Ischemic heart disease in Kiruna - Risk factors and sequelae

AKADEMISK AVHANDLING

Som med vederbörligt tillstånd av Rektor vid Umeå Universitet för avläggande av medicine doktorsexamen kommer att offentligen försvaras i sal 933, Norrlands Universitetssjukhus fredagen den 26 april 1996 kl 09.00

av

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University of Umeå
Umeå 1996
Ischemic heart disease in Kiruna - risk factors and sequelae

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Abstract

Kiruna, a Swedish community situated 300 km north of the Arctic Circle, has a very high mortality in ischemic heart disease (IHD). A case-control study was undertaken to find out if the risk factors for IHD or their impact differed from those in other populations. The survey methods comprised questionnaires, physical examinations, laboratory tests, a food diary, ecological studies, and a register study. The study group consisted of 219 men who had suffered an acute myocardial infarction (cases) and 438 men without known ischemic heart disease (controls).

The main risk factors were: a family history of IHD, hypertension, hyperlipidemia, diabetes mellitus, and smoking. Also psycho-social risk factors like lack of job support constituted a risk factor.

Cholesterol ester and adipose tissue triglyceride fatty acids have a slower turn-over rate than other routinely analysed lipids and lipoproteins and thus reflect dietary habits over a longer period of time. They were measured in a subset of our cohort, showing that the cases, judged from lipid and fatty acid composition, lived on a diet comparable to that of the controls. A prospective diet diary showed few differences between cases and controls and between the whole cohort and a reference cohort in Uppsala in the central part of Sweden. Most notable differences were a low level of y-tocopherol, a low proportion of linoleic acid, and a high proportion of palmitic acid in serum cholesterol esters and adipose tissue triglycerides in the Kiruna cohort.

The expected reduced morbidity in ischemic heart disease related to alcohol consumption was not seen in our material. This finding was further examined in an ecological study on a national Swedish level, longitudinally, cross-sectionally, and with time-series methodology. There was an inverse correlation between wine consumption and mortality in IHD for women but no correlation between the consumption of beer and distilled spirits, and mortality in IHD.

Heart failure, a common sequela of IHD, has an increasing incidence in a hospital-based population. In spite of improved treatments the prognosis has not improved during the last seven years and is still as bad as or worse than that of many malignant diseases. Male sex and high age implied a worse prognosis.

Consumption of acetylsalicylic acid (ASA) for pain relief resulted in a greater risk of developing an acute myocardial infarction in our cohort. This was further examined in an ecological study on a national Swedish level also showing a correlation between ASA consumption and mortality in IHD both in the geographical and the longitudinal analysis for the surveyed years, but not in the time series analysis.

Key words: Ischemic heart disease, risk factors, alcohol, acetylsalicylic acid, lipids, fatty acids, diet, psychosocial risk factors, migration, smoking, mortality, diabetes mellitus, family history, heart failure.
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by

Torbjörn Messner

Umeå and Kiruna
1996
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Livet forstår baglæns, 
men må leves forlæns. 

Kierkegaard
# ABBREVIATIONS

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<th>Description</th>
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<tbody>
<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
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<tr>
<td>Apo A</td>
<td>Apolipoprotein A</td>
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<tr>
<td>Apo B</td>
<td>Apolipoprotein B</td>
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<tr>
<td>Apo E</td>
<td>Apolipoprotein E</td>
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<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CVD</td>
<td>Cardiovascular Disease</td>
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<td>DDD</td>
<td>Defined Daily Dose</td>
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<tr>
<td>df</td>
<td>degree(s) of freedom</td>
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<td>E%</td>
<td>Energy%</td>
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<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
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<td>ICD8</td>
<td>International Classification of Diseases, Eighth Revision</td>
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<td>ICD9</td>
<td>International Classification of Diseases, Ninth Revision</td>
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<td>IDDM</td>
<td>Insulin-Dependent Diabetes Mellitus</td>
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<td>IHD</td>
<td>Ischemic Heart Disease</td>
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<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
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<tr>
<td>Lp(a)</td>
<td>Lipoprotein(a)</td>
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<tr>
<td>MONICA</td>
<td>Multinational Monitoring of Determinants and Trends in Cardiovascular Disease</td>
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<tr>
<td>NIDDM</td>
<td>Non Insulin-Dependent Diabetes Mellitus</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PTCA</td>
<td>Percutaneous transluminal coronary angioplasty</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>TG</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>t-PA</td>
<td>tissue plasminogen activator</td>
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<td>WHO</td>
<td>World Health Organization</td>
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ABSTRACT

Kiruna, a Swedish community situated 300 km north of the Arctic Circle, has a very high mortality in ischemic heart disease (IHD). A case-control study was undertaken to find out if the risk factors for IHD or their impact differed from those in other populations. The survey methods comprised questionnaires, physical examinations, laboratory tests, a food diary, ecological studies, and a register study. The study group consisted of 219 men who had suffered an acute myocardial infarction (cases) and 438 men without known ischemic heart disease (controls).

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Key words
Ischemic heart disease, risk factors, alcohol, acetylsalicylic acid, lipids, fatty acids, diet, psychosocial risk factors, migration, smoking, mortality, diabetes mellitus, family history, heart failure.
ORIGINAL PAPERS


DEFINITIONS

Epidemiology, as many other sciences, has its own vocabulary, sometimes not easy to comprehend for the uninitiated, sometimes even causing confusion since different epidemiologists have different meanings for the same expression. To facilitate the understanding of the methodology in this thesis, part of the terminology used is explained below. The "translations" are from Rothman (1), Clayton and Hills (2), Kleinbaum, Kupper and Morgenstern (3), Estève, Benhamou and Raymond (4), Box, Jenkins and Reinsel (5), and Parmar and Machin (6).

<table>
<thead>
<tr>
<th>Term</th>
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<tr>
<td>Bias</td>
<td>An effect that produces a systematic deviation from the true values.</td>
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<tr>
<td>Case</td>
<td>An individual with a disease or some other attribute of interest.</td>
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<tr>
<td>Case-control study</td>
<td>A study where individuals with a disease are compared to controls without the disease, looking for differences in previous exposures.</td>
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<tr>
<td>Confounding</td>
<td>When the exposure-disease relationship under study is mixed up with the effects of extraneous variables.</td>
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<td>Control</td>
<td>An individual who is free from the disease under study.</td>
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<tr>
<td>Cross-sectional study</td>
<td>A study where the exposure to a possible risk and the presence of disease at one point in time are assessed in a population group.</td>
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<tr>
<td>Ecological study</td>
<td>The study of groups of people, or populations, rather than individuals.</td>
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<tr>
<td>Ecological fallacy</td>
<td>The potential for misleading inferences from an ecological study where correlations on a group level not are comparable to results among individuals.</td>
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<tr>
<td>Epidemiology</td>
<td>The study of the distribution of diseases over time and place and according to individual or group characteristics.</td>
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<tr>
<td>Etiologic fraction</td>
<td>The proportion of all new cases in a given period that are attributable to the risk factor of interest.</td>
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<tr>
<td>Incidence</td>
<td>The number of new cases of disease within a specified population and a specified time period.</td>
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<tr>
<td>Independent risk factor</td>
<td>A risk factor which exerts its effects directly and not via other risk factors.</td>
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<tr>
<td>Term</td>
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<td>Interaction</td>
<td>The effects of exposure to one risk factor varies with level(s) of one or more other risk factors.</td>
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<tr>
<td>Intervention trial</td>
<td>A study where an effort is made to reduce disease occurrence by some type of prevention or treatment e.g. vaccinations or diet restrictions.</td>
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<td>Logistic regression</td>
<td>A method where a logarithmic transformation is done, enabling a linear regression model to accommodate a non-linear relation. This model allows control of confounding and interaction.</td>
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<tr>
<td>Longitudinal study</td>
<td>A study where differences in disease occurrence and risk factor levels are studied during consecutive time periods, allowing for a time interval corresponding to a meaningful induction period.</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>The analysis of several smaller studies aggregated to gain greater statistical power.</td>
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<tr>
<td>Morbidity</td>
<td>A measure of disease frequency.</td>
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<tr>
<td>Mortality</td>
<td>A measure of disease frequency measured as a relative number of deaths in a specified disease.</td>
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<tr>
<td>Non-stationary series</td>
<td>A series where the variation in the variables over time is not compensated for.</td>
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<tr>
<td>Odds ratio</td>
<td>The ratio of exposure odds among cases to exposure odds among controls.</td>
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<tr>
<td>Prevalence</td>
<td>The total number of individuals in a defined population who have a disease at a specific time point.</td>
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<td>Risk factor</td>
<td>An attribute associated with an increased risk of a disease among the exposed.</td>
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<td>Risk ratio</td>
<td>The ratio of the risk of disease or death among the exposed to the risk among the non-exposed.</td>
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<td>Standardised mortality ratio</td>
<td>The ratio of the number of deaths observed in a study population to the number of expected deaths had the study population had the same age distribution as a standard population.</td>
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<td>Survival study</td>
<td>A study where the survival time can be compared for groups with different characteristics. This can be done with linear methods (e.g. life-table analysis or actuarial analysis) or with non-linear methods (e.g. Cox's proportional hazards analysis) where interaction and confounding can be controlled.</td>
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<tr>
<td>Time series analysis</td>
<td>The analysis of the co-variation in two or more variables over time.</td>
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INTRODUCTION

Background to the study
Many studies have addressed the problems related to the incidence, morbidity, and mortality in ischemic heart disease (IHD) from an epidemiological point of view. It is probably one of the most and best studied disease entities. Why then another study? The outset for this investigation was not primarily to find new risk factors for IHD. Several hundred risk factors have been identified and no new study can be expected to find biologically significant hitherto unknown causes of IHD or contributors to IHD risk. Our goal was rather to study the local risk factors for coronary heart disease in Kiruna to decide which priorities to make in the battle against a disease which is expected to kill almost half of us, many prematurely, both directly in an acute myocardial infarction, and indirectly via its sequelae, e.g. congestive heart failure.

There is a gradient with increasing morbidity and mortality in ischemic heart disease in Sweden from the south to the north (7), and also from the east to the west (8, 9). Consequently, in the north-western part of Sweden the mortality in IHD is very high. This has been apparent to us working at the Kiruna District Hospital for many years. The myocardial infarction standardised mortality ratio for men in Kiruna aged 15 to 74 years during the time period 1974 to 1983 was 1.79 compared with Sweden as a whole, and 1.29 compared with the county of Norrbotten (10).

There are many sources of inspiration to our study, among them the Framingham Heart Study. This study was initiated in 1948 to study cardiovascular disease risk. The term "risk factor" was coined in this study (11), and several statistical and epidemiological tools were developed and refined. Still after over 40 years this study produces valuable findings and has contributed knowledge that has stemmed the United States epidemic of cardiovascular morbidity and mortality, which after a peak in the 1960's has declined (12). A later follower is the Tromsø study (13) which showed that it is important to study risk factors in a defined geographic area since the impact of them seems to differ between different populations. Our hope was that a similar study in Kiruna would help to unveil the reasons for the increased IHD mortality in Kiruna and in a longer perspective be used to reduce the incidence of and mortality in ischemic heart disease.

We thus decided to perform a case-control study to chart some of the important differences between myocardial infarction patients and patients free from overt coronary heart disease especially with regard to constitutional and environmental risk factors. Were the risk factors for acute myocardial infarction (AMI) in Kiruna different from those
described in the literature? Or was the impact of the risk factors different in Kiruna? An important entry point was that it may be difficult to detect risk factors in a population with a very high disease prevalence.

Rather unexpectedly we found from a questionnaire:

1. That alcohol consumption was *not* associated with a decrease in IHD risk, and

2. That the consumption of acetylsalicylic acid (ASA) for pain relief was associated with an *increased* risk of IHD.

This prompted two ecological studies, on consumption of alcoholic beverages and mortality in IHD, and on ASA consumption and mortality in IHD, respectively, using the whole of Sweden as denominator.

An important sequela to acute myocardial infarction and chronic ischemic heart disease is congestive heart failure. It has been suggested that this is an increasing problem both in terms of incidence and prevalence (14). It has also been stated that the prognosis of heart failure has improved with the advent of new treatments (15, 16). Since these observations were made within the framework of controlled studies on selected populations we found it important to find out if this was the case also among our patients. This was the reason for our study on survival in heart failure.

**Local risk factors**

Many risk factors for coronary heart disease have been described (17). Naturally, not all of them have been possible to analyse in our studies. Three of them that are not specifically addressed (two of them are shared by cases and controls alike) but may be of a special local importance are:

**Cold**

It has been known since the mid 1960’s that deaths from IHD are considerably higher in winter than summer (18). Several hypotheses why a cold climate should increase the risk of developing a myocardial infarction have been put forward. In the Caerphilly study (19), it was found that a temperature drop of 16°C caused sizeable and unfavourable changes in blood pressure, HDL cholesterol, platelet count, and $\alpha_2$-macroglobulin, a protein that inhibits fibrinolysis. All changes were about one third of a standard deviation.

In Europe the mortality gradient in IHD increases from the Mediterranean countries to Scandinavia. Even within European countries, mortality increases from the south to the north (20 - 23) with the exception of Belgium where the opposite situation exists (24, 25) attributed to differences in serum cholesterol levels which are high in the south, in turn
ascribed to dietary differences. Cold has been implicated in explaining this north-south gradient where the mortality in IHD in some winters has been as much as 70% higher than in the summers (26). A Swedish thesis (27) further examined this issue by constructing a cold index. This index took account of how many times daily (out of five measurements) during a ten-year period the temperature was below preset cut-off points. Even when controlling for water hardness, socio-economic factors, tobacco use, sales of antihypertensive drugs, and sales of butter fat, cold remained a strong predictor of coronary mortality, explaining 39% of regional variations in coronary heart disease. Kiruna’s geographical position some 300 km north of the Arctic Circle infers long, dark, and cold winters.

**Early life experience**

Since the publication of the paper by Forsdahl (28) which suggested that great poverty in childhood and adolescence followed by prosperity in adult age was a risk factor for arteriosclerotic heart disease, many studies have tried to link adverse conditions during intrauterine, neonatal, childhood, and adolescent life with an increased risk of developing premature coronary heart disease (29 - 31). In the first quarter of the 20th century, the living conditions in the countryside of Norrbotten were characterised by hardship and poverty, with a high infant death rate and a high prevalence of tuberculosis. Still today, the infant mortality rate is higher in Norrbotten than the national Swedish average. Adult height is most influenced by genetic factors and early life experiences, e.g. infant nutrition (32). A short stature has been linked with more unfavourable growth experiences. In our studies, cases were shorter than controls, although not to a statistically significant degree.

**Water hardness**

Soft drinking water is associated with an increased mortality in coronary heart disease, a fact known for some 30 years. Consistent results from investigations of the relation between water quality and IHD have been reported from different parts of the world (33 - 35). When adjusting for socio-economic and climatic factors the water hardness effect seems to be non-linear with approximately 10-15 per cent excess of all cardiovascular deaths when areas of very soft water are compared to areas with medium water hardness (36). The factors responsible for water hardness are mainly calcium and magnesium. Since the calcium intake from water is almost negligible compared to that from other sources, a protective effect of magnesium has been postulated (37, 38), possibly mediated via an antihypertensive effect of the magnesium ion (39). It has been shown that people in soft water areas have lower concentrations of magnesium in heart muscle compared to those living in hard water areas (40). The water in Kiruna has until the winter 1994-1995 been extremely soft.
GENERAL REMARKS ON RISK FACTORS FOR ISCHEMIC HEART DISEASE

Life-style factors
This label serves as a comprehensive cover for several risk factors which are mainly caused by such circumstances the individual himself or herself to some degree can influence the level of (e.g. smoking, sedentary lifestyle, alcohol consumption, and habitual diet) although some of them are partly genetically determined (e.g. obesity, lipid levels, hypertension, diabetes mellitus, and hemostatic factors). Our way of life affects our disease risks. Already Hippocrates suggested that we should study the water people use, the way the inhabitants live, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labour (41). A later follower, the Alameda County study, reported that the average life expectancy of men aged 45 who reported six or seven good habits was more than eleven years longer than that of men reporting fewer than four (42). The habits studied were: smoking, obesity, alcohol consumption, hours of sleep, regularity of meals, eating between meals, and physical exercise in leisure time. Some of these risk factors have been studied in this thesis.

Hypertension
The increased risk for IHD associated with both systolic and diastolic hypertension is continuous and graded. There is no evidence of a J-shaped curve (43). In middle-aged men it is estimated that a 20 mm Hg higher systolic blood pressure is associated with 60 per cent higher cardiovascular mortality and with a 40 per cent higher all-cause mortality over a ten year period (44). However, the results from intervention trials and meta-analyses of such trials have partly been disappointing, since the estimated reduction in IHD events amounts to only fourteen per cent compared to the 20-25 per cent predicted from observational data.

Smoking
In most epidemiological risk factor studies cigarette smoking carries an odds ratio of just below 2. However, considering the great number of nicotine abusers, cigarette smoking is a major preventable cause of IHD. The US Surgeon General report "The health consequences of smoking" in 1983 (45) summarised the facts then known about smoking and still valid:
1 It should be considered the most important of the known modifiable risk factors for IHD.
2 Cigarette smokers experience a 70 per cent greater IHD risk than non-smokers.
3 The IHD risk increases the earlier the habit started, the more pack-years one has smoked and with an increasing degree of inhalation.
4 The use of oral contraceptives together with smoking increases the myocardial infarction risk tenfold compared to women not smoking and not using oral contraceptives.

PASSIVE SMOKING
Several studies (46 - 50) have shown a consistently increased risk of IHD after exposure to passive smoking, although in only one of these studies the results were significant. Since more people are exposed to passive smoking than the number of active smokers, this is an important study area from a public health perspective.

COFFEE
Coffee consumption has in some studies been shown to be a risk factor for IHD mortality (51) although this could not be verified in a Swedish study (52). A possible reason could be the effect of boiled but not brewed or filtered coffee in raising the s-cholesterol levels (53). There is a preference for boiled coffee in the northern parts of Sweden that separates it from most other parts of the country.

SERUM LIPIDS
A high total serum cholesterol concentration is firmly established as a risk factor for IHD. Intervention studies, both pharmacological (54) and dietary (55), have shown that a reduction in the cholesterol levels reduces IHD mortality in the setting of established coronary heart disease. High triglyceride levels and low HDL cholesterol levels are also associated with an increased risk of IHD, most often as part of a syndrome, consisting of dyslipidemia, obesity, hypertension, glucose intolerance, and hyperinsulinemia (56).

DIABETES MELLITUS
Diabetes mellitus seems to be more dangerous for women then for men. In the Framingham Study (57) the relative risk for IHD was 2.4 in men and 5.1 in women. IDDLM is associated with an even higher risk of IHD than NIDDM, with a similar sex difference.

HEMOSTATIC FACTORS
The insight that a coronary thrombus causes the majority of myocardial infarctions have caused a great therapeutic step forwards with the advent of thrombolytic therapy. The rapid adhesion of platelets to damaged endothelium is the pivotal point in the
thrombogenic pathway, and acetylsalicylic acid prophylaxis has caused the second revolution for AMI risk reduction in the setting of established coronary artery disease, after thrombolysis. The formation and incorporation of fibrin is a slower process although fibrin and platelets seem to be equally important in the thrombus formation (58). Fibrin is probably also important as a promoter of plaque growth by encouraging smooth muscle migration and proliferation (59). Prospective studies (60 - 62) have shown that an increased fibrinogen level is a risk factor for IHD in men, although after adjustment for other risk factors in the Gothenburg study, only the increased risk of stroke was significant. However, as pointed out by Meade (63), fibrinogen levels are usually high together with other recognised risk factors. The main environmental determinant of fibrinogen concentration is smoking, which causes an increase in fibrinogen levels (64), as do central obesity, high blood pressure, raised total cholesterol and hypertriglyceridemia (65).

Also fibrinolysis affects the risk for IHD. A defect fibrinolysis increases the risk of recurrence of myocardial infarction both in cross-sectional (66, 67) and in longitudinal studies (68). In the Northwick Park study, the impact of fibrinolytic activity was stronger than that of cholesterol - one standard deviation difference in fibrinolytic activity was associated with a 40% difference in IHD incidence.

SEDENTARY LIFESTYLE
Since the early reports by Morris that physically active bus conductors and postmen seemed to be protected from IHD compared to sedentary government workers (69), the benefit of physical activity and the independence of a sedentary lifestyle as an IHD risk factor has been verified in several studies (70 - 73) and meta-analyses (74). From a public health point of view, motivating the population to engage in regular exercise is second to smoking the most effective way to reduce the risk factor burden: weight, blood pressure, and pulse rate decreases, glucose tolerance and dyslipidemia improves. Maybe it is even more efficient than primary smoking cessation since smokers participating in sports activities often reduce or quit their smoking habits.

ALCOHOL CONSUMPTION
International studies on an individual level have shown that an increasing alcohol consumption causes a decrease in the risk of AMI (75, 76). Ecological studies have shown similar results but with different results in different cultural settings, with different beverage type consumption, and with different consumption patterns. Although all types of alcoholic beverages have each been shown to be the most efficient in reducing the risk for IHD, present opinion seems to favour wine (77, 78). Binge drinkers, however, appear to have an increased risk for sudden death compared to teetotallers (79).
NUTRITION
The type and amount of food people eat sets the basal level for several risk factors, e.g. obesity, diabetes mellitus, hypertension, and some hemostatic factors. Aside from personal preferences, food intake is closely associated with choice of life-style and economy. From a physician's perspective, it seems irrational to subsidise dairy fat and meat while fish is not subsidised at all. In fact, consumer prices in Sweden increased more for products like vegetables and fish than for cigarettes, alcohol and dairy fat in the years 1969-1981 (80).

OBESITY
Several cohort studies have reported a J- or U-shaped association between weight, and all-cause mortality and cardiovascular mortality (81, 82). Waaler's study in Norway found that the risk of death from CVD increased by two per cent for each kilogram increase in body weight above BMI 23. In multivariate analyses controlling for hypertension, glucose intolerance, and hyperlipidemia attenuates but does not abolish the excess IHD risk associated with obesity, suggesting that part of the excess risk is mediated via these risk factors which are more common among the obese, part is caused by obesity as an independent risk factor. Also the fat distribution affects the IHD risk. Several studies (83 - 85) have shown that abdominal (central) obesity increases the CVD risk partly mediated via the factors constituting the metabolic syndrome.

FAMILY HISTORY
Many of the above mentioned risk factors could be mediated via a positive family history for IHD. Several studies have argued that a family history is an independent risk factor, e.g. the Western Collaborative Study (86) and the Framingham study (87). This view has been challenged by the St Vincent Heart Study (88) which found little evidence to confirm a positive family history as an important independent risk factor for coronary heart disease.

PSYCHO-SOCIAL FACTORS
Cassel (89) in 1976 claimed that psycho-social factors acted as "conditional" stressors by changing an endocrine balance in the body. The result would be an increased susceptibility of the organism to direct stimuli. The clinical manifestation of this susceptibility would be determined by microbiological and physico-chemical agents within the organism, or any inborn weakness. This terminated the earlier prevailing discussion that each social process should result in a specific disease and that there should be a dose-response relationship between the social processes and the diseases. There is now scientific evidence of a causal association between e.g. a limited social network and mortality (90 - 92) as well as shift work and increased myocardial infarction risk (93).
Socio-economic factors

There is an association between a low socio-economic status and poor health. In the literature, the term "socio-economic status" has covered a wide range of factors, related to the level of education, income and income inequalities, and many other socio-economic aspects of life, sometimes referred to as "social class." Although for purpose of clarity separated here, socio-economic factors cannot and must not be regarded in isolation since they may set the stage for life-style factors.

Education

Education is a commonly used measure of socio-economic status. Questions regarding education are easy to construct and answer, highly valued by the usually well-educated researcher, and the non-response rates are low. Also, the levels of education are fairly stable after young adulthood, and not influenced by subsequent illness. However, it is possible that poor health in childhood could influence the subsequent education (94). The US National Longitudinal Mortality Study (95) showed that for those aged 25 years or older, the standardised mortality decreased as the educational level increased. Other studies (96, 97) have shown similar results.

Income

The measurement and interpretation of levels of income are complex. A low income can both reflect the influence of poor health and be an indirect cause of poor health in many parts of the world. A higher income means better access to among other things health care. Although income can be compared between different population groups, it has to be standardised for family size, type of housing and area of living. Also, other sources of income than wages have to be included (e.g. housing and child benefits) and the total wealth of the family has to be measured. Many people are unwilling to give this information. In spite of these difficulties, measures of income are strongly associated with risk of death from all causes. Rogot's study (95) showed that white men with incomes of less than $5,000 had a standardised mortality ratio 1.8 times greater than that of men with incomes of $50,000 or more. The Alameda County Study (98) showed that the association between income and mortality persisted throughout a nineteen year follow-up period. After adjusting for family size, income was grouped into four levels: very adequate, adequate, marginal and inadequate. Those in the "inadequate" group had 2.2 times the mortality of those in the "very adequate" group.

In a series of studies, Wilkinson (99 - 101) has in cross-sectional and time-series analyses found that it is not the wealth of a nation that determines life expectancy at birth but rather the distribution of the income. However, more recently, this view has been challenged with the use of more recent data than Wilkinson's (102).
**Occupation**

Also measures of occupation are difficult to evaluate. Several different ranking systems are used in epidemiologic investigations. In the USA twelve ordered categories are used, in Great Britain the population has been divided into six classes. In some of the classifications used a small farm owner could be grouped together with the chief executive officer of a multinational corporation and a skilled manual worker could have an income exceeding that of an academic. Occupation is, however, an important sign of social status in modern societies. To avoid these difficulties in classification and to provide a better correlate with measures of disease and death, Karasek (103) has suggested models based on other work-related characteristics, e.g. decision latitude and time pressure.

In the National Longitudinal Study (95) blue-collar workers had standardised mortality ratios of 1.15 or greater whereas those in professional technical occupations had a ratio of 0.80. Similar relations with increased all-cause mortality and mortality in IHD among those employed in low-status jobs have been described in several studies (104 - 107).

**Unemployment**

Several cardiovascular risk factors are associated with unemployment. Studies have shown associations with higher serum cholesterol concentrations (108, 109), heavier smoking (110), greater alcohol consumption (111) and, at least in some studies, a raised blood pressure (112). A still unanswered question is whether unemployment is an independent risk factor. A recent thesis (113) addressed this question and concluded that the traditional risk factors for ischemic heart disease only partly explained the correlations between unemployment and morbidity and mortality from cardiovascular disease.

**Living Conditions**

The material conditions under which people live can be adequately described. Often these measures are highly correlated with income level but can also be a sign of choices of different life-styles. In a longitudinal study in England and Wales (114), individuals who owned a house and a car had a lower mortality than those not owning these items. In the highest socio-economic group, the standardised mortality was 18% higher among those who rented their homes compared to those who owned their homes. In the Whitehall study (29) not owning a car was associated with a 49% higher mortality risk. After adjustment for employment grade, there was still a remaining difference of 28%.

**Migration**

There are several studies describing the relation between migration and cardiovascular risk factors. Most of these studies have described international migration, e.g. the studies on Japanese living in Hawaii and San Francisco (115), on Finnish immigrants to Stockholm (116), and the migration from the remote Pacific island of Tokelau to the
industrialised New Zealand (117). A recent thesis (118) showed that among foreign-born people, low social class, poor social network, and not feeling secure in daily life were associated with ill-health. Most previous studies have focused on ethnicity and environmental factors rather than on the migration process and few studies have described "internal" migration within a country, the cultural changes, and the subsequent changes in psycho-social circumstances as risk factors for ischemic heart disease.

ARE SOCIO-ECONOMIC FACTORS INDEPENDENT RISK FACTORS FOR IHD?
The only possibility to answer this question comes from observational studies. Essentially, this is a problem of confounding since the statistical methodology used comprises different kinds of multivariate analyses. Traditionally, in these analyses, the association between socio-economic factors and a cardiovascular outcome is tested after adjusting for other risk factors. If the relation between the socio-economic factor(s) of interest and IHD weakens with the addition of another risk factor, then this is regarded as confounding. However, the situation regarding socio-economic factors is more complex than that. Even if confounding is present, the socio-economic status could act as a determinant of the levels of the other risk factors, thus remaining an independent risk factor in spite of the evidence for statistical confounding. The question of independence is also complicated by another matter since the strongest predictive relationships are not necessarily with those factors that are causal but rather with those that most reliably can be characterised by a single measurement (119).

It is however possible to obtain indications of the independence of socio-economic status from the results of studies. The Whitehall study (120) showed a substantial gradient of cardiovascular events related to employment grades among British civil servants. The established coronary risk factors hypertension, smoking, sedentary life-style, and obesity were more prevalent in the lower employment grades but these differences did not explain all of the increased risk. When adjusting a logistic regression model for other risk factors, the relative risk of a cardiovascular event if being in a lower employment grade was still more than doubled. In a Gothenburg study (121) the relation between social class and the risk of non-fatal myocardial infarction was reduced only by 17% after adjustment for several other covariates, still remaining a strong risk factor. Other European studies (122 - 124) have shown similar findings. Taken together, this seems to imply that socio-economic factors should be regarded as independent risk factors.

OTHER RISK FACTORS?
When embarking on a study of this type it is important to realise that only about 50% of the variability in risk of cardiovascular morbidity and mortality can be explained by the well-recognised biomedical risk factors, e.g. family history, hypertension, diabetes mellitus, dyslipidemia, and smoking. This assumes that there are one or more still
unidentified factors accounting for large variances in IHD. From a biological point of view it seems unlikely that a factor which gives a large contribution to the rates of cardiovascular disease has been "missed." Rather, many of our measurements are crude and serve only as approximations for a lifetime exposition and variation in their levels. Could we make a better evaluation of the impact of an exposition during longer periods, maybe a larger proportion of the variance could be accounted for.

HEART FAILURE

PREVIOUS STUDIES
Several studies (125 - 129) have examined heart failure epidemiologically in defined populations. Incidence figures differ widely between different populations, ranging between 1 and 5 per thousand inhabitants, generally somewhat higher for males than for females. Prevalence figures are more scarce. The few reported span from 0.4% to 1%.

IMPACT OF HEART FAILURE
There are several reasons why heart failure should be an increasing problem. One is a decreased case-fatality ratio in acute myocardial infarction leading to an increased population prevalence of individuals with reduced left ventricular function, another the increasing mean population age, also leading to more people with chronic ischemic heart disease, since this primarily is a disease of the elderly. It is not known whether the incidence of acute myocardial infarction has decreased. Recent unpublished MONICA data suggests that the number of reinfarctions has decreased but a small shift in age upwards of age at myocardial infarction could have caused this finding since MONICA only takes account of persons up to age 65.
AIMS OF THE STUDIES

General aim
To evaluate major risk factors for acute myocardial infarction in Kiruna.

Specific aims
1  To quantify the main risk factors for IHD in Kiruna.
2  To study the psycho-social risk factors in Kiruna.
3  To evaluate the lipid and cholesterol ester fatty acid profiles in serum and adipose tissue as risk factors, and as possible markers for a change in habitual diet.
4  To conduct a food diary survey to evaluate the dietary risk factors for acute myocardial infarction of the inhabitants of Kiruna.
5  To make an ecological reference study on the consumption of distilled spirits, wine and beer, and mortality in IHD to use as reference to the Kiruna cohort.
6  To study the magnitude and tendencies of an important sequela of chronic ischemic heart disease, i.e. congestive heart failure.
7  To make an ecological reference study on acetylsalicylic acid consumption and mortality in IHD to compare with the situation in the studied cohort.
STUDY AREA (PAPER I)

Kiruna, the northernmost city in Sweden, covers a very large area and is sparsely populated. It is separated from the nearest neighbour city by some 300 kilometres of wilderness with some smaller villages. It was founded in the year 1900 with the exploitation of iron ore from the world's largest underground mine. The city is highly industrialised with an ongoing shift from heavy to light industry. During the years surveyed, the population decreased from about 30,000 to 27,000.

STUDY POPULATION (PAPERS I - IV)

The cases and controls were males who had been residents in Kiruna for at least five years before the AMI (or the selection as controls), they lived less than five kilometres from the city centre and they were or had previously been employed in Kiruna. Since the community is young there is a large proportion of migrants into the city. The place of origin of our cohort is according to table I. The population genetic admixture is 63% Finnish, 34% Sami, and 3% Swedish (130). Many men in the "infarction ages" received different forms of disability pensions during the time period studied and moved back to the place where they were born and raised, mainly in the Swedish part of the River Torne Valley. This in turn could have resulted in a situation with a "healthy worker effect" since the young and healthy were left in Kiruna. In turn this would give a false low mortality and morbidity in ischemic heart disease.

IDENTIFICATION OF CASES

The cases were found in the hospital register of diagnoses between 1 January 1973 and 30 April 1985. The diagnosis of AMI was based on the fulfilment of at least two of the following three criteria:

- A typical history of chest pain.
- Serial cardiac enzyme elevations.
- A typical ECG pattern of recent onset.

We found 219 patients fulfilling the medical and population-based criteria. This group constituted the cases.
Table I. Place of origin of cohort, absolute numbers and per cent. 188 individuals out of 239 (78.7%) born in "Sweden, city" were born in Kiruna.

<table>
<thead>
<tr>
<th>Origin</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland, city</td>
<td>4 (2.4)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Finland, countryside</td>
<td>11 (6.7)</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>Finland, River Torne Valley</td>
<td>1 (0.6)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Other foreign</td>
<td>1 (0.6)</td>
<td>14 (4.0)</td>
</tr>
<tr>
<td>Sweden, city</td>
<td>65 (39.4)</td>
<td>174 (49.2)</td>
</tr>
<tr>
<td>Sweden, countryside</td>
<td>48 (29.1)</td>
<td>77 (21.8)</td>
</tr>
<tr>
<td>Sweden, River Torne Valley</td>
<td>35 (21.2)</td>
<td>69 (19.5)</td>
</tr>
<tr>
<td>Total</td>
<td>165 (100)</td>
<td>354 (100)</td>
</tr>
</tbody>
</table>

IDENTIFICATION OF CONTROLS

The controls (two for each case) were matched for age and sex and selected from the internal revenue register in Kiruna, for the corresponding year, for each case. The control group thus consisted of 438 individuals. With this type of selection, some controls could have suffered an acute myocardial infarction and later have become cases, thus having been counted twice, both as cases and controls. However, in this study, there were no such events among the controls.

ACQUISITION OF DATA (V AND VII)

Statistics Sweden supplied age and sex standardised mortality statistics for ischemic heart disease (ICD9 diagnosis numbers 410 to 414), and data on the percentage of daily smokers in each county, from the Swedish Survey of Living Conditions. The Swedish Alcohol Retailing Monopoly provided data on the consumption of distilled spirits and wine countywise, the Swedish Brewers' Association supplied data on the consumption of beer for the whole nation for the surveyed years, and The National Corporation of Swedish Pharmacies provided the ASA delivery data in DDD/county.

STUDY POPULATION (VI)

This part of the study was based on in-patients on the wards of the Department of Internal Medicine at the Kiruna District Hospital. All patients discharged dead or alive after a first
event of heart failure (ICD9 numbers 428 A-X) in the years 1987 to 1994 were included in the study.
STUDY DESIGN AND METHODS

Methodological aspects
Sweden is divided into 24 administrative units, in this thesis referred to as counties, each responsible for the health care in their respective geographical area. These counties are also from other points of view separate units. It is thus possible to obtain mortality statistics for each county, and also feasible to obtain delivery data for acetylsalicylic acid and alcohol countywise.

The case-control methodology was chosen because of its cost-efficiency (1). Its main strengths are that many causal hypotheses can be evaluated simultaneously, new as well as previously evaluated, that causal as well as protective factors can be assessed, and that evaluation and control of interaction and confounding can be performed (131). The controls were randomly and retrospectively selected the same year as the case experienced the event, thus the study is a concurrent case-control study.

The Kiruna District Hospital gives care to all patients living in the catchment area. Very few patients with a symptomatic myocardial infarction (chiefly those who experienced their myocardial infarction somewhere else) have been missed. Two other groups not accounted for are most of the ones who died a sudden cardiac death (since they never reached the hospital) and those who had a "silent" myocardial infarction. These groups are fairly large, together maybe constituting as much as 50% of the total AMI population. However, it is likely that the same risk factors operate on these patients, possibly with the exception of diabetes mellitus which is more common among patients with a silent myocardial infarction (132, 133).

In defence of the ecological study
The ecological analysis has a place in the study of the etiology of diseases (134 - 137) provided that appropriate precautions are taken. The major limitation is the potential for bias in the effect estimation since the variables describe groups of individuals rather than the individuals themselves. The classical problem is the "ecological fallacy" mathematically described in 1950 (138). The most frequently cited example of this potential problem is Durkheim's study (139) of the correlation between suicide rates and religious denominations in four areas of western Europe in the nineteenth century where he found that there was a correlation between the number of Protestants and the suicide rates. In Durkheim's data it could have been the Catholics in predominantly Protestant provinces who committed suicide the more they found themselves in the minority and experienced social pressures predisposing to suicide. However, since this explanation
would have required an extremely rapid increase in the suicide rate among Catholics as the proportion of Protestants increased it seemed unlikely. Durkheim ultimately showed that this was not the case. Logically, however, it was not implausible and reveals a major contradiction in the ecological approach: the average level of an exposure factor can have a positive association with the incidence rate in the group, even when that factor is associated negatively with individual risk within the group.

Like analyses on individuals, the ecological analyses become faulty when there is confounding, but the consequences of confounding are more severe in ecological analyses. It is often difficult or impossible to control for confounding in these analyses since the existence and levels of other risk factors often is not known. The proper role of this type of analyses is to generate hypotheses about etiology and for evaluating the effects of intervention programs on the health status of target populations (4). Even if ecological analyses are confounded by factors not controlled for or even unknown, differences between populations can at least signal the presence of effects worthy of further investigation (1). Problems of studying variations in mortality between countries are reduced when looking at variations within one country or state, since there is a uniform system of death certification and registration, socio-economic and life-style differences are smaller than in international comparisons (140), and where culture and traditions are more homogeneous than in international comparisons. In addition to environmental factors, culturally determined factors, e.g. diet, are sometimes better studied on group level with regard to exposure measurement. Ecological studies are not necessarily less accurate than studies of individuals. Some biases such as interviewer bias and recall bias may even be avoided. Studies on alcohol consumption among individuals are especially hampered by "recall" bias.

**Paper I**

In 1988, a questionnaire was sent by mail to all cases (219 individuals) and controls (438 individuals) or their next-of-kin if deceased (spouse, son/daughter or brother/sister, in that order). If no reply was received, a second questionnaire was sent, and finally an attempt was made to establish contact by telephone. The persons who had left Kiruna were traced through references to other parish offices or through a central population address register (SPAR DATA).

We asked questions about birthplace, year for moving to Kiruna (for those not born in Kiruna), education, occupations, work load, psycho-social conditions on the job, tobacco use, alcohol consumption, food habits, acute and chronic diseases (stomach ulcer, diabetes, hypertension), and drug consumption. From those still alive we asked about social support. The questions asked concerned the situation during the surveyed time period 1973 to 1985.
The surviving cases and controls who still lived in Kiruna were invited to a clinical examination where we measured blood pressure, weight, height, waist and hip circumferences, serum cholesterol, triglyceride, and HDL cholesterol concentrations, and blood glucose. They also answered to a second questionnaire about their leisure time physical activity.

The occupations of the cases and controls were classified according to the Swedish socio-economic classification (141). These classes were aggregated into three groups for the social group classification: 1) professionals, higher civil servants, and executives; 2) foremen and lower white-collar workers; and 3) unskilled and semi-skilled workers.

**Paper II**
The answers from the questionnaire sent to the cases and the controls were used for the evaluation of psycho-social conditions as risk factors for IHD. The questions pertained to aspects of psycho-social risk factors on the work-site and in the social network. We asked how well the respondents got along with their work-mates and superiors, if they experienced stress (physical or psychological) at work. To get a good insight into their social network we asked how many trustworthy friends they had, from how many people they could borrow kitchen equipment, how many people they could visit without an invitation, how many that visited them without invitations, etc.

**Paper III**
Fifty cases and fifty controls were randomly selected from the original study cohort for further analyses of the serum lipoprotein and apolipoprotein concentrations and the serum cholesterol ester fatty acid composition. Comparisons were made between cases and controls and for different life-style characteristics.

**Paper IV**
We randomly selected 100 persons (34 cases and 66 controls) from the original study cohort. After having been informed by one dietician, these persons kept a food diary for seven days. Ninety-one persons (33 cases and 58 controls) completed the study. After the end of the week they returned the diary and had serum samples and an adipose tissue biopsy taken. In this study, cases and controls were compared, and the nutrition habits and results from the serum samples and adipose tissue biopsies of the whole cohort was compared to an age-matched reference cohort in Uppsala, in central Sweden.
Paper V
The national Swedish consumption of distilled spirits, wine, and beer during the years 1973 to 1986 were regressed against Swedish ischemic heart disease mortality for the years 1979 through 1987. This material was analysed longitudinally, cross-sectionally, and with time series methodology, with a time-lag with a maximum delay of fourteen years. Also the confounding effect of smoking was assessed.

Paper VI
All patients with a first event of cardiac failure, treated as in-patients at the Kiruna District Hospital between 1987 and 1994, were included. To exclude those with a prior admission with the same diagnosis, the hospital register of diagnoses was also searched for the ICD8 numbers 427.00, 427.10 and 428.99 in the time interval 1982 to 1986. Dates of admission and discharge, age, and sex of each patient were recorded. The vital status of each patient was ascertained as on 30 April 1995. For those deceased, date of death was noted and survival time from the first admission was calculated. Only the total mortality was used in this analysis since fatalities attributed to cardiac failure usually are grossly underestimated due to the coding of the underlying cause of death rather than heart failure.

Paper VII
National Swedish age standardised and sex specific death rates for IHD (ICD9 numbers 410 to 414) for the years 1979 to 1987 were modelled against acetylsalicylic acid consumption in defined daily doses (DDD)/county in multiple least squares regression. The material was analysed both for geographical and longitudinal trends, and with a time-lag with a maximum delay of fourteen years. Also in this study, smoking was analysed as a possible confounder. A re-analysis with time-series methodology was done for this thesis.
DATA QUALITY

Reliability of the data

Memory
How reliable are our data? Questionnaires are sensitive to what the respondents remember. If a long time has passed, or if the data pertain to another person, the risk of imperfect data increases. Many of the questions asked in the questionnaires in our studies were however quite specific, e.g. about pharmaceutical drugs used, tobacco and alcohol use, and certain medical diagnoses. Since the cases in our case-control study probably both were more aware of health problems and had had more contact with health care centres, there could be selective under-reporting among controls, thus giving a false high OR for hypertension, but high blood pressure has been under-reported in one study (142). For other long-standing illnesses, like diabetes, the prevalence estimation is probably more reliable (143). The questions relating to life-style, psycho-social conditions on the work-site, and social support are probably more difficult to answer, especially for the next-of-kin. If not well known, these questions were left unanswered.

Migration
Internal migration could affect the reliability of our data. Out of the 523 who answered the question on "internal migration," 335 were not born in Kiruna. Many of these people were born in the Finnish or Swedish part of the River Torne Valley. Other internal migration in our study was small (188 out of 239 born in a Swedish city were born in Kiruna) and unlikely to have had any effect on mortality rates on a county level. A study on the migration in the northern Swedish county of Västerbotten showed that 90% of those who died in that county in 1969-1978 also were resident there in 1960 (144).

Measurements
The actual measurements made on the cohort during the examinations were subjected to measurement errors. Blood pressure was recorded to the nearest 5 mm Hg. This probably has eliminated the problem of digit preference, to the cost of reduced precision. Weight was recorded to the nearest 1/10 of a kilogram and height, waist, and hip circumferences to the nearest 1/2 of a centimetre. These "anthropometric" data are probably fairly accurate. The measurement error (coefficient of variation) of "dry chemistry" for the glucose measurements is about 2.8%. Glucose tolerance varies over time (145) and also with ambient temperature (146). All serum samples were drawn and analysed during a two month period in the spring of 1989. All the lipid analyses were made in batch, and at the same time. A greater problem than the possible laboratory measurement error is the within-subject variation. It has been estimated that of middle-aged men with a single total
cholesterol value above 6.9 mmol/l, 28% have a true average value below that level (147). This error can be reduced by taking at least three samples and use the average (similarly to what is done when diagnosing hypertension). Due to limited funding this was not possible in our studies. Other biochemical measurements are probably affected to a lesser degree.

**Menu Diary Study**

The reported food intake in the food menu-diary depends on short-term memory and psychological processes since there is a selective underestimation of energy intake related to body mass index (148). Even if the recording of nutrient intake is done correctly, the diary method used in Kiruna underestimates the actual food intake by about 20%, as validated by studies with a seven day weighed food record, doubly labelled water, and measurement of urinary nitrogen excretion. The Uppsala method, with optical reading of the diary, underestimates the intake by a further 10%. The total energy underestimation in Uppsala was thus 30%. However, the relative composition of nutrients in energy% is not affected by these methodological errors. The food consumed is converted via food tables in a computer software to nutrients and non-nutritive substances. However, the nutrient content of the same food can vary depending on food type, storage conditions and methods of processing and preparation.

**Non-fasting Laboratory Measurements**

In all studies but paper IV the laboratory measurements of lipids and B-glucose were made on non-fasting subjects. This has affected the s-triglyceride levels to the greatest degree. However, most people in affluent societies are unexposed to the fasting state except for a short time in the early morning. A non-fasting sample thus more closely mirrors the milieu of the vascular endothelial cell.

**Regression Dilution Bias**

The imprecision in measurement in several variables causes distortion of the outcome in cohort studies. The (sometimes substantial) fluctuations in measurement of baseline variables, such as lipid concentrations and blood pressure, which also deviate from the individuals' usual value can lead to an underestimation of the true strength of the relationship, the so called regression-dilution bias. Is this bias also taken into account, the proportion of IHD explained by these variables is probably increased. By the use of repeated blood pressure measurements from the Framingham study, MacMahon et al (43) found that blood pressure was underestimated as a risk factor by approximately 60%. They also suggested that the same mechanism operates for cholesterol and smoking.

**Register Data**

In the ecological studies, several registers have been used: the Swedish Mortality Register, the Swedish Survey of Living Conditions, the register of the National Corporation of Pharmacies of drug delivery, The Swedish Alcohol Retailing Monopoly
on alcohol sale, and the Swedish Brewers' Association on beer sale. The first three of these registers have been validated (138, 149 - 151) and found to be reliable. Since alcohol was traded via a monopoly in Sweden during the years surveyed, all but the home-made spirits, wine, and strong beer consumption is accounted for. Thus also this register should be reliable. The figures for imported beer are obtained from official customs returns and for domestically produced beer from the Swedish Tax Authority and are thus also fairly complete.

**Hospital diagnoses**
The diagnosis of myocardial infarction was based on standard criteria, i.e. typical chest pain, typical elevations of cardiac enzymes and ECG changes. These diagnoses are probably accurate and fairly complete.

**Diagnostic criteria for heart failure**
The study of heart failure in general has been hampered by the lack of uniformly applied diagnostic criteria. In the Framingham study (152), major and minor criteria for heart failure have been used, in the British study (153) other sets of clinical criteria, and in a Scottish study (154) hospital discharge diagnoses were used. Recently more specific criteria for heart failure have been defined (155, 156) but have not been used extensively in clinical studies.

In our study we used discharge diagnoses and validated in the 1993 cohort. The diagnosis "heart failure" should be regarded as a symptom of an underlying disease which also should be noted as a diagnosis. It is probable that in some cases only the underlying diagnosis, e.g. acute myocardial infarction, has been recorded and not the episode of cardiac failure, leading to an underestimation of the problem size since false negative diagnoses have not been accounted for. The cases analysed in this study are only in-hospital patients. The milder cases of heart failure presumably treated as out-patients are not accounted for.

**Non-responders**
Among the cases there were 51/219 (23%) non-responders and among the controls there were 61/438 (14%) non-responders to the first questionnaire; most of the next-of-kin of the deceased answered to the questionnaire. The drop-out rate was higher for the clinical examinations (and thus also the second questionnaire). Out of 96 eligible cases, 58 were examined (60%) and out of 332 controls, 224 were examined (67%). In the case group 72 (43%) and in the control group 45 (12%) were deceased (see inside cover page for figure).

The answers in the questionnaires were compared for the three groups 1) examined, 2) not examined, and 3) deceased. Diabetes mellitus and a family history of AMI were
significantly more common among those deceased but there were no statistically significant differences in the prevalence of hypertension, smoking, or a family history of AMI before age 50. When only the two groups "examined" and "not examined" were compared, there were no differences at all in risk factor status, still judged from the answers to the questionnaire. Earlier analyses of non-responders in Swedish population-based studies have shown an over-representation of diseased people and people with social problems (157, 158). There is no reason to believe that the persons in our study differed from this. However, based on the comparisons between not examined and examined, there seems to be small differences in risk factor load between those two categories.
EXAMINATION PROCEDURES

PHYSICAL EXAMINATIONS
All examinations relating to papers I - III were made by a registered nurse. Blood pressure was measured in the supine position with a mercury sphygmomanometer to the nearest 5 mm Hg, after a five minute rest. The diastolic blood pressure was measured at the disappearance of the sounds (Korotkoff phase V). Weight was recorded to the nearest 1/10 of a kilogram, height, and waist and hip circumferences were recorded to the nearest 1/2 of a centimetre.

All adipose tissue biopsies were performed by the three doctors locally engaged in the study (paper IV) in Kiruna. The biopsies were sampled according to the method described by Beynen and Katan (159) where a biopsy sample was taken from the upper outer quadrant of a buttock with a needle attached to a vacuum tube. The specimens were collected in the connector between the needle and the tube and was stored frozen at -70°C protected from light.

HABITUAL DIET ASSESSMENT
The participants were given a 15-minute individual instruction by one dietician how to register their food intake in the precoded menu diary. They estimated their food intake by using full-size illustrations of portion sizes. Each registration was performed during seven consecutive days. The participants were asked to maintain their ordinary dietary habits during the period of registration. Amounts consumed were reported in household measures. The nutritional composition of the recorded intakes was calculated by using the data base at the National Food Administration (160). A validation study has been performed on the method (161).

BIOCHEMICAL ANALYSES
Non-fasting blood samples (papers I-III) were drawn and immediately frozen at -70°C for a maximum period of 2 months before analysis in batch. The lipid analyses were performed at one central laboratory using standard procedures. Cholesterol was analysed with the CHOD-PAP-method (Boehringer-Mannheim, Germany), triglycerides were determined fluorometrically after enzymatic hydrolysis, and HDL cholesterol was measured enzymatically after precipitation with sodium phosphotungstate and magnesium chloride. B-Glucose was measured immediately with a Reflotolux Glucometer (Boehringer-Mannheim, Germany).

The blood samples (paper IV) were drawn at the laboratory of the Kiruna District Hospital after an overnight fast. All samples were sent frozen to Uppsala for analyses in
batch. Triglyceride and cholesterol concentrations were determined in serum by enzymatic methods using Boehringer-Mannheim kits (Boehringer-Mannheim, Germany). The high density lipoprotein lipid concentration was determined after precipitation with a sodium phosphotungstate and magnesium chloride solution (162). The concentrations of serum apolipoproteins B and A-I were determined by turbidimetry in the Multistat III F/LS apparatus using monospecific polyclonal antibodies against apo B and A-I, respectively. Before assay the samples were preincubated with triglyceride lipase as suggested by DaCol and Kostner (163). The coefficients of variation in the apolipoprotein assays for apo B and A-I were 2.5 and 2.4 per cent respectively. The fatty acid composition in plasma cholesterol esters was determined by gas liquid chromatography (164). The concentrations of the fatty acids were expressed as relative percentage of the total number of fatty acids analysed.

Serum α-, β- and γ-tocopherol concentrations were assayed by high performance liquid chromatography (HPLC), using a fluorescence detector (165).

The adipose tissue specimens were weighed, dissolved in 1 ml hexane and homogenised in a tissue grinder at the time of analysis. The hexane was pipetted off and the residue was evaporated to dryness. Methanol was added and the fatty acids were separated by gas-liquid chromatography as described above. The concentrations of the fatty acids were expressed as relative percentage of the total number of fatty acids analysed.
STATISTICAL METHODS

The distribution curve of each continuous variable was inspected, skewness and kurtosis were measured, and occasionally the Shapiro-Wilk W (166) test was used to verify that the data were a random sample from a normally distributed variable.

The means for normally distributed variables were compared with Student's t-test and for non-normally distributed variables the Mann-Whitney U test was used for medians' comparisons. Two-sided tests were used where appropriate and p values below 0.05 were generally considered significant irrespective of the number of comparisons except for the paper on diet and coronary heart disease (paper IV) where the significance level 0.005 was chosen because of a large number of comparisons. Very small p values are denoted "<0.0001, or <0.001" others are given as exact values rather than using limits by earlier conventions.

The distribution of categorical variables between cases and controls was analysed with the Mantel-Haenszel and Pearson chi-square tests, and in case there were few persons in the cells, by the Fisher exact test. Odds ratios (OR) and 95% confidence intervals (CI) were determined. In fact, since the concurrent strategy was used, the odds ratios equal the rate ratios.

The ecological surveys were analysed with multiple linear regression. The fit of the models was assessed by the adjusted $R^2$ values and by inspection of the residual plots. In the cross-sectional analyses, least squares regression, weighted by population density was performed since the number of inhabitants varied almost 30-fold between the smallest and the largest county.

Since ASA consumption was highly intercorrelated for successive years, ridge regression technique was used (167). Ridge regression is one of several methods that has been suggested for use when there are multicollinearity problems in an analysis. In this method, a small bias is introduced into the analysis. The result is then a biased but more precise estimate since it will have a larger probability of being closer to the true parameter value (168).

Time series analyses were performed according to the method proposed by Box, Jenkins and Reinsel (5). In many time series, it is common that the data contain long-time trends. This was the case for both alcohol consumption and mortality in our series. These trends were removed by filtering. Several different filtering methods exist. In this study,
differencing (taking the difference between one years' consumption and that in the preceding year) was used (169). This means that instead of analysing the correlation between the consumption of alcohol and the mortality in IHD, we analysed the correlation between the change in consumption and the change in mortality. The removal of the long-time trends was checked by means of ACF plots (autocorrelation function; this function is obtained by calculating the correlation between a time series and itself at different lags). These filtered series were checked by means of cross-correlations to discover any time-lag effects.

The test for trend in the multiple comparisons tables was calculated according to the formula (2):

\[
\frac{(\bar{x}_1 - \bar{x}_0)^2 - (N-1)}{s^2 \left( \frac{1}{n_1} + \frac{1}{n_0} \right)}
\]

where

- \( N \) = total number of cases and controls
- \( n_1 \) = number of cases
- \( n_0 \) = number of controls
- \( \bar{x}_1 \) = mean score for the cases
- \( \bar{x}_0 \) = mean score for the controls
- \( s \) = standard deviation of the score when cases and controls are combined.

The groups were coded as ordinal variables. This equation has a \( \chi^2 \) distribution with one degree of freedom, since a straight line is supposed. This test measures the probability of monotonicity of the increase or decrease in the risk levels for exposed versus unexposed.

When testing the trend in the heart failure investigation, the Cuzick (170) extension of the Wilcoxon rank-sum test was used, with a correction for ties.

The case-control study was also analysed with unconditional maximum likelihood logistic regression techniques to control for interaction and confounding. Polytomous categorical independent variables were coded as indicator variables (171). The parameters that made a significant contribution with a p value < 0.05 in the likelihood ratio test were retained.

In the analysis of the food diary the food consumption habits and the serum levels of lipoproteins, fatty acids and tocopherols of the whole cohort was compared in a one group t-test against that of the reference cohort of 70-year old males in Uppsala.
In an effort to simplify the structure of the factors related to psycho-social well-being both at home and at the work-site and to combine several correlated variables into a smaller number of underlying dimensions, principal components analysis was performed (172). The scree curve was inspected and usually the Kaiser criterion was used for variable selection.

Life-table analysis and Kaplan-Meier product-moment correlation (173) were used for survival analysis of heart failure. For comparison of dicotomized variables, the Mantel method (174) was used since there were censored observations, and for polytomous variables the logrank test (175). To control for interaction and confounding, Cox's proportional hazards analysis (176) was performed after verification that the proportional hazards' assumption was applicable.

The software used in these analyses were SPSS (177), SYSTAT (178), STATISTICA (179) and STATA (180) for the Macintosh microcomputer.

ETHICAL ASPECTS

The studies involving patients with myocardial infarction and the controls were approved by the Ethics Committee for Human Research at Umeå University.

The computer data handling procedures were approved by the National Computer Data Inspection Board.
RESULTS

Paper I (Risk factors for acute myocardial infarction in the subarctic area).

SHORT SUMMARY: In a case-control study among men in Kiruna, 219 cases who had suffered a myocardial infarction and 438 controls without known coronary heart disease were identified. They answered to a questionnaire and were subsequently clinically examined. The main risk factors were: hypertension, a family history of AMI, diabetes mellitus, and smoking.

PARTICIPATION
The participation rate was according to table II (see also graph inside front cover).

Table II. Study cohort participation.

<table>
<thead>
<tr>
<th></th>
<th>Living</th>
<th>Deceased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Total number</td>
<td>147</td>
<td>393</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>48</td>
<td>85</td>
</tr>
<tr>
<td>The number of</td>
<td>58</td>
<td>224</td>
</tr>
<tr>
<td>survivors who</td>
<td></td>
<td></td>
</tr>
<tr>
<td>attended the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>examination</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FAMILY HISTORY
A family history of AMI carried a high OR for myocardial infarction (OR 2.2, CI 1.5, 3.2), especially if parents, or brothers or sisters had had a diagnosis of ischemic heart disease before the age of 50 (OR 2.6, CI 1.5, 4.5). In the logistic regression likelihood ratio test, a family history was still a significant risk factor when controlling for hypertension, smoking, diabetes, total s-cholesterol, s-triglycerides, and s-HDL-cholesterol, suggesting that a family history is an independent risk factor in our study population.

DIABETES MELLITUS
With the two group of diabetes, IDDM and NIDDM, considered together, OR was 2.2 (CI 1.2, 3.9).
**Hypertension**

In the questionnaire we asked whether the cohort members used drugs for hypertension during the time period 1973 to 1985. An affirmative answer to this question was considered diagnostic of hypertension. A high blood pressure was the strongest risk factor in our survey, with OR 3.5 (CI 2.3, 5.3). Dyslipidemia was more common in the group treated with antihypertensive drugs than among non-treated (Table III).

**Table III.** Treated hypertension and lipid concentrations.

<table>
<thead>
<tr>
<th></th>
<th>Treated (n=143)</th>
<th>Non-treated (n=359)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>58</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>6.56</td>
<td>6.49</td>
<td>0.68</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.9</td>
<td>2.3</td>
<td>0.008</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.99</td>
<td>1.1</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Smoking**

The label "smoker" was designated to a man smoking at least one cigarette daily, or the equivalent (one gram of tobacco). In most analyses, ever smoking, i.e. past and present smokers, were grouped together and assessed against life-long non-smokers. The OR for ever smoking was 1.7 (CI 1.1, 2.7). The stratification of the number of cigarettes smoked did not give significantly increased risks with increasing cigarette consumption, neither was the test for trend for increasing cigarette consumption significant (p=0.14). There was no significant difference in the proportion of smokers among the three social groups nor was there any difference with regard to educational level. Smoking seemed to potentiate the effect of other risk factors, with the exception for a family history of myocardial infarction (Table IV).

**Table IV.** Odds ratios for main biomedical risk factors, for smokers and non-smokers.

<table>
<thead>
<tr>
<th></th>
<th>Smokers (n=384) OR (95% CI; p value)</th>
<th>Non-smokers (n=129) OR (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (n=143)</td>
<td>3.8 (2.2, 6.4; &lt;0.0001)</td>
<td>2.4 (0.94, 6.2; 0.07)</td>
</tr>
<tr>
<td>Family history (n=204)</td>
<td>1.6 (0.99, 2.7; 0.06)</td>
<td>2.4 (0.95, 6.1; 0.06)</td>
</tr>
<tr>
<td>Diabetes mellitus (n=50)</td>
<td>2.2 (0.98, 4.9; 0.06)</td>
<td>1.2 (0.22, 7.0; 0.8)</td>
</tr>
</tbody>
</table>

**Coffee**

There were more ever smokers among those consuming more than eight cups of coffee daily (100 smokers versus 13 non-smokers). Among smokers, there was no relation between coffee intake and risk of myocardial infarction. Among non-smokers, there was
a trend with increasing risk of myocardial infarction with increasing coffee consumption (p test for trend=0.06). There was no significant correlation between number of cups of coffee/day and total cholesterol level neither for smokers nor for non-smokers but the s-cholesterol values tended to increase with increasing coffee consumption, up to eight cups of coffee per day. In the multivariate analysis, coffee was not a significant risk factor.

**USE OF WET SNUFF**

Use of snuff is common in Kiruna. Most persons used snuff together with smoking tobacco (Table V).

**Table V. Use of snuff and smoking tobacco.**

<table>
<thead>
<tr>
<th></th>
<th>Non-snuffer</th>
<th>Sniffer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-smoker</strong></td>
<td>87</td>
<td>32</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>256</td>
<td>99</td>
</tr>
</tbody>
</table>

The OR for use of wet snuff only was 0.61, CI 0.23, 1.62 and for use of both wet snuff and smoking tobacco OR was 1.14, CI 0.70, 1.85.

There was a difference among the social groups in the use of snuff, which was more common among the lower groups (Table VI).

**Table VI. Number of snuff users among the social groups.**

<table>
<thead>
<tr>
<th></th>
<th>Social group 1 (%)</th>
<th>Social group 2 (%)</th>
<th>Social group 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-snuffer</strong></td>
<td>48 (79)</td>
<td>164 (75)</td>
<td>105 (64)</td>
</tr>
<tr>
<td><strong>Sniffer</strong></td>
<td>13 (21)</td>
<td>56 (25)</td>
<td>59 (36)</td>
</tr>
</tbody>
</table>

Test for trend $\chi^2(1 \ df)=6.49$, $p=0.01$.

**MIGRATION**

Men who had moved into Kiruna had an insignificantly increased odds ratio for myocardial infarction of 1.3 (CI 0.9, 1.9). When migrants into the community were stratified by the length of their residence in Kiruna, a significant trend was noted with decreasing risk the longer time having been resident in Kiruna. The immigrants who had arrived most recently had an almost three-fold risk increase compared to Kiruna-born (Table VII).
Table VII. Crude odds ratios for myocardial infarction by length of residence in Kiruna.

<table>
<thead>
<tr>
<th></th>
<th>Kiruna-born*</th>
<th>Migrants by length of residence in Kiruna</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25+ years</td>
<td>15-24 years</td>
</tr>
<tr>
<td></td>
<td>5-14 years</td>
<td>cases</td>
</tr>
<tr>
<td>Cases</td>
<td>53</td>
<td>80</td>
</tr>
<tr>
<td>Controls</td>
<td>135</td>
<td>176</td>
</tr>
<tr>
<td>OR</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>CI</td>
<td>0.8, 1.8</td>
<td>0.8, 2.8</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*=reference category.

Test for trend $\chi^2 (1 \text{ df})=4.13, p=0.04.$

EDUCATION

Very few in the cohort had a higher education. There were no statistically significant differences in educational levels between cases and controls (Table VIII). All persons (who had answered this question) in the cohort had a complete primary school education.

Table VIII. Educational level.

<table>
<thead>
<tr>
<th></th>
<th>Cases (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary education</td>
<td>66 (100)</td>
<td>231 (100)</td>
</tr>
<tr>
<td>Vocational school</td>
<td>17 (25.8)</td>
<td>64 (27.7)</td>
</tr>
<tr>
<td>High school</td>
<td>9 (13.6)</td>
<td>36 (15.6)</td>
</tr>
<tr>
<td>University</td>
<td>2 (3.0)</td>
<td>8 (3.5)</td>
</tr>
<tr>
<td>Trained labour</td>
<td>92 (56.1)</td>
<td>191 (53.5)</td>
</tr>
</tbody>
</table>

CLINICAL EXAMINATION

There were small differences between cases and controls in individual values, not reaching statistical significance but 93% of the cohort subjected to the clinical examination (282 persons had their s-cholesterol levels measured) had cholesterol concentrations above 5.0 mmol/l (Figure 1).

LDL cholesterol concentrations were not calculated since the non-fasting triglyceride levels would have caused underestimation of the LDL levels.

High non-fasting triglyceride concentrations predicted individuals sharing many of the characteristics of the metabolic syndrome, with increased risk for myocardial infarction, high serum cholesterol concentrations, low HDL cholesterol concentrations, obesity with predominant abdominal fat distribution, and diabetes (Table IX).
Figure 1. Distribution of s-cholesterol concentrations in the Kiruna cohort. Vertical bar at s-cholesterol=5.0 mmol/l.

Table IX. Triglyceride levels as indicators of the metabolic syndrome.
(Cut-off point between upper quartile and lower three quartiles 3.6 mmol/l).

<table>
<thead>
<tr>
<th></th>
<th>Lower three triglyceride quartiles</th>
<th>Highest triglyceride quartile</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with myocardial infarction</td>
<td>40/208</td>
<td>24/74</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean s-total cholesterol (mmol/l)</td>
<td>6.43</td>
<td>7.30</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean s-HDL-cholesterol (mmol/l)</td>
<td>1.24</td>
<td>0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean body mass index (kg/m²)</td>
<td>26.4</td>
<td>27.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean waist/hip ratio</td>
<td>0.92</td>
<td>0.94</td>
<td>0.018</td>
</tr>
<tr>
<td>Number with diabetes</td>
<td>9/208</td>
<td>13/74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number with hypertension</td>
<td>48/208</td>
<td>24/74</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Among migrants there was a significant difference in HDL-cholesterol concentrations, with controls having 1.15 mmol/l, compared to 1.00 mmol/l for cases (p=0.02).
was also a significant difference in the proportion of hypertensives, 18% among controls vs. 63% among cases, p<0.001.

The differences were even greater between Kiruna-born and migrants. Migrants were more obese (BMI 27.2 vs. 25.9, p=0.004), their HDL-cholesterol concentrations were lower (1.12 vs. 1.23, p=0.02), and their triglyceride concentrations were higher (3.2 vs. 2.6, p=0.02).

**Physical Exercise**

There was no difference in the amount of exercise performed by cases and controls. Overall, 70% of cases and 79% of controls exercised regularly, giving an insignificant OR = 0.62 (CI 0.34, 1.14) for regular exercise in the classical analysis. In the multivariate analysis the OR was 0.7 (CI 0.3, 1.5) when controlling for hypertension, smoking, body weight, and a family history of IHD and the p-value in the likelihood ratio test was 0.06. There was no difference when stratifying for leisure time physical activity in winter and summer.

**Acetylsalicylic Acid Consumption**

The outset for the ecological study on ASA consumption and mortality in IHD was the unexpected finding that significantly more cases than controls used ASA several times weekly, in doses effective for pain relief (Figure 2).

![Figure 2. Distribution of consumers of acetylsalicylic acid among cases and controls in the study cohort.](chart)
Paper II (Psycho-social risk factors for ischemic heart disease among men in Kiruna, a mining town with a high cardiovascular mortality).

SHORT SUMMARY: Based on the answers to a questionnaire, the psycho-social risk factors at work and the social support were evaluated as potential risk factors for AMI. We found that the main psycho-social cardiac risk factors were job related. Strain and low decision latitude were important. We also found that the migrants had a significantly higher risk for AMI than non-migrants due to low social support and solidarity at work.

WORK
The men who had good control over their work tasks seemed to be protected from AMI (OR 0.7, CI 0.5, 0.9, p=0.02). Physical (OR 2.0, CI 1.1, 3.6, p=0.02) exhaustion on the job was also an independent and significant risk factors while mental (OR 1.5, CI 0.8, 2.7, p=0.19) exhaustion was not significant. The combination of a feeling of physical and mental exhaustion was a particularly sinister experience (OR 3.5, CI 1.6, 7.8, p=0.002. When the answers to the fifteen questions concerning well-being at work were analysed with principal components analysis, five factors were retained.

SOCIAL NETWORK
There were no significant differences in social or marital status or in social class belonging between the cases and the controls after stratification for age group. Both groups had a well established social network, insignificantly larger for the controls. The classical analysis yielded some important factors, but in the logistic regression, when controlling for the other psycho-social variables none remained significant, and in the factor analysis of five questions concerning social network only one factor was retained, suggesting that the five questions measured the same dimension that not separated the cases from the controls to a significant degree.

MIGRATION AND PSYCHO-SOCIAL FACTORS
For migrants, heavy physical work was a significant risk factor (OR 3.4, CI 1.1, 10.1, p=0.03) but not for those native to Kiruna. There were no significant differences in risk between the men born in Kiruna and those who were not born in Kiruna with regard to job-related psycho-social strains (decision latitude, dexterity, and monotony). Both the cases born in Kiruna and the migrants who experienced poor solidarity at work had an increased risk of AMI but the risk was significant (p=0.006) only among the men who were not born in Kiruna.
Paper III (Fatty acid composition in serum after myocardial infarction. Do survivors change their dietary habits?).

**SHORT SUMMARY:** Serum lipid and apolipoprotein concentrations and the cholesterol ester fatty acid composition in serum were analysed in a subset of our cohort. Judged from the serum fatty acid composition, the diet was not nutritionally more favourable after the myocardial infarction. The difference in fatty acid composition between cases and controls and also between the men in our cohort and other Swedish male populations is compatible with a dietary origin of the high lipid levels in serum.

**Lipoproteins**
There were no significant differences with regard to serum lipid or lipoprotein lipid concentrations between cases and controls.

**Cholesterol ester fatty acid**
Also for the cholesterol esters the differences were small. The cases had significantly higher proportion of palmitoleic acid compared to controls (4.9% and 4.0%, respectively, p=0.004) and somewhat higher concentrations of palmitic acid (12.5% versus 12.1%, p=0.06) than controls while the mean value for linoleic acid was lower among cases (50.3% versus 51.6%, p=0.21), although not to a significant degree.

When controlling for serum lipids, HDL-cholesterol, serum apolipoproteins and the different cholesterol ester fatty acids, the proportion of palmitoleic acid (16:1) was significantly associated with myocardial infarction (p=0.001), whereas oleic acid was significantly protective (p=0.027).

There were strong correlations (p<0.001) between body mass index (BMI) and the proportions of 16:1, 18:1, 18:2 n-6, 18:3 n-3, and 20:3 n-6, but no statistically significant correlations between waist-hip ratio and the same cholesterol ester fatty acids.
Paper IV (Dietary habits and fatty acid composition in serum and adipose tissue in survivors after myocardial infarction. A case-control study in Kiruna, a mining town with high mortality in ischemic heart disease).

SHORT SUMMARY: Based on a seven day food menu-diary, the habitual food intakes of cases and controls, and of the Kiruna cohort and that of a reference population in Uppsala were compared. Also lipoproteins, fatty acids in serum cholesterol esters and adipose tissue triglycerides, and serum tocopherols were measured. There were small differences between cases and controls, and also between the two cohorts but our results could indicate a more favourable antioxidative status in the Uppsala cohort.

DIFFERENCES BETWEEN CASES AND CONTROLS
There were no significant differences in intake of nutrients, vitamins, or trace metals. There was a non-significant greater intake of monounsaturated fatty acids among controls.

DIFFERENCES BETWEEN THE KIRUNA AND UPPSALA COHORTS
The diet of the Kiruna men was characterised by higher intake of carbohydrates but there were no differences in relative food composition. Compensating for the methodological error, the men in Uppsala consumed slightly more calories than the men in Kiruna. The intake of polyunsaturated fatty acids was higher in Uppsala than in Kiruna and the intake of selenium higher in Kiruna. There was no difference in intake of vitamin E, measured as α-tocopherol equivalents (Table X).

DIFFERENCES IN SERUM LIPIDS, LIPOPROTEINS, CHOLESTEROL ESTER FATTY ACIDS, AND ANTIOXIDANTS BETWEEN THE KIRUNA AND UPPSALA COHORTS
The serum composition of fatty acids differed between Kiruna and Uppsala, with higher proportions of short-chain fatty acids in Kiruna and lower proportion of linoleic acid. The γ-tocopherol was significantly lower in Kiruna (0.15 µg versus 0.20 µg, p<0.001) but there were no differences in α- and β-tocopherol levels (Table XI).

DIFFERENCES IN ADIPOSE TISSUE FATTY ACIDS BETWEEN THE KIRUNA AND UPPSALA COHORTS
There were no major differences in the composition of adipose tissue triglyceride fatty acids between Kiruna and Uppsala. The differences in serum were largely mirrored in the adipose tissue triglycerides but the Kiruna cohort had a greater proportion of 22:5 n-3 and 22:6 n-3. Thus, the proportions of short-chain fatty acids was higher and the proportion of linoleic acid was lower in Kiruna than in Uppsala.
Table X. Differences between the Kiruna and Uppsala male cohorts in reported daily intake of energy and some nutrients (E%=energy%, SFA=short-chain fatty acids, MUFA=monoun-saturated fatty acids, PUFA=polyunsaturated fatty acids).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kiruna (SD)</th>
<th>Uppsala (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>91</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Energy, kcal/MJ</td>
<td>1,942 (492)/8.1 (2.1)</td>
<td>1,798 (531)/7.5 (2.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Energy, kcal (corrected for method error)</td>
<td>2,400</td>
<td>2,550</td>
<td>0.03</td>
</tr>
<tr>
<td>Protein, g</td>
<td>73 (20)</td>
<td>68 (19)</td>
<td>0.01</td>
</tr>
<tr>
<td>Protein, E%</td>
<td>15.5 (2.4)</td>
<td>15.7 (2.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>238 (64)</td>
<td>211 (67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbohydrates, E%</td>
<td>50.0 (6.4)</td>
<td>47.6 (5.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fat, g</td>
<td>73 (26)</td>
<td>72 (25)</td>
<td>0.82</td>
</tr>
<tr>
<td>Fat, E%</td>
<td>32.6 (6.0)</td>
<td>35.3 (5.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>E% SFA</td>
<td>14.4 (3.4)</td>
<td>15.3 (3.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>E% MUFA</td>
<td>11.3 (2.0)</td>
<td>12.4 (1.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>E% PUFA</td>
<td>4.7 (1.2)</td>
<td>5.3 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α-tocopherol equivalents, μg</td>
<td>5.7 (2.5)</td>
<td>6.1 (2.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Selenium, mg</td>
<td>31.1 (10.6)</td>
<td>26.7 (7.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table XI. Differences between the Kiruna and Uppsala cohorts of 70-year old males in lipid corrected serum tocopherol (μg/mmol) and cholesterol ester fatty acid composition (expressed as percentage distribution).

<table>
<thead>
<tr>
<th>Serum</th>
<th>Kiruna (SD)</th>
<th>Uppsala (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>91</td>
<td>855</td>
<td></td>
</tr>
<tr>
<td>α-tocopherol</td>
<td>1.60 (0.36)</td>
<td>1.61 (0.30)</td>
<td>0.85</td>
</tr>
<tr>
<td>β-tocopherol</td>
<td>0.04 (0.01)</td>
<td>0.04 (0.01)</td>
<td>0.93</td>
</tr>
<tr>
<td>γ-tocopherol</td>
<td>0.15 (0.06)</td>
<td>0.20 (0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>16:0</td>
<td>12.26 (0.88)</td>
<td>11.77 (0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>16:1 n-7</td>
<td>4.57 (1.63)</td>
<td>3.75 (1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18:0</td>
<td>1.25 (1.23)</td>
<td>0.96 (0.21)</td>
<td>0.035</td>
</tr>
<tr>
<td>18:1</td>
<td>21.34 (2.26)</td>
<td>20.50 (2.26)</td>
<td>0.001</td>
</tr>
<tr>
<td>18:2 n-6</td>
<td>49.91 (4.80)</td>
<td>52.21 (4.52)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Paper V (Alcohol and ischemic heart disease mortality in Sweden).

**SHORT SUMMARY:** The relation between alcohol consumption and coronary heart disease mortality was examined in an ecological study in the total Swedish population. There was a negative correlation between consumption of wine and mortality in IHD for both men and women, in spite of a positive correlation between smoking and wine consumption. There was no correlation between distilled spirits and beer consumption and IHD mortality.

**CROSS-SECTIONAL ANALYSIS**
In the geographical univariate analysis, consumption of spirits and wine ethanol did not seem to have any statistically significant influence on IHD mortality for either sex.

In the cross-sectional multiple regression model, controlling for cigarette smoking, spirits ethanol consumption was associated with an increased mortality and wine ethanol consumption with a decreased mortality for males. The adjusted $R^2$ for the whole model was 0.10 ($p=0.02$). Also for females, spirits consumption was associated with increased mortality whereas wine seemed to be protective. The adjusted $R^2$ for this model was 0.31 ($p<0.001$).

**LONGITUDINAL ANALYSIS**
In the longitudinal analysis spirits ethanol was associated with an increased IHD risk for both males (correlation coefficient 0.66, $p=0.01$) and females (correlation coefficient 0.72, $p=0.003$). Wine seemed to be protective for both sexes (correlation coefficient for males -0.74, $p=0.002$, for females correlation coefficient -0.99, $p<0.001$). For males, beer ethanol consumption was not associated with IHD mortality, but for females beer ethanol consumption was associated with increased IHD mortality (correlation coefficient 0.70, $p=0.006$). In the time lag analyses there were no correlations between spirits, wine and beer consumption and IHD mortality.

**TIME-SERIES ANALYSIS**
There was a statistically significant negative correlation between female mortality and wine consumption (-0.57, $p=0.04$) but no statistically significant correlations, positive or negative, between any other female or male ethanol consumption and mortality. There were neither any significant correlations in the time-lagged analyses between mortality and ethanol consumption.
Paper VI (Clinical epidemiology of heart failure. Experience in a rural hospital).

**SHORT SUMMARY:** The incidence and prognosis of heart failure was calculated from a hospital-based population between the years 1987 and 1994. The incidence increased during the surveyed years, approximately equal for males and females. The prognosis did not seem to be better during the later years. Female sex carried a better prognosis with a 27% risk reduction. Being one year older increased the hazard ratio by 3.5%.

The incidence of heart failure increased during the surveyed years. For males, the incidence was 1.4 in 1987 and 2.7 in 1994 (p=0.17). For females, the figures were 1.4 and 2.5 (p=0.08), respectively.

The causes of heart failure (based on the 1993 cohort) were according to table XII.

**Table XII.** Etiology of heart failure.

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>28 (47)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (28)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>60 (100)</strong></td>
</tr>
</tbody>
</table>

The one-year survival was 67% for the whole group. The survival decreased with increasing age (Table XIII).

Age was of profound importance in several aspects of heart failure. With increasing age, survival worsened, incidence increased, and demand of in-hospital care increased (Table XIV).

In Cox's proportional hazards analysis, female sex carried a 27% reduced hazard ratio, an age increase of one decade increased the hazard ratio by 35% and each additional day spent on the ward increased the hazard ratio by 1.8%.
Table XIII. One- and three-year survival experiences in different groups expressed as proportion surviving.

<table>
<thead>
<tr>
<th>Group</th>
<th>One-year survival</th>
<th>Three-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group</td>
<td>0.67</td>
<td>0.48</td>
</tr>
<tr>
<td>Males</td>
<td>0.65</td>
<td>0.46</td>
</tr>
<tr>
<td>Females</td>
<td>0.68</td>
<td>0.50</td>
</tr>
<tr>
<td>1987-1990 cohort</td>
<td>0.66</td>
<td>0.47</td>
</tr>
<tr>
<td>1991-1994 cohort</td>
<td>0.67</td>
<td>0.48</td>
</tr>
<tr>
<td>Age &lt;61</td>
<td>0.95</td>
<td>0.79</td>
</tr>
<tr>
<td>Age 61-70</td>
<td>0.73</td>
<td>0.50</td>
</tr>
<tr>
<td>Age 71-75</td>
<td>0.64</td>
<td>0.51</td>
</tr>
<tr>
<td>Age 75-80</td>
<td>0.61</td>
<td>0.46</td>
</tr>
<tr>
<td>Age &gt;80</td>
<td>0.60</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Table XIV. Mean duration of in-patient stay by age-group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;61</td>
<td>6.2</td>
</tr>
<tr>
<td>61-70</td>
<td>9.8</td>
</tr>
<tr>
<td>71-75</td>
<td>11.6</td>
</tr>
<tr>
<td>76-80</td>
<td>12.8</td>
</tr>
<tr>
<td>&gt;80</td>
<td>12.8</td>
</tr>
</tbody>
</table>
Paper VII (Mortality in ischemic heart disease and consumption of acetylsalicylic acid – an ecological study).

SHORT SUMMARY: An ecological study was performed to study the relationship between ASA consumption and mortality in IHD on a national Swedish level. Even taking the potential confounding of smoking into account there was a positive relation between the ASA consumption and the mortality in IHD in the geographical and longitudinal analyses but not in the time-series analysis.

CROSS-SECTIONAL ANALYSIS
In the geographical study there was a positive relation between amount of ASA in DDD/1,000 inhabitants sold (1 DDD = 3 g) and the mortality in IHD, for both males (p=0.003, $R^2=0.32$) and females (p=0.04, $R^2=0.17$).

LONGITUDINAL ANALYSIS
In the time trend analysis, for all tested age groups and both sexes, there was a significant positive correlation between amount of ASA sold and mortality for successive years (p<0.001, $R^2=0.96$).

TIME-SERIES ANALYSIS
The material was also re-analysed with time-series methodology, after the original publication. After filtering of the series, the removal of non-stationary trends was checked with ACF (autocorrelation function) plots and cross-correlation with different time-lags were done. In this analysis type, there was no significant correlation, positive or negative, between mortality in IHD and consumed ASA neither the same year nor with the consumption in the preceding years (Table XV).

Table XV. Results of the filtered time-series analysis of male and female IHD mortality and consumption of ASA.

<table>
<thead>
<tr>
<th></th>
<th>$R^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>0.0001</td>
<td>0.985</td>
</tr>
<tr>
<td>Males</td>
<td>0.36</td>
<td>0.07</td>
</tr>
</tbody>
</table>
DISCUSSION

Case-control studies

FAMILY HISTORY (PAPER I)
The reason for the family history of IHD to act as a risk factor is multifactorial. There could be a genetic susceptibility to the effects of individual risk factors, a greater predisposition to individual risk factors, a primary genetic predisposition to atherosclerosis, or to these factors in any combination. The high genetic admixture of Finnish genes makes one expect an increased mortality in IHD (130). On the other hand, many intrafamilial shared environmental factors operate within this category, e.g. cooking traditions, smoking habits, leisure time physical activity, etc. Hypertension, the most powerful risk factor in our study, could be caused by both genetic and environmental factors, as could dyslipidemia.

A study from South Africa (181) has shown that a family history of IHD appeared to exert its effect partly independently of known risk factors and partly dependently through age, total cholesterol minus HDL cholesterol, and HDL cholesterol, suggesting that genetic as well as reversible environmental risk factors contribute to the incidence of myocardial infarction. Several possible genetic mechanisms have been described. The best understood disorder is probably familial hypercholesterolemia which arises from mutations of the LDL receptor gene, leading to accumulation of LDL particles in plasma. More than 150 mutant alleles have been described, resulting in the occurrence of familial hypercholesterolemia in between one in 50 and one in 500, depending on ethnicity and geographic location (182). Familial combined hyperlipidemia consists of increased levels of cholesterol, or triglyceride, or both, in patients with IHD and their relatives (183). There is also a strong association between serum levels of Lp(a) and IHD. Lp(a) is under strong genetic influence (184).

Apolipoprotein E is a protein constituent of several plasma lipoproteins. A Finnish study (185) showed that the frequency of the apo E4 allele was significantly higher in the group with IHD when compared to a non-IHD group. It has been shown that the E4 allele is more frequent in Finland and Sweden than in non-Nordic countries (186).

A family history score has been developed that identifies IHD cases better than simple family-history definitions (187). Further studies with this score have pleaded for gene-environment interaction contributing to phenotypic expression. In high-risk families
(defined by hypertension and dyslipidemia) cigarette smoking was particularly dangerous (188).

However, there are at least two good reasons for assuming a limited impact of genetic factors:

Firstly, international migration studies have shown that the migrants bring their pattern of disease with them and that the morbidity and mortality in IHD with time approaches those of the host country, e.g. the study of Finnish men in Stockholm (116) reducing their incidence of myocardial infarction or the study of Japanese in Hawaii and California (189) increasing their rates. Genes do not change that quickly.

Secondly, there have been large changes in mortality rates in several countries (190). In the USA the death rate from IHD decreased by 48% from 1970 to 1985, in Japan the rate decreased by 39% in males and 30% in females during the same period. In Eastern Europe, rates have increased among males in Bulgaria by over 60% and Poland by almost 40% during the period 1970 to 1985. Genetic changes do not occur at those rates.

**Diabetes mellitus (Paper I)**

Both insulin-dependent diabetes mellitus (IDDM) and non insulin-dependent diabetes mellitus (NIDDM) are associated with an increased risk for IHD (191). The Framingham study found that the diabetics in the study cohort after 20 years of follow-up had a twofold to threefold increased risk of clinical atherosclerotic disease (192). As well the odds ratio (2.2) as the etiologic fraction (8%) are probably underestimated since the patients with a silent myocardial infarctions not coming to the hospital are not accounted for. Diabetes mellitus is also associated with several other diseases leading to death (e.g. stroke and renal insufficiency) possibly causing a premature death before these patients could have suffered a myocardial infarction.

**Hypertension (Paper I)**

In our study hypertension was defined as being treated with a drug for hypertension during the time period 1973 to 1985. Some patients could thus have developed overt hypertension after the event of myocardial infarction. Since the patients with a myocardial infarction have been more in contact with the health care system, there is also a greater chance that a hypertensive state would been discovered among them. However, it is likely that the metabolic disturbances are present early in the hypertensive process or even precede the raised blood pressure (193).

Since treatment of hypertension alone has not reduced the mortality in IHD as much as expected, it seems likely that the metabolic aberrations are of equally great significance to
the heart as the blood pressure *per se*. It has been suggested that one reason for this could be an adverse effect of commonly used antihypertensive drugs (chiefly diuretics and betablockers) on serum lipid concentrations. Also in our cohort there were differences in lipid concentrations between hypertensives and normotensives. This could in part account for the increased risk among treated hypertensives. However, even when controlling for HDL cholesterol and triglycerides in a logistic regression model, antihypertensive treatment remained a strong risk factor in the likelihood ratio analysis, suggesting that hypertension indeed is an independent risk factor also in our population.

There is a possibility that some of the drugs could have been instituted for other diagnoses than hypertension (e.g. diuretics for heart failure and betablockers for heart rhythm disturbances or angina pectoris) but, since the drugs are used also for hypertensive patients, the patients might have believed that they also had hypertension. In this case the number of people with hypertension are overestimated as is the OR. A British study (cited in 194) found that over 80% of patients in surveyed age classes were aware of the purpose of their medicine. If the two groups, "Knows purpose of medicine" and "Knows something of purpose" were combined, 95% of respondents answered affirmative. It thus seems reasonable to believe that the diagnosis of hypertension was fairly accurate. In the subset who met up for the clinical examinations, there were no differences in systolic blood pressure (150 for normotensives vs. 155 for treated, p=0.07) but the diastolic blood pressures were higher for treated hypertensives (89 vs. 86, p=0.02).

**TOBACCO USE (PAPER 1)**

Smoking is a powerful risk factors for several diseases (195), among them ischemic heart disease, which has been known since the mid-1960s (196). The 40 years' observation on British male doctors (197) revealed that the earlier estimated risks had been underestimated and that the death rate ratios during 1971-91 were approximately threefold at ages 45-64 and twofold at ages 65-84 comparing continuing cigarette smokers with life-long non-smokers. It is also important to realise that risk factors act synergistically. Our figures with increased odds ratios for smoking in combination with either hypertension or diabetes mellitus, compared to non-smoking diabetics and hypertensives, attest to this.

In the northern part of Sweden use of snuff is common. The WHO MONICA study (198) did not find an increased risk for acute myocardial infarction in connection with snuff dipping. Neither did our study show an increased risk for IHD with use of wet snuff.
COFFEE (PAPER I)
Recent studies (199, 200) have shown that the diterpenes cafestol and kahweol, present in oil droplets in boiled but not filtered coffee, raise s-cholesterol levels in humans. In the northern part of Sweden, 47% of the men and 33% of the women drink at least five cups of coffee daily, 48% in the form of boiled coffee (201). Since there is a correlation between smoking and coffee drinking, and smoking is a strong risk factor, the effect of coffee was seen only as a tendency among non-smokers in the univariate analysis and not in the logistic regression.

MIGRATION (PAPER I-II)
Relocation can be a risk factor for disease. Already in 1961 it was suggested that recent migrants to an industrial milieu are likely to manifest increased risks of psychosocial, somatic, and social ill health (202). A study among Finnish immigrants to Sweden (116) concluded that the environmental factors dominated the explanation for the difference in the relative risk of developing myocardial infarction since the relative risk decreased from the indigenous Finnish to approach the Swedish risk. The studies on Japanese immigrants to Hawaii and California (115, 189) showed that the rates for heart disease increased to approach those of the host country. The reasons for this was hypothesised to be factors related to social support and life-style.

Most migrants to Kiruna came from rural areas surrounding Kiruna, in particular the Finnish and Swedish River Torne Valley. The admixture of Finnish genetic material is even higher in this area than in Kiruna [75% Finnish, 25% Sami, and 0% Swedish (130)]. The resettlement in Kiruna meant for many of those migrants loss of social network, loss of social ranking and living alone during the weekdays and returning "home" for the weekend. It also meant a different life-style where the pace of work following the natural variations in daylight and season of the year was lost for industrial work following a clock.

LIPID LEVELS (PAPER I, III AND IV)
In the classical analysis the triglyceride concentration was a significant risk factor (OR 2.0, CI 1.1, 3.6) but as has been found in numerous studies it lost its significance in multivariate regression analysis. The reasons for this in our study appears to be the close association of the metabolic syndrome with raised non-fasting triglyceride levels where cholesterol, body mass index, waist/hip ratio, and diabetes mellitus act as confounders.

There was no significant difference in total cholesterol concentration between cases and controls. One reason for this might be that over 90% of the cohort had levels where some sort of intervention is considered necessary, i.e. above 5.0 mmol/l. If almost the whole group has hypercholesterolemia this factor per se cannot constitute a statistical risk factor.
in our population even if it is recognised as a biological risk factor in several studies. On
the other hand, an increased risk with increasing cholesterol concentrations would have
been expected. The statistical outcome depends upon how the comparisons were made.
We chose to compare the top quartile with the three lower quartiles agglutinated. Had we
instead chosen to compare the top quartile with the lowest quartile, OR would have been
2.4, CI 1.1, 5.2, suggesting that it is more dangerous to have a high cholesterol
concentration than a low one.

**Physical Exercise (Paper I)**

Several studies have addressed the question of whether a high level of physical activity
protects from coronary heart disease. The Harvard Alumni Study (203) showed that even
when controlling for hypertension, smoking, body weight, and a family history of IHD,
physical activity was protective. In the Whitehall studies (204) there was a strong trend to
decreasing mortality in IHD with increasing levels of physical activity as in the London
Transport studies (205) where the physically active conductors ran a lower risk of
myocardial infarction than the more sedentary drivers. Several other studies (71, 73, 206
- 209) have confirmed that a sedentary life-style is associated with about twice the risk of
a heart attack.

In our study physical exercise was marginally significantly protective with a p value in the
likelihood ratio test of 0.06. There could be two possible explanations to the lack of
significance:

Firstly, the questions about exercise concerned the situation at the time of the second
questionnaire. Some myocardial infarction victims may have taken up a healthier life style
after the event, diluting the difference between cases and controls.

Secondly, hunting, fishing, and trekking have always been an integral part of the life
style of many men in Kiruna probably to an equal degree among cases and controls. This
may also account for the lack significance of physical activity.

**Psycho-Social Factors (Paper II)**

Unfavourable factors in the social environment increase the risk for ischemic heart
disease. The paper by Cassel (89) initiated much research in this area. The Whitehall
study (29) found that differences in smoking, obesity, physical activity, blood pressure
and plasma cholesterol only partly explained differences in morbidity and mortality and
that there was a steep inverse association between social class and mortality from several
diseases, although the use of social class as an index of socio-economic position led to
underestimation of the association between social factors and mortality. The Whitehall II
study 20 years later (204) showed the same inverse association between employment
grade and angina pectoris and ECG evidence of ischemia. There were employment-grade
differences in health-risk behaviour including smoking, diet and exercise. Differences were also found in low control over the work situation, low satisfaction with work and in social support among the lower grades.

The results of our study suggest that the concept of well-being at work is complex since five factors were needed to explain only 62% of the combined variance of the fifteen variables. The five factors could broadly be grouped into 1) control over the work tasks, 2) pace of work, 3) how well the worker got along with superiors and work-mates, 4) self-esteem and appreciation of work, and 5) variability of the job tasks. In the classical analysis, control over job tasks seemed to be the most important (p=0.025) but the saturated logistic regression model selected social network on the worksite, i.e. the questions on how well the worker got along with superiors and work-mates as the most important (p=0.042). In the logistic model none of the other factors were significant.

Swedish studies have largely reported similar findings. Orth-Gomér (210) reported that lack of social support and smoking were the two leading risk factors for IHD in the Gothenburg study of 50-year-old men. The study of men born in 1913 and 1923 in Gothenburg found from multivariate analysis that a low level of social activities was significantly related to cardiovascular mortality (211). The result is similar in our study, especially with regard to the factor analysis, where only one factor accounting for almost 60% of the combined variance of the six variables was retained.

The social class concept was invented to account for differences in material well being, among other factors. In our study the social classes were constructed with regard to type of work, much like the grading of the Whitehall Civil Servants. In Kiruna, however, differences in social class belonging are not reflected in differences in material well being to the same extent as in other societies which could account for the lack of effect of social grouping.

The work organisation also has an impact on the risk for IHD. The London Transport study (205) showed that bus drivers had a higher mortality in IHD than the conductors because of differences in systolic blood pressure and serum cholesterol concentrations, the two major risk factors. One proposed explanation was the difference in the amount of physical exercise during work, but psychosocial factors were touched upon. Interestingly, reference was made to the "nervous strains of bus-conducting," although the drivers ran the higher risk of myocardial infarctions. With knowledge of today's central London traffic, we would assume that the nervous strain was higher among the drivers. Karasek (212) originally showed that the combination of high demands and low decision latitude was a work related health risk factor. Subsequent studies (213 - 216)
also have related monotonous and non-learning work to an increased risk for myocardial infarction.

Deficiencies in social support at home and at work are thus risk factors for myocardial infarction. This does not explain why a person exposed to these risk factors eventually will get his disease. There are at least two reasons for why a person has a limited social network, why he does not get along with work-mates etc. One reason might be that he is shy and reserved and actively rejects close contacts, the other that his surrounding rejects contacts with him and repels him. It is reasonable that these two different mechanisms may result in different risks. We could not discriminate between these two causes of a limited social network in our study.

What is then the link between the psychological signal and the pathophysiological response, leading to plaque instability and rupture, increased thrombocyte aggregability, vasospasm, reduced fibrinolysis, and ultimately acute myocardial ischemia? It has been suspected that catecholamines mediate at least part of this relationship. A poor social network and a boring job has been associated with elevated plasma adrenaline levels at rest (217) and high urinary catecholamine excretion (218). Poor decision latitude has also been found to be correlated to a high urinary catecholamine excretion (219) and mental stress has been shown to increase platelet aggregability (220) and activation of the fibrinolytic system with increases in t-PA activity (221, 222).

Another biological link is the relation between coagulation factors and catecholamines. A boring work or work strain has been related to high plasma fibrinogen levels (223).

The third possible "missing link" is serotonin. At least depression is associated with a disorder of serotonin metabolism. A novel effective treatment is serotonin receptor uptake inhibitors. Thrombocytes, macrophages, and coronary arteries (224) contain serotonin receptors. Animal studies (225, 226) have shown that the serotonin receptor antagonists enhances the effects of conventional thrombolytic therapy. Patients with a recent acute myocardial infarction suffer a substantially increased risk of death if depressed.

**LDL CHOLESTEROL**

A high concentration of LDL cholesterol is associated with an increased risk of coronary heart disease (227, 228). The Northern Sweden MONICA study confirmed high levels of serum cholesterol in the area (229). In our study, the LDL cholesterol concentrations were not calculated since the triglyceride concentration was measured non-fasting.

**HDL CHOLESTEROL (PAPER I, III AND IV)**

The importance of a low HDL cholesterol concentration has been controversial (230, 231). British studies have found that a high HDL concentration independently offers
protection against coronary heart disease (232, 233). A Swedish study found a strong protective effect of HDL2, among males who had survived a myocardial infarction below the age 45 and with normal triglyceride values (234). In the Framingham study (235), the ratio \( \frac{\text{Total cholesterol}}{\text{HDL cholesterol}} \) provided the best lipid risk profile. In the Kiruna cohort, the values of this derived variable were very skewed. The median for cases was 6.5 and for controls 5.7 (p=0.02).

**TRIGLYCERIDES (PAPER I, III AND IV)**

Also the role of triglycerides in coronary heart disease has been controversial. In many epidemiological studies, triglycerides have not been independent risk factors in multivariate statistical modelling (236). However, several studies have revealed that the triglyceride concentrations were independently related to IHD risk, also in multivariate modelling (237 - 239). A Swedish study on elderly men showed that the incidence of coronary heart disease was related to blood pressure, smoking habits and serum triglycerides both in univariate and multivariate analyses (240). The PROCAM study (241) and the Helsinki Heart Study (242) showed that if the LDL/HDL ratio was above 5, the triglyceride concentration was related to IHD incidence.

Most studies on triglycerides as risk factors for IHD have been carried out in the fasting state. However, a recent study (243) found that non-fasting triglyceride concentrations were independent predictors of CAD in multivariate modelling and equal to that of apolipoprotein B, the most discriminatory fasting parameter.

**LIPID-LOWERING STUDIES**

An indirect evidence of the importance of serum lipid levels, especially the LDL cholesterol concentration, comes from the atherosclerosis regression studies. As well regression of atherosclerotic plaques (244) as regression of plaques and reduced incidence of cardiovascular events (245) have been shown after lipid lowering therapy.

Recently published studies have shown a decrease in coronary atherosclerosis (246) and reduced mortality, reduced incidence of myocardial infarctions, as well as reduced need for by-pass surgery and PTCA (54) for patients treated with the lipid-lowering drug simvastatin. A clue as to whether cholesterol reduction could act as primary prevention is given by a Scottish study (247), which found that treatment with a lipid-lowering drug significantly reduced the incidence of myocardial infarction and death from cardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction.

**FOOD DIARY STUDY (PAPER IV)**

Our prospective food diary study illustrates well the difficulties that are inherent in efforts to chart food habits (248). The reported caloric intake was after correction for
methodological error that expected. However, food habits are affected by any intervention, be it only recording of what people eat. A possible reason for the absence of a difference between cases and controls (apart from the possibility that there is no difference) is that the cases in the study cohort became more aware of their consumption habits and made nutritionally better choices. This may also account for the few differences in intake between Kiruna and Uppsala. The men in Uppsala in fact consumed more fat than the men in Kiruna (35.3 energy% versus 32.6 energy%) but one of the few statistically significant differences in fat consumption was a relatively greater intake of polyunsaturated fats in Uppsala.

The interpretation of differences in proportions of fatty acids is difficult because of the mathematical interdependence of the constituents. Thus, differences between cases and controls should be interpreted cautiously but differences between the two cohorts in Uppsala and Kiruna have been affected to a lesser degree. There were small differences in the fatty acid composition in cholesterol esters as well as in adipose tissue triglycerides between cases and controls, suggesting that they had changed their food intake to an equal degree. Substantial differences were found between the whole Kiruna cohort and the reference cohort in Uppsala. These differences were mainly to the disadvantage of the Kiruna cohort and the low serum γ-tocopherol concentrations, high proportion of short-chain fatty acids and low proportion of linoleic acid could increase the risk of IHD in the whole Kiruna population provided these results could be extrapolated.

The men in Kiruna had a greater intake of selenium. Probable sources for this trace metal are reindeer meat and fish, supported by the fact that the adipose tissue triglyceride proportion of 22:5 n-3 and 22:6 n-3 (fish fatty acids) was greater in Kiruna than in Uppsala. Several studies have found an increased risk of cardiovascular disease with low intake and serum levels of vitamin E (249, 250) and selenium (251). However, the "selenium hypothesis" has been contested (252 - 254), also a Swedish study (255) failed to show an association between selenium and CVD. Ecological studies have shown that dietary α-tocopherol may provide at least as good an explanation as wine consumption for the paradoxically low rates of IHD in the Mediterranean countries (256). The biological and antioxidant effects of the different forms of vitamin E differ, however. γ-Tocopherol has about one-half the antioxidant activity and one-tenth the biologic activity of α-tocopherol (257) but γ-tocopherol more efficiently detoxifies nitrogen dioxide into nitrogen oxide than α-tocopherol (258), thus scavenging free radicals that otherwise can increase lipid oxidation.

A recent study from Uppsala (259) comparing a group of patients with ischemic heart disease and a control group free from this disease, showed that the patients had significantly lower levels of γ-tocopherol than the control group. Also in our studies the
l lipid corrected \(\gamma\)-tocopherol concentration was lower, although not to a statistically significant degree, among cases than controls but the level in the Kiruna cohort was significantly lower that of the age-matched reference cohort in Uppsala. In the menu-diary it is not possible to chart differences in intake of the different subtypes of tocopherol. Only \(\alpha\)-tocopherol equivalents could be measured. However, since the intake of \(\alpha\)-tocopherol equivalents did not differ between the cohorts but the serum concentration of \(\gamma\)-tocopherol did, this could signal that the dietary fat composition is more favourable in Uppsala than in Kiruna with a greater intake of oils from rapeseed and soybean, which is also confirmed by a higher intake of \(\alpha\)-linolenic acid (18:3 n-3) in Uppsala. Both rapeseed and soybean oils are rich in 18:3 n-3.

The lower linoleic acid (18:2 n-6) content in serum cholesterol esters and adipose tissue triglycerides is a risk factor for IHD. Studies on individuals (260, 261) have shown that myocardial infarction patients without previous coronary heart disease have lower adipose tissue values. Also epidemiological comparisons, between Stockholm and Edinburgh (262), and between Italy and Finland (263) have shown a higher IHD mortality in populations with low adipose tissue linoleic acid.

The Mediterranean diet which is characterised by among other things a high content of complex carbohydrates, a "normal" lipid proportion but high in polyunsaturated fatty acids, omega-3 fatty acids from fish, high consumption of antioxidant vitamins C and E, and a moderate but regular wine consumption, has been put forward as the most ideal diet for the retardation of the atherosclerotic process (264). A prospective randomised study (265) has shown that patients eating a typically Mediterranean diet had a 70% reduction in fatal and non-fatal myocardial infarctions during a five year follow-up.

Even if our findings do not explain the difference between cases and controls, the results in the whole Kiruna cohort, compared to the Uppsala cohort, with increased proportion of short-chain fatty acids, lower proportion of linoleic acid, and a lower serum concentration of \(\gamma\)-tocopherol could be a partial explanation to why the mortality in IHD is so high in Kiruna, if our results can be extrapolated to the whole Kiruna population.

**Ecological studies**

**Alcohol and IHD (Paper V)**

Studies on an individual level suffer from the difficulty in estimating the reliability of answers to questions about alcohol drinking habits either from interviews or from questionnaires. Ecological analyses, eliminating the need for individual answers, do not suffer this draw-back. Most earlier studies, however, have compared the consumption of alcohol and the IHD mortality between different countries but it is difficult to separate the
confounding effect of different culturally related drinking habits from the direct effects of alcohol. This problem is reduced by making the ecological comparisons within a country that is fairly homogenous as far as culture and drinking habits are concerned, where there is a uniform system of death certification and registration, and where socio-economic and life-style differences are smaller than in international comparisons.

Several large studies have shown that alcohol consumption decreases the IHD risk, either following a linear relation (75,76) or a U-shaped (266) curve. In the follow-up study on British doctors (267) no significant trend of decreasing risk with increasing dose of alcohol was seen but the mortality rates for IHD were significantly lower among regular drinkers than in non-drinkers. In France, a higher alcohol consumption has been found in the northern parts of the country, e.g. Normandy, which have higher mortality rates (268).

Most earlier studies have compared raw data on ethanol consumption. The interpretation of these data is rather difficult, since any two trends going in the same (or opposite) direction tend to be related, positively or negatively, to one another. These correlations are difficult to interpret since many etiologic factors may change over time. When these risk indicators, positive as well as negative, change simultaneously, the total result may be rather different from the result to be observed, if only the alcohol consumption had changed (169). It is advisable to perform also a time series analysis of the data. If they show the same tendencies as the analyses on raw data, the foundation for the interpretation of the data is much better. However, filtering removes much of the systematic variance in the series while much of the error variance in the dependant variable remains. Especially if the time series is short, it could be difficult to demonstrate relations which actually exist. The absence of a significant correlation does not necessarily imply the absence of a causal relation.

A controversy exists about which factor is eventually protective. The increased levels of HDL-cholesterol caused by alcohol consumption (269) and other factors, e.g. antioxidants, mainly in wine (270 - 272) have been advocated. Red wine contains antioxidative substances that may explain why this type of wine seems to be more protective. In our study it was not possible to separate the effects of red and white wine, respectively. Approximately equal amounts of red and white wines are sold in Sweden.

Smoking was a confounder, since it is related to both wine consumption and mortality in IHD. However, if anything, this would tend to decrease the magnitude of the inverse relation between wine consumption and mortality in ischemic heart disease.
Bradford Hill (273, 274) recommended a systematic analysis of eventual causation, consisting of determination of 1) temporal relation; 2) plausibility; 3) consistency; 4) strength; 5) specificity; 6) dose-response relationship; and 7) reversibility. Applying these criteria on the study on alcohol and IHD is difficult concerning the temporal relation, since alcohol is analysed as a protective agent. There are plausible biological mechanisms whereby alcohol could protect against IHD. Consistent results have been found in many studies, also of considerable strength. Specificity, i.e. a simple, one-to-one relationship between cause and effect is rare in epidemiological studies and not present here. Bradford Hill emphasised that since these one-to-one relations are so infrequent, specificity of any observed association cannot be insisted on. All ecological studies have demonstrated a graded, dose-response relationship. Reversibility is inherent in ecological studies - if a protective agent is discontinued, the risk of disease/death increases.

**ACETYLSALICYLIC ACID CONSUMPTION AND IHD (PAPER I AND VII)**

When testing the strength of association between a risk factor and a disease or cause of death, ecological analyses, case-control studies and randomised trials are graded in that order of explanatory power. Contrary to our hypothesis we found that a high consumption of aspirin was associated with an increased risk of developing a myocardial infarction. This was partly supported by the ecological study. It must however be pointed out that the association between IHD and a variable need not indicate a causal relationship even if the association is strong but may reflect the presence of confounding variables.

Although smoking is accounted for as a confounder and the $R^2$ gave a high value for the influence of ASA on the mortality, this study only provides fairly weak evidence of the association between ASA and mortality in IHD. Anyway, there are possible biological explanations since ASA in low doses irreversibly inhibits cyclo-oxygenase only in the thrombocytes whereas ASA in high and repeated doses reversibly inhibits cyclo-oxygenase in the vessel wall increasing the risk for thrombosis and causing vasoconstriction. High-dose ASA also leads to decreased t-PA activity (58). Earlier studies among patients with rheumatoid arthritis have not shown an increased incidence of IHD (275, 276) but one cohort study in the elderly (277) showed that the risk of ischemic heart disease was almost doubled among male regular users of ASA but not in female users. Also our study on raw data showed a stronger association for men than for women.

Since most ASA is sold as an "over the counter" drug it was not possible to obtain figures for consumption separated for men and women. The dependent variable (mortality in IHD) is thus for each sex but the independent variable (ASA consumption) is agglutinated for both sexes. Still, correlations are fairly strong. Since so much ASA is consumed these findings ought to be verified or refuted by other studies.
The time series analysis did not support our hypothesis that ASA increases the risk of IHD. However, as stated in the discussion concerning alcohol consumption and mortality, there are limitations also in the time series methodology. The series with ASA consumption and mortality is even shorter (comprising only nine years) than the alcohol series, which would require very strong correlations to find a significant relation between ASA consumption and mortality in IHD for males and females.

One possible but far-fetched explanation to our findings is that ASA could be used as pain relief for angina pectoris. In that case the group with the most severe heart disease takes ASA and thus results in a higher frequency of myocardial infarctions. However, were this the case, drugs containing paracetamol should presumably be used for the same purpose and to the same extent. Sixty-four out of 495 persons (12.9%) used paracetamol several times weekly for pain relief, 11.2% of cases and 13.7% of controls. Eighty-eight out of 501 (17.6%) used aspirin, 26.8% of cases and 13.5% of controls. Twenty-seven persons used both aspirin and paracetamol. Thus, ASA was used to a greater extent among cases than paracetamol, which makes it less likely that these drugs were used for relief of cardialgia.

Applying the above mentioned "Bradford Hill criteria" also on the question of ASA and AMI would give the following results: since this is an ecological study, the temporal relation cannot with certainty be accounted for. From biological point of view there are mechanisms whereby ASA can cause an increased risk for thrombosis and reduced thrombolysis. The question of ASA and increased risk for acute myocardial infarction has not been studied before. Consistency is thus not accounted for, even if the same result has been obtained in the case-control study and part of the ecological study. ASA was also a strong risk factor with an OR of 2.3, well above that for smoking. Specificity and dose-relationship can not be accounted for, but in the ecological studies a dose-response has been shown.

**HEART FAILURE SURVIVAL STUDY (PAPER VI)**

This study highlights the fact that it is dangerous to extrapolate controlled clinical trials to free-living populations. Several studies have shown a better prognosis in later years. Although the hospital has followed the latest guide-lines in treating heart failure, no statistically significant improved prognosis can be seen when the late cohort (1991 to 1994) is compared to the early cohort (1987 to 1990). A possible reason for this (apart the possibility that there is no difference) is the short observation time. Congestive heart failure has a very bad prognosis, shown in several studies (278, 279). In our study, less than half of the patients survived three years after the first event.

The contemporary major cause of heart failure is chronic ischemic heart disease but there seems to have been a shift in the spectrum of underlying diseases in the last half century.
In 1939, Bedford (280) noted that 84% of 132 consecutive patients with heart failure were hypertensive. In the Framingham study (150) hypertension was judged to cause 75% of cases with heart failure. Fourteen years later Killip (281) found that hypertension was the cause in 31%. Six years later this figure had decreased to 3.8% (282). This puts our figure of 8% into perspective. A possible reason for the decreasing importance of hypertension could be the more aggressive treatment of high blood pressure. However, hypertensive disease still indirectly causes a substantial part of congestive heart failure by causing coronary heart disease even if the high blood pressure is well controlled.

An understanding of the disorders predisposing to or leading to heart failure may open a possibility to reduce the incidence and prevalence of heart failure but so far the importance of heart failure as a major health problem in the community has passed largely unnoticed. Since the average time between the first hospitalisation for angina pectoris and the first hospital-treated event of heart failure in Kiruna is about 7 years (unpublished data), it is still too early to decide whether we will see a reduced mortality in heart failure.

Acute myocardial infarction occurs at an older age among females than among males. The reasons for this are supposed to be hormonal. This is reflected in a female advantage in survival as far as heart failure is concerned. However, after controlling for age, the difference in survival even increased, suggesting that other factors than age also operate. The sex and age differences found in are in agreement with other studies (283).

It can be expected that coronary heart failure will be an increasing medical, public health, and economic problem in industrialised societies with ageing populations, as has been previously suggested (284). Reports from the USA (285) and Scotland (152) have confirmed that the hospitalisation rates for cardiac insufficiency have increased. Studies on the cohort of men born in 1913 in Gothenburg (286, 287) have shown that both prevalence and incidence rates of heart failure increase in Gothenburg but point out that it is difficult to make comparisons between different studies since the definitions of heart failure differ between studies.
GENERAL DISCUSSION AND IMPLICATIONS FOR PREVENTION

It is a truism, but, as elsewhere, ischemic heart disease is multifactorial in Kiruna. Although several risk factors have been identified, the intervention against any one of them in selected high risk individuals is unlikely to influence the overall mortality in ischemic heart disease. It is unethical not to treat high risk individuals but for maximal public health benefit a population perspective must be considered.

The distribution of risk factors follows a normal curve whether it be skewed or peaked, whether we are discussing serum cholesterol concentrations, smoking habits, or leisure time physical activity. We have a tendency to alienate us from individuals with a high risk factor load - "we" in the middle part of the curve against "them" in the tails, in both discussions concerning prevention and treatment. We do, however, all belong to the population regardless of our position in the normal curve.

Implicit in this is also that public health measures to reduce cholesterol concentration, to eliminate smoking, to counteract social isolation and in a broad sense unhealthy workplaces, and to promote a healthy life-style, must apply to the whole population. More in terms of mortality and morbidity will be gained if the whole distribution (and normal curve) can be shifted to the left than if a few individuals in one of the tails of the normal distribution curve can be moved within +/-2SD. The paradox is that a preventive measure that brings large benefits to the community offers little to each individual (288).

The methods to achieve a reduction in the morbidity and mortality in IHD are not for scientists alone, they are for politicians with the aid of scientists and cover a wide range of moves, e.g. less subsidies to meat and high-fat dairy products and more to vegetables, fish, and low-fat dairy products. Increased legislation against smoking and smoking advertisement is important, knowing that the tobacco industry has to recruit a cohort of 30,000 smokers only in Sweden each year to keep their revenues constant. The promotion of a healthy life-style in general is also important. It is, however, difficult to change long-standing habits. Most likely we have at least one "lost generation" in Kiruna as far as coronary heart disease risk is concerned. To be effective, measures to counteract unhealthy habits and to promote a healthy life-style must be started already among children and young adults since the atherosclerotic process starts early in life. However, knowing that this process can be reversed, it is never too late to "start a new life."
Like what has been described for peptic ulcer (289), IHD passes through society in a wave, at first affecting the privileged and subsequently the less privileged, and declining in the same order (290). In agreement with Rose (291) "The primary determinants of disease are mainly economic and social, and therefore its remedies must also be economic and social. Medicine and politics cannot and should not be kept apart."
CONCLUSIONS

1. The main risk factors for IHD in Kiruna pertain to life-style: hypertension, smoking, high serum cholesterol concentration, and diabetes mellitus. Their impact, measured as odds ratios, is of the same size as that published in other studies.

2. The psycho-social risk factors are mainly related to the work situation: physical exhaustion was a risk factor, whereas good control over work tasks was protective. Recent immigration into the society seemed to increase the risk of having an acute myocardial infarction.

3. A high proportion of palmitoleic acid was associated with an increased risk of myocardial infarction but in general there were few differences between cases and controls, suggesting that few changes in dietary habits had taken place.

4. In the Kiruna cohort the concentration of γ-tocopherol was lower than in the Uppsala cohort. This could indicate a less favourable antioxidative status and endothelial function in Kiruna. There were also differences in the proportion of fatty acids in serum cholesterol esters and adipose tissue triglycerides to the disadvantage of the Kiruna cohort. Again, there were few differences between cases and controls.

5. Alcohol consumption was not in general associated with a protective effect. However, there was a protective effect of wine in women.

6. Heart failure carries a grim prognosis with less than 50% three-year survival. Being male and being old is associated with a worse prognosis.

7. The unfavourable effect of acetylsalicylic acid consumption in the Kiruna cohort was found also in the geographical and longitudinal ecological analyses but could not be verified in the time-series analysis.

I en fall-kontrollstudie (en typ av studie, där friska individer jämförs med sådana som har eller har genomlifit en sjukdom av intresse) visade det sig, att högt blodtryck, sockersjuka och rökning gav en ökad risk för att få en hjärtinfarkt. Risken var även högre om någon nära släktning genomlidit en hjärtinfarkt.

Även ogynnsamma psykosociala omständigheter var förenade med en ökad risk för hjärtsjukdom. De psykosociala faktorerna omfattar bl a sådant som trivsel på arbetsplatsen, psykiskt eller fysiskt stresstade arbete, dåliga relationer till arbetsledning, monotont arbete respektive hur många goda vänner man har, hur ofta man umgås med dem, osv.

I Kiruna är nivån av blodfetter mer ogynnsam än hos män i jämförbara åldrar på andra orter i landet. De som genomlifit en hjärtinfarkt hade i genomsnitt något högre kolesterolvärden än de hjärtfriska individerna. När vi gjorde mer förfinade analyser av vilka fettsyror man har i blod och i fettväv fann vi emellertid små skillnader mellan hjärtfriska och hjärtinfarkt. En koststudie visade små skillnader i val av föda mellan hjärtfriska och infarktpatienter och även mellan Kirunaborna och en jämförelsegrupp av män i Uppsala.

Blodprover tagna i samband med koststudien visade låga halter av vitamin E-gruppen och linolensyra och höga halter av palmitinsyra, samtliga förändringar ogynnsamma ur hjärtsynpunkt.

Alkohol har i flera studier visat sig ha en skyddande effekt mot hjärtsjukdom. Detta kunde vi inte verifera bland våra patienter. Däremot visade en studie på registerdata på riksnivå (ej på individnivå), att vin kan ha en skyddande effekt för kvinnor, medan övriga alkoholhaltiga drycker ej var hjärtskyddande. Vinkonsumtionen var vid tiden för vår undersökning liten i Kiruna, och understiger fortfarande riksgenomsnittet. Detta kan vara en orsak till att vi inte fann någon skyddande effekt av alkoholkonsumtion i Kiruna.

Hjärtvikts sinviktande pumpfunktion hos hjärtat) är ofta orsakad av kroniska åderföröreningar sjukdomar i hjärtats kranskärl. Trots förbättrad terapi har prognosen vid detta tillstånd inte förbättrats, utan är fortfarande lika dålig, eller sämre, än vid många cancersjukdomar. Ett årsöverlevnaden är för de patienter, som vårdades vid medicinkliniken vid Kiruna Sjukhus under åren 1987 ill och med 1994 67,%, ungefär samma för män och kvinnor och oberoende av om man behandlades sent eller tidigt under perioden. Prognosen var bättre för kvinnor (27% minskad risk för död) och för yngre människor (varje års ökande ålder ökade risken för död med 3,5%).

En studie av läkemedelskonsumtion visade, att de som regelbundet åt läkemedel innehållande acetylsalicylsyra (t ex Magnecl, Albyl, Bamyl) löpte en ökad risk att få en hjärtinfarkt. Detta fynd kunde inte med säkerhet veriferas i en registerstudie, där konsumtion av acetylsalicylsyra och dödlighet i hjärtinfarkt undersöktes, på nationell nivå.
ACKNOWLEDGEMENTS

I wish to express my gratitude to:

KJELL ASPLUND
For generous help, support and encouragement in tying the final knots of this work together.

ÅKE DANIELSSON
My mentor, friend and tutor. By personal example you have shown that it is possible to be a doctor in the best sense of the word at the same time as it is possible to do fruitful research.

MERJA LEINONEN
For helping me with an endless amount of references.

MY EMPLOYER
For generous grants making it possible to carry out these studies.

MY FAMILY
For being there.

BO PETERSSON
My co-author and partner for intellectually stimulating discussions.

HAROLD SIHM
Harold, you opened my eyes to the problems of our patients and showed me the virgin territory of epidemiological studies in Kiruna and the need for such studies. Your guidance, patience and knowledge has been of decisive importance.

BENGT VESSBY
Friend, co-author and most valued advisor.

THE CASES AND CONTROLS
You patiently answered strange questions and came for interviews and examinations when called for. Without your patience and co-operation my job would have been an arduous task.

MY MACINTOSH COMPUTERS (THREE HAVE BEEN WORN OUT BY THIS THESIS)
- absolutely essential companions and obedient servants in this job.

This study was made possible by research grants from the County Council of Norrbotten and the Swedish Work Environment Fund.
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