI	MI n	CFR n	%	MI n	CFR n	%	MI n	CFR n	%	*P* for trend
MEN										
35-44	41	12	29.3	21	6	28.6	6	2	33.3	
45-54	171	36	21.1	102	33	32.4	43	20	46.5	
55-64	136	37	27.2	79	32	40.5	36	19	52.8	
Total	348	85	24.4	202	71	35.1	85	41	48.2	<.0001*
										<.0001**
WOMEN										
35-44	3	0	-	2	0	-	0	0	-	
45-54	35	9	25.7	21	6	28.6	10	4	40.0	
55-64	24	5	20.8	16	5	31.3	14	6	42.9	
Total	62	14	22.6	39	11	28.2	24	10	41.7	.0878*
										.1324**

MI indicates myocardial infarction; CFR, 28-days' case fatality rate

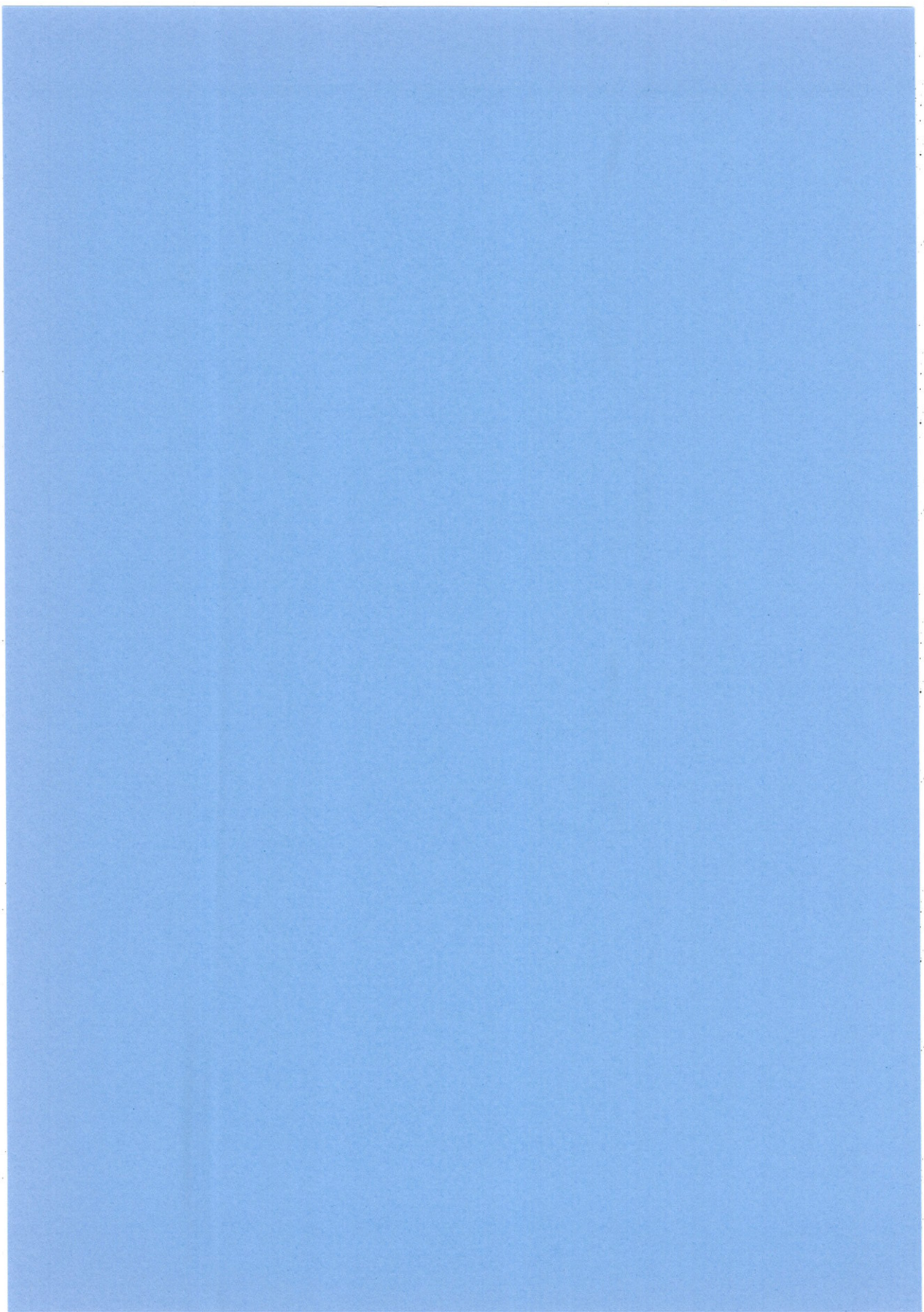
* crude ** age adjusted

Table 5. Predictors of death after first myocardial infarction (MI).* Adjusted relative risk and 95% confidence interval (CI): The Finnmark Study 1974-1989

Risk factor	Relative risk	95% CI
Sex, m/f	1.08	0.79 - 1.44
Age at MI, 5 years	1.12	1.01 - 1.24
Systolic BP, 15 mmHg	1.22	1.13 - 1.31
Total cholesterol, 1mmol/L	1.02	0.95 - 1.11
Triglycerides (log)	0.94	0.74 - 1.18
Body mass index, 1 kg/m^2	0.98	0.96 - 1.01
Daily smoking, y/n	1.40	1.07 - 1.85
Physical activity,low/high	1.01	0.72 - 1.42
Treated hypertension, y/n	0.76	0.50 - 1.14
Angina pectoris, y/n	1.43	0.90 - 2.27
Diabetes mellitus, y/n	1.97	0.86 - 4.49

* 754 cases (346 fatal) with data on all variables, adjusted for variables shown and ethnicity

Paper III



Trends in incidence and case fatality in myocardial infarction:
The Finnmark Study 1975-1989

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ABSTRACT

Objectives. To investigate trends in incidence and case fatality in myocardial infarction (MI) from 1975 to 1989 in a defined cohort.

Design. Population based cohort study.

Setting. In Finnmark county, northern Norway, 11 604 men and women born 1925 to 1939 were followed for 15 years. Surveys in 1974/75, 1977/78 and 1987/88 were used to assess changes in cardiovascular risk factors during follow-up.

Main outcome measures. Sex specific incidence and 28-days' case fatality in first MI, determined for three 5-year birth cohorts and three 5-year periods.

Results. 614 first events of MI in men and 123 events in women were registered. Despite an ageing cohort, the overall 28-days' case fatality did not increase, and was non-significantly lower in the last (30.7%) compared to the preceding (34.4%) period among men. The incidence rates in 46-50 year old men were 7.1, 6.4, and 7.1 per 1000 personyears in the three 5-year periods. Corresponding case fatality rates were 27.1%, 41.0% and 19.1% (χ^2 =7.64, d.f.=2, p=0.0219). Hypertension treatment increased greatly, while smoking frequency and mean serum total cholesterol changed heterogeneously in the different sex- and age-groups during follow-up. Thrombolytic therapy and coronary bypass grafting did not have a large impact on incidence and case fatality.

Conclusions. A stable level in major cardiovascular risk factors coincided with an unchanged MI incidence among 46-50 year old men, while case fatality decreased by 30% (p=0.2641) from 1975 to 1989. Overall case fatality remained quite constant despite an ageing cohort, possibly due to favourable risk factor changes in some age groups and improved secondary prevention.

KEY WORDS

cohort study, population based, coronary heart disease, incidence, case fatality, epidemiology

A dramatic increase in coronary mortality was observed in industrialized countries after World War II [1]. In some countries, the peak was reached in the 1960s. In Norway, the coronary mortality among middle aged men rose sharply and culminated around 1970 [2]. Thereafter, the mortality declined and is now back to the level of the early 1950s. A similar, but less pronounced trend was seen among women [2]. Within Norway, Finnmark county in the north has had the highest coronary mortality since regional data became available [3], although coronary mortality among 30 - 69 year old men in Finnmark decreased by 21% from 1966 to 1987 [4]. No official registry of incident myocardial infarction (MI) exists, and it is not known whether the decreasing mortality is due to a decreasing incidence, a lower case fatality, or both.

The purpose of this study was to analyze trends in incidence and case fatality in MI in a cohort of middle aged men and women in Finnmark. In a population based study we registered first events of MI and sudden death during 15 years (1975 to 1989) among 11,604 subjects born from 1925 to 1939. Incidence and case fatality rates were determined for three 5-year birth cohorts and three 5-year time periods. Changes in risk factor levels during follow-up were assessed from repeated measurements performed 10 years apart in a subcohort.

MATERIAL AND METHODS

Study population

All 35 to 49 years old residents in Finnmark county and a sample of those aged 20 to 34 years, were invited to a cardiovascular survey in 1974/75. Three years later the survey was replicated. Residents who did not attend, and subjects who immigrated after the first survey, were invited to the second. A total of 22,612 persons were invited to the first and/or second survey through a personal, mailed letter. The surveys were conducted by the National Health Screening Service, in cooperation with the University of Tromsø and local health authorities. Details of the study design have been published [5, 6]. The present analysis is limited to those born from 1925 to 1939. In this age group, all residents were invited and 11,670 subjects (91.6%) participated. Sixty-six subjects were excluded from follow-up because of a verified MI. Out of 11,604 subjects available for analysis, 36% were of Sami or Finnish origin, and the rest were of Norse (48%) or unknown ethnicity.

A third population based survey which was carried out in 1987/88, included the present birth cohorts. Out of 8,674 participants born from 1925 to 1939 (82% of those invited), 7,887 subjects participated in survey II and survey III and were used to assess population changes in risk factors during follow-up.

Survey data and procedures

On the reverse of the invitation letter was a questionnaire that covered history and symptoms of cardiovascular disease, ethnicity, physical activity, and smoking habits. The questionnaire was to be completed at home and brought to the examination site, where it was checked for inconsistencies. An identical questionnaire was used in all surveys, and each municipality was visited at the same time of the year in the three surveys. The examination

comprised measurements of weight, height, and blood pressure, and collection of a nonfasting blood sample. Details of screening procedures and laboratory methods have been published [5-7]. The serum was analyzed for total cholesterol and triglycerides at Ullevål Hospital in Oslo. Between survey II and survey III, laboratory methods changed from the Liebermann-Burchard method for total cholesterol and a fluorometric method for triglyceride determination into enzymatic methods using a Technicon Autoanalyzer. An extensive test program revealed systematic differences between the methods, and allowed correction formulas to be developed [6]. This article presents values from survey I and II transformed to the enzymatic methods in survey III. HDL cholesterol was determined only at survey II, and was analyzed at the Institute of Medical Biology, University of Tromsø, by the cholesterol esterase cholesterol oxidase method after precipitation of LDL and VLDL with heparin and manganese [7]. In the two first surveys, blood pressure was measured twice with one minute's interval, after 4 minutes' rest and with the subject seated. A mercury sphygmomanometer (Erca) was used. Survey III used an automatic device (Dinamap 845 XT, Tampa, Florida) and three measurements, which yielded approximately 4 mmHg lower readings for mean diastolic pressure and almost similar systolic pressure as the manual method [8]. The deviations were not uniform throughout the blood pressure distributions, and no correction formula has been developed.

Follow-up and case identification

The participants were followed from January 1, 1975 through December 31, 1989. The national 11-digit identification number enabled a linkage to the Causes of Death Registry at Statistics Norway. Date and causes of death are known for all deceased subjects. For persons with an underlying or contributory death certificate diagnosis which accorded to International Classification of Diseases (ICD) 8th and 9th revision codes 410-414 or 795 (ICD-8) or 798.1 (ICD-9), medical information was collected from the relevant hospital or attending physician for case validation. Possible cases were also detected through hospital discharge diagnosis lists and through a survey of the medical record files in the Finnmark hospitals. When cardiovascular disease was indicated, the medical record was reviewed by one of the authors (I.N.) to determine if and when a first MI had occurred. The diagnosis of MI was based on symptoms and changes in ECG and cardiac enzymes, and on autopsy results, if performed. Classification criteria have been published [9]. Maximum serum concentrations of cardiac enzymes were recorded in those who had been hospitalized because of suspected MI. Streptokinase treatment in the acute phase of MI was recorded. Events of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty (PTCA) were registered.

Altogether 15% of the cohort emigrated from Finnmark during follow-up. To detect ambulant and out-of-county nonfatal events, a questionnaire was sent to all 10,484 participants who were alive by June 1, 1991. The Central Population Registry of Norway provided updated addresses regardless of current area of residency. The questionnaire response rate was 81%. When a questionnaire reply indicated

cardiovascular disease, medical information was obtained from the relevant hospital or physician, with the respondent's written consent. In all, 97% of the participants were followed up by means of the postal survey and/or diagnosis registers and hospital record surveys. The linkage to the Causes of Death Registry ensured a 100% follow-up on vital status.

For this analysis, all incident events which occurred from January 1, 1975 through December 31, 1989, were included. Baseline data on risk factors were taken from the first survey attended. Three subjects had a nonfatal heart attack before the baseline examination. The same validation criteria were used for events which occurred before and after the examination.

The study was approved by the Regional Committee for Medical Research Ethics and by the Norwegian Data Inspectorate. The Directorate of Health permitted access to medical record files.

Data analysis

The total cohort was divided into three successive 5-year birth cohorts (1925 to 1929, 1930 to 1934, and 1935 to 1939). The birth cohorts were almost equally sized, and the ethnic composition was similar in all subgroups. Incidence rates were based on person-years from January 1, 1975 until first event of MI or sudden death, with date of death from other reasons, emigration or December 31,1989 as the censoring date. Incidence rates were calculated separately for three successive 5-year periods (1975 to 1979, 1980 to 1984, and 1985 to 1989). Case fatality was calculated as death from any cause within 28 days after first MI. For reasons of brevity we used the term "age-specific" for subgroups defined by age at the onset of each 5-year period. All analyses were sex specific.

RESULTS

Baseline variables by birth cohort and sex are shown in Table 1. Blood pressure and serum lipids increased by age; more so in women than in men. Mean sex difference in systolic blood pressure was 8.4 mmHg in the youngest, but only 1.3 mmHg in the oldest cohort. In the oldest cohort, women were more obese, and had an average serum cholesterol similar to men. More men than women were daily smokers, but the age trends were opposite in the sexes.

During 15 years, 614 events of first MI among men and 123 events among women were registered. The overall age-adjusted incidence rate was 7.0 per 1,000 person-years in men and 1.5 per 1,000 person-years in women. Age-, sex-, and birth-cohort-specific incidence rates are shown in Table 2 for the three 5-year periods. The incidence increased over the 15 years' time span in all three birth cohorts. There was no indication of a decline in age specific incidence (Table 2). The incidence rate in 46-50 year old men was 7.1, 6.4 and 7.1 per 1,000 personyears in the three time periods, respectively. The 28-days case fatality rate showed a somewhat different pattern (Table 3). The overall case fatality rate increased slightly from the first to the second 5-year period and decreased thereafter, but the differences were not significant. Among men, the MI case fatality rate was lower in 1985-89 than in the preceding period for all three birth cohorts, but the difference was significant only for men born 1930-

34 (χ^2 =5.41, d.f.=1, p=0.0201). Case fatality in 46-50 year old men changed significantly over the three time periods (χ^2 =7.64, , d.f.=2, p=0.0219). From the middle to the last 5-year period, case fatality decreased from 41.0% to 19.1% (p=0.0065) in this age group, but the difference in case fatality between the first period (27.1%) and the last period (19.1%) was not significant (p= 0.2641).

A total of 631 men and 256 women died during follow-up; for 239 men and 41 women the death certificate stated ICD-8 codes 410-414 or 795, or ICD-9 codes 410-414 or 798.1 as the underlying cause of death (data not shown).

Table 4 shows the extent of coronary bypass grafting and PTCA in the cohort. Almost 70% of the interventions were performed during the last 5-year period. Sixtyseven subjects (50.4%) underwent surgery or angioplasty after a verified MI. The percentage was similar in the three periods, and only one subject was operated within 4 weeks after the heart attack. Eight subjects (7 men and 1 woman) developed an infarct in connection with bypass surgery or later. Altogether 14 (10 men, 4 women) of the 133 bypass-operated subjects died during follow-up.

None of the hospital-admitted subjects who suffered from MI before 1986 received streptokinase. Among 244 men with a first MI during 1986-89, 58 died out of hospital or did not survive long enough in hospital to have an ECG recorded. Eight subjects were admitted one or several days after symptom onset. Out of the remaining 178 subjects who could have been eligible for thrombolytic treatment, 46 men may have received streptokinase; one died within 28 days (2.2%).There were 12 deaths among those who were not treated, but 6 were in a terminal phase at hospital admission; thus a maximum of 6 could theoretically have been "saved" by streptokinase (data not shown).

Among the 421 subjects with MI who had adequate serial measurements of cardiac enzymes taken, maximum serum aspartat aminotransferanse (ASAT) concentrations were non-significantly lower in 1975-79. Median values among men were 158.5 U/L in the first, 188 U/L in the second and 180 U/L in the third 5-year period. Corresponding values in women were 113.5 U/L, 175.5 U/L and 186 U/L. No consistent differences in maximum ASAT concentrations were noted between smokers and non-smokers or between different age groups (data not shown).

To assess whether changes in coronary risk factors during follow-up may have influenced MI incidence and case fatality heterogeneously, we analyzed changes in major risk factors by birth cohort, first between survey I and survey II, and then between survey II and survey III. Table 5 presents means and frequencies of risk factors, and the absolute and relative changes over 3 years in those who participated in survey I and survey II. Total cholesterol declined in all subgroups except the oldest women. Diastolic blood pressure increased by 2-3 mmHg in all groups. Smoking frequency declined, but less so among women. Table 6 presents risk factor levels in those who participated in survey II and survey III. During the ten years, smoking frequency decreased by 16% in the oldest, but was unchanged in the youngest birth cohort. Despite the increase in age, serum total cholesterol changed very little in men, in contrast to women who had up to

12% increase in serum cholesterol. A great increase in antihypertensive treatment was reported by both sexes and all age groups. By 1987, 21% of the women and 15% of the men who were 58-62 years old, were treated for hypertension.

Taken together, Tables 5 and 6 show that the smoking frequency declined in all subgroups between 1974 and 1987. The absolute and relative decrease was greater among men than women, and greater in the older than in the youngest birth cohort within each sex. In contrast, time trends for serum total cholesterol diverged in the sexes. Mean serum cholesterol increased by 0.38 mmol/L in the oldest and by 0.55 mmol/L in the youngest women, but decreased by 0.26 mmol/L in the oldest and increased by 0.10 mmol/L in the youngest men.

DISCUSSION

Secular trends in mortality from coronary heart disease are a function of age, period and cohort effects, which all act in combination. Further, a decrease in coronary mortality may be artificial, due to changes in classification criteria, or real, reflecting a decrease in coronary disease incidence, better treatment and increased survival in those with "soft" disease manifestations, or a lower case fatality in myocardial infarction. An analysis based on official mortality statistics showed that from 1977-82 to 1983-87 the coronary mortality in Finnmark declined by 29% among men aged 40-49 years, by 16% among those aged 50-59 years, and by 16 % among those aged 60-69 years [4]. The present study showed that age-specific 5-year incidence rate of MI in 46-50 year old men in Finnmark was unchanged from 1975-79 to 1985-89, while the case fatality rate decreased from 27% to 19% in the same age group. However, there were few cases in each stratum and the 30% reduction in case fatality was not significant.

Data for case validation and classification were collected from medical records in retrospect. New and more sensitive diagnostic tools came into clinical use but were not used for case validation to ensure consistent classification criteria. Silent MIs were not included in the coronary endpoint, and we avoided therefore a possible time dependent detection bias due to more widespread use of ECG in general practice during follow-up. Several sources were used to detect incident cases of MI. However, an underregistration of nonfatal events must be expected, mainly among those who had moved from Finnmark and who did not respond to the postal survey in 1991. We estimated the number of missed events to less than 20.

The lower 28-days' case fatality during the last part of the 1980s was unexpected, since case fatality in MI increases with age [10,11]. There was no reduction in case fatality in a study among men in New Zealand 1974 to 1986 [12], while case fatality decreased from 38% in 1985 to 27% in 1990 among men in the MONICA-Toulouse population [13]. Changes in major risk factors explained the decline in coronary mortality between 1972 and 1986 among men in Finland [14], but from 1986 to 1992 the observed decline was larger than predicted, suggesting that improved treatment or other factors not accounted for became relatively more important for mortality reduction from the late 1980s.

A change in hospitalization policy towards minor infarcts could have introduced a time dependent detection bias and would contribute both to a higher incidence and to a lower case fatality. Our data do not indicate that this was the case. Serum concentrations of cardiac enzymes indicate infarct size and predict mortality [15]. We registered maximum ASAT values, and whether adequate serial measurements had been taken. Although the enzyme measurements were not standardized, neither according to time since symptom debut nor by laboratory method, the data indicate that maximum ASAT values tended to be lower in the first 5-year period, especially among women.

As expected in a cohort study, the crude incidence of MI increased with duration of follow-up. The study allowed an assessment of age-specific 5-year incidence rates through all three time periods only for those who were 46-50 years at the beginning of each 5-year period, and this incidence did not change.The finding was surprising, given the downward trend in age specific coronary mortality known from vital statistics [2-4]. However, smoking was the strongest risk factor for MI incidence in this study population, while blood pressure and serum lipids were additional independent predictors [9]. On the other hand, blood pressure was the most important predictor of case fatality, and smoking, but not serum cholesterol, was an additional independent predictor [16]. Could changes in risk factors during follow-up influence incidence and case fatality heterogeneously in the different birth cohorts and time periods? In the age groups under study, several changes in major cardiovascular risk factor levels took place from the first to the second survey, and from the early part (1977) to the late part (1987) of follow-up. Overall, the frequency of daily smoking decreased from 55% to 49% between among men, and from 42% to 40% among women from 1977 to 1987, but age differences were seen. The smoking frequency was reduced by 17% in those born from 1925 to 1929, but remained unchanged among men and women who were 10 years younger. As a result, the smoking frequency in the oldest birth cohorts dropped below the percentage among the younger subjects, and the age specific smoking frequency among 46-50 years old subjects remained approximately 50% throughout follow-up. Similarly, mean serum cholesterol in men remained unchanged in the two oldest but increased by 0.20 mmol/L in the youngest birth cohort from survey II to survey III. Thus, total cholesterol in 46-50 years old men decreased by less than 0.10 mmol/L from 1977 to 1987. The change in methods of blood pressure measurement with no systematic intermethod validation precludes an assessment of changes in blood pressure to be made.

Atherosclerosis is the main intermediate step in the causal chain for myocardial infarction, with blood cholesterol as the major determinant. The lag time from risk factor exposure to disease incidence in not firmly established, neither is the lag time for risk reduction when intervention is introduced. In recent trials the clinical effect of lipid lowering medication in high risk individuals was seen within 6 months after randomization in primary [17] and within 2 years in secondary [18] prevention. Based on 40-49 year old men in the Seven Countries' Study, Rose [19] estimated the lag time for serum cholesterol, blood pressure and

smoking exposure to overt coronary disease to more than ten years in the general population. However, a rapid decline in coronary mortality in Norway during World War II, followed by an immediate and great increase after 1945 [20], indicate that when great changes in diet and lifestyle occur, the lag time is much shorter than would be expected if the risk was mediated only through long term atherosclerosis. The stable levels of total cholesterol and smoking among 46-50 year old men correspond with the unchanged MI incidence in the same age group in this study.

Hypertension treatment increased during follow-up. By 1987, 15% of the men and 21% of the women who were born from 1925 to 1929, were on blood pressure lowering medication. No data were collected on type of drug used. In a sub-sample, diuretics (60%) and β-blockers (30%) were the main classes of antihypertensives used in 1977 [21]. β-blockers prevent reinfarctions and sudden death after an initial infarct [22], while the primary prevention effect in hypertension treatment is uncertain [23]. A twofold sales increase in β-blockers in Finnmark from 1976 to 1988 [24,25] reflects an absolute increase in hypertension treatment, a shift from other antihypertensives and diuretics to β-blockers, and increased use of β-blockers in secondary prevention. In the mid-1980s there was also a shift to low-ceiling and potassiumsaving diuretics [26] following studies that focused on risk of sudden death associated with high doses of thiazides [27,28]. In this study population, hypertension treatment was associated with an increased risk of MI [9], but with a (non-significantly) reduced risk of dying after the heart attack [16]. No firm conclusions can be drawn, but increased hypertension treatment and changes in treatment policy may have affected incidence and case fatality heterogeneously in the three time periods.

The effect of PTCA on the outcome of angina pectoris is uncertain [29], but coronary artery bypass grafting improves long term survival in some types of coronary artery disease [30] and may influence coronary mortality in the general population. However, those intervention procedures were not of importance for the endpoints in this study. One half of the surgical interventions were performed on patients who had already suffered from MI. Most operations were performed during the last 5-year period, and could therefore at best contribute to lower MI incidence in the last rather than in the preceding time periods. The delay from MI to bypass surgery was too long to affect case fatality; only one man was operated within 4 weeks.

Thrombolytic therapy came into regular clinical practice towards the end of follow-up. The main admitting hospital participated in the ISIS-2 trial, which included patients from March 1985 to December 1987 [31]. Because of the blinded randomization, the actual treatment is not known for all 46 subjects whom we recorded as treated. Most coronary deaths occurred suddenly and out of hospitals or shortly after hospital admission.We estimated that a maximum of 6 subjects could have been "saved" during the last 5-year period, had streptokinase been administered to all subjects theoretically eligible for treatment; thus, streptokinase cannot have had a major impact on case fatality in this study. Aspirin was used in ISIS-2 [31], but was not unequivocally recommended for pre-hospital admission treatment until the 1990s in

Norway [32]. We did neither record such treatment nor other acute phase therapy regimens for which treatment policy changed during follow-up and which may have influenced case fatality positively [33] or negatively [34].

In conclusion, this study showed that overall case fatality rate in MI in Finnmark remained quite constant from 1975-79 to 1985-89 in this cohort in spite of ageing. Coronary risk factors remained stable and no trend in the incidence of MI was observed among 46-50 year old subjects from 1975-79 to 1985-89. The case fatality rate in this age group was nonsignificantly lower in 1985-89 than in preceding periods. Improved secondary prevention may possibly have contributed to a lower case fatality and a lower coronary mortality without affecting the incidence of MI.

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Table 1. Baseline characteristics in men and women by year of birth.
The Finnmark Study, 1974 or 1977.

	Year of birth		
	1925-1929	1930-1934	1935-1939
MEN	*n=2025*	*n=2031*	*n=2070*
Age (year)	47.2	42.3	37.3
Blood pressure (mmHg)			
Systolic	137.0	133.9	132.8
Diastolic	85.4	84.1	82.2
Serum lipids (mmol/L)			
Total cholesterol	7.11	6.95	6.65
Triglycerides	1.94	1.93	1.90
HDL cholesterol	1.31	1.30	1.27
Self reported			
Daily smoking (%)	67.1	66.7	60.4
Antihypertensive treatment (%)	4.0	2.1	1.6
WOMEN	*n=1875*	*n=1746*	*n=1857*
Age (year)	47.2	42.3	37.2
Blood pressure (mmHg)			
Systolic	135.7	129.3	124.4
Diastolic	82.9	79.7	77.3
Serum lipids (mmol/L)			
Total cholesterol	7.07	6.65	6.34
Triglycerides	1.54	1.39	1.31
HDL cholesterol	1.52	1.53	1.51
Self reported			
Smoking (%)	46.5	47.5	48.8
Antihypertensive treatment (%)	6.6	3.8	1.7

Table 2. Incidence rates of myocardial infarction (MI) per 1000 person years by sex and year of birth. The Finnmark Study, 1975-1989

	Time of event								
	010175-311279			010180-311284			010185-311289		
Year of birth	Person years	MI n	Rate/ 1000	Person years	MI n	Rate/ 1000	Person years	MI n	Rate/ 1000
MEN									
1925-29	9865	70	7.1	9207	96	10.4	8316	127	15.3
1930-34	10003	39	3.9	9561	61	6.4	8973	105	11.7
1935-39	10264	22	2.1	10032	26	2.6	9637	68	7.1
Total	30132	131	4.4	28799	183	6.4	26926	300	11.1
WOMEN									
1925-29	9272	15	1.6	9041	23	2.5	8707	30	3.5
1930-34	8706	3	0.3	8599	11	1.3	8384	20	2.4
1935-39	9247	2	0.2	9138	10	1.1	8997	9	1.0
Total	27225	20	0.7	26779	44	1.6	26088	59	2.3

Table 3. 28-days case fatality rate in myocardial infarction by sex and year of birth. The Finnmark Study, 1975-1989

	Time of event								
	010175-311279			010180-311284			010185-311289		
	Total*	Fatal	CFR**	Total*	Fatal	CFR**	Total	Fatal	CFR**
Year of birth	n	n	%	n	n	%	n	n	%
MEN									
1925-29	70	19	27.1	96	31	32.3	127	54	42.5
1930-34	39	13	33.3	61	25	41.0	105	25	23.8
1935-39	22	5	22.7	26	7	26.9	68	13	19.1
Total	131	37	28.2	183	63	34.4	300	92	30.7
WOMEN									
1925-29	15	3	20.0	23	8	34.8	30	12	40.0
1930-34	3	0	-	11	4	36.4	20	2	10.0
1935-39	2	0	-	10	2	20.0	9	3	33.3
Total	20	3	15.0	44	14	31.8	59	17	28.8

* Total, total number of myocardial infarction; ** CFR, case fatality rate

Table 4. Coronary artery bypass grafting and PTCA* in men and women by year of birth and 5-year periods. The Finnmark Study, 1975-1989

	Year of intervention procedure					
	1975-79		1980-84		1985-89	
Year of birth	Total n	After MI ** n	Total n	After MI* * n	Total n	After MI** n
MEN						
1925-29	4	2	18	9	26	10
1930-34	3	1	10	6	27	15
1935-39	3	2	3	1	17	12
1925-39	10	5	31	16	70	37
WOMEN						
1925-29	1	-	1	-	9	4
1930-34	-	-	2	2	7	1
1935-39	-	-	2	1	-	-
1925-39	1	1	5	3	16	5

* PTCA, percutaneous transluminal coronary angioplasty

** Coronary artery bypass grafting/PTCA performed after a first myocardial infarction (MI) had occurred

Table 5. Characteristics at survey I (1974) and survey II (1977), difference and percent change between surveys by sex and year of birth in subjects who participated in both surveys. The Finnmark Study

	Year of birth											
	1925-1929				1930-1934				1935-1939			
	1974	1977	Diff I-II	%chg	1974	1977	Diff I-II	%chg	1974	1977	Diff I-II	%chg
MEN (n)		1683				1592				1545		
Total cholesterol (mmol/L)	7.14	6.88	- 0.26	- 4	6.99	6.86	- 0.13	- 2	6.67	6.58	- 0.09	- 3
Systolic BP (mmHg)	136.7	137.5	0.8	0.6	134.2	134.4	0.2	0.1	132.9	132.8	- 0.1	- 0.1
Diastolic BP (mmHg)	84.9	87.8	2.9	3	83.9	86.9	3.0	4	81.6	84.9	3.3	4
Daily smoking (%)	67.0	59.2	- 7.8	- 12	66.1	58.1	- 8.0	- 12	60.6	52.7	- 7.9	- 13
Antihypertensive treatment (%)	3.8	6.6	2.8	74	1.8	4.3	2.5	139	1.5	2.5	1.0	67
WOMEN (n)		1578				1490				1506		
Total cholesterol (mmol/L)	7.06	7.15	0.09	4	6.67	6.53	- 0.14	- 2	6.38	6.21	- 0.17	- 3
Systolic BP (mmHg)	135.8	136.7	0.9	0.7	129.5	130.6	1.1	0.8	124.7	125.0	0.3	0.2
Diastolic BP (mmHg)	82.8	85.6	2.8	3	79.6	82.5	2.9	4	77.2	79.8	2.6	3
Daily smoking (%)	44.8	40.2	- 4.6	- 10	47.3	44.5	- 2.8	- 6	49.5	45.5	- 4.0	- 8
Antihypertensive treatment (%)	6.9	12.2	5.3	77	3.8	6.1	2.3	61	1.6	2.9	1.3	81

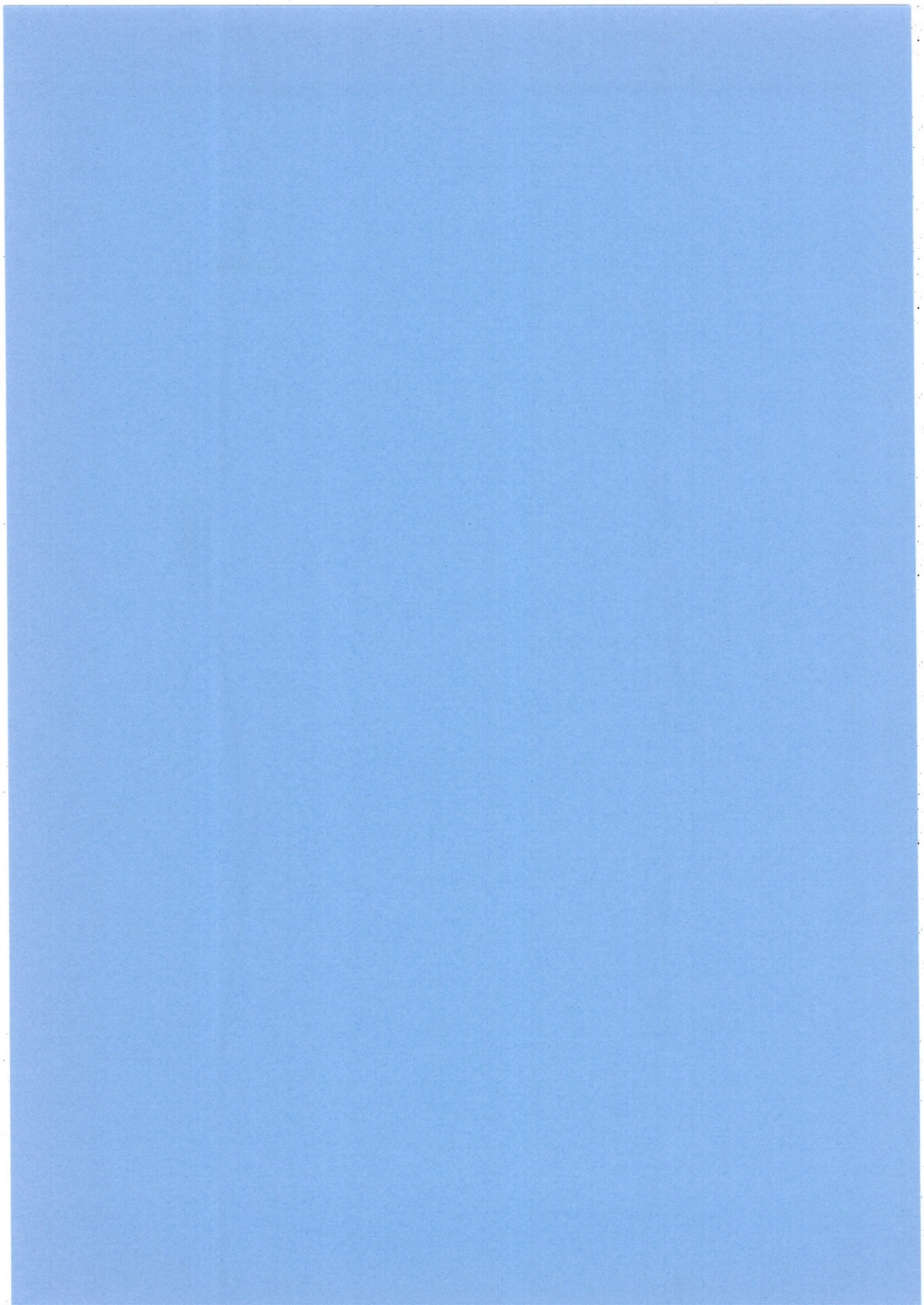
Diff, difference; %chg, per cent change from survey I to survey II

Table 6. Characteristics at survey II (1977) and survey III (1987), difference and percent change by sex and year of birth in subjects who participated in both surveys. The Finnmark Study

	Year of birth											
	1925-1929				1930-1934				1935-1939			
	1977	1987	Diff II-III	%chg	1977	1987	Diff II-III	%chg	1977	1987	Diff II-III	%chg
MEN (n)		1352				1332				1258		
Total cholesterol (mmol/L)	6.85	6.88	0.03	0.4	6.84	6.88	0.04	0.6	6.57	6.77	0.20	3
Blood pressure (mmHg)												
Systolic	136.9	143.6			133.4	140.0			132.6	136.7		
Diastolic	87.5	85.6			86.2	82.4			84.7	84.2		
Daily smoking (%)	57.4	47.7	- 9.7	- 17	56.5	50.3	- 6.2	- 11	51.2	50.2	- 1.0	- 2
Antihypertensive treatment (%)	5.6	15.3	9.7	173	3.9	10.4	6.5	167	2.4	8.2	5.8	242

Diff. difference; %chg. per cent change from survey II to survey III

Paper IV



Body Height, Cardiovascular Risk Factors, and Risk of Stroke in Middle-aged Men and Women

A 14-Year Follow-up of the Finnmark Study

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Background Geographical differences in stroke mortality are not fully explained by population variations in blood pressure and antihypertensive treatment. Some studies have suggested that factors connected with health and nutrition in early life may be related to stroke morbidity and mortality. Body height is a sensitive marker for socioeconomic conditions, but results are conflicting as to whether height is associated with stroke.

Methods and Results In a population-based study, we investigated stroke incidence in relation to height and classic cardiovascular risk factors. A total of 13 266 men and women 35 to 52 years of age were followed for 14 years, and 241 first events of stroke were registered. Stroke incidence was 36% higher in men. Height was inversely related to stroke in a dose-response manner. Per 5-cm increase in height, the age-adjusted risk of stroke was 25% lower in women ($P<.0001$) and 18% lower in men ($P=.0007$). Systolic blood pressure and daily smoking were positively associated with stroke in both sexes, while serum triglyceride level was a significant risk factor in women only (relative risk per 1 mmol/L, 1.3; 95% CI, 1.1 to 1.5). The associations remained after adjustment for possible confounders and were also observed in certain subtypes of stroke.

Conclusions The results are consistent with the theory that factors influencing early growth as well as adult lifestyle factors contribute to cerebrovascular disease in adult age. (*Circulation.* 1996;94:2877-2882.)

Key Words • risk factors • stroke • epidemiology • cerebrovascular disorders

Official Norwegian statistics show that stroke mortality is higher in northern Norway than farther south.[1] Curiously, there are no corresponding geographical differences in blood pressure distributions in the general population.[2] Additional stroke determinants that are unevenly distributed between the northern and southern regions therefore should be sought. One such factor is body height,[3] which is determined both by genetics and by nutrition and health status in early life.[4]

Height is inversely associated with all-cause and cardiovascular mortality.[5] In England, stroke mortality varies inversely with average body height in different regions,[6] but the association between height and stroke is as yet not clarified.[7-15] From observations in Norwegian counties, Forsdahl[16,17] postulated poor childhood living conditions followed by prosperity to be associated with a high cardiovascular mortality in adult age. Studies from England and Wales support the view that unfavorable factors in fetal and infant life may be important for later coronary heart disease and stroke.[18]

In the present study we had the opportunity to assess height as a risk factor for stroke in addition to classic cardiovascular risk factors and ethnicity in a free-living population of more than 13 000 men and women who were 35 to 52 years old at study entry.

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Methods

Study Population

In 1974, a cardiovascular disease study was initiated in Finnmark, the northernmost county in Norway. The survey was conducted by the National Health Screening Service in cooperation with the University of Tromsø and local health authorities.[19] All resident men and women 35 to 49 years of age and a 10% random sample of those 20 to 34 years of age were invited through a personal, mailed letter. In four small municipalities, all residents 20 to 49 years of age were invited. Three years later, a nearly identical screening was carried out.[2] A total of 7073 men and 6339 women (90.5% of those invited) who were born from 1925 to 1942 attended one or both screenings. Both surveys comprised a questionnaire on cardiovascular history and symptoms, smoking habits, physical activity, and ethnicity. The questionnaire was to be filled in at home and was checked for consistency at the examination. Height was measured to the nearest centimeter and weight to the nearest half-kilogram. Blood pressure was measured twice with a mercury sphygmomanometer in sitting subjects and after 4 minutes' rest. Nonfasting total cholesterol, triglycerides, and glucose were determined in chilled sera. Serum HDL cholesterol was determined only at the second screening.[2]

The questionnaire used these questions to define ethnicity: "Are two or more of your grandparents of Saami origin?" and "Are two or more of your grandparents of Finnish origin?" Fifty percent were classified to be of Norse, 17% of Finnish, and 13% of Saami (Lappish) origin. The remaining persons were of Saami/Finnish (4%) or unknown (16%) ethnicity. In all, 77% of the subjects were born in Finnmark.

Follow-up and Case Identification

A total of 13 266 participants free from stroke at baseline and with a nonmissing value for height were followed; excluded were 16 men and 13 women with verified or possible stroke before screening. Mean follow-up was 14 years. First fatal or nonfatal stroke was the outcome measure.

Strokes were detected through hospital discharge diagnosis lists (International Classification of Diseases 8th and 9th revision

TABLE 1. Baseline Characteristics in Men and Women: The Finnmark Study, 1974-1989

Variable	Men (n=7002)	Women (n=6264)
Age, y	41.5 (4.6)	41.4 (4.7)
Blood pressure, mm Hg		
Systolic	134.2 (16.2)	129.0 (17.6)
Diastolic	83.9 (11.0)	79.8 (10.5)
Body mass index, kg/m²	25.2 (3.1)	25.0 (4.4)
Height, cm		
All ethnic groups	172.8 (7.0)	160.0 (6.5)
Norse	175.3 (6.4)	162.2 (5.7)
Finnish	172.9 (6.2)	160.0 (5.9)
Saami	166.8 (6.2)	154.4 (6.0)
Saami/Finnish	168.2 (6.3)	156.2 (5.9)
Unknown ethnicity	171.1 (6.4)	158.7 (6.1)
Serum lipids, mmol/L		
Total cholesterol	6.9 (1.4)	6.6 (1.4)
Triglycerides	1.9 (1.2)	1.4 (0.8)
HDL cholesterol*	1.3 (0.4)	1.5 (0.4)
Smoking habits		
Never-smokers, %	14.7	38.6
Ex-smokers, %	21.7	13.8
Current smokers, %	63.6	47.6
Prevalent conditions		
Diabetes, %	0.5	0.3
Treated hypertension, %	2.4	3.7

Values are mean (standard deviations in parentheses) or percentages. To convert cholesterol values to mg/dL, multiply by 38.76. To convert triglycerides to mg/dL, multiply by 88.57.
*In 5876 men and 5410 women and measured at the second screening.

codes 430-438) and through a systematic survey of the record files in the only two Finnmark hospitals. Deceased persons, with dates and causes of death, were identified by linkage to the Norwegian Registry of Deaths. A postal questionnaire to all 12 028 participants alive by June 1991 aimed to detect out-of-county and nonhospitalized events. The response rate was 81%. A total of 346 postal survey nonrespondents had moved from Finnmark during follow-up. Strokes among these (3% of the entire cohort) are likely to have been missed, while nonfatal cases among nonrespondents who resided in Finnmark throughout the follow-up period were detected through the hospital record surveys. Nonhospitalized events in the latter group may have escaped registration but are assumed to be very few in these young persons. If a death certificate, medical record, or postal survey response indicated a stroke, additional information was collected from hospitals and physicians for case verification and subtype classification of the first-ever stroke event. The World Health Organization definition of stroke was followed.[20] Strokes were classified as subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, or unclassified stroke. Cases with bloody spinal fluid but no further information to distinguish between subarachnoid or intracerebral hemorrhage (n=10) were included in the unclassified subgroup.

The validation process included inspection of medical records or discharge letters, autopsy reports, and radiograph and cerebral computer tomography descriptions. Eleven cases with a physician's diagnosis of stroke but inaccessible further medical information were included. One person did not give written consent for validation and was assigned as probable stroke. Not included as cases were 27 persons with some symptoms of stroke but with information suggestive of trauma or another disease.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The State Health Directorate permitted access to medical record files.

Data Analysis

Incidence rates were based on the person-years from the date of the first screening attended until the first stroke, with the date of death from other reasons, emigration, or December 31, 1989, as censoring date. Age adjustment of incidence rates was performed by the direct method on 5-year age groups and with all attenders as the standard population. Age- and multivariate-adjusted relative risks were obtained from Cox proportional hazards analysis, in which these continuous variables were considered: age, systolic blood pressure, height and body mass index (weight/height²), and serum total cholesterol, triglycerides, and glucose. Relative risks were determined for units arbitrarily chosen to approximate standard deviations for both sexes. Daily smoking (yes/no), self-reported diabetes (yes/no), medically treated hypertension (yes/no), and ethnic groups were included as covariates. In one analysis, height was examined by sex-specific quartiles. The numbers included vary slightly between individual analyses as the result of missing values. All significance tests were two-tailed, and significance level was chosen at 5%. The SAS statistical package version 6.09 was used.

TABLE 2. Distribution of Stroke Subtypes by Sex: The Finnmark Study, 1974-1989

	Men		Women	
Stroke Subtype	Cases	%	Cases	%
Subarachnoid hemorrhage	20	13.9	28	28.9
Intracerebral hemorrhage	9	6.3	14	14.4
Cerebral infarction	64	44.4	18	18.6
Unclassified stroke	51	35.4	37	38.1
Total	144	100.0	97	100.0

Results

Baseline mean values and frequencies are given in Table 1. Serum lipids and blood pressure were higher in men, and more men were daily smokers. Large ethnic differences in height were observed. The differences in mean height between Saami (shortest) and Norse (tallest) men and women were 8.4 cm and 7.8 cm, respectively. The age distributions were similar in all ethnic groups.

During 187 336 person-years, 144 first-ever strokes among men and 97 first events among women were registered. Sex differences in stroke distribution were seen (Table 2). Almost 40% of the cases could not be subclassified.

Overall stroke incidence was 1.08 per 1000 person-years in women and was 36% higher among men (Table 3). Higher age-adjusted rates of stroke were observed among Finnish and Saami/Finnish men than among men of Norse origin, but the relative risks were only of borderline significance when controlled for height. In general, relative risks associated with ethnicity were attenuated once height was taken into account.

In both sexes, height, systolic blood pressure, and daily smoking were highly significant risk factors for stroke when adjusted for age (Table 4). The estimates changed only slightly when controlled for other variables. There was an apparent threshold level for smoking; incidence rates were similar in nonsmokers and smokers of <10 cigarettes per day (men, 1.1 per 1000 person-years; women, 0.8 per 1000 person-years). The incidence among smokers of ≥ 10 cigarettes was 1.8 per 1000 person-years in both men and women, with no additional risk increase among those who smoked ≥ 20 cigarettes (data not shown). Being treated for hypertension was a strong risk factor for men only. Body mass index was a highly significant predictor in the univariate but not the multivariate model. Few reported to be diabetics at baseline in this young cohort, but diabetes was nevertheless a strong risk factor among men,

TABLE 3. Age-Adjusted Incidence Rates of Stroke per 1000 Person-Years, Relative Risks, and 95% CI by Ethnic Group and Sex: The Finnmark Study, 1974-1989

	Men							Women						
Ethnic Group	Person-Years	Cases, n	Rate/1000	Relative Risk*	95% CI	Relative Risk†	95% CI	Person-Years	Cases, n	Rate/1000	Relative Risk*	95% CI	Relative Risk†	95% CI
Norse	48 108	55	1.15	1.00		1.00		44 597	46	1.03	1.00		1.00	
Finnish	16 605	33	1.92	1.68	1.09-2.59	1.54	1.00-2.39	15 808	15	0.94	0.91	0.51-1.62	0.78	0.43-1.40
Saami	13 127	21	1.62	1.35	0.82-2.24	0.99	0.57-1.71	12 413	14	1.16	1.11	0.61-2.01	0.64	0.33-1.24
Saami/Finnish	3714	11	2.97	2.54	1.33-4.86	1.95	1.00-3.83	3371	5	1.50	1.43	0.57-3.61	0.93	0.36-2.40
Unknown	15 968	24	1.46	1.29	0.80-2.08	1.10	0.68-1.80	13 625	17	1.24	1.19	0.68-2.08	0.93	0.52-1.64
Total	97 522	144	1.47					89 814	97	1.08				

*Relative risk adjusted for age.
†Relative risk adjusted for age and body height.

while serum glucose did not predict stroke in either sex. To examine the role of HDL cholesterol, a separate analysis was performed with the 1977 survey as baseline and with 5876 men (115 strokes) and 5410 women (67 strokes) in the cohort. Adjusted for all variables in Table 4 except triglycerides, a nonsignificant inverse relation was seen between serum HDL cholesterol and stroke in men (relative risk per 0.4 mmol/L increment in HDL cholesterol, 0.8; 95% CI, 0.6 to 1.0) and women (relative risk, 0.8; 95% CI, 0.6 to 1.1).

Table 5 presents stroke in relation to sex-specific quartiles of body height. Controlled for age, ethnic group, and independent risk factors, an inverse association between height and stroke with a clear dose-response pattern was observed. The stroke risk was halved in the tallest compared with the shortest quartile among men and was reduced by 66% in women. The χ^2 test for linear trend was highly significant in both sexes ($P<.002$).

Next, we examined the relation between several risk factors and stroke subtypes in four separate Cox analyses (Table 6). There were too few cases to warrant a sex-stratified subtype analysis. The multiple adjusted relative risks were virtually unchanged from relative risks adjusted only for age and sex (not shown). Height seemed inversely related to all stroke subtypes; the strongest relation was with intracerebral hemorrhage, while a borderline significance was seen for cerebral infarction and statistical significance was not reached for subarachnoid hemorrhage. Daily smoking was associated with a twofold-increased relative risk for all stroke subtypes except intracerebral hemorrhage. Also, daily smoking was the only variable significantly associated with subarachnoid hemorrhage. No significant relation was observed between total cholesterol and any stroke subtype, but the data suggested a positive association with cerebral infarction and a negative association with subarachnoid and intracerebral hemorrhage.

Finally, we investigated risk factors for fatal stroke. Altogether, 23 men and 34 women died within 28 days after a first stroke. In all, 37 of these had a confirmed intracerebral or subarachnoid hemorrhage. In a Cox regression analysis as in Table 6, the relative risk associated with height was 0.64 (95% CI, 0.53 to 0.78). Daily smoking (relative risk, 3.06; 95% CI, 1.65 to 5.67) and systolic blood pressure (relative risk, 1.34; 95% CI, 1.09 to 1.65) were significant risk factors. Serum cholesterol was inversely related to fatal stroke (relative risk, 0.77; 95% CI, 0.61 to 0.95) (data not shown in table).

Discussion

Body height was a significant predictor of stroke in this population-based prospective study. The inverse relation between height and stroke was continuous, independent from obesity and classic cardiovascular risk factors, and observed in both sexes. In the tallest compared with the shortest quartiles, the risk of stroke was 55% lower among men and 66% lower among women. Our data suggest that the inverse relationship may hold for all subtypes of stroke except subarachnoid hemorrhage. Furthermore, blood pressure and cigarette smoking were significant independent predictors, whereas serum lipids and stroke were inconsistently related.

The population-based approach and the high attendance rate make selection bias unlikely. The follow-up on vital status was complete, and death certificate diagnoses were known for all deceased persons. A thorough search for fatal and nonfatal events was made in the hospitals serving

TABLE 4. Risk Factors for Stroke: Adjusted Relative Risks and 95% CI by Sex: The Finnmark Study, 1974-1989

	Men (144 Cases)				Women (96 Cases)			
	Relative Risk				Relative Risk			
Variable	Adj*	95% CI	Adj†	95% CI	Adj*	95% CI	Adj†	95% CI
Systolic blood pressure, 15 mm Hg	1.46	1.29-1.65	1.34	1.18-1.52	1.29	1.12-1.49	1.25	1.08-1.46
Daily smoking (yes/no)	1.48	1.02-2.13	1.64	1.13-2.37	1.85	1.23-2.79	2.12	1.39-3.23
Height, 5 cm	0.82	0.73-0.92	0.84	0.74-0.96	0.75	0.65-0.87	0.73	0.62-0.87
Body mass index, 3 kg/m^2	1.26	1.09-1.45	1.13	0.97-1.32	1.19	1.06-1.34	1.11	0.98-1.26
Total cholesterol, 1 mmol/L	1.16	1.05-1.29	1.08	0.96-1.22	1.03	0.89-1.19	0.89	0.75-1.05
Triglycerides, 1 mmol/L	1.12	1.00-1.25	1.01	0.88-1.15	1.30	1.14-1.48	1.29	1.05-1.57
Glucose, 1 mmol/L	1.08	0.95-1.24	...	...	1.02	0.83-1.26	...	...
Diabetes (yes/no)	4.69	1.49-14.7	4.88	1.55-15.4	...	...	...	...
Treated hypertension (yes/no)	4.62	2.70-7.92	3.19	1.80-5.64	1.70	0.78-3.70	1.13	0.50-2.54

*Relative risk adjusted for age.
†Relative risk adjusted for age, ethnic group, and for all variables listed.

TABLE 5. Age-Adjusted Incidence Rates of Stroke per 1000 Person-Years, Relative Risks, and 95% CI by Sex-Specific Quartiles of Body Height: The Finnmark Study, 1974-1989

Men (97 522 Person-Years)					Women (89 814 Person-Years)				
Height, cm	Cases, n	Rate/1000*	Relative Risk†	95% CI	Height, cm	Cases, n	Rate/1000*	Relative Risk†	95% CI
<168	47	2.08	1.00		<157	49	1.85	1.00	
168-172	45	1.77	0.83	0.55-1.27	157-160	23	1.04	0.54	0.33-0.91
173-177	31	1.19	0.58	0.36-0.94	161-164	11	0.54	0.28	0.14-0.55
178+	21	0.86	0.45	0.26-0.79	165+	14	0.70	0.34	0.18-0.64
P, test for linear trend			.0017					.0001	

*Rate adjusted for age.
†Relative risk adjusted for age at entry, ethnic group, systolic blood pressure, triglycerides, daily smoking, diabetes, and treated hypertension.

the inhabitants of the county. The high response rate on the postal survey makes any large influence from missed nonfatal events unlikely, although 15% of the subjects moved from Finnmark during follow-up. If incidence rates of nonfatal stroke among postal survey responders are applied to the nonresponders, 28 cases would be expected among these persons. Actually, 28 cases were detected through the medical record surveys. Events in which a possible trauma or alternative disease could not be ruled out were not defined as cases. However, almost 40% of the strokes could not be subtype-classified because of nonperformed investigations or lack of detailed information, and the results should be interpreted in the light that "unclassified stroke" is a heterogeneous group in which intracerebral hemorrhages and cerebral infarctions probably make up different proportions in the two sexes.

Cardiovascular Risk Factors and Stroke

Daily smoking was a significant predictor of stroke in both sexes and for all subtypes except intracerebral hemorrhage. A positive relation between cigarette smoking and stroke was also seen in recent prospective studies among men[12] and women.[21] Furthermore, our results are in line with a large meta-analysis[22] that demonstrated that smoking in particular was associated with subarachnoid hemorrhage and cerebral infarction.

Systolic blood pressure has been a better stroke predictor than diastolic pressure in several studies.[23] We observed no sex difference in the relation between systolic blood pressure and stroke, but being treated for hypertension was a strong risk factor only for men. In the Copenhagen City Heart Study, the risk of stroke was 1.5 times higher among treated than among untreated subjects for a given systolic blood pressure with both sexes combined.[24]

When controlled for other risk factors, no association persisted between serum total cholesterol and all stroke in either sex. Specified by stroke subtype, our data show an inverse relationship between serum cholesterol and subarachnoid as well as intracerebral hemorrhage and a positive relation with cerebral infarction. Though nonsignificant, these results are consistent with the large Multiple Risk Factor Intervention Trial[25] and other prospective studies of cholesterol and cerebral hemorrhages[26] and thromboembolic stroke[26-28] and as reviewed by Qizilbash et al.[29] Controlled for confounders, serum triglyceride level was associated with stroke only in women, at variance with a Scandinavian study of mostly ischemic strokes.[28]

Body Height and Stroke

To our knowledge, the Nurses' Health Study[15] is the only previous study on the association between height and stroke in women and the only prospective study on height in relation to stroke subtypes. This large study found no association between height and stroke incidence or between height and stroke subtypes.[15] However, no baseline biological measurements were undertaken, the study used self-reported height, and it was not population based. Results from studies among men vary. In a nested case-control study of stroke mortality, Paffenbarger and Wing[7] found future cases to be on average 1 inch shorter than control subjects. Tverdal[9] reported a significant inverse relation between height and stroke mortality in a follow-up study of 53 000 Norwegian middle-aged men, which included men from the present cohort. An inverse, however nonsignificant, relation between height and stroke incidence and mortality was observed in the Oslo study of men 40 to 49 years of age.[12] A large cohort study among Amer-

TABLE 6. Selected Risk Factors for Stroke Subtypes*: Adjusted Relative Risks and 95% CIs: The Finnmark Study, 1974-1989

	Subarachnoid Hemorrhage (48 cases)		Intracerebral Hemorrhage (23 cases)		Cerebral Infarction (82 cases)		Unclassified Stroke (87 cases)	
Variable	Relative Risk†	95% CI	Relative Risk†	95% CI	Relative Risk†	95% CI	Relative Risk†	95% CI
Sex (M/F)	0.75	0.32-1.74	2.08	0.67-6.48	4.43	2.22-8.86	2.42	1.32-4.44
Systolic blood pressure, 15 mm Hg	1.17	0.92-1.49	1.36	0.98-1.88	1.37	1.16-1.61	1.31	1.12-1.54
Smoking (yes/no)	2.09	1.12-3.91	0.88	0.38-2.06	2.15	1.30-3.58	1.88	1.18-2.99
Total cholesterol, 1 mmol/L	0.89	0.71-1.12	0.76	0.54-1.08	1.12	0.97-1.30	1.07	0.92-1.24
Height, 5 cm	0.91	0.72-1.15	0.61	0.45-0.82	0.85	0.71-1.01	0.77	0.65-0.88
Body mass index, 3 kg/m²	1.01	0.81-1.26	1.07	0.80-1.43	1.16	0.98-1.37	1.18	1.02-1.36
Treated hypertension (yes/no)	1.90	0.55-6.51	0.94	0.12-7.49	1.62	0.67-3.89	3.01	1.55-5.88
Diabetes (yes/no)	...	...	...	...	3.26	0.45-23.5	5.76	1.40-23.7

*13 221 persons (240 cases) with nonmissing values for all variables analyzed in four separate Cox regression analyses.
†Adjusted for age at entry, the other variables, and for ethnic group.

ican physicians found a small, nonsignificant decrease in stroke risk in the tallest compared with the shortest height quintile. No significant trend across height categories was seen.[11]

What, then, could explain the inverse association between height and stroke in the present study? At least two different etiologic paths are conceivable. First, a short stature per se might physically increase the risk of stroke. Height is inversely associated with heart rate,[30] positively correlated to coronary artery lumen diameter,[31] and could possibly affect stroke risk through physiological mechanisms, although we are not aware of any such evidence. Alternatively, the final attained height may be regarded as a marker of the sum of factors operating in early life, with some unfavorable factor related to height causing the association between adult height and stroke. Average body height reflects the socioeconomic level of a society.[32-34] In individuals, height is both influenced by hereditary factors[4] and associated with family economy in childhood[35] and with social class.[36,37] Importantly, due to the finely tuned mechanisms of catch-up growth,[38] a permanent stunting of growth must be expected to have occurred either during a sensitive intrauterine or infant period or must be due to a prolonged period of poor nutrition or illness. Undernutrition during intrauterine life may permanently affect body size, and, depending on its timing, structures, metabolism, or hormonal activity.[39,40]

Some evidence of an early life influence on stroke risk does exist. Forsdahl[16] demonstrated a strong positive correlation between past infant mortality and adult stroke mortality among Norwegian men but not women. Current stroke mortality in England and Wales correlates with past neonatal rather than postneonatal mortality.[41] The correlation was even stronger with past maternal mortality exclusive of puerperal fever,[18] indicating a prenatal influence on later stroke risk.

Blood pressure and serum lipids are modifiable risk factors associated with adult lifestyle. However, in utero growth and adult blood pressure seem related,[42] and increased blood pressure has been suggested as the physiological link between early living conditions and stroke risk in adult age.[17] In our study, no baseline correlation between height and systolic blood pressure was observed in men (Pearson $r=.003$, $P=.8052$), and a weak but significant correlation was present in women ($r=-.053$, $P<.0001$). In both sexes, systolic blood pressure and height were highly significant independent predictors in the multivariate model, suggesting that they may influence the risk of stroke through different mechanisms.

Serum cholesterol in adults is associated with past infant mortality[17] and with intrauterine growth.[43] An inverse relation between height and cholesterol was reported from a cohort of 19 000 adult men and women.[30] Serum cholesterol is positively associated with cerebral atherosclerosis,[44] but a low cholesterol concentration in blood and cell membranes may add to the fragility of small intracerebral vessel walls and contribute to the association between low serum cholesterol and intracerebral hemorrhage.[45] A protein-rich diet counteracts negative effects of salt on blood pressure and prevents stroke in stroke-prone rats,[46] and the declining stroke mortality in Japan seems closely related to postwar socioeconomic improvements, which include a diet with less salt and increased animal fat and protein content.[34,45] Thus, a large body of evidence points to the importance of nutrition, whether it be during pregnancy, childhood, or adult age in stroke epidemiology.

We have no reason to believe that this study population is genetically predisposed for stroke. Stroke mortality shows a declining trend in Finnmark as in other Norwegian counties, although the mortality rates are higher.[1] Hereditary factors could possibly play a role in the observed association between height and stroke. It is not known to what extent the interethnic height differences in this population are due to genetics or to possible group-related differences in living conditions. Apparent ethnic differences in stroke were reduced when height was taken into account. The present cohort was born from 1925 to 1942. Living conditions in Finnmark, as indicated by infant mortality rates, lagged far behind the central areas of Norway throughout this period[47] and were probably tougher for the Saami and Finnish than for the average Norse population.[17] The secular growth curve for army recruits from Finnmark born from 1925 to 1942 was steeper than for the whole country,[48] but even in those born as late as 1942 the mean height was 3.7 cm lower than the national average.[3] One may speculate whether the socioeconomic conditions for this particular study population have allowed stroke determinants to come forward that will not be apparent in societies with more optimal conditions for pregnant women and children. Furthermore, if this reasoning is correct, the different selections of study participants may possibly explain some of the discrepancies between the findings on height and stroke in the present study in contrast to the two large cohort studies among US physicians[11] and nurses.[15]

Conclusions

Body height was negatively associated while blood pressure and daily smoking were positively associated with the risk of stroke in this cohort. It is suggested that a short stature is a marker for unfavorable conditions during early life that contribute to the risk of stroke, together with factors connected with adult lifestyle. Epidemiological studies of stroke are needed that more specifically address nutrition and other health factors in pregnancy, childhood, and adult age.

Acknowledgments

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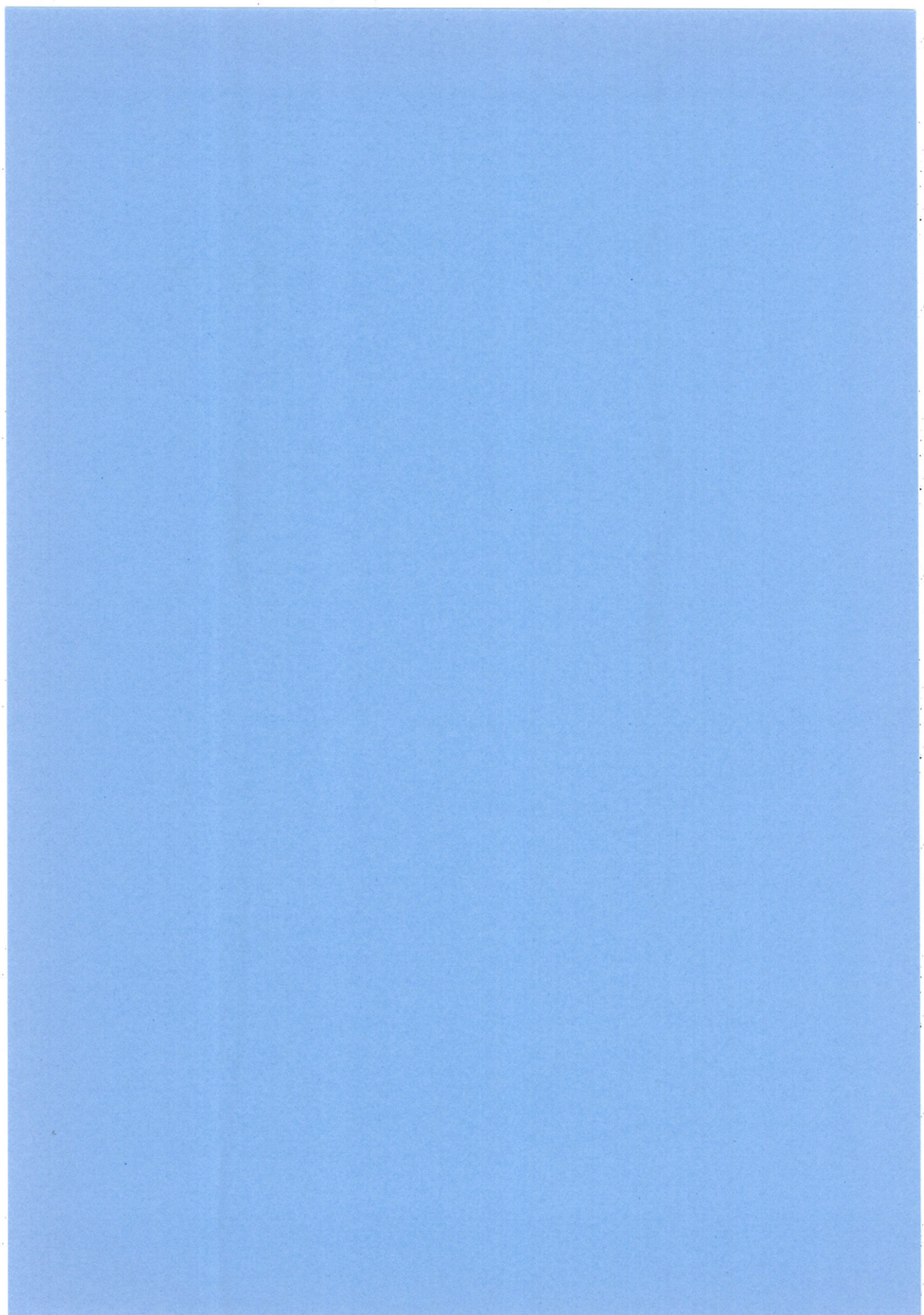
Paper V



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Sex Differences in Risk Factors for Clinical Diabetes Mellitus in a General Population: A 12-Year Follow-up of the Finnmark Study

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The associations among obesity, height, cardiovascular risk factors, and the incidence of clinical diabetes mellitus were investigated in the Norwegian population-based Finnmark Study of 11,654 men and women aged 35–52 years at baseline in 1977–1978. A total of 87 cases of diabetes among men and 75 cases among women were registered during 12 years of follow-up. The incidence of diabetes was 1.1 per 1,000 person-years in women and 1.2 per 1,000 person-years in men, but sex-related differences in risk factors were noted. Body mass index was the dominant risk factor in men and predicted diabetes in a dose-response relation in both sexes. However, in women, the association between body mass index and diabetes was greatly attenuated after multivariable adjustment. Serum lipid concentrations were similar in prediabetic men and women; thus, prediabetic women had a relatively more adverse metabolic risk profile as compared with nondiabetics of the same sex. In multivariable analysis, high density lipoprotein cholesterol was inversely related to diabetes in women (relative risk per 0.3 mmol/liter, 0.53; 95% confidence interval 0.41–0.70) but not in men (relative risk, 0.97; 95% confidence interval 0.78–1.19). Serum glucose was a highly significant predictor in both sexes, while height was inversely related to diabetes only in women (relative risk per 5 cm, 0.71; 95% confidence interval 0.58–0.87). *Am J Epidemiol* 1998;147:49–58.

diabetes mellitus, non-insulin-dependent; prospective studies; risk factors; sex

The incidence and prevalence of non-insulin-dependent diabetes mellitus (NIDDM) are increasing in many populations (1), and diabetes mellitus has become one of the most prevalent chronic diseases worldwide. NIDDM is believed to have a strong genetic basis (2), but rapid changes in lifestyle including diet and physical activity are rapidly followed by changes in diabetes incidence and prevalence (3–5). This points to a large influence of modifiable risk factors and to a great potential for disease prevention. Still, the causes and pathogenesis of NIDDM are not fully clarified (2), justifying further studies on risk factors for and consequences of diabetes.

There is increasing evidence that cardiovascular disease and NIDDM share some common antecedents (6–8). Further, coronary heart disease is the major cause of death among persons with diabetes, with a twofold to fourfold increased mortality compared with the general population (9). Importantly, the coronary mortality is relatively more increased in diabetic women than in diabetic men (9–11), which may imply that women with diabetes for some reason have lost their "female protection" against cardiovascular disease. It has been advocated that the diabetic state has a more atherogenic effect in women (12). However, both diabetic (11, 12) and prediabetic (7) women are reported to have serum lipid concentrations similar to those in men, in contrast to the nondiabetic population, where women have a more favorable lipid profile (7, 11, 12). The question then arises: Are risk factors for diabetes mellitus similar in men and women, or could the attenuated sex differential in coronary disease among diabetics be associated with sex-related differences in diabetes determinants? This possibility has been little investigated. Population-based studies of risk factors for diabetes in middle-aged women are sparse (7, 13, 14). Few prospective studies had the opportunity to investigate the association between obesity and NIDDM in both men and women (13, 15, 16), and few studies (7, 13, 16) published data on cardiovascular risk factors and subsequent diabetes in both sexes within the same study population. Moreover, several of the few prospective studies on diabetes were carried out in populations with a high prevalence of diabetes but a low prevalence of cardiovascular disease (7, 15, 17).

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Abbreviations: NIDDM, non-insulin-dependent diabetes mellitus; HDL, high density lipoprotein.

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The aim of the present 12-year follow-up study was to investigate risk factors for diabetes mellitus among 11,654 free-living middle-aged men and women. Sex-stratified analyses with validated and identical endpoints allowed a comparison of risk factor patterns in the two sexes. We focused mainly on cardiovascular risk factors and height in addition to obesity and glucose, which are established risk factors for NIDDM (2).

MATERIALS AND METHODS

Subjects

A population-based survey of cardiovascular risk factors and disease was performed in 1977–1978 in Finnmark, the northernmost county in Norway. The survey was conducted by the National Health Screening Service in collaboration with the University of Tromsø and local health authorities, and details of study design and procedures have been published (18, 19). All resident men and women aged 35–52 years and a sample of those aged 20–34 years were invited through a personal, mailed letter. The present analysis is restricted to those aged from 35 to 52 years at screening. The attendance rate in this age group was 87.8 percent. Fifty percent of the cohort were defined as Norse, 36 percent were of Finnish or Saami (Lappish) origin, and 14 percent were of unknown ethnicity.

Screening procedures and baseline data

Enclosed with the letter of invitation was a questionnaire that included cardiovascular history and symptoms, smoking habits, ethnicity, and usual level of leisure physical activity (self reported as low, moderate, regular training, or hard training). At the examination, the questionnaire was checked for consistency. Menopausal status in women was recorded. Time since the last meal was recorded in hours. Body height was measured to the nearest centimeter and weight to the nearest half kilogram. Body mass index was defined as weight (kg)/height $(m)^2$. Blood pressure was measured twice with a mercury sphygmomanometer with the subject sitting and after 4 minutes' rest. The lower values were used. Details of laboratory methods have been published (18, 19). Nonfasting serum glucose, total cholesterol, and triglycerides were analyzed at the Central Laboratory, Ullevål Hospital, Oslo (20). Serum high density lipoprotein (HDL) cholesterol was determined at the Institute of Medical Biology, University of Tromsø, after precipitation of low density lipoprotein and very low density lipoprotein with the heparin-manganese method (19).

Follow-up and case identification

Among the 12,785 persons who participated, 35 men and 21 women were excluded from follow-up because of a physician-verified diagnosis of diabetes before screening or within 3 months thereafter, or because of a screening serum glucose concentration of $\geq$11.1 mmol/liter. Persons with missing values for body height or HDL cholesterol were also excluded, leaving 6,098 men and 5,556 women available for analysis. They were followed from screening through December 31, 1989, for an average of 12 years.

Incident cases of diabetes were detected through hospital discharge diagnosis lists and a systematic survey of hospital records in the only two hospitals in Finnmark. To detect cases among unhospitalized persons and among those who had moved from the county during follow-up, a postal survey was undertaken among all 10,714 participants who were alive by June 1991; 81.8 percent responded. Replies that indicated diabetes were validated by medical records in hospitals and primary health care with the respondent's written consent. We then accepted a doctor-confirmed diagnosis without an evaluation of whether World Health Organization diagnostic criteria (21) had been met. Eight cases were not confirmed because of nonresponse from the doctor in charge, and nine subjects who reported diabetes did not give a written permission for validation. They were not included as cases. If no exact date of diagnosis was given, the date midway in the time interval stated was used. Deceased persons, with date and underlying and contributing causes of death, were identified by linkage to the Norwegian Registry of Deaths.

Study approval

The study was approved by the Regional Ethical Committee for Medical Research and by the Norwegian Data Inspectorate. The Norwegian State Health Directorate permitted access to medical record files.

Statistical methods

Incidence rates were based on person-years from the date of screening until the diagnosis of diabetes, with the date of death, emigration, or December 31, 1989, as censoring date, whichever came first. Two persons were censored when secondary diabetes mellitus was diagnosed. Age adjustment of the incidence rates was done by the direct method on 5-year age groups and with the total cohort as standard population. Baseline variables were age adjusted and compared by analysis of covariance. Age-adjusted and multiple-adjusted relative risks were obtained by Cox proportional hazards analysis. Preliminary analyses revealed significant in-

teractions between sex and serum HDL cholesterol and between sex and body mass index. Accordingly, all analyses were sex stratified. Systolic blood pressure was not included in the multivariable model because of a high correlation with diastolic blood pressure (Pearson's $r > 0.6$ in both sexes), and serum triglycerides were omitted because of a high correlation with HDL cholesterol ($r = -0.4$ in both sexes). Relative risks for continuous variables are shown for units of increase arbitrarily chosen to approximate standard deviations for both sexes. Adjustment for ethnicity was done in analyses that include height, since the two variables are strongly correlated in this study population. Adjustment for time since the last meal and for menopausal status at baseline (in women) did not change relative risk estimates materially and was omitted from the final analyses.

Because of different distributions for several baseline variables, the relative risk by sex-specific rather than combined quartiles was used. The quartile (Q1-Q4) cutpoints were the following: body mass index (kg/m^2): men: <23.2, 23.2–25.0, 25.1–27.0, ≥27.1; women: <22.0, 22.0–24.1, 24.2–27.1, ≥27.2; height (cm): men: <168, 168–172, 173–177, ≥178; women: <156, 156–160, 161–164, ≥165; HDL cholesterol (mmol/liter): men: <1.05, 1.05–1.22, 1.23–1.45, ≥1.46; women: <1.26, 1.26–1.48, 1.49–1.73, ≥1.74; glucose (mmol/liter): men: <5.38, 5.38–5.76, 5.77–6.37, ≥6.38; women: <5.27, 5.27–5.76, 5.77–6.21, ≥6.22; systolic blood pressure (mmHg): men: <123, 123–132, 133–142, ≥143; women: <119, 119–126, 127–138, ≥139; and diastolic blood pressure (mmHg): men: <79, 79–86, 87–92, ≥93; women: <75, 75–80, 81–88, ≥89.

The number of subjects included in the individual analyses varies slightly because of missing values. Significance tests were two tailed, and the significance level was chosen at 5 percent. SAS version 6.09 software (SAS Institute, Inc., Cary, North Carolina) was used.

RESULTS

In total, 87 incident cases of diabetes among men and 75 cases among women were registered. The mean age at entry was higher in future diabetic subjects, and baseline variables adjusted for age are shown for prediabetic and nondiabetic subjects in table 1. Future diabetic subjects were more obese and less physically active, and they had higher blood pressure, serum glucose, and triglycerides than did the others. Prediabetic women were shorter than other women, but no relation between height and diabetes was seen among men. A significantly larger proportion of prediabetic women than of prediabetic men were treated for hypertension (age-adjusted $p = 0.0277$). In general, baseline values were relatively more adverse for female than for male future diabetic subjects, and the

TABLE 1. Age-adjusted baseline variables in men and women initially free of diabetes by future diabetic status, the Finnmark Study, 1977–1989

	Age not adjusted for age (years)		Blood pressure (mmHg)				Body mass index (kg/m^2)		Body height (cm)	
			Systolic		Diastolic					
	Mean	SD†	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Men										
Developed diabetes ($n = 87$)	45.9	4.2	140.3	17.1	93.4	11.4	29.6	4.6	173.2	6.6
Remained nondiabetic ($n = 6,011$)	43.4	5.3	134.2	16.2***	86.0	11.1***	25.3	3.1***	172.7	7.0§
Women										
Developed diabetes ($n = 75$)	46.9	4.5	141.7	22.7	89.7	12.2	31.5	6.1	157.2	6.9
Remained nondiabetic ($n = 5,481$)	43.3	5.3	129.2	17.5***	81.8	10.8***	25.0	4.3***	159.8	6.5***

	Nonfasting serum (mmol/liter)										
	Glucose		Total cholesterol		HDL cholesterol†		Triglycerides		Current smokers (%)	Physically active‡ (%)	Hypertension treatment (%)
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Men											
Developed diabetes ($n = 87$)	6.45	1.07	6.80	1.42	1.17	0.33	2.36	1.34	45.7	66.8	14.1
Remained nondiabetic ($n = 6,011$)	5.92	0.90***	6.70	1.23§	1.29	0.35**	1.81	0.99***	57.0*	77.4*	3.4***
Women											
Developed diabetes ($n = 75$)	6.64	1.34	6.76	1.42	1.22	0.27	2.24	1.16	35.7	67.9	28.3
Remained nondiabetic ($n = 5,481$)	5.81	0.75***	6.51	1.30§	1.52	0.36***	1.34	0.72***	44.3§	77.2§	5.3***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
† SD, standard deviation; HDL cholesterol, high density lipoprotein cholesterol.
‡ Those who reported moderate leisure physical activity or regular or hard training.
§ Not significant.

sex differences in baseline variables seen in the nondiabetic population (table 1) were largely eliminated. Serum HDL cholesterol was relatively more reduced in the prediabetic women; the mean HDL cholesterol was not significantly different from that of prediabetic men. The mean HDL cholesterol was lower in prediabetic subjects who were treated for hypertension than in those who were not (age-adjusted means in men, 1.03 mmol/liter vs. 1.20 mmol/liter; in women 1.12 mmol/liter vs. 1.27 mmol/liter) (not shown in table).

Pearson's correlation coefficients between baseline serum lipids were generally similar in men and women but were different for body mass index and height ($r = -0.05$ in men, $r = -0.21$ in women, $p < 0.0001$), in contrast to the correlation coefficients for body mass index and triglycerides ($r = 0.3$), HDL cholesterol ($r = -0.2$), total cholesterol ($r = 0.2$), and diastolic blood pressure ($r = 0.3$), where no sex differences were seen. In men, there was no correlation between body mass index and glucose ($r = 0.0$), whereas a weak, positive correlation ($r = 0.1$, $p < 0.001$) was seen in women. An inverse correlation between height and HDL cholesterol was seen in men ($r = -0.1$, $p < 0.001$) but not in women ($r = 0.0$) (not shown in tables).

Figure 1 presents the relative risk of diabetes by sex-specific quartiles of various baseline variables. A strong dose-response relation between diabetes and body mass index was present in both sexes. Sex-related differences in the relations between diabetes and height, HDL cholesterol, and glucose are apparent in figure 1. Adjustment for body mass index attenuated in particular the relation of diabetes with blood pressure (in both sexes) and HDL cholesterol (in men).

The 12-year incidence rate of diabetes was 1.1 per 1,000 person-years in women and 1.2 per 1,000 person-years in men (table 2). However, the distribution of cases according to serum HDL cholesterol differed by sex. In table 2, common cutoff points were chosen to allow comparison between the sexes. HDL cholesterol concentrations less than 1.5 mmol/liter were associated with a higher incidence of diabetes in women than in men, while the situation was reversed at HDL cholesterol concentrations greater than 1.5 mmol/liter. Correspondingly, age-adjusted relative risk estimates were 0.07 (95 percent confidence interval 0.03–0.16) in women and 0.43 (95 percent confidence interval 0.22–0.82) in men in the highest compared with the lowest HDL cholesterol group, and the sex differences were even more pronounced when adjusted for other risk factors, of which body mass index was the major confounder.

The relation between body mass index and diabetes was explored in more detail in table 3, subdividing subjects with a body mass index ≥ 27.1 kg/m^2 into strata with common cutoff points for men and women. The age-adjusted relative risk rose greatly with increasing body mass index. However, in women the relation was heavily confounded. At a body mass index ≥ 35.0 kg/m^2, the relative risk in women was reduced from 36.6 to 11.1 (95 percent confidence interval 4.6–26.5) after multiple adjustment, while the relative risk among men was less influenced.

Table 4 presents age-adjusted and multiple-adjusted risk factors for diabetes. Adjusted only for age, systolic and diastolic blood pressures were highly significant risk factors, and the relative risks were similar in the sexes, whereas serum triglycerides and HDL cholesterol were stronger risk factors for women. Total cholesterol did not predict diabetes in either sex and was not included in the final model. Adjusted for age, HDL cholesterol was a significant predictor in both sexes. In the fully adjusted model, the risk of diabetes was 47 percent lower in women but only nonsignificantly 3 percent lower in men for every 0.3-mmol/liter increment in HDL cholesterol. Physical activity was inversely associated with diabetes in the age-adjusted model, but the association was weaker after adjustment for other risk factors. In a multivariable analysis that included only those with a body mass index ≥ 27.1 kg/m^2, leisure physical activity had a protective effect of borderline significance among men (relative risk per level increase, 0.69; 95 percent confidence interval 0.46–1.04). Otherwise, the risk factor patterns remained virtually unchanged (data not shown).

One third of the prediabetic women but only 15 percent of the prediabetic men were treated for hypertension at baseline. Therefore, a multivariable analysis similar to the one in table 4 was performed, but without those on antihypertensive treatment. The analysis included 74 cases among men and 51 cases among women. Only small changes in relative risk estimates occurred. In particular, the relative risk associated with HDL cholesterol was 0.63 (95 percent confidence interval 0.46–0.85) in women and 0.99 (95 percent confidence interval 0.80–1.24) in men (data not shown in table).

At baseline, 1,169 women (21 percent) reported having undergone menopause. Serum total cholesterol and triglycerides, body mass index, and smoking frequency differed significantly by menopausal status, while diastolic blood pressure, serum HDL cholesterol, and glucose did not (not shown). Menopausal status (yes/no) did not predict diabetes when included in an analysis as in table 4 (relative risk, 0.67; 95 percent confidence interval 0.37–1.22), did not confound the associations between other risk factors and diabetes, and was not included in the final model.

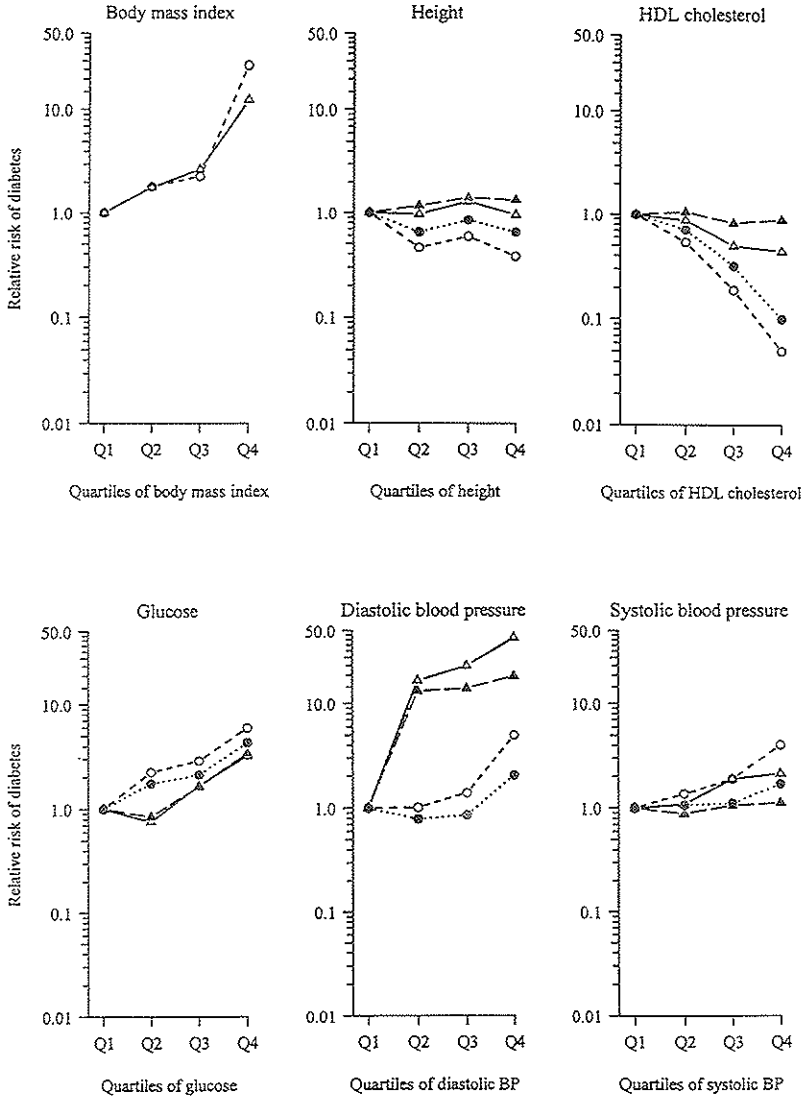

FIGURE 1. Relative risk of diabetes mellitus in men and women by sex-specific quartiles of baseline factors, the Finnmark Study, 1977–1989. Quartile (Q1-Q4) cutpoints: *body mass index* (weight (kg)/height (m)^2): men: <23.2, 23.2–25.0, 25.1–27.0, ≥27.1; women: <22.0, 22.0–24.1, 24.2–27.1, ≥27.2; *height* (cm): men: <168, 168–172, 173–177, ≥178; women: <156, 156–160, 161–164, ≥165; *glucose* (mmol/liter): men: <5.38, 5.38–5.76, 5.77–6.37, ≥6.38; women: <5.27, 5.27–5.76, 5.77–6.21, ≥6.22; *high density lipoprotein cholesterol* (HDL cholesterol) (mmol/liter): men: <1.05, 1.05–1.22, 1.23–1.45, ≥1.46; women: <1.26, 1.26–1.48, 1.49–1.73, ≥1.74; *systolic blood pressure* (BP) (mmHg): men: <123, 123–132, 133–142, ≥143; women: <119, 119–126, 127–138, ≥139; *diastolic blood pressure* (mmHg): men: <79, 79–86, 87–92, ≥93; women: <75, 75–80, 81–88, ≥89. △, age-adjusted relative risk, men; ▲, age- and body mass index-adjusted relative risk, men; ○, age-adjusted relative risk, women; ●, age- and body mass index-adjusted relative risk, women.

DISCUSSION

This population-based study demonstrates several sex-related differences in risk factors for diabetes mellitus. First, body mass index was the dominant risk factor in men, and a dose-response relation was seen in both sexes. However, in women, the strong relation

TABLE 2. Age-adjusted incidence rates of diabetes per 1,000 person-years and age-adjusted and multiple-adjusted relative risk by high density lipoprotein cholesterol (HDL cholesterol) and sex, the Finnmark Study, 1977–1989

HDL cholesterol (mmol/liter)	Men					Women				
	Person-years	Cases (no.)	Rate/1,000†	Relative risk		Person-years	Cases (no.)	Rate/1,000	Relative risk	
				Age adjusted	Multiple adjusted†				Age adjusted	Multiple adjusted
<1.0	13,491	26	1.98	1.00	1.00	3,289	14	4.47	1.00	1.00
1.0–1.49	42,234	47	1.14	0.58	1.06‡	30,369	51	1.71	0.39	0.60‡
≥1.5	15,812	14	0.85	0.43	1.06‡	33,036	10	0.30	0.07	0.17**
Total	71,537	87	1.22			66,694	75	1.12		
p, test for trend					0.8514					<0.0001

* $p < 0.05$; ** $p < 0.001$.

† Adjusted for age, body mass index, glucose, diastolic blood pressure, height, smoking, antihypertensive treatment, physical activity, and ethnicity.

‡ Not significant.

TABLE 3. Relative risk of diabetes according to body mass index (BMI), by sex, the Finnmark Study, 1977–1989

BMI (kg/m^2)	Men (87 cases)			Women (75 cases)		
	Cases (no.)	Relative risk		Cases (no.)	Relative risk	
		Age adjusted	Multiple adjusted*		Age adjusted	Multiple adjusted
≤27.0	27	1.00	1.00 (ref.)	10	1.00	1.00 (ref.)
27.1–28.9	16	3.19	2.53 (1.34–4.79)†	12	7.85	5.60 (2.36–13.28)
29.0–31.9	20	6.72	5.47 (2.97–10.07)	24	18.94	9.23 (4.25–20.02)
32.0–34.9	13	20.04	13.05 (6.23–27.32)	10	14.18	6.49 (2.53–16.65)
≥35.0	11	42.00	27.89 (12.27–63.42)	19	36.60	11.07 (4.63–26.46)
p, test for trend		<0.0001				<0.0001

* Relative risk adjusted for age, diastolic blood pressure, high density lipoprotein cholesterol, glucose, smoking, height, antihypertensive treatment, physical activity, and ethnicity.

† Numbers in parentheses, 95% confidence interval.

between body mass index and diabetes was confounded by other factors. Second, there were sex-related differences in the associations between serum HDL cholesterol and diabetes and between height and diabetes. Physical activity was inversely related with diabetes, especially among obese subjects. This observation accords with previous studies (22) and carries an important public health message. Physical activity increases insulin sensitivity in working muscles (23) and may exert a direct protective effect among those who are otherwise at a high risk for diabetes.

In general, a strong positive association between obesity and NIDDM has been noted in prospective studies among men (13, 15, 16, 24–28) and women (13, 14–16, 29) but, with few exceptions (15), possible differences by sex have not been taken into account. Therefore, the observed sex-related difference in the relation between body mass index and diabetes is of particular interest. Multivariable adjustment greatly attenuated the association between body mass index and diabetes in women, while the relation was less influenced in men. The Nurses' Health Study reported a strong, continuous relation between body mass index and diabetes in women (29) but did not adjust for serum lipids or blood pressure.

In men, adipose tissue tends to accumulate in the abdominal region. In women, both "feminine" and "masculine" obesity may occur, with adipose tissue preponderance for the gluteofemoral or the abdominal region, respectively (30). Abdominal obesity is associated with metabolic aberrances in both sexes (30–32) and with hyperandrogenicity in women (33). It is an independent risk factor for NIDDM in both men and women (14, 15, 25). The clustering of high serum triglycerides, low HDL cholesterol, hypertension, hyperinsulinemia, and insulin resistance, which was labeled the metabolic syndrome or Syndrome X (34), is often accompanied by abdominal obesity (35). A study by Krotkiewski et al. (30) showed that women seemed to tolerate moderate obesity better than men do. Only the most obese women in their study had metabolic aberrances similar to those of men. The future diabetic women in our study "were like men" in a metabolic sense with regard to baseline levels of HDL choles-

TABLE 4. Risk factors for diabetes mellitus in men and women, the Finnmark Study, 1977–1989

Variables	Men (87 cases)		Women (75 cases)	
	Relative risk*	Relative risk†	Relative risk*	Relative risk†
Age (5 years)	1.61 (1.30–1.99)‡	1.52 (1.21–1.90)	2.02 (1.58–2.58)	1.44 (1.10–1.89)
BMI§ (3 kg/m²)	2.22 (1.98–2.50)	2.09 (1.79–2.43)	1.72 (1.57–1.88)	1.35 (1.21–1.51)
Body height (5 cm)	1.07 (0.90–1.26)	1.15 (0.97–1.35)	0.65 (0.53–0.79)	0.71 (0.58–0.87)
Systolic BP§ (15 mmHg)	1.33 (1.13–1.55)		1.50 (1.30–1.72)	
Diastolic BP (10 mmHg)	1.73 (1.47–2.05)	1.17 (0.96–1.43)	1.79 (1.49–2.13)	1.19 (0.95–1.50)
Total cholesterol (1 mmol/liter)	1.08 (0.91–1.28)		1.14 (0.97–1.34)	
HDL cholesterol§ (0.3 mmol/liter)	0.71 (0.57–0.88)	0.97 (0.78–1.19)	0.41 (0.32–0.52)	0.53 (0.41–0.70)
Triglycerides (1 mmol/liter)	1.48 (1.28–1.72)		2.14 (1.83–2.50)	
Glucose (1 mmol/liter)	1.68 (1.39–2.01)	1.67 (1.38–2.02)	2.46 (2.04–2.96)	2.34 (1.91–2.87)
Daily smoking (yes/no)	0.66 (0.43–1.01)	0.85 (0.55–1.30)	0.72 (0.45–1.16)	0.79 (0.47–1.31)
Hypertension treatment (yes/no)	4.23 (2.33–7.68)	1.98 (1.03–3.80)	5.52 (3.32–9.18)	2.68 (1.53–4.67)
Physical activity (one level)	0.67 (0.49–0.92)	0.84 (0.61–1.16)	0.66 (0.44–0.99)	0.91 (0.61–1.36)

* Relative risk adjusted for age (height also adjusted for ethnicity).
† Relative risk adjusted for the other risk factors and for ethnicity.
‡ Numbers in parentheses, 95% confidence interval.
§ BMI, body mass index; BP, blood pressure; HDL cholesterol, high density lipoprotein cholesterol.

terol, triglycerides, and blood pressure, but their mean body mass index was higher. Our data cannot disclose, but may support, a possible connection between abdominal obesity, androgenicity, and diabetes.

Serum HDL cholesterol was a strong independent risk factor of diabetes in women. An increment of 0.3 mmol/liter in HDL cholesterol was associated with a 47 percent lower risk among women but did not predict diabetes in men after multiple adjustment. Among men in the British Regional Heart Study (27), the highest versus lowest quintile of HDL cholesterol carried a relative risk of 0.7 (95 percent confidence interval 0.5–1.2, p for linear trend = 0.03) after multiple adjustment. Only two prospective studies (7, 36) offer data on HDL cholesterol levels in prediabetic women. Future diabetics in the San Antonio Heart Study (7) had lower HDL cholesterol concentrations than did nondiabetics, and the differences of 0.3 mmol/liter in women and 0.09 mmol/liter in men were almost identical to our findings. However, that study included only 17 male and 26 female prediabetic subjects. Among elderly persons in the Framingham Study, HDL cholesterol was 0.2 mmol/liter lower in prediabetic men and women (36). To our knowledge, no prospective analysis of HDL cholesterol and diabetes with relevant multivariable adjustment has been published for women until the present one. Sex differences in the relations of body mass index and serum lipids with diabetes warrant further investigations.

Antihypertensive treatment was associated with a twofold (men) to threefold (women) increased risk of diabetes in this study. Antihypertensive agents may precipitate diabetes (26, 37), but the coincidence between hypertension and diabetes could be due to insulin resistance (38). In this study, serum HDL cholesterol was lower in prediabetic subjects who were treated for hypertension at screening compared with those who were not. Whether this was a treatment side effect or whether it simply reflects the common association between hypertension and serum lipids (34) is not known.

Serum glucose was a highly significant predictor of diabetes, in accordance with previous findings in men (7, 13, 16, 25, 26) and women (7, 13, 14, 16). A high serum glucose concentration may indicate glucose intolerance and may be regarded as an intermediate step along the causal pathway to diabetes. The relative risk associated with glucose was significantly higher in women than in men. No glucose tolerance test or other indices of insulin resistance were performed at baseline. We treated a casual serum glucose ≥11.1 mmol/liter as prevalent diabetes (21) and excluded those subjects from follow-up. Of the 162 subjects who later developed diabetes, 14.2 percent (14 women, 9 men) had a random serum glucose concentration from 7.8 mmol/liter to 11.0 mmol/liter, while the percentage was 2.6 among the remaining subjects, suggesting that baseline manifest glucose intolerance was not a major feature of this study population.

Of the classic cardiovascular risk factors, only blood pressure emerged as a significant risk factor for diabetes in our study after age adjustment, and relative risks were slightly higher (nonsignificant) in women. Diastolic blood pressure was not a significant risk factor after multiple adjustment. The study confirms previous findings that blood pressure is increased in prediabetic subjects, (7, 16, 25–28, 36) but is not always a significant risk factor in multivariable models (13, 27, 28). Serum total cholesterol did not predict diabetes in this and several other studies (16, 27, 28).

We observed a nonsignificant, inverse relation between smoking and diabetes in both sexes, while others reported smoking and diabetes to be positively (27, 28, 39) or not (16, 25) related.

This is the first prospective study to report an inverse relation between height and diabetes in women, and the finding is at variance with the Nurses' Health Study where no association was seen (29). The risk of diabetes was 29 percent lower per 5-cm increase in height after adjustment for age, body mass index, and other risk factors. There seems to be no obvious explanation for the observed sex difference. Adult height is determined by genetics and by environmental factors during early life (40). An inverse correlation between adult height and glucose tolerance was noted in men and women in the Isle of Ely Diabetes Project (41). In a study of 50-year-old men and women, those with Syndrome X were shorter than others (42), but there was no such association in a sample of men aged 59–70 years (42). In a diabetes prevalence study from Bangladesh, adult women with hyperglycemia were significantly shorter than other women, but no similar association was observed among men (43). The authors ascribe this finding to more prevalent malnutrition among girls than among boys in early childhood. As recently reviewed by Stern (8), increasing evidence connects low birth weight and possibly inadequate nutrition in early life to the metabolic syndrome and to NIDDM in adults. Glucose intolerance (44), insulin resistance (45), and Syndrome X and NIDDM (42) have been linked to reduced fetal and infant growth. Theoretically, the association between height and diabetes in women in the present study may express an adverse influence from early life factors. On the other hand, the lack of such an association among men should caution against premature conclusions.

The population-based approach, the large study size, and factual, not self reported, biologic baseline measurements are strengths of the present study, but some limitations should be considered. No baseline data were collected to identify glucose-intolerant subjects. The diagnosis of diabetes during follow-up was clinical. Preferably, screening for diabetes using fasting glucose and a glucose tolerance test (21) should be undertaken in the whole cohort by the end of follow-up, since diabetes may go clinically unrecognized (21), but this was not feasible. A recent Norwegian population-based prevalence study that did make use of fasting glucose and glucose tolerance tests (46) showed that the prevalence of undetected diabetes was far less than the estimated 50 percent commonly referred to from the United States (47). Among subjects >40 years old, 83 percent of the cases had been detected prior to the screening. Misclassification of cases would tend to dilute the observed associations between risk factors and disease. Based on the incidence rates of diabetes among those who responded to the postal survey in 1991, we estimated that 11 cases of diabetes were missed among the questionnaire nonresponders. Available data on insulin treatment could not be used to distinguish between insulin-dependent and non-insulin-dependent diabetes, since the latter may be treated with insulin. However, insulin-dependent diabetes mellitus is relatively rare in Finnmark (48), and all study subjects were at least 35 years old at study entry.

Alcohol consumption raises HDL cholesterol (49), and heavy alcohol intake may induce secondary diabetes, but no baseline data were collected on this potential confounder. However, alcohol use is rather modest in Norway, with alcohol-related disease accounting for less than 1 percent of all deaths (50). By 1987, 40 percent of the women and 13 percent of the men in Finnmark were alcohol abstainers (51). Among users, alcohol intake was more frequent in men. In the present study, among the 531 men and 195 women who died during follow-up, 44 men and three women had some alcohol-related condition mentioned on the death certificate. None of them had diabetes. Only two subjects in this cohort had a diagnosed secondary (pancreatic) diabetes and were not included as cases. A sex difference in drinking habits may therefore have influenced our findings through an effect on HDL cholesterol, but this is unlikely to be a major confounder.

Existing knowledge of the role of menopause with regard to diabetes incidence is very limited. At baseline, 21 percent of the women in this study had undergone menopause. We observed higher serum total cholesterol and triglyceride concentrations in post- than in premenopausal women, while HDL cholesterol, glucose, and diastolic blood pressure did not vary by menopausal status. This finding accords with previous studies (52, 53). Menopausal status at baseline did not predict diabetes and did not act as a confounder in multivariable models. In the San Antonio Heart Study, there was no significant interaction between menopausal status and conversion to NIDDM (54).

No information on hormonal replacement treatment was collected in the baseline survey. However, by 1987, only 2 percent of Finnmark women aged 45–62 years used exogenous estrogen (51). Further, few data exist to assess whether estrogen could be a true confounder of the relative risks reported. Postmenopausal estrogen use may affect the levels of HDL cholesterol (55) and of triglycerides and glucose (56) but did not increase the risk of clinical diabetes in the Nurses' Health Study (57).

Diabetes is an important risk factor for coronary heart disease (10, 11), but risk factors for the two diseases overlap only partially in the present study population. Total cholesterol and smoking were not related to the risk of diabetes, and blood pressure was not a significant predictor in the multivariable model. On the other hand, the classic cardiovascular risk factors, but not body mass index, were significant predictors of myocardial infarction in both sexes (58). Walden et al. (12) found HDL cholesterol to be more reduced in women with type 2 diabetes than in men, and they concluded that diabetes has a more adverse effect on lipoproteins in women. However, lipid abnormalities preceded and were indeed a strong predictor (in women) for diabetes in our study, not a consequence of the diabetic state. Since HDL cholesterol is an equally important coronary risk factor in men and women (58), the sex-specific relations between serum lipids and diabetes may be one reason for diluted sex differences in coronary disease among diabetic subjects, and they may be involved in the apparently accelerated atherosclerotic process in diabetic women (12).

In conclusion, several sex-related dissimilarities were noted in the relations between body mass index, height, serum lipids, and glucose and subsequent diabetes mellitus in this middle-aged population. After multivariable adjustment, body mass index was a stronger predictor in men, possibly because an increased body mass index is more directly related to abdominal obesity and the amount of visceral fat in men. Serum HDL cholesterol and glucose were stronger risk factors among women. The risk factor patterns were suggestive of insulin resistance and may shed some light on attenuated sex differences in coronary disease among diabetic subjects. Further studies are needed to elucidate the temporal sequence of events that lead to diabetes and concomitant coronary disease and to explore the sex-related differences that seem to be involved.

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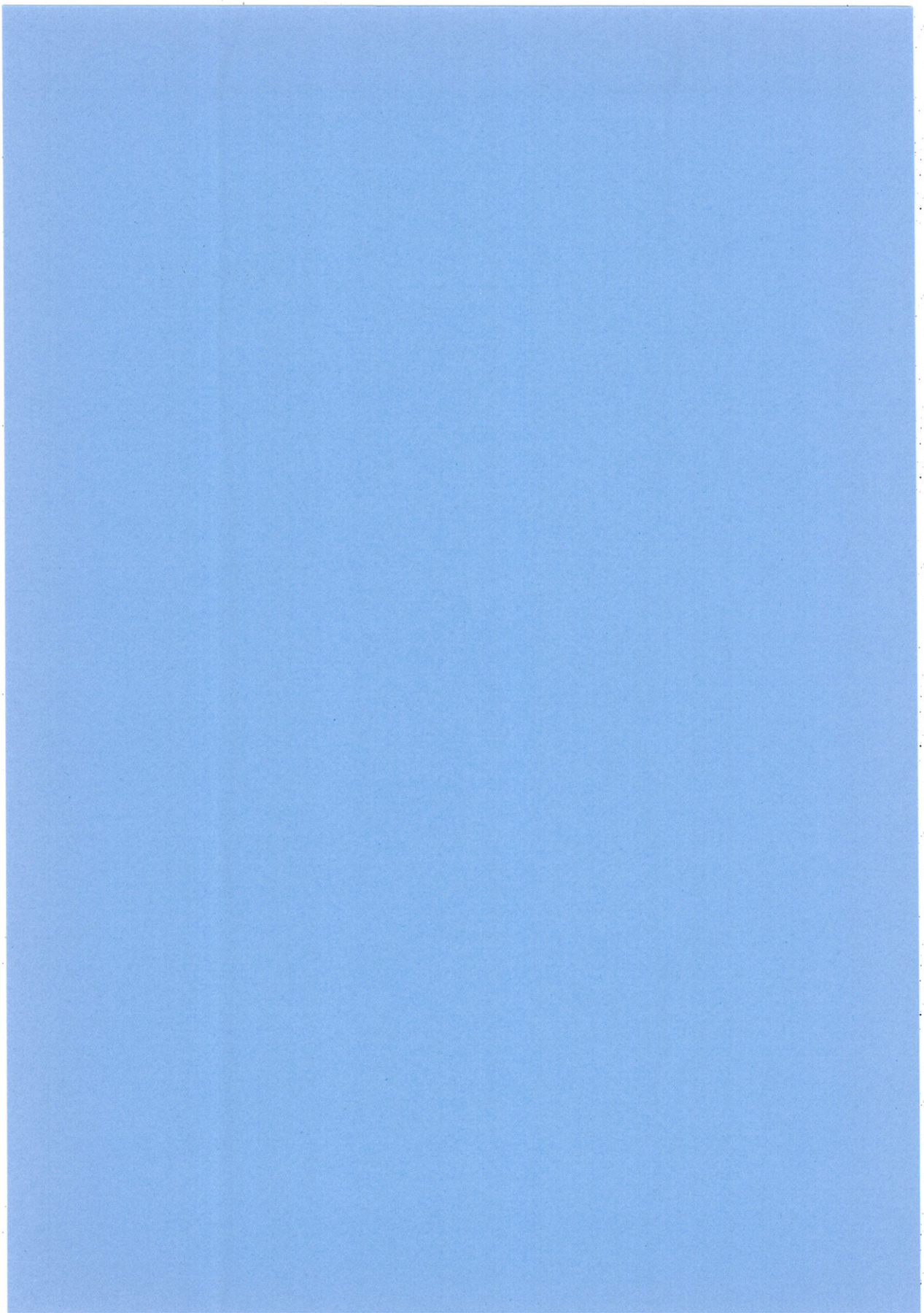
ADDENDUM

Note added in proof: The following study was published after the submission of this article: Haffner SM, Miettinen H, Stern MP. Relatively more atherogenic coronary heart disease risk factors in prediabetic women than in prediabetic men. Diabetologia 1997;40:711–17.

Paper VI



Cardiovascular Diseases and Diabetes Mellitus in Different Ethnic Groups. A Prospective Analysis from The Finnmark Study.

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Running head:
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ABSTRACT

The mortality from coronary and cerebrovascular diseases is higher in the northernmost Finnmark County than in other Norwegian counties. In a population based cohort study, we compared the incidence of myocardial infarction, stroke, and diabetes mellitus in different ethnic groups in Finnmark. A total of 10,622 subjects of Norse, Sami and Finnish origin were followed for 14 years. During approximately 150,000 person-years we identified 509 and 84 cases of myocardial infarction among men and women, respectively, 107 and 75 cases of stroke, and 96 and 73 cases of clinical diabetes mellitus. A total of 533 men and 199 women died. Norse subjects born out of Finnmark had the most favorable risk factor levels and, in general, the lowest incidence of disease. Men of Finnish origin had a higher incidence rate of all end points than other men, and Finnish women had a higher incidence rate of myocardial infarction than other women. Sami women were more obese, but did not have a higher diabetes incidence than other women. After adjustment for major cardiovascular risk factors and height, most ethnic differences were attenuated.

Key words: myocardial infarction, stroke, diabetes mellitus, incidence, epidemiology, cohort studies

Finnmark County in northern Norway has had a higher mortality of ischemic heart disease and stroke than other Norwegian counties for several decades.[1] The population of this county is an ethnic mix of Norse, Sami (Lappish) and Finnish descendants. In a cross-sectional study in Finnmark in 1974, the prevalence of coronary heart disease (CHD) was only one-quarter of the expected among Sami men.[2] Fewer Samis reported myocardial infarction among first degree relatives as compared with those of Norse origin,[2-4] while people of Finnish descent seemed particularly prone to coronary heart disease.[5] A lower coronary mortality in Sami than in Norse subjects was observed in a recent study, and it was suggested that the Samis may be genetically protected against CHD.[6] In addition, a correlation, based on county ecological data, was reported between previous infant mortality and present cardiovascular mortality among adult men in Norway,[7] raising the hypothesis that adverse living conditions in childhood increase the risk of cardiovascular disease in adulthood.[7,8]

Diabetes mellitus is strongly associated with cardiovascular disease irrespective of ethnicity.[9-12] However, a high diabetes prevalence is not always accompanied by a high incidence of CHD,[11,13] warranting concomitant studies of both diseases. To our knowledge, no previous study investigated non-insulin-dependent diabetes mellitus (NIDDM) in the different ethnic groups of northern Scandinavia.

In this study we examine the incidence of myocardial infarction, stroke, and diabetes mellitus among 10,622 middle aged men and women of Norse, Finnish and Sami origin. We investigate whether ethnic differences in cardiovascular disease and diabetes exist, and, where present, whether such differences can be explained by ethnic variations in cardiovascular risk factors and height.

SUBJECTS AND METHODS

Study population

A population-based cardiovascular survey was undertaken in Finnmark in 1974/75 by the National Health Screening Service, in collaboration with county health authorities and the University of Tromsø. All residents 35 to 49 years old and a sample of those 20 to 34 years old were invited. Three years later, the survey was replicated. A total of 13,412 subjects (90.5% of those invited) who were 35 years or more attended one or both surveys.

Details on screening procedures and methods have been published.[14-16] Briefly, all subjects were invited to participate by personal letter which included a questionnaire about symptoms and history of cardiovascular disease and diabetes mellitus, ethnicity, smoking habits, and usual leisure and occupational physical activity level. At the examination, the questionnaire was checked for inconsistencies, municipality of birth and time since the last meal was recorded, and height and weight were measured. Blood pressure was measured twice with the person sitting and after four minutes' rest. Non-fasting serum total cholesterol, triglycerides, and glucose were determined at Ullevål Hospital, Oslo.[14]

The questions on ethnicity read: Are two or more of your grandparents of Sami origin? Are two or more of your grandparents of Finnish origin? (yes/no/do not know). The subjects

were divided into Finnish (17%), Sami (13%), Finnish/Sami (4%) and "unknown" (15%) ethnicity. The rest (51%) were classified as Norse, since admixture of persons of foreign origin was known to be negligible. Twentytwo percent of the participants reported to be born out of Finnmark. The percentage varied from 37% among the Norse to 8% in the other ethnic groups. Information on municipality of birth was missing for 136 subjects.

Follow-up and case identification

A total of 126 subjects had a verified history of myocardial infarction, stroke, or diabetes mellitus diagnosed before screening and were excluded from follow-up. Subjects who reported "unknown" ethnicity or had a missing value for height were excluded. Included in the prospective analysis were 8,349 subjects born in Finnmark and 2,273 Norse subjects born in other Norwegian counties. They were followed from the first screening attended through December 31, 1989; on average 14 years. The 11-digit personal identification number allowed a linkage to the Causes of Death Registry, and underlying and contributory causes of death are known for all deceased participants. Cases of myocardial infarction, stroke and diabetes mellitus were registered through discharge diagnosis registers and through a survey of the medical record files in the two Finnmark hospitals.

In all, 14% of the present cohort moved from Finnmark during follow-up. The percentage varied by ethnic group; from 37% among Norse born out of Finnmark to 5% among Sami subjects. To detect ambulant and out-of-county events, we mailed a questionnaire to all 9,693 participants who were alive by June 1991, using updated addresses provided by Statistics Norway. A total of 82% responded to the postal survey; the response rate did not vary by ethnicity. When a reply indicated cardiovascular disease or diabetes, we obtained additional information from the relevant hospital or physician with the respondent's written consent. We classified each event according to pre-set diagnostic criteria. We included as outcomes definite and probable first events of myocardial infarction and stroke, and verified clinical cases of diabetes mellitus. Details on classification criteria are available.[17-19]

Variable definitions

Subjects reported their usual leisure physical activity as either: reading, watching TV or other sedentary activities (L1), light physical activity for at least four hours per week (L2), exercise to keep fit, heavy gardening etc for at least four hours per week (L3), or regular hard training (L4). They reported their physical activity at work as either: mostly sedentary work (W1), much walking (W2), work with much lifting and walking (W3), or heavy manual work (W4). We classified those who reported L3 or L4 and/or W3 or W4 as "physically active".

Data analysis

We allocated the subjects into four mutually exclusive groups, based on ethnicity and municipality of birth: Norse I (Norse born in Norwegian counties except Finnmark), Norse II (Norse born in Finnmark), Finnish, and Sami. All analyses were sex specific. Baseline variables were age adjusted. We calculated observation years from date of first examination until first event

of a non-fatal or fatal myocardial infarction (including sudden death), a first stroke, or until diabetes mellitus was diagnosed, with date of death from other reasons, emigration, or December 31, 1989 as censoring date. Observation years were calculated for each endpoint independently from the others. We age adjusted the incidence rates by the direct method, using 5-year groups, with the total study population as standard. We used Cox's proportional hazard analysis to estimate multiple adjusted relative risks. Norse subjects born in Finnmark (Norse II) were chosen as the reference group.

The 222 women and 268 men (4%) who reported a mixed Sami/Finnish origin had baseline characteristics between Sami and Finnish values. Their inclusion in the Sami subgroup did not materially alter the results and conclusions for this group.

RESULTS

Age adjusted baseline characteristics are shown for men (Table 1) and women (Table 2), by ethnic group. The age distributions were similar, but inter-ethnic differences in a number of risk factors were noted. Norse men born out of Finnmark were taller, smoked less and had lower total cholesterol than other men (Table 1). A larger percentage among Norse men born out of Finnmark reported low physical activity at work. Norse women born out of Finnmark were taller and had a more favorable risk factor profile than other women (Table 2). Together with Sami women, they smoked less than the others.

During approximately 150,000 person-years, there were 509 and 84 first events of myocardial infarction among men and women; 107 and 75 first events of stroke; and 96 and 73 new cases of clinical diabetes mellitus. A total of 533 men and 199 women died during followup. The age adjusted total mortality rates per 1,000 person-years in men were: 5.3 (Norse I), 6.6 (Norse II), 8.0 (Finnish), and 7.3 (Sami). Corresponding rates for women were 2.6, 2.5, 2.4, and 3.7 deaths per 1,000 person-years. Age adjusted incidence rates and rate ratios for men and women are shown in Tables 3 and 4 for each endpoint. Norse men born out of Finnmark had the lowest rates while Finnish men had the highest. While Norse women born out of Finnmark tended to have lower rates, the patterns across the other groups were not consistent. This may, in part, be due to the small number of cases in each ethnic group. Sami women had a similar diabetes incidence rate as other women, despite a higher mean BMI.

We used Cox' regression analysis to examine whether the ethnic differences in known risk factors explained the differences in incidence rates. Adjustment for physical activity did not influence relative risk estimates for any endpoint, and was therefore omitted from further analyses. In Tables 3 and 4 , relative risk estimates are shown for each endpoint, adjusted first for age only, then for age plus potential confounders, and finally, for age, potential confounders and height. The addition of serum total cholesterol, blood pressure and smoking to the model generally attenuated the inter-ethnic differences in relative risk of myocardial infarction. The inclusion of height in the model did not change the estimates materially, except to lower the relative risk in Sami women.

For stroke, the adjustment for blood pressure, cholesterol and smoking attenuated the differences among men, without much change in the differences among women. The inclusion of height generally resulted in modest attenuation, except for Sami women where the relative risk estimate changed from 1.1 to 0.8.

BMI was the most important confounder of the relation between ethnicity and diabetes, while smoking did not affect relative risk estimates (not shown). In models adjusting for age and BMI, the relative risk in men were 1.0 for Norse I, 1.1 for Finnish, and 0.7 for Sami ethnicity; for women they were 0.6, 1.0, and 0.6 respectively. Further adjustment for blood pressure, triglycerides and glucose attenuated the estimate for Sami women (Table 4). The addition of height to the multivariable model altered the estimates slightly for Sami subjects (Table 4).

The role of height as a disease predictor was further explored. In models that included the whole study population, and controlling for age and ethnicity, height was inversely related to stroke in men (relative risk (RR) per 5 cm = 0.8; 95% confidence interval (CI) = 0.7-1.0) and women (RR = 0.7; 95% CI = 0.6-0.9) (not shown in tables). The inverse relation between height and stroke seemed to be present within all ethnic groups, except Norse men born out of Finnmark, but there were few cases within each group and the confidence intervals did not preclude unity (Table 5). Among women, there was an inverse relation between height and myocardial infarction (RR per 5 cm = 0.9; 95% CI = 0.8-1.0), and height and diabetes (RR per 5 cm = 0.8; 95% CI = 0.7-0.9), but no such association was seen among men (myocardial infarction: RR per 5 cm = 1.0; 95% CI = 0.9-1.1), (diabetes: RR per 5 cm = 1.0; 95% CI = 0.9-1.2) (not shown in tables). The relations between height and myocardial infarction and height and diabetes were inconsistent across the ethnic groups (Table 5). Again, few cases within each subgroup limit the value of subgroup comparisons.

DISCUSSION

We observed differences in risk factor levels as well as in age adjusted rate ratios of cardiovascular disease and diabetes among the different ethnic groups living in Finnmark County, Norway. Adjustment for major risk factors attenuated most, but not all of these ethnic differences. Our study on myocardial infarction incidence did not support the recent finding of a much lower coronary mortality among Sami than among Norse men in Finnmark [rate ratio 0.4 (95% CI= 0.2-0.7), adjusted for major risk factors].[6]

No genetic markers were included, and the relative contributions of hereditary and environmental factors to disease susceptibility are difficult to separate. Serum total cholesterol is the main intermediate factor on the causal pathway to coronary heart disease and was included in our analyses. However, serum cholesterol may be influenced by genes,[20] fetal environment,[21] dietary fat,[22] and consumption of boiled, unfiltered coffee.[23] Apolipoprotein E phenotype E4/4, which is is associated with high serum total cholesterol,[20] is common in the Finnish population,[24] but may be more frequent among Samis than among Finns.[25] A high consumption of cholesterol-increasing[23] boiled coffee is more common in Finnmark than in southern Norway,[26]

and may have been more common among Samis than among Norse subjects.[27] Furthermore, the diet may contain several factors which enhance and protect against atherosclerosis and thrombogenicity. Traditionally, Sami reindeer herders lived on a diet which differed considerably from that of the general population, with lean, antioxidant-rich reindeer meat as the staple food.[27] In a Finnish study, serum concentrations of α-tocopherol correlated with the consumption of reindeer meat, and the observed lower coronary mortality among Samis than among Finns in that study was attributed to diet rather than to genetics.[25] In contrast, coronary and total mortality among Swedish reindeer breeding Samis did not differ from that of the general Swedish population.[28]

All ethnic groups in our study had a low incidence of diabetes mellitus compared with other populations of a similar age.[29] In contrast to indigenous populations who are experiencing a westernization in lifestyle and diet with a concordant increase in the prevalence of diabetes,[30] the Samis in our study had a reduced risk of diabetes compared with the Norse population. After multivariable adjustment, the relative risk associated with Sami origin was 0.8 in women and 0.9 in men. The similar diabetes incidence rates in Sami, Finnish and Norse women born in Finnmark were unexpected, since these groups differed considerably in body mass index. Obesity is closely associated with the high diabetes prevalence in some ethnic minorities,[31] and body fat distribution and abdominal fat amount are additional important diabetes determinants.[32,33] No data are available on body fat distribution in the ethnic groups of northern Norway.

A low level of physical activity may explain some of the excess diabetes incidence in minority groups.[34,35] Traditionally, the nomadic part of the Sami population was engaged in physically demanding reindeer herding, while fishing, farming and mining are other traditional occupations in Finnmark. At present, only a minority of the Samis is engaged in reindeer herding. Nevertheless, Sami men reported a higher level of physical activity at work, and Sami men were overall more physically active than others in this study. Physical activity protects against diabetes, regardless of body mass index,[36,37] but did not influence the ethnicity associated estimates for the endpoints in our study.

Cases of diabetes were based on clinical diagnoses, and an ethnic bias in case detection must be considered. The formal access to health services is similar for all inhabitants, but a lesser use of health care facilities among the Samis due to language and cultural barriers has been reported.[38] On the other hand, the well known association between obesity and diabetes could favor case finding among Sami women. Most cases among non-hospitalized persons were registered through the postal survey. From rates among postal survey respondents we estimated that altogether 11 cases of diabetes were missed among non-respondents. None were expected among Sami or Finnish women, and only 3 cases were expected in the group with the highest frequency of emigration from Finnmark (Norse I), and who therefore were least likely to be detected through the record survey in local hospitals. A distinction between IDDM and NIDDM could not be made, but only seven normal weighted subjects started insulin treatment when

diabetes was diagnosed. This, and a low IDDM incidence in Sami sub-populations [37] and in Finnmark compared with other Norwegian counties,[38] argues against a strong influence from late onset IDDM. The total mortality rate was higher among Samis than among Norse, but not large enough to let selective mortality be a likely explanation for the lower diabetes incidence in the Sami group.

In addition to well known risk factors, we examined the role of body height. Adult height is determined by genetics and by environmental factors in fetal life and childhood.[41,42] The present cohort was born between 1925 and 1942. Poor nutrition was common in Finnmark throughout that period.[5] Living conditions, as indicated by infant mortality rates and average height, lagged far behind central areas in Norway, and were probably tougher for the Sami and Finnish than for the average Norse population in Finnmark.[5] An inverse relation between height and stroke has been reported from the Finnmark Study.[18] In the present study, height was inversely related to stroke in all ethnic subgroups except men born out of Finnmark. Thus, the association between height and stroke may indicate that environmental factors early in life are involved in stroke disposition, as suggested by some authors.[43,44] By contrast, height was related to myocardial infarction and diabetes only in women, and the point estimates varied between ethnic groups. An inverse relation between height and all cause mortality was observed in a large Norwegian study,[45] but the relation between height and cardiovascular diseases,[46-49] and height and glucose intolerance[50,51] has been inconsistent in epidemiologic studies.

Immigrant Norse men and women had lower incidence of cardiovascular diseases and diabetes than Norse subjects born in Finnmark in the present study. They were taller, reflecting known geographical differences in body height in the Norwegian population,[52] and had more favorable risk profiles including lower serum total cholesterol and a lower proportion of smokers. No data were collected on occupation and social class, but sedentary work was reported more often by Norse men born out of Finnmark than by other men. This could indicate a higher social class. Thus, it is not possible from this analysis to discern to what extent the more favorable risk factor levels and the lower risk of disease among Norse immigrants to Finnmark reflect genetic differences, more favorable conditions during early life and childhood or rather social class and associated lifestyle factors in adulthood.

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TABLE 1. Baseline Characteristics in Men by Ethnic Group*: The Finnmark Study

Baseline Characteristic	Born out of Finnmark	Born in Finnmark		
	Norse N = 1,167	Norse N = 2,172	Finnish N = 1,120	Sami N = 1,142
Age (years)	41.0 (4.8)	41.5 (4.5)	41.7 (4.5)	41.5 (4.4)
Blood pressure (mmHg)				
Systolic	132.5 (14.8)	133.9 (15.5)	136.7 (17.3)	133.5 (16.2)
Diastolic	83.3 (10.4)	83.9 (10.8)	85.0 (11.3)	82.8 (10.8)
Serum (mmol/l)				
Total cholesterol	6.5 (1.2)	6.8 (1.4)	7.0 (1.4)	7.0 (1.5)
Triglycerides	1.8 (1.0)	1.9 (1.1)	2.0 (1.3)	2.0 (1.5)
Glucose	5.7 (0.9)	5.8 (1.0)	5.8 (0.9)	5.8 (0.9)
Body mass index (kg/m^2)	25.0 (3.0)	25.1 (3.1)	25.5 (3.1)	25.3 (3.1)
Body height (cm)	176.7 (6.0)	174.6 (6.4)	172.9 (6.3)	167.2 (6.2)
Self reported (%)				
Daily smoking	56.9	62.5	64.4	66.2
Leisure physcial inactivity (L1)	22.9	22.2	22.0	22.4
Physical inactivity at work (W1)	44.2	29.3	24.5	19.5
Physically active	43.1	56.7	60.4	66.0
Antihypertensive treatment	2.5	2.1	3.2	1.6
Angina pectoris	0.8	1.0	2.1	1.2

Values are means (SD) or percentages.
* All variables, except age, are adjusted for age.

TABLE 2. Baseline Characteristics in women by ethnic group*: The Finnmark Study

Baseline Characteristic	Born out of Finnmark	Born in Finnmark		
	Norse N = 1,106	Norse N = 1,912	Finnish N = 967	Sami N = 1,036
Age (years)	41.0 (4.8)	41.5 (4.7)	41.7 (4.7)	41.4 (4.6)
Blood pressure (mmHg)				
Systolic	126.8 (16.1)	128.6 (17.2)	130.9 (18.1)	128.8 (19.0)
Diastolic	78.9 (10.4)	79.5 (10.0)	80.5 (10.4)	79.5 (10.9)
Serum (mmol/l)				
Total cholesterol	6.4 (1.5)	6.5 (1.3)	6.8 (1.4)	6.7 (1.3)
Triglycerides	1.3 (0.8)	1.4 (0.7)	1.4 (0.8)	1.4 (0.9)
Glucose	5.7 (0.8)	5.7 (0.8)	5.7 (0.8)	5.6 (0.8)
Body mass index (kg/m^2)	24.2 (3.9)	24.6 (4.2)	25.2 (4.2)	26.4 (4.9)
Body height (cm)	163.3 (5.6)	161.6 (5.6)	160.0 (5.8)	154.7 (5.9)
Self reported (%)				
Daily smoking	43.3	49.4	49.4	42.7
Leisure physical inactivity (L1)	23.1	26.1	25.3	30.9
Physical inactivity at work (W1)	10.8	16.2	12.0	9.0
Physically active	20.1	18.7	20.4	22.7
Antihypertensive treatment	3.4	3.1	3.3	4.6
Angina pectoris	0.7	0.6	1.1	0.8

Values are means (SD) or percentages.
* All variables, except age, are adjusted for age.

TABLE 3. Age Adjusted Incidence Rates of Myocardial Infarction, Stroke and Diabetes Mellitus per 1000 Person-years, Adjusted Relative Risks and 95% Confidence Intervals (CI) in Men by Ethnic Group: The Finnmark Study

	Born out of Finnmark	Born in Finnmark		
	Norse	Norse	Finnish	Sami
Myocardial infarction				
No. of cases	89	199	125	96
Person-years at risk	16016	29817	15342	15876
*Incidence rate**	*5.8*	*6.7*	*8.0*	*6.1*
Rate ratio*	0.9	ref	1.2	0.9
Relative risk A	1.0		1.1	0.9
Relative risk B	1.0		1.1	0.9
95% CI	0.8-1.3		0.9-1.4	0.7-1.1
Stroke				
No. of cases	14	36	29	28
Person-years at risk	16258	30310	15654	16100
*Incidence rate**	*0.9*	*1.2*	*1.8*	*1.8*
Rate ratio*	0.8	ref	1.5	1.5
Relative risk A	0.9		1.4	1.4
Relative risk B	0.9		1.3	1.1
95% CI	0.5-1.7		0.8-2.2	0.6-1.9
Diabetes mellitus				
No. of cases	17	38	25	16
Person-years at risk	16221	30247	15625	16141
*Incidence rate**	*1.1*	*1.3*	*1.6*	*1.0*
Rate ratio*	0.9	ref	1.3	0.8
Relative risk C	1.0		1.1	0.7
Relative risk D	1.0		1.1	0.9
95% CI	0.6-1.7		0.7-1.9	0.5-1.6

adjusted for: *age A:age,systolic blood pressure,serum total cholesterol,daily smoking, B: as A + height, C:age,systolic blood pressure,body mass index, serum triglycerides, serum glucose, D: as C + height

TABLE 4. Age Adjusted Incidence Rates of Myocardial Infarction, Stroke and Diabetes Mellitus per 1000 Person-years, Adjusted Relative Risks and 95% Confidence Intervals (CI) in Women by Ethnic Group: The Finnmark Study

	Born out of Finnmark	Born in Finnmark		
	Norse	Norse	Finnish	Sami
Myocardial infarction				
No. of cases	12	32	22	18
Person-years at risk	15720	27388	14040	15019
*Incidence rate**	*0.8*	*1.2*	*1.5*	*1.2*
Rate ratio*	0.7	ref	1.3	1.1
Relative risk A	0.8		1.2	1.0
Relativ e risk B	0.9		1.1	0.8
95% CI	0.4-1.7		0.6-1.9	0.4-1.5
Stroke				
No. of cases	13	32	11	19
Person-years at risk	15712	27374	14080	15008
*Incidence rate**	*0.8*	*1.2*	*0.8*	*1.3*
Rate ratio*	0.7	ref	0.7	1.1
Relative risk A	0.8		0.6	1.1
Relative risk B	0.9		0.6	0.8
95% CI	0.5-1.7		0.3-1.2	0.4-1.6
Diabetes mellitus				
No. of cases	8	30	17	18
Person-years at risk	15691	27338	14062	14968
*Incidence rate**	*0.5*	*1.1*	*1.2*	*1.2*
Rate ratio*	0.5	ref	1.1	1.1
Relative risk C	0.4		1.0	0.9
Relative risk D	0.4		1.0	0.8
95% CI	0.2-1.1		0.5-1.8	0.4-1.5

adjusted for: *age A:age,systolic blood pressure,serum total cholesterol,daily smoking, B: as A + height, C:age,systolic blood pressure,body mass index, serum triglycerides, serum glucose, D: as C + height

TABLE 5. Relative Risk and 95% Confidence Interval (CI) of Myocardial Infarction, Stroke and Diabetes Mellitus Aassociated with Height, by Ethnic Group: The Finnmark Study

End point	Norse I RR* (95% CI)	Norse II RR* (95% CI)	Finnish RR* (95% CI)	Sami RR* (95% CI)
MEN				
Myocardial Infarction				
Age adjusted	0.9	1.0	1.0	1.1
Multivariably† adjusted	1.0 (0.8-1.1)	1.0 (0.9-1.1)	1.1 (0.9-1.2)	1.1 (1.0-1.3)
Stroke				
Age adjusted	1.0	0.8	0.7	0.9
Multivariably† adjusted	1.1 (0.7-1.7)	0.9 (0.7-1.1)	0.7 (0.5-1.0)	0.9 (0.7-1.3)
Diabetes				
Age adjusted	1.3	1.0	1.1	1.0
Multivariably‡ adjusted	1.4 (0.9-2.1)	1.2 (0.9-1.5)	1.1 (0.8-1.5)	1.0 (0.7-1.6)
WOMEN				
Myocardial infarction				
Age adjusted	0.9	0.7	0.8	0.9
Multivariably† adjusted	0.9 (0.5-1.5)	0.8 (0.6-1.0)	0.8 (0.6-1.2)	0.9 (0.6-1.3)
Stroke				
Age adjusted	0.7	0.8	0.6	0.8
Multivariably† adjusted	0.8 (0.5-1.3)	0.8 (0.6-1.0)	0.6 (0.4-1.1)	0.8 (0.6-1.2)
Diabetes				
Age adjusted	1.3	0.8	0.7	0.9
Multivariably‡ adjusted	2.3 (1.1-5.1)	0.9 (0.7-1.3)	0.8 (0.5-1.2)	1.0 (0.6-1.5)

* RR, relative risk per 5 cm increase in height.
† Adjusted for age, systolic blood pressure, serum cholesterol, daily smoking.
‡ Adjusted for age, systolic blood pressure, body mass index, serum triglycerides, serum glucose.

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
   Av Anders Forsdahl, 1976. (nytt opplag 1990)

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7.* Blodtrykksovervåkning og blodtrykksmåling.
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