OLLI SUHONEN

Sudden Coronary Death in Middle-age in Finland

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Abstract


The purpose of the study was to prospectively investigate the incidence, risk factors and attendant circumstances of sudden coronary death (SCD) in a representative population sample in Finland. The study population consisted of 6510 men and 5800 women aged 30-59 years, drawn from 4 regions in Finland. The four-year incidence of coronary heart disease (CHD) death per thousand was 13.0 among men and 1.8 among women, and the incidence of SCD was 7.8 among men and 0.7 among women. The corresponding figures for definite nonfatal myocardial infarction (MI) were 15.1 and 2.7. SCD most commonly occurred at home and the most common time was forenoon. Later SCD victims had an initially higher prevalence of typical angina pectoris than those dying nonsuddenly of CHD. In comparison with men free from CHD, the risk of SCD was ten-fold in men with a history of MI and almost three-fold in men with ischemic ECG-changes. Smoking and alcohol consumption were independent risk factors for SCD but not for nonsudden CHD death both in men without and with CHD.

Key words: sudden coronary death, coronary heart disease, myocardial infarction, risk factors

Tiivistelmä


Avainsanat: äkkikuolema, sepelvaltimotauti, sydäninfarkti, vaaratekijät
FOREWORD

This study is part of the Social Insurance Institution's Coronary Heart Disease Study, which was initiated in 1966 to investigate the epidemiology of coronary heart disease in middle-aged men and women in Finland. Some ten years ago Professor Kalevi Pyörälä, M.D., kindly asked me to join the research group, and as one part of the study my special task was to elucidate the epidemiological aspects of sudden coronary death. I am very grateful to Professor Pyörälä for his constant encouragement and enthusiasm, without which this long-term project might never have been completed.

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The author
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1. LIST OF ORIGINAL PAPERS


2. ABBREVIATIONS

AP = angina pectoris
BP = blood pressure
CHD = coronary heart disease
ECG = electrocardiogram
MC = Minnesota code
MI = myocardial infarction
NFMI = nonfatal myocardial infarction
NSCD = nonsudden coronary death
SCD = sudden coronary death
VEB = ventricular ectopic beat
VF = ventricular fibrillation
3. INTRODUCTION

Cardiovascular diseases have been the main cause of mortality and morbidity in industrialized countries for decades, and today they have increasing significance as a cause of ill-health and death in many developing countries, too. Despite its declining incidence in several western countries, Finland included, coronary heart disease (CHD) remains the most important cardiovascular disease because of its grave prognosis and high incidence in working-aged populations, especially among men.

Cardiac arrest is one essential manifestation of CHD and, although potentially treatable, it usually leads to death. In about 20 per cent of cases, sudden coronary death (SCD) is the first manifestation of CHD, and more than half of CHD deaths are sudden, i.e. occurring within an hour of the onset of symptoms. SCD is thus an important cause of premature death in populations with a high incidence of CHD.

In western countries, especially the U.S.A., the key role of SCD has prompted numerous studies on its epidemiology, pathology and clinical features. Many efforts have been made on the basis of extensive prospective studies to establish its specific risk factors and predictors and thus to devise measures for prevention. Many aspects of SCD in Finland have been described in an earlier retrospective study (Romo 1973) and in connection with the North Karelia Project (Salonen 1982). However, there is a need for a more comprehensive study including populations from different parts of the country and with a more thorough study of SCD as a manifestation of CHD.

In 1966, when CHD mortality in Finland was the highest in the world (Epstein and Krueger 1969), the Social Insurance Institution of Finland initiated a prospective population study designed to investigate the prevalence, incidence, risk factors and prognosis of CHD among middle-aged men and women in Finland. In that study, interest was focused on SCD, too, and the following report summarizes the results of five separately published studies on its incidence, attendant circumstances and risk factors in the study population.
4. REVIEW OF THE LITERATURE

4.1. Definition of sudden coronary death

The definition of SCD has varied widely in the vast literature on its epidemiology and clinical aspects. Most definitions have used the time span from the onset of symptoms to death, which ranges from a few minutes to 24 hours or even longer. Definitions without a precise time interval have also been used, using the circumstances linked with the event as a basis for selection.

In 1969, an international committee supported by the International Society of Cardiology and the American Heart Association agreed upon the following definition: "Sudden unexpected (natural) death is defined as death occurring instantaneously or within an estimated 24 hours of the onset of acute symptoms and signs" (Paul and Schatz 1971). The definition involved no etiological considerations. In spite of the above recommendation, the time span has tended to be shorter in subsequent definitions, and today most investigators have adopted a one-hour definition, which Myerburg (1978) has expressed as follows: "Natural death due to cardiac causes occurring either instantaneously or up to one hour after the onset of symptoms in a patient who may or may not have known pre-existing heart disease, but in whom the time and mode of death occur unexpectedly." Extensive analyses of so-defined sudden death have consistently shown that in the vast majority of cases, CHD is the etiology, and abrupt arrhythmia the mechanism of death. As the time span increases the etiological spectrum definitely widens, and in CHD cases, the mechanism of death is increasingly often cardiogenic shock or intractable pump failure with secondary fatal arrhythmia.

Other constraints have also been included in the definition of SCD. In the Framingham study, coronary death was defined as sudden "when apparently well persons were observed to suddenly and unexpectedly collapse and die within one hour" (Gordon and Kannel 1971). In the Anturane Reinfarction Trial, symptoms and findings indicative of myocardial infarction were used as criteria excluding SCD (The Anturane Reinfarction Trial Research Group 1980). A WHO Scientific Group (1983) on Sudden Cardiac Death recently emphasized the importance of defining the specific characteristics linked with cardiac arrest instead of trying to define the word "sudden" in the context of death. Such an approach would contribute to a better understanding of the pathogenic mechanisms involved. In the present review, unless indicated otherwise, SCD is defined as death of coronary origin within one hour of the onset of symptoms.
4.2. Proportion of sudden coronary death in relation to natural sudden deaths, and coronary heart disease deaths, and the incidence of sudden coronary death

The following questions are of interest in the characterization of SCD occurrence: What is the proportion of SCD in relation to all natural sudden deaths? How often is CHD death sudden? What is the incidence of SCD by age and sex? Answers to these questions have been sought through autopsy studies, short-term surveillance studies and prospective studies of defined populations in Europe and the U.S.A.

4.2.1. Proportion of sudden coronary death in relation to all natural sudden deaths

An overwhelming majority of sudden natural deaths is attributed to cardiovascular diseases, especially CHD. Aortic stenosis, hypertrophic obstructive cardiomyopathy and myocarditis are emphasized as other cardiovascular causes, as is pulmonary embolism. Some rhythm disturbances and some forms of heart block have significantly increased risks of sudden death. Cerebral and subarachnoid hemorrhage are possible causes of sudden death, and a residue of cases remains in which no definite cause can be identified by postmortem investigation.

In a material of 1329 consecutive autopsies performed in Brooklyn, U.S.A., CHD was the cause of death in 91 per cent of males and in 48 per cent of females aged 30 years or more who died within one hour of the onset of the fatal episode (Spain et al. 1960). The corresponding percentages for unwitnessed cases, which constituted 44 per cent of all unexpected deaths, were 61 and 33. In another American autopsy study of males under 50 years, 50 per cent of deaths occurring within one hour were caused by CHD (Oalmann et al. 1980). In a two-year surveillance study in Baltimore, U.S.A., arteriosclerotic heart disease was the cause of death in 67 per cent of all natural deaths occurring within 24 hours of the onset of symptoms among men and women aged 25 to 64 years (Kuller et al. 1973). In a study of medically unattended deaths in Stockholm, 90 per cent of deaths among men over 50 years were caused by CHD, provided that they had no history of fatal disease (Wikland 1971). In Lund, forty-nine out of 100 consecutive nonviolent deaths among adults and occurring outside hospital, were caused by CHD (Lundberg and Voigt 1979). In a retrospective study of 352 medico-legal autopsies performed on men aged 25 to 64 years in the district of Helsinki in 1976, CHD was the cause of death in 71 per cent of all natural deaths occurring within 24 hours (Penttilä 1980). In another retrospective Finnish study on non-traumatic sudden deaths connected with leisure exercise and sports, the cause of death was cardiac in 91 per cent, being CHD in 81 per cent (Vuori et al. 1983). In an autopsy series of 77 deaths in northern Finland, CHD was the etiology in 50 per cent of deaths occurring within 24 hours among persons aged 50 years or less (Särkioja and Hirvonen 1983).
4.2.2. Proportion of sudden coronary death in relation to all coronary heart disease deaths

According to myocardial infarction community registers set up by WHO, the proportion of SCD in relation to all witnessed CHD deaths was 40 per cent among males and 35 per cent among females aged 65 years or less (WHO 1976). The figures varied rather much from centre to centre, perhaps mainly because information about cases of SCD was lacking. About 60 per cent of all CHD deaths occurred outside hospital, and about 33 per cent of them were un witnessed. The Ischaemic Heart Disease Register in Helsinki showed that the proportion of SCD in relation to all CHD fatalities was 53.1 per cent among men and 38.5 per cent among women aged 30 to 64 years (Romo 1973). In Stockholm the proportion of one-hour deaths in relation to all medically unattended CHD deaths was 72 per cent among men and 59 per cent among women (Wikland 1971). In Kaunas, the proportion of deaths occurring within 6 hours was 61 per cent in relation to all CHD deaths, and about half of them occurred within one hour (Janushkevichi us et al. 1978). In Belfast 38 per cent of deaths due to CHD occurred within one hour (McNeilly and Pemberton 1968). In prospective population studies the numbers have been of the same order. In the North Karelia study the proportion of SCDs was 47 per cent (Salonen 1982). In the U.S.A. the proportion of SCDs has been about 50 per cent among men (Chiang et al. 1970; Friedman et al. 1975; Doyle et al. 1976; Stamler 1976; Kannel and Thomas 1982) and about 40 per cent among women (Kannel and Thomas 1982).

4.2.3. Incidence of sudden coronary death by age and sex

The incidence of SCD has been estimated on the basis of several short-term and prospective population studies. The studies have consistently shown the appearance of SCD in early middle age among men and some ten years later among women. The incidence rises steeply with age, and has a distinct male preponderance in all age groups. In Helsinki in 1970-1971 the annual incidence per thousand SCDs among men aged 40 to 44 years was 0.7, and rose to 6.4 in the age group 60-64 years. The corresponding figures among women were 0.1 and 0.7 (Romo 1973). In Stockholm the incidence was considerably lower: 0.3 per mille among men aged 40 to 44 years, 3.5 per mille among men aged 60 to 64 years and only about a sixth of the above figures among women (Wikland 1971). In a Danish population the incidences per thousand by age group (50-69) were 0.19 and 3.6 among men and 0.12 and 1.0 among women (Madsen 1983). In a Scottish community study the incidences among men per thousand by age group (40-49, 50-59) were 1.2 and 3.2, and 1.4 and 2.8 among women by age group (50-59, 60-69) (Fulton et al. 1969). In short-term surveillance studies in the U.S.A., the incidence among middle-aged men has varied between 0.5 and 2.1 per thousand (Hagström et al. 1971; Kuller et al. 1975; Margolis et al. 1976). Among women the incidence was only one-third that of men (Kuller et al. 1975). In American prospective studies the incidence has been somewhat
higher: in the Framingham study it was 1.9 per mille among men and 0.5 per mille among women aged 45 to 74 years (Kannel and Thomas 1982); in Tecumseh the overall incidence per thousand among men and women aged 50-59 was 2.0 (Chiang et al. 1970); in Chicago the corresponding figure was 2.6 among men aged 40-59 at entry (Stamler 1976).

4.2.4. Conclusions

In a vast majority of cases the etiology of sudden natural death is CHD, and about half of all CHD fatalities are sudden deaths. SCD appears in early middle age among men, and its incidence rises steeply with age, a distinct male preponderance being noticeable at all ages. The variation in the incidence mainly reflects varying incidences of CHD in different populations, but to some extent it can be explained by differences in data collection and definitions. It is also possible that the mode of death from CHD varies from one population to another.

4.3. Pathology of sudden coronary death

By definition, in SCD the heart shows signs of coronary atherosclerosis. Of special interest as prerequisites of sudden death are the extension and distribution of chronic changes in coronary vessels and the myocardium, the role of acute occlusive changes in coronaries and acute lesions in the myocardium, and the possible existence of specific lesions.

The state of the coronary arteries and the myocardium in SCD has been investigated in several extensive postmortem studies in Europe, the U.S.A, and Australia (Spain et al. 1960; Friedman et al. 1973; Liberton et al. 1974; Bashke et al. 1973; Lie and Titus 1973; Margolis et al. 1973; Myers and Dewar 1973; Perper et al. 1975; Lovegrove 1977; Reichenbach et al. 1977; Ulrich and Schmittova 1977; Janushkevichius et al. 1978; Rissanen et al. 1978; Rissanen V 1979; Davies 1981; Newman et al. 1982; Davies and Thomas 1984; El Fawal et al. 1987). Comparison of the results of different series is hampered by the diverse selection criteria, study methods and definitions. Recently, as a result of successfully resuscitated sudden-death cases, intravital information has been obtained about coronary vessels and the myocardium (Weaver et al. 1976; Tresch et al. 1981).

4.3.1. Coronary atherosclerosis and acute occlusive changes

In general, postmortem studies carried out by the quantitative dissection method or by coronary angiography or both have disclosed severe atherosclerotic occlusive changes in the coronary arteries of SCD victims. The prevalence of single-vessel disease (other vessels not affected to a critical degree) has varied between 8 (Reichenbach et al. 1977) and 38 per cent (Janushkevichius et al. 1978). The prevalence has been 10-20 per cent in
most studies. The prevalence of single-vessel disease among survivors has been 12 (Tresch et al. 1981) and 33 per cent (Weaver et al. 1976). Two vessels have been critically affected somewhat more often, from 15 (Perper et al. 1975) to 39 per cent (Janushkevichius et al. 1978), usually in about one in four cases. Among survivors the prevalence has been about 30 per cent. The prevalence of three-vessel disease has been distinctly highest, between 39 and 86 per cent, except in the study of Janushkevichius, in which the rate was only 13 per cent. Almost half of the survivors had three-vessel disease. Total occlusion in any vessel has been disclosed in more than half of the cases in most postmortem studies and in both intravital studies. Stenosis has most often been located in the left anterior descending and right coronary arteries, corresponding to the distribution of stenoses in patients with nonfatal coronary artery disease (Gensini 1980). Over-representation of stenosis in the right coronary artery was detected in one study (Davies and Thomas 1984).

According to a hitherto widely held opinion, the appearance of acute changes in the coronary arteries - thrombosis or plaque rupture, or both - depends on the survival time of the SCD victim; hence acute lesions are seldom seen in instantaneous deaths. In Friedman's series of instantaneous coronary deaths, only 4 per cent had intraluminal thrombosis (Friedman et al. 1973). However, in a recent study the prevalence of acute thrombosis was high and independent of the survival time of up to six hours (Davies and Thomas 1984). Acute thrombosis was detected in 65 per cent of cases dying within 15 minutes of the onset of symptoms. In other studies in which the inclusion criteria differed from one to 24 hours, the prevalence of acute thrombosis varied from 10 (Reichenbach et al. 1977) to 68 per cent (Newman et al. 1982). The essential role of plaque rupture was clearly shown in Friedman's study, in which acute thrombosis was almost always preceded by rupture of a necrotic atheromatous plaque (Friedman et al. 1973). This result has been confirmed in later studies (Davies and Thomas 1984; El Fawal et al. 1987). Different studies have uniformly shown that the acute occlusive changes occur at the site of severe old stenosis. Cases with no acute changes in coronary arteries were rather common in earlier studies, e.g. in Lovegrove's series of 499 SCDs, the proportion was 74 per cent (Lovegrove 1977). In contrast, Davies found only five cases out of 100 SCDs without acute changes in the coronaries. An intraintimal thrombus, most often associated with plaque fissuring, was found in 21 of the 26 cases without intraluminal thrombi (Davies and Thomas 1984). Recently, Davies et al. have demonstrated platelet aggregates in the small intramyocardial vessels in 27 of 90 patients who had died suddenly (Davies et al. 1986).

4.3.2. Chronic and acute myocardial lesions

Simultaneous investigation of the coronary arteries and the myocardium in cases of SCD shows clearly that lesions in the coronaries and the myocardium are positively correlated. For example, a positive association has been found between the prevalence of old infarctions and the number
of affected coronaries (Perper et al. 1975). The prevalence of old myocardial infarctions has varied from 22 (Friedman et al. 1973) to 78 per cent (Janushkevichius et al. 1978). The presence of diffuse or local myocardial fibrosis has been more uniform, being verified in 43 to 72 per cent of cases. Prior myocardial infarction has been clinically diagnosed in 18 to 59 per cent of cases. Interestingly, pathological changes in the conductive tissue have been uncommon: Friedman could find no changes in 59 autopsies (Friedman et al. 1973); in another study, two of 49 cases had histological changes in conductive tissue, each in connection with a massive septal infarction (Lie 1975).

The uncovering of acute myocardial lesions in SCD depends essentially on the histological survey method as well as the time elapsing between the onset of symptoms and the moment of death. The prevalence of fresh or recent infarction has varied from 5 (Reichenbach et al. 1977) to 76 per cent (Rissanen et al. 1978), usually having been disclosed in one-third of cases. Among survivors the clinical diagnosis of myocardial infarction (MI) has been settled in about 30 per cent of cases (Libethson et al. 1974; Weaver et al. 1976; Tresch et al. 1981). In most studies the infarctions have been distributed equally between the anterior and the posterior surface of the heart. Rupture of the cardiac wall has been confirmed as a terminal event in about 5 per cent of cases (Rissanen et al. 1975; Lovegrove 1977; Ulrich and Schmittova 1977; Lundberg and Voigt 1979).

4.3.3. Conclusions

Viewed from the aspect of coronary vasculature, SCD most often means the presence of extensive occlusive atherosclerosis with precipitating acute occlusive intraluminal or intraintimal thrombosis, frequently initiated by plaque rupture or fissuring. In accordance with the former, in SCD the myocardium usually has single or multiple, and old and/or acute lesions of ischemic origin. There seem to be no chronic or acute lesions specific to SCD.

4.4. Pathophysiology of sudden coronary death

Since the end of the last century, it has been suggested that sudden death is due to ventricular fibrillation (Lown 1980). Other alternatives for the abrupt breakdown of effective blood flow are extreme bradycardia or asystole; severe pump failure caused by massive myocardial infarction or cardiac wall rupture can also be manifested as sudden death. In rare cases, the abrupt breakdown of pump function without initiating rhythm disturbance or mechanical catastrophe (what is referred to as electromechanical dissociation) has been demonstrated (Raizes et al. 1977).

The era of coronary care units and resuscitation facilities outside hospitals has given abundant information about the pathophysiology of SCD. Even
more detailed knowledge has been obtained from CHD patients succumbing to SCD during long-term out-patient monitoring. In the last few years electrophysiological stimulation studies on CHD patients have augmented our knowledge of electrical phenomena in the myocardium, providing data valuable in explaining later SCD.

4.4.1. Electrophysiological mechanisms

Early experience in coronary care units confirmed that unexpected ventricular fibrillation (VF) during the early hours of definite or even suspected MI is not a rare event irrespective of the hemodynamic consequences of the myocardial injury (Lawrie et al. 1968). Out-of-hospital resuscitation experience, too, has shown that VF is the initial rhythm disturbance in the vast majority of cases (Liberthson et al. 1974; Weaver et al. 1976; Iseri et al. 1978; Goldstein et al. 1981; Tresch et al. 1981). In a review of 82 cases of SCD during out-patient monitoring, VF was the prevailing terminal arrhythmia, often preceded by ventricular ectopic beats (VEBs). Asystole, extreme sinus or junctional bradycardia or complete atrioventricular block has been verified only occasionally (Roelandt et al. 1984). It is probable that VF has been the initial arrhythmia in some of the cases with asystole, as has been demonstrated in a published case of out-patient monitoring (Hinkle et al. 1977).

4.4.2. Predisposing factors to ventricular fibrillation

Animal experiments (Lown et al. 1977) and electrical stimulation tests in healthy men (Greene et al. 1978) have demonstrated that VF is not the response of the healthy heart to electrical stimuli. Under experimental conditions induction of myocardial ischemia profoundly lowers the threshold to VF (Lown et al. 1977). Clinical experience, too, has inevitably indicated that ischemic myocardium is a precondition of VF. Presumably, VF is initiated and sustained by a re-entry circuit mechanism, for which the ischemic myocardium, with varying conduction velocities and unidirectional blocks, forms a structural basis (Lown 1979). Out-patient monitoring has shown that the event triggering VF is often a VEB like thousands before it. At that moment, an acute worsening of ischemia, and the release of catecholamine or even neural stimulus may have lowered the threshold to VF (Engel 1973; Lown 1979). The high prevalence of acute structural changes in the coronaries of SCDs indicates the importance of acute worsening of ischemia as a precondition of VF. Coronary spasm, induced by local or neural factors, can also worsen the ischemia (Maseri et al. 1982). Sometimes an exceptionally short coupling interval has been detected before the initiating VEB, which by itself can explain the VF (Roelandt et al. 1984). Recent electrophysiological stimulation studies have revealed post-myocardial infarction patients who responded to experimental cardiac stimulus with repetitive VEBs or self-terminating ventricular tachycardia or VF (Hamer et al. 1982; Richards et al. 1983). These patients
have been especially prone to subsequent SCD. Conversely, electrical stability during stimulation has meant a very low short-term risk for SCD after MI.

4.4.3. Conclusions

In most cases of SCD the electrophysiological mechanism is VF. The prerequisite is electrically unstable ischemic myocardium, whose threshold to VF is reduced by acutely worsening ischemia or the release of catecholamine or perhaps neural stimulus. The immediate triggering event is often a VEB which by a re-entry mechanism develops into sustained VF.

4.5. Risk factors of sudden coronary death

4.5.1. Conventional coronary heart disease risk factors

Without doubt hypertension, high serum cholesterol and smoking are risk factors for various manifestations of CHD (The Pooling Project Research Group 1978). The majority of prospective studies investigating the associations between these risk factors and SCD have been conducted in the U.S.A. In the Framingham study the general risk profile of a candidate for SCD was the same as that of persons with other manifestations of CHD (Kannel and Thomas 1982). It was noted that cigarette smoking had a somewhat greater effect on SCD than on nonsudden coronary death (NSCD). A large-scale prospective study of male telephone-industry workers compared the risk factor levels between men dying abruptly (arrhythmic deaths) and those dying insidiously (circulatory failure deaths) (Hinkle 1982). Hypertensives were more prone to arrhythmic deaths than normotensives, both kinds of death were more common among heavy smokers than among nonsmokers, and high serum cholesterol was more of a predisposing factor to death from circulatory failure. In the Kaiser-Permanente study, the risk factor levels of 214 men who died of CHD within 24 hours of the onset of symptoms were compared with the levels of age-matched men (Friedman et al. 1975). The SCD group had higher levels of systolic and diastolic blood pressure (BP) and a higher prevalence of smoking, but the serum cholesterol level was of the same order in both groups. No comparison was made with men dying non-suddenly of CHD. In a Yugoslavian prospective study, all three risk factors yielded an increased incidence of SCDs (Kozarevic et al. 1984). In the North Karelia prospective study, a high serum cholesterol level, above 310 mg/100 ml, was the only risk factor positively associated with the suddenness of CHD death (Salonen 1982).

4.5.2. Alcohol as a risk factor

In the last ten years, increasing evidence has accumulated that there is an interrelationship between alcohol consumption and manifestations of CHD. International comparison has shown an inverse relationship between alcohol
consumption - especially of wine - and CHD mortality (St Leger and Cochrane 1979). A time-trend comparison in the U.S.A. has shown the same trend, especially concerning the consumption of beer (LaPorte et al. 1980). Several cross-sectional (Hennekens et al. 1978; Klatsky et al. 1979) and prospective population studies (Kozarevic et al. 1980; Klatsky et al. 1981; Marmot et al. 1981; Cullen et al. 1982; Gordon and Kannel 1983; Hulley et al. 1983), in which other common risk factors, smoking in particular, were taken into account, have consistently shown an inverse or U-shaped relationship between alcohol consumption and CHD mortality. In some studies heavy drinkers or alcoholics have had an increased risk of coronary death (Pell and D’Alonzo 1973; Wilhelmsen et al. 1973; Dyer et al. 1977; Poikolainen and Simpura 1983; Wilhelmsen et al. 1983). A Japanese study of male physicians failed to show any significant association between alcohol consumption and subsequent CHD death during 13 years of follow-up (Kono et al. 1983). In the North Karelia study, men consuming spirits at least once a week had a reduced risk of nonfatal myocardial infarction (NFMII), but not of CHD death (Salonen et al. 1983a).

The association between alcohol consumption and SCD has been analysed extensively in recent years. In a long-term prospective study in Chicago, the increased risk of CHD among problem drinkers was especially pertinent to SCD (Dyer et al. 1977). A Swedish prospective study corroborates this finding (Lithell et al. 1987). In the Framingham study, SCD was an exception in the otherwise inverse relationship between alcohol consumption and the incidence of cardiovascular disease (Gordon and Kannel 1983). It was especially noted that truly unexpected sudden death was more usual among drinkers than among other men. The negative correlation between alcohol consumption and CHD mortality did not apply to SCD in urban populations in Yugoslavia (Kozarevic et al. 1980, 1983). A British prospective study found no significant relation between reported alcohol intake and the incidence of major cardiac events, SCD included (Shaper et al. 1987). Retrospective studies have implied that alcohol intake predisposes to SCD (Myers and Dewar 1975; Fraser 1978; Fraser and Upsdell 1981). However, a case-control study indicated that moderate alcohol consumption provides protection from primary cardiac arrest (Siscovick et al. 1986). The possible mechanisms of the influence of alcohol were thoroughly discussed in a recent review (Marmot 1984).

4.5.3. Other risk factors

Controversy exists about the significance of obesity as an independent risk factor of clinical CHD (The Pooling Project Research Group 1978). In the Framingham study obese young men had a somewhat increased risk of SCD (Kannel and Thomas 1982). In the Tecumseh study, SCD victims had a higher relative weight than the Tecumseh population as a whole (Chiang et al. 1970). In yet another American study, there was no association between the thickness of the triceps skinfold and incidence of SCD (Friedman et al. 1973).
Since the study of Morris et al. (1953), physical activity has been considered to be negatively associated with CHD. In a later study it was suggested that, among middle-aged men, vigorous exercise reduces the risk of SCD (Morris et al. 1973). A case-control study supported this conclusion (Siscovick et al. 1982). The incidence of SCD among American dockers was lower for heavy physical workers than for those with moderate or light work (Paffenbarger and Hale 1975). In contrast, in a later study of Harvard College alumni, the diminished coronary mortality among physically active men did not apply to SCD (Paffenbarger et al. 1978). In the Framingham study, physical activity seemed to have a somewhat greater effect on SCD than on NSCD (Kannel and Thomas 1982). Animal studies have given some evidence that daily physical exercise reduces the susceptibility of the ischemic heart to VF (Billman et al. 1984).

The incidence of all manifestations of CHD is elevated in diabetics: CHD is manifested earlier, the case-fatality is higher and the prognosis after nonfatal events is less favourable than among non-diabetics (Pyörälä and Laakso 1983). In a study in Israel, CHD mortality among men aged 40 years and over was 3.5 times higher and the incidence of SCD was 3.6 times higher among diabetics than among non-diabetics (Herman et al. 1977). In many prospective studies the number of diabetics has been too small to reveal any difference in the mode of death from CHD as compared with non-diabetics.

4.5.4. Conclusions

The conventional risk factors of CHD, i.e. hypertension, high serum cholesterol and smoking, also apply to SCD. Whether a person's risk profile for SCD is different from that for NSCD or other manifestations of CHD has not been fully established. There is some evidence that heavy smoking and hypertension predispose a person to SCD. There seems to be rather strong epidemiological evidence that moderate alcohol consumption is inversely associated with the risk of different manifestations of CHD, with the possible exception of SCD. Heavy consumers' increased risk seems to apply to SCD in particular. Physical activity may provide protect from SCD, but vigorous exercise may have some precipitating effect on its occurrence. Diabetics' enhanced risk of CHD probably applies to SCD, too.

4.6. Precursors of sudden coronary death

4.6.1. Prior clinical coronary heart disease

The prevalence of angina pectoris (AP) and sustained MI before SCD varies considerably from study to study, presumably mostly because of methodological differences. Earlier American studies indicated that SCD was the first manifestation of CHD in 20-25 per cent of cases (Kuller et al. 1966). Later retrospective studies in the U.S.A. have shown varying prevalences:
in one study 42 per cent of men and women dying from CHD outside hospital had no prior history of MI or AP (Simon and Alonzo 1973); in another study 23 per cent of patients dying within 24 hours had no prior evidence of CHD, and in 53 per cent CHD had been diagnosed earlier (Friedman et al. 1973); in a third study 84 per cent of SCD victims had a history of prior MI or AP, and only 3 per cent died suddenly with no history of cardiac symptoms (Reichenbach et al. 1977). In the Tecumseh prospective study, 40 per cent of those dying suddenly of CHD during the six-year follow-up period had established CHD at the initial examination (Chiang et al. 1970). In the Framingham study, SCD was preceded by a history of MI in 21 per cent, and by a history of AP in an additional 9 per cent (Kannel and Thomas 1982). In 57.5 per cent of 270,000 male telephone industry workers in the U.S.A., SCD during 5 years was preceded by clinical heart disease at the initial examination (Hinkle 1982). The Helsinki Ischaemic Heart Study showed a 38 per cent prevalence of prior MI among male SCD victims, and when AP was included, the prevalence of prior CHD rose to 74 per cent (Romo 1973). In a study from Denmark, the prevalence of prior MI was 54 per cent, and that of AP 23 per cent (Madsen 1983). In both studies the prevalence of prior manifestations increased with age among both sexes.

4.6.2. Prior electrocardiographic changes

The predictive value of electrocardiogram (ECG) for SCD has been investigated both in unselected populations and in post-infarction patients. In the Tecumseh study, 38 of 45 SCD victims (84 per cent) had codable ECG changes at the initial examination (Chiang et al. 1970). In the Framingham study, CHD-free men with ECG signs of left ventricular hypertrophy had an almost sixfold risk of SCD (Kannel and Thomas 1982). The prevalence of VEBs in later SCD victims was about 20 per cent in the Tecumseh study and about 15 per cent in the Framingham study.

The predictive value of VEBs has been studied more thoroughly in post-infarction populations. In the Coronary Drug Project, 2035 male survivors of MI were screened by resting ECG and followed for three years (The Coronary Drug Project Research Group 1973). The SCD incidence was about twofold for men with any VEBs and about fourfold for men with VEBs ≥ 10/100 beats as compared with men without VEBs at the screening examination. In that study, VEBs seemed to be an independent predictor of SCD. In a study of 940 patients after MI, a three-year follow-up period showed increased cardiac mortality among those who had had VEBs during the initial six hours of monitoring (Moss et al. 1979). The excess mortality was highest when complex VEBs were present, but the occurrence of VEBs of any type did not differentiate between SCD and NSCD. In yet another post-infarction material of 1739 men, the occurrence and type of VEBs were classified on the basis of one hour ECG monitoring at baseline (Ruberman et al. 1981). During the follow-up, men with R-on-T phenomenon or runs of VEBs had a fourfold incidence of SCD as compared with
men without VEBs. Among men with other types of VEBs, the incidence of SCD was between the other groups. The rate of SCD was fairly constant during the follow-up, indicating a long-term effect of VEBs. The value of VEBs as predictor of NSCD was less distinctive. In a Finnish study of 158 post-infarction men, the occurrence of ectopic beats during an exercise test shortly after MI predisposed them to later SCD (Kentalo and Sarna 1976). Comparison of the predictive value of ECG changes in healthy people and in patients with clinical CHD has clearly shown that VEBs are of importance only in the presence of cardiac disease (Pedoe 1978). This applies to younger age groups in particular (Kennedy et al. 1982).

A study of 55 patients with recent MI showed that prolongation of corrected QT interval (QTC) constituted a twofold risk of SCD during seven years of follow-up (Schwartz and Wolf 1978). Recently, the predictive value of the QTC interval was studied among 1157 patients with angiographically established CHD. Initially, no group with prolonged QTC could be identified, but during the follow-up prolongation of QTC emerged in 61 per cent of the 82 patients who suffered SCD. Among survivors, prolongation of QTC occurred in only 15 per cent (Puddu and Bourassa 1986).

4.6.3. Noncardiac factors

Long before any scientific proof had been obtained, a popular opinion among laymen held that psychosocial and environmental stress affect the occurrence of the various manifestations of cardiac disease. The occurrence of sudden death, in particular, has been ascribed to emotional shock, such as fear, rage, grief or even joy. In a material of 170 sudden deaths collected from newspapers and other sources of information, the death of a close person, other acute grief or personal danger were the most common life settings before sudden death (Engel 1971). Although such reports contain many inaccuracies and unreliable details, the possible cause-effect relationship is congruent with approved pathophysiological principles in SCD.

The role of psychosocial stress in the incidence of SCD has hitherto been studied only retrospectively (Engel 1978). A study concerning recent life changes of 226 SCD victims in Helsinki detected a marked elevation in the magnitude of recent life changes - such as recent illness, dismissal from work, the death of a spouse, divorce or marital problems - as compared with life changes one year earlier (Rahe et al. 1974). Studies from Finland (Koskenvuo et al. 1980) and the U.S.A. (Weinblatt et al. 1978) have shown that low social and educational class is associated with an enhanced risk of SCD. It has been hypothesized that such a situation might serve as a marker of life stresses or inability to cope with them, and thus explain the finding. However, further analysis of the American study population failed to show any marked differences in the magnitude of psychosocial stress according to the level of education. In fact, nonstrivers in the low-education group and those with the lowest time urgency in the high-
education group had a greater probability of SCD than did other men (Ruberman et al. 1983).

4.6.4. Conclusions

In most cases SCD is preceded by clinical evidence of CHD, and in approximately a third of cases by MI. In some 20 per cent, SCD is the first manifestation of CHD. ECG changes before SCD mostly reflect a diseased myocardium, but the occurrence of complex VEBs is presumably an independent predictor of SCD. It is possible that acute emotional shock can discharge SCD. The role of long-standing psychosocial stress in the incidence of SCD is inconclusive, because it is difficult to evaluate such associations in the absence of information on psychosocial stress in appropriate control populations.

4.7. Premonitory symptoms of sudden coronary death

It has been known for decades that in the majority of cases MI is preceded by various warning symptoms lasting for several days or weeks before the acute attack (Feinleib et al. 1975). The occurrence of symptoms during the prodromal phase of SCD has been elicited retrospectively from relatives and other witnesses (Kinlen 1969; Fulton et al. 1972; Küller et al. 1972; Friedman et al. 1973; Romo 1973; Simon and Alonzo 1973; Fraser 1978; Haghfelt 1980; Madsen 1985), in successfully resuscitated cases also from the patients themselves (Liberson et al. 1974; Goldstein et al. 1986). The chief symptoms during the preceding four weeks have been new or worsening AP, new or worsening dyspnea and unusual fatigue and tiredness. In Romo's study, 53 per cent of SCD victims had premonitory symptoms, and 38 per cent went to the doctor because of these symptoms during the four weeks before the final attack. Undue fatigue was the most prevalent symptom (Romo 1973). Findings in the other aforementioned studies were about the same, and the occurrence of symptoms did not correlate with age or sex. In Simon's material only four out of 147 SCD victims (2.7 per cent) died without any history of heart disease, prodromata or acute symptoms of some duration (Simon and Alonzo 1973). Thus, when all evidence of CHD is collected, truly unexpected SCD is a rare phenomenon.

4.8. Attendant circumstances of sudden coronary death

The Myocardial Infarction Community Registers have been a source of extensive material for the analysis of environmental factors in nonfatal and fatal myocardial infarctions (WHO 1976). Regrettably, only the Helsinki Register contains separate analyses referring to SCD (Romo 1973). In Helsinki and in all centres combined, the incidence of all attacks was somewhat higher than average from February to June, and lower from July to October. The same applied in a Scottish study concerning mortality from
CHD while in hospital (Dunnigan et al. 1970), and in New Zealand, where SCDs were significantly more common in the cooler months (Fraser 1978). The distribution of all attacks over the days of the week was uniform in various Myocardial Infarction Registers. The pooled figures show a slightly higher incidence on Mondays and Saturdays than on other days of the week (WHO 1976). In a study of 100 autopsied SCD cases, the most common day of death was Saturday (Myers and Dewar 1975); in another study it was Monday (Rabkin et al. 1980). The pooled figures of Myocardial Infarction Registers show an increased incidence of all attacks in mid-morning and late afternoon. In Helsinki the distribution of SCD was quite even throughout the day (24 hours) except from 12 p.m. to 6 a.m., when the incidence was lower than expected (Romo 1973). In a recent American study, the incidence of SCD was highest from 7 to 11 a.m. (Muller et al. 1987).

The preponderance of the home as the place where SCD occurs has been documented in several studies (Kuller et al. 1966; Wikland 1971; Romo 1973, Simon and Alonzo 1973; Rissanen et al. 1975; Hejl et al. 1976; Ulrich and Schmittova 1977; Wennemblom 1982; Madsen 1985). More than half of the patients were at home at the onset of SCD. The same studies have consistently indicated that SCD occurs at work in only about 5-10 per cent of cases. The proportion of those dying during transport or after admission to hospital has likewise been small.

The role of strenuous work or exercise as a precipitating factor of SCD has been analysed in some studies. Romo found that 3.7 per cent of men and one in 36 women were engaged in strenuous activity at the onset of SCD (Romo 1973). In Lovegrove's material of 500 autopsied SCD cases, 7.4 per cent had been engaged in strenuous activity immediately before death (Lovegrove 1977). One study demonstrated a 37 per cent prevalence of strenuous activity immediately before instantaneous death, compared with a prevalence of only 3 per cent before noninstantaneous SCD (Friedman et al. 1973). In recent years, efforts have been made to assess the risk of SCD during vigorous activity. Over a six-year period in Rhode Island, U.S.A., a total of 12 men died while jogging; it was calculated that the rate of SCD was seven times the estimated death rate during more sedentary activities (Thompson et al. 1982). In another American study, the relative risk of cardiac arrest during vigorous exercise was 56 as compared with that at other times among men with low levels of habitual activity. Among men with the highest level of habitual activity, the risk during exercise was elevated by a factor of only 5 (Siscovick et al. 1984). In a Finnish study, the age-adjusted risk of SCD related to exercise was 4.5 times higher than that unrelated to exercise (Vuori et al. 1983).

4.9. Prevention of sudden coronary death

Prevention is of great importance for SCD, as therapy after cardiac arrest is difficult and seldom even possible. A number of secondary prevention intervention measures in post-MI patients have been undertaken, including
beta-blockers, antiplatelet drugs, coronary artery bypass grafting and multifactorial programmes. A number of studies have demonstrated that SCD as well as overall cardiac mortality can be reduced by the administration of beta-blockers within one to two years of MI (Green et al. 1975; Hjalmarson et al. 1981; The Norwegian Multicenter Study Group 1981; B-Blocker Heart Attack Trial Research Group 1982; Hansteen et al. 1982). In patients with unstable AP the Veterans Administration aspirin trial produced a nearly statistically significant reduction in cardiac deaths during a 12-week period; this applied also to SCD (Lewis et al. 1983). Other studies with antiplatelet drugs have shown the same trend less conclusively (The Persantin-Aspirin Reinfarction Study Research Group 1980; Aspirin Myocardial Infarction Study Research Group 1980). In Finland a multifactorial intervention programme was applied to 183 patients under 65 years who had been treated in hospital for MI (Kallio et al. 1979). After three years of follow-up, the cumulative coronary mortality was significantly smaller in the intervention group than among the controls; this difference was mainly due to the reduction in sudden deaths in the intervention group.

In a European coronary surgery study, patients with stable AP were given surgical or medical treatment on a random basis. A significant reduction in SCD was recorded for patients with triple vessel disease who had undergone surgical treatment (European Coronary Surgery Study Group 1982). In the Coronary Artery Surgery Study in the U.S.A., surgical treatment had a highly significant independent effect on SCD during five years of follow-up (Holmes et al. 1986).

Since SCD is one clinical manifestation of coronary atherosclerosis, the most effective way to prevent SCD would be to prevent coronary atherosclerosis by reducing risk factors in populations. Primary prevention studies to date have not unambiguously resulted in reduced SCD (Oliver 1983). However, the decline in mortality from CHD that has occurred in many industrialized countries during the past 15 years is partly due to a reduction in risk factors; in particular, this applies to SCD (Piza and Uemura 1982; Kuller et al. 1986).
5. PURPOSE OF THE STUDY

The present study was undertaken to investigate prospectively in a representative Finnish middle-aged population

- the occurrence of SCD and other manifestations of CHD
- the incidence of SCD by sex and age group, and its regional variation
- the characteristics of the SCD event and SCD victims
- the risk factors of SCD.
6. STUDY POPULATIONS AND SURVEY METHODS

6.1. General design

The Social Insurance Institution's Coronary Heart Disease Study is part of the larger prospective Mobile Clinic Health Survey carried out in adult populations in 1966-72. The study population of the CHD study was drawn from four geographical areas in Finland, and in each study area three population groups were investigated (Figure 1). The population groups from southwestern, northwestern and central Finland were investigated in 1966-68, the population groups in eastern Finland in 1972. After a median follow-up period of six years, a re-examination was carried out in 1973-76.

Figure 1. Geographic location of the 12 population cohorts.
The re-examination contained basically the same investigations as the baseline examination, but included a more detailed questionnaire and the analysis of some additional risk factors. The mortality of the whole population invited to participate in the study has been monitored until the end of 1979. Detailed descriptions of the study design and baseline results have been published (Pyörälä et al. 1974; Reunanen 1977; Reunanen et al. 1983).

6.2. Baseline examination

6.2.1. Study population

The study population comprised all men and women aged 30-59 years invited to come for a health examination, carried out at a mobile clinic unit in 12 population groups (Figure 1). The population groups consisted of

**Figure 2.** Number of men (M) and women (F) invited to and participating in the baseline survey and the re-examination, and the number of people dying during the follow-up. The number of people constituting the baseline population of the Social Insurance Institution's Coronary Heart Disease Study is given in parentheses.
either the whole population or a random sample of the population of a geographical area or the employees of a factory. Four of the population groups were urban or semi-urban (Vammala, Saloien, Jämsä and Joensuu), five were rural (Mouhijärvi, Merijärvi, Koskenpää, Kiihtelysvaara and Tohmajärvi) and three consisted of factory employees (Kauttua, Rautaruukki and Jämsänkoski).

There were 5765 men and 5261 women participating in the baseline examination; the overall participation rate was 89.6 per cent (88.6 for men and 90.7 for women) (Figure 2). The number of men and women examined and for whom complete data were obtained, according to study area, is presented in Table 1.

A questionnaire was sent to most non-participants regarding the reason for not participating. More than half of the non-participants had moved from the study area, and about a third had a basically medical reason for not participating.

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<th>Table 1.</th>
<th>Number of men and women examined, with complete data by age group and study area.</th>
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<td>Women</td>
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6.2.2. Survey methods

A questionnaire concerning known diseases, use of drugs, and smoking habits was filled in by the participants at home, and checked by a nurse during the field examination. Questions about chest pain symptoms were asked by a trained nurse, using the structured London School of Hygiene Cardiovascular Questionnaire (Rose 1962). Typical AP was defined as chest pain located behind the sternum or both the left of the chest and the left arm, appearing while walking and disappearing within 10 minutes of stopping or slowing down. Pain was defined as atypical when located elsewhere, or when the symptoms did not necessitate stopping or slowing down, or when the pain did not disappear in 10 minutes. An attack of chest pain was defined as severe chest pain across the front of the chest, lasting for half an hour or more. The symptom questionnaire included questions concerning effort dyspnea and claudication.

A resting 12-lead ECG was recorded on a 4-channel Mingograf 34 (Elema Schönander), at a paper speed of 50 mm per second. The changes in ECGs were coded according to the revised Minnesota code (MC) (Rose and Blackburn 1968) by specially trained technicians under the supervision of two cardiologists. The small ST segment depressions (MC 4,3) and small negative or isoelectric T waves (MC 5,3) were also coded when the changes appeared only in the lead aVF. The ectopic beats were coded according to the criteria of The Scandinavian Committee on ECG Classification (1967).

Height was measured barefoot and read to the nearest centimetre. Weight was measured with indoor clothing, subtracting 1 or 2 kg. Quetelet's body mass index (weight in kilograms / height in metres squared) was used as an index of overweight (Keys et al. 1972). Blood pressure (BP) was measured in the sitting position after a 3-5 minute rest. A semiautomated device (Elag BPM-A) was used, and BP was read to the nearest 2 mmHg. The disappearance of sounds was recorded as diastolic BP. An oral glucose tolerance test was carried out on all examinees except known diabetics. Plasma glucose was measured, by using an autoanalyzer modification of the ferricyanide reduction method, one hour after ingestion of glucose. Serum cholesterol was determined by an autoanalyzer modification of the method of Huang et al. (1961).

6.3. Re-examination

6.3.1. Study population

The re-examination was carried out in 1973-76, approximately 5½ years (range 49-82 months) after the baseline examination. All men and women invited to come for the baseline examination and still alive were asked to come for re-examination. There were 5519 men and 5166 women participating in the re-examination, giving an overall participation rate of 90.2
per cent (89.8 per cent for men, 90.6 for women) (Figure 2). A question-naire concerning the reasons for non-attendance and asking for information about known diseases was mailed to all non-participants. The response rate was 63 per cent for men and 72 per cent for women. Accordingly, no information on health status was available for only 3.8 per cent of the men and 2.6 per cent of the women.

6.3.2. Survey methods

The survey methods were basically the same as in the baseline examina-tion. The questionnaire filled in by the examinees was more comprehen-sive, and included items on possible vascular events during the follow-up. All participants who stated that they had suffered a definite or suspected MI since the baseline examination were asked to give details of hospital admissions. Questions on the dates of the attack and hospital admissions were also asked in a second letter that was sent to all non-participants who had given a history of MI.

Drinking habits were also enquired in the questionnaire. There were separate items for the consumption of beer, wine and spirits. Examinees who stated that they had not drunk alcohol of any kind during the preceding 12 months were classified as abstainers. Consumption of beer was recorded as the average number of bottles (at 1/3 litre) drunk per week during the preceding month. The consumption of wine and spirits was recorded as the total number of bottles (one bottle of wine being 3/4 litre, one bottle of spirits being 1/2 litre) drunk during the preceding month. The pre-coded choices for the answers were less than 1/2, 1/2-1, 1-2, 2-5, 5-10 or 10+ bottles for wine and less than 1/4, 1/4-1, 1-2, 2-3, 3-5, 5-10 or 10+ bottles for spirits. In addition, for each type of drink a further question enquired whether the respondent's usual monthly consumption during the preceding twelve months had been equal to, at least double, or at most half of the amount given for the preceding month. For subjects stating that their usual average consumption was twice as high, the number of bottles of beer was doubled; for wine and spirits consumption the next higher class was used to describe usual average consumption. For respondents stating that their usual average consumption was only half of the amount stated, the number of bottles of beer was divided by two, and for wine and spirits the next lower class was selected. Finally, the usual average total monthly consumption of absolute alcohol was calculated as a sum of the amount of all types of alcohol consumed. The alcohol content used in the calculation was 3.6 per cent by weight for beer, 8.9 for wine and 35 per cent by weight for spirits.

The questionnaire contained questions about the date and cause of death of the respondent's parents. The causes of the parents' deaths reported as in the questionnaire were ascertained by consulting local registrars, without checking the original death certificates.
6.4. Follow-up investigations

The mortality of the examinees has been monitored continuously since the baseline investigation. A copy of the death certificates of all examinees dying before the end of 1979 has been obtained from the Central Statistical Office of Finland. A detailed analysis of deaths was begun after completion of the follow-up investigation. The causes of death were coded using the 8th revision of the international classification of diseases. All death certificates with coronary death as an underlying or contributory cause were thoroughly examined. If the death certificate indicated - in addition to coronary death (codes 410-414) as the underlying diagnosis - the time and place of death and the duration of the terminal illness, no additional information was sought. In other cases with CHD as an underlying or contributory cause of death, the hospital records and autopsy reports were checked. Autopsy was performed in 40 per cent of the SCD cases. In non-hospitalized and non-autopsied cases, the subscriber of the death certificate was consulted. In five cases, additional information was obtained from relatives.

Fatal MI was defined as fatal outcome for a patient hospitalized for MI or death outside hospital probably caused by CHD. Death within one hour of the onset of acute symptoms was classified as definite SCD. If the death was unwitnessed, and the duration of the terminal illness was therefore inexacty documented, it was inferred that death had probably occurred suddenly (probable SCD). Unless otherwise indicated in subsequent analyses, definite and probable SCDs were grouped together.

Hospital records of all but three of the 237 men and 92 women reporting hospital admissions because of unequivocal or suspected MI after the initial survey were scrutinized. NFMI was defined according to the criteria applied in the WHO co-ordinated infarction register study (WHO 1976). Definite NFMI was thus defined as an attack with a typical history together with serial enzyme changes or unequivocal serial ECG changes. Possible NFMI was defined as an attack with a typical history without ECG and enzyme changes and without evidence for another diagnosis for the attack. Those without history of NFMI between the initial survey and the re-examination but with new unequivocal Q/QS changes on the ECG at re-examination constituted the group of silent ECG-infarction.

In nonfatal cases the first event during the follow-up period was used for classification. An attempt to investigate the previous history of possible nonfatal events was also made in fatal cases. A previous history of nonfatal event during the follow-up, and before the fatal event, was found for eight people dying from MI. However, because the previous history of many fatal cases could not be settled, all those dying from CHD during the follow-up were counted as fatal cases only.
6.5. Statistical methods

The indirect method was applied in computing the age-adjusted prevalences using the whole Finnish population aged 30-59 in 1970 as weights (Armitage 1971). Age-adjusted risk ratios were calculated according to a method described by Miettinen (1972). Age-adjusted prevalences in various subgroups of the population were estimated with the linear logistic model (Cox 1970). The differences in prevalences between different groups were tested by the likelihood ratio test and Wald's test based on the model. The F-test based on the general linear model was also used (Searle 1971).

The estimation of mortality in various age groups was based on an exponential survival distribution. Age-adjusted mortality rates were calculated with the direct method. The proportional hazards model of Cox (1972) was used to estimate the association between different risk factors and mortality. Age and other confounding factors and effect-modifying factors were included in the models. An exponential modification of the model was also used (Kalbfleisch and Prentice 1980). Relative risk estimates, likelihood ratio test statistics, and Wald's test statistics were based on the model. The assumption that the relative mortality risk between classes of the independent variable is constant over the follow-up was analysed by the stratified survival model of Cox (Kalbfleisch and Prentice 1980). Systematic changes with time in the differences in the hazards between the different classes were tested with Cox's model including time-dependent variables.

In the study of incidence during a short follow-up period with low incidence rates and no withdrawals alive during the period, age-adjustment was based on the direct method, and the differences in the age-adjusted rates were tested by the Mantel-Haenszel method (Mantel and Haenszel 1959). If the exact date of onset was unknown in the incidence studies, a multiple logistic model was used.

6.6. Discussion

The study population was not a strictly representative sample of the whole middle-aged population of Finland, and thus the results concern only the 12 cohorts studied. However, the cohorts were chosen to represent populations with low (the southwestern study area), intermediate (the northwestern and central study areas) and high (the eastern study area) CHD mortality, and the distributions by age, occupation and social class of the people studied were close to the distributions for the whole country.

In order to study the representativeness of the study population, the mortality among the people in our study was compared with the mortality among people of the same age in the provinces, from which the study cohorts were chosen (Table III/Paper II, p. 86). The total, cardiovascular and CHD mortality in the study areas did not differ markedly from those observed in the corresponding province.
The attendance rates at the examinations were rather high by international standards, and although the prevalence of CHD manifestations was higher in non-participants, the prevalence of various CHD indicators would not have increased substantially if all those invited had been examined. In addition, fatal end points were checked equally for participants and non-participants.

The CHD death rates presented in this study are based on a thorough check of death certificates of everyone who died during the follow-up. The autopsy rate was rather low, and in the majority of cases the CHD diagnosis was based on the clinical disease history. Especially in SCD cases outside hospital, the CHD diagnosis was often based on scanty clinical documentation. However, when a physician, usually aware of the health state of the deceased, assumes that cases of sudden unexpected death are due to MI, he usually determines the correct etiology, because in about 90 per cent of the cases there is a causal relationship between sudden death and coronary atherosclerosis (Spain et al. 1960).

The one-hour limit in the definition of SCD is presumably relevant in differentiating cases by mechanism of death; death ensuing within an hour is most often due to fatal arrhythmia, usually VF; longer duration of the symptoms makes pump failure and secondary arrhythmia a more plausible mechanism of death. What is more important, the chosen cut-off is relevant from the therapeutical standpoint; in most cases of so-defined SCDs, prevention is the only therapy. On the other hand, this kind of definition naturally leads to some disagreement about the allocation of fatal CHD cases to appropriate categories, because it is sometimes very difficult to determine when the terminal event begins. However, in most cases, the onset of symptoms has clearly disrupted the usual activities of the person affected.

In a substantial number of cases, the terminal illness had no witnesses. However, enough information was obtained to make it possible to reconstruct the probable course of events, thus justifying their classification as sudden deaths.

The incidence of NFMI may be an underestimate, as information was lacking in a few cases. No information on known diseases could be obtained for 3.8 per cent of the men and 2.6 per cent of the women living at the time of re-examination. Had the incidence of NFMI in these non-respondents been the same as in the whole study population, the number of men with NFMI would have increased by five (from 141 to 146) and of women by one (from 41 to 42). In addition, it is possible that some respondents with a NFMI in the follow-up period did not mention the event in the questionaire. According to an analysis with record linkage to the national hospital discharge register (Heliövaara et al. 1984), there were very few false negative cases, and the number of incidence cases identified in this study but not by the discharge register was about the same as the number of false negatives.
7. RESULTS

7.1. Distribution of different manifestations of coronary heart disease between baseline and re-examinations (Paper I)

The assessment of the incidence of different manifestations of CHD was based on the people in the initial study population who had complete initial data and were either alive at the time of re-examination and had complete re-examination data or who had died before the re-examination. The population at risk consisted of 5438 men and 4924 women, and the mean follow-up time was six years.

7.1.1. Results

The age-adjusted annual mortality per thousand from all causes was 10.3 for men and 2.4 for women, and for cardiovascular diseases 5.7 for men and 1.0 for women. The average annual rates of CHD death and SCD were 3.8 and 2.4 for men, 0.4 and 0.2 for women. The percentage distribution of all cases with a new CHD event or new symptoms is depicted in Figure 1/Paper I (p. 76). Forty-one per cent of all events in men, but only 13 per cent in women, consisted of various forms of MI or CHD death. SCD comprised 8.3 per cent of all new events among men, and only 0.8 per cent among women.

The incidence of different manifestations of CHD in the group from which persons with overt CHD were excluded is presented in Figure 2/Paper I (p. 76). Overt CHD at baseline was defined as a history of MI or typical AP symptoms or unequivocal resting ECG changes of past MI (MC 1.1 or 1.2 and 5.1-2). The age-adjusted average annual incidence of all CHD manifestations combined was 19 per cent lower among men and 7 per cent lower among women without CHD than among all men and women. The incidence of CHD death was 4.9 times higher among men with CHD at entry, than among men without CHD; the corresponding figure for women was 4.1 (Figure 3/Paper I, p. 77).

7.1.2. Discussion

In many prospective population studies, the incidence of CHD events is only reported for people free of CHD at entry; the incidence of events in the whole population studied remains unknown. In this study the risk of new MI or CHD death among people with evidence of CHD at entry was 4-5 times higher than among people without. One third of all 'hard criteria' CHD events consisted of the 9 per cent of the study population with overt CHD at entry. On the other hand, if those with evidence of CHD at entry were excluded, the incidence rates declined by a maximum of 10-20 per
cent. The rates obtained for the CHD-free population are thus not very different from the rates for all those participating in the study.

The comparability of various population studies is hampered by differences in the composition of the study populations and by the variability of definitions of end points. However, the percentage distribution of CHD death, NFMI and new AP in various incidence studies may be compared with the results of this study (Table III/Paper I, p. 78). Fatal CHD constitutes one-fifth of all events among men in nearly all the studies. The distribution of events among men in our study was very close to that of two other Finnish studies applying similar survey methods (Karvonen et al. 1970; Pyörälä et al. 1973).

7.2. Incidence of sudden coronary death and other 'hard criteria' coronary heart disease events (Paper II)

A fixed four-year follow-up time common to all population groups was used to allow analysis of regional variability. During the follow-up, 297 of the 6310 men and 61 of the 5800 women in the original cohorts had died. A check of the hospital records confirmed the diagnosis of NFMI in 141 men and 41 women during the four-year follow-up.

7.2.1. Results

The total, cardiovascular and CHD mortality rates in four years are presented in Table I/Paper II (p. 84). The four-year CHD mortality per thousand by age group (30-39, 40-49, 50-59) was 2.0, 8.5 and 31.5 among men and 0.5, 1.4 and 3.4 among women, respectively. The incidence of SCD by age group was 0.4, 3.6 and 21.5 among men and 0.2, 1.0 and 1.1 among women, respectively. The age-adjusted total CHD mortality in four years was 13.0 per thousand among men and 1.8 per thousand among women. The corresponding figures for SCD were 7.8 and 0.7 among men and women, respectively. Thus, 59 per cent of the fatalities among men and 40 per cent among women were SCDDs.

The incidence of NFMI as well as all 'hard criteria' CHD events in four years is presented in Table II/Paper II (p. 84). The age-adjusted incidence of definite NFMI was 15.1 per thousand among men and 2.7 per thousand among women. The incidence of all 'hard criteria' CHD per thousand by age group (30-39, 40-49, 50-59) was 11.0, 29.0 and 71.8 among men and 0.5, 7.2 and 19.8 among women, respectively. The total age-adjusted four-year incidence of all 'hard criteria' CHD was 35.2 among men and 9.1 among women.

The four-year incidence of fatal CHD and NFMI in the 12 population cohorts is illustrated in Figure 3. The highest CHD death rate for men (29.6 per thousand) was observed in Merijärvi, a small rural community in northwestern Finland, and the lowest (2.6 per thousand) in Vammala, an
urban community in southwestern Finland. The highest incidence of all 'hard criteria' CHD events for men was observed in a North Karelian rural community, Kihhtelysvaara (66.7 per thousand), and the lowest for men from Mouhijärvi (9.2 per thousand), a rural community in southwestern Finland. Among women, the differences between the incidence rates were rather small. As among men, the highest CHD death rate (3.9 per thousand) was found in Merijärvi.

**Figure 3.** The incidence of coronary death and NFMI in 12 population cohorts. N = number of examinees.

A systematic variation was observed when the incidence of CHD events was examined by study area, each comprising three population cohorts (Figure 4/Paper II, p. 85). The total CHD mortality per thousand among men in four years was 4.7 in the southwestern, 14.4 in the northwestern, 14.3 in the central and 17.5 in the eastern study area. The incidence of SCD per thousand was 2.5, 8.1, 7.7 and 11.9, respectively. Although both total coronary mortality and the incidence of SCD were significantly higher among men from North Karelia than among men from the other study areas combined (p < 0.05), the regional differences were more striking when the incidence rates of CHD death and SCD for men from
southwestern Finland were compared with the rates for men from the other three areas combined ($p < 0.001$ and $< 0.01$, respectively). Total CHD mortality as well as the incidence of SCD among women were low, and the difference in rates by study area was not significant.

The age-adjusted mortality from CHD was significantly higher for the non-participants among both men ($p < 0.01$) and women ($p < 0.001$) (Figure 3/Paper II, p. 85). The incidence of SCD was also significantly higher among the non-participating men than among the participants ($p < 0.05$). The number of women who died suddenly was too small to permit a meaningful analysis.

In addition, the four-year incidence of 'hard criteria' CHD was estimated in the subpopulation initially free of overt CHD. The four-year incidence of CHD death per thousand was 7.6 among men and 0.9 among women. The corresponding figures for SCD were 3.8 and 0.4. The incidence of NFMI and all 'hard criteria' CHD events among CHD-free men and women are presented in Table II/Paper II (p. 84). The regional variation in the incidence rates for CHD-free men was similar to that for all men. The rate of fatal CHD was about 40 per cent and that of NFMI about 20 per cent lower among the CHD-free men than among all participants. Among women, the corresponding figures were 50 and 40.

7.2.2. Discussion

The incidence of SCD in this study was very close to that of the Helsinki infarction register (Romo 1973). Other Scandinavian short-term surveillance studies have shown much lower rates of SCD. In Stockholm the estimated incidence of SCD was 0.5 per thousand among men and 0.1 per thousand among women aged 45-54 (Wikland 1971). In a Danish population it was 3.6 per thousand among men and 1.0 per thousand among women aged 50-69 years (Madsen 1985).

American prospective studies in initially CHD-free populations have shown rates that are much closer to our results. The Framingham 20-year follow-up study showed an annual incidence of 1.1 per thousand among men and 0.3 per thousand among women aged 45-54 at entry (Kannel and Thomas 1982); in another study with a 10-year follow-up, the annual incidence was 2.6 per thousand among men aged 40-59 at entry (Stamler 1976).

The regional differences in the incidence of fatal CHD and NFMI in this study correspond closely to the regional pattern of CHD mortality in the whole country (Pyörälä and Valkonen 1981) and with the data both in MI registers (Pohjola et al. 1980) and in hospital discharge records (Romo et al. 1982).

The high total, cardiovascular and CHD mortality of non-participants compared with participants in this study corroborates the findings of other studies (Wiigelmsen et al. 1976; Criqui et al. 1978).
7.3. Characteristics of sudden coronary death (Paper III)

Characterization of the SCD event was based on the whole male population invited to participate in the baseline survey and followed up to the re-examination (study population I/Paper III, p. 90). The previous health status could only be checked among the participants of the baseline study. Consequently, SCD was correlated to the former health status of its victims in that part of study population I which participated in the baseline study (study population II/Paper III, p. 90). Since information about the participants' parents was not collected until during the re-examination, the hereditary aspects of SCD were only investigated in the population participating in the re-examination (study population III/Paper III, p. 90). The vital status of this population was followed up to the end of 1978, giving a median follow-up time of 3½ years. As described earlier, the causes of the parents' deaths were checked by consulting local registrars. The 1966 deaths among all Finns aged 30 years or over were used as references (Causes of death in Finland 1966).

7.3.1. Results

There were 57 definite and 20 probable SCDs in study population I/Paper III (p. 90). The age distribution of the men at the moment of death is presented in Table 2. The distribution of the SCD cases by place of attack is presented in Table 3. Attacks were most common at home; only 10 per cent occurred at work. No deaths occurred in traffic. The most common time

<table>
<thead>
<tr>
<th>Age, years</th>
<th>SCD cases</th>
<th>Percentage of all coronary deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35 - 39</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>40 - 44</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>45 - 49</td>
<td>11</td>
<td>61</td>
</tr>
<tr>
<td>50 - 54</td>
<td>19</td>
<td>58</td>
</tr>
<tr>
<td>55 - 59</td>
<td>30</td>
<td>71</td>
</tr>
<tr>
<td>60 -</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>100</td>
</tr>
</tbody>
</table>
for SCD was between 7 a.m. and 3 p.m., but the difference from the rates at other times of day was not statistically significant. Deaths were evenly distributed throughout the seasons of the year. Friday was the most common and Tuesday the least common day when SCD occurred, but the difference from the rates of other days of the week was not statistically significant.

Table 3. Distribution of SCD cases by place of attack.

<table>
<thead>
<tr>
<th>Place</th>
<th>SCD cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Home</td>
<td>33</td>
</tr>
<tr>
<td>Work place</td>
<td>8</td>
</tr>
<tr>
<td>Public place</td>
<td>12</td>
</tr>
<tr>
<td>Hospital</td>
<td>10</td>
</tr>
<tr>
<td>During transport to hospital</td>
<td>4</td>
</tr>
<tr>
<td>Sauna</td>
<td>2</td>
</tr>
<tr>
<td>Other place</td>
<td>4</td>
</tr>
<tr>
<td>No information</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
</tr>
</tbody>
</table>

Owing to the method of study used, symptoms experienced immediately before death were poorly documented. In 28 cases (49 per cent) of definite SCD, death was described as instantaneous. In 21 cases (37 per cent) preceding symptoms, most often chest pain, were reported. In the remaining 28 cases (36 per cent of all SCDs), no data about preceding symptoms could be obtained.

In study population II/Paper III, the health status of the 66 (49 definite, 17 probable) subsequent SCD victims was evaluated at the baseline study, an average of 3½ years (range 1-85 months) before death. The prevalence of moderate or severe dyspnea, typical AP, a history of MI, the presence of treated heart failure or hypertension and ECG signs of past MI among men subsequently dying suddenly were compared with the respective prevalences among men with subsequent NSCD and NFMI and among men without CHD events during the follow-up (Table III/Paper III, p. 91). The prevalence of symptoms of effort dyspnea and typical AP as well as heart failure was highest in the SCD group. The probable SCD group seemed to be the least healthy. The use of cardiovascular drugs, especially nitro-
glycerin, was more common in the SCD group than in other groups (Table V/Paper III, p. 92). In the comparison between SCD and NSCD groups, the prevalence of typical AP was significantly higher in the SCD group (Table 4).

**Table 4.** Age-adjusted prevalences (%) and risk ratios (RR) for certain signs and symptoms reflecting cardiovascular disease at the time of the baseline study in men with subsequent SCD compared with men with subsequent NSCD.

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>SCD N = 66 %</th>
<th>RR</th>
<th>NSCD N = 38 %</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or severe dyspnea</td>
<td>41</td>
<td>1.6</td>
<td>27</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Typical AP</td>
<td>35</td>
<td>4.7</td>
<td>9</td>
<td>1.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>History of MI</td>
<td>23</td>
<td>2.4</td>
<td>11</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20</td>
<td>1.9</td>
<td>11</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>1.6</td>
<td>11</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Infarction ECG</td>
<td>14</td>
<td>3.0</td>
<td>5</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>None of above symptoms or signs</td>
<td>43</td>
<td>0.7</td>
<td>57</td>
<td>1.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Subjects were regarded as healthy at the time of the baseline study if they reported no symptoms of effort dyspnea, chest pain or claudication; if they did not give a history of organic heart disease, hypertension or diabetes; and if there were no codable ECG changes suggestive of CHD. The mean age at death of those eight men (12 per cent) who were healthy at the time of the baseline investigation, but who suffered SCD during the follow-up, was 48.4 years, and the mean survival time was 46 months (42 months for the entire SCD group). In the corresponding NSCD group of five men (13 per cent) the mean age at death was 42.8 years, and the survival time 38 months.

In study population III/Paper III, 64 men died of CHD under the age of 60 years, 41 of the deaths being definitely or probably sudden. Of their parents, 122 were registered (60 fathers and 62 mothers). The mean age at the death of the fathers of the SCD victims was 63.2 years (range 30-85 years) and mothers 66.3 years (range 40-86 years). The ages of parents at death in the SCD group did not differ significantly from the ages at death
of the parents of the NSCD group and of those who died from other causes. Table VI/Paper III (p. 93) shows the percentage distribution of the causes of death of the parents. The combined mortality from heart and vascular diseases was significantly higher among both SCD and NSCD mothers than in the reference population (p < 0.01).

7.3.2. Discussion

This report is the first effort to describe SCD in a nationwide prospective population study.

In keeping with earlier investigations, the most common place of death was the home, where the major part of the day is spent. The small number of SCDs at work may reflect the fact that the victims were either retired or on sick leave. The small number of hospital deaths was also natural. They probably included some home or transport deaths that had been registered as hospital deaths because of resuscitation efforts. This study revealed no cardiac arrests that had begun outside hospital and been successfully resuscitated and classified as NFMIs.

The result of this report is consistent with a study recently published in the U.S.A. (Muller et al. 1987), which shows that the peak incidence of SCD is between 7 and 11 a.m. This fact may reflect the importance of the activated sympathetic nervous system in the mechanism of SCD. Another explanation would be the enhanced aggregability of platelets in the morning (Tofler et al. 1987). SCD was evenly distributed over the calendar year, suggesting that seasonal variations in climate have no measurable effect on the occurrence of SCD. This finding does not rule out the possibility that climatological factors might have some precipitating effect on the occurrence of SCD (Vuori 1987).

The results showed that some years before death, SCD victims had significantly more signs of cardiovascular disease than men with other subsequent CHD events. These signs also distinguished the SCD group from the NSCD group. This result seems to justify the opinion that sudden death befalls patients with the most severe CHD. A healthier heart needs a large infarction for death to ensue, as is often the course of events in NSCD cases. In the Helsinki register study (Romo 1973), however, earlier coronary morbidity was higher in the NSCD than in the SCD group, although this difference was not significant. Comparison of the results is hampered by the fact that in the present study, the health status was registered much earlier in relation to death than it had been in the Helsinki study.

The SCD group contained only eight healthy men, most of whom were in the age group 40-49. The follow-up time of five of them was longer than 3½ years. In the NSCD group there were five healthy men, and in only one was the follow-up until death more than 3½ years. This difference, although not
significant, would seem to suggest that it takes longer for CHD to result in SCD than NSCD.

The material on which the investigation of hereditary aspects of SCD was based was rather small. In addition, in a substantial number of cases the causes of the parents' deaths were not established. The results suggest that especially the mother's cardiovascular death predisposes her working-aged son to the same fate. This claim is in line with another Finnish study, which showed that excess mortality from CHD was a characteristic of mothers in the youngest age group of CHD patients (Rissanen A 1979). The negative result regarding the fathers can be attributed to the high prevalence of CHD among men, which obscures the appearance of its hereditary influence in this kind of study.

7.4. Risk factors of sudden coronary death (Papers IV and V)

The population in which the association between certain risk factors and SCD was studied consisted of 3589 men aged 40-59 participating in the baseline examination. The mortality of all examinees has been followed continuously, and deaths up to the end of 1979 have been included in the analysis of this report. A total of 570 deaths, out of which 234 were coronary deaths, occurred during the follow-up. One hundred and fifty of the coronary deaths were definite or probable SCDs (64 per cent). The mean follow-up was eleven years.

7.4.1. Earlier coronary heart disease as a risk factor (Paper IV)

To analyse the relationship of different CHD indicators to subsequent SCD and NSCD, the study population was hierarchically divided into five groups as follows: Group I was men with a history of MI or ECG infarction who had VEBs or supraventricular ectopic beats in the resting ECG; Group II was other men with a history or ECG evidence of MI; Group III was men with ischemic ECG changes; Group IV; was men with typical or atypical chest pain symptoms; Group V was other men.

7.4.1.1. Results

The incidence of SCD and NSCD in these hierarchic groups after adjustment for age, systolic BP, serum cholesterol, smoking, obesity and diabetes is shown in Table 5. The incidence of both SCD and NSCD was highest among men with past MI. The proportion of SCDs was also highest in this group, especially among the few men with ectopic beats in their resting ECG. In the combined group of men with past MI or ischemic ECG changes, the proportion of SCDs in relation to all CHD deaths was 70 per cent; in other men it was 59 per cent.
Table 5. Age and risk factor\(^1\) adjusted mean annual incidence (per 1000) and relative risk of SCD and NSCD in men with different signs of CHD initially. The last column indicates the percentage of SCD of all CHD deaths. Number of men in parentheses.

<table>
<thead>
<tr>
<th>Group(^2)</th>
<th>N</th>
<th>SCD Incidence</th>
<th>Relative Risk</th>
<th>NSCD Incidence</th>
<th>Relative Risk</th>
<th>SCD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>(15)</td>
<td>43.8</td>
<td>17.4***</td>
<td>7.6</td>
<td>4.4(\text{ns})</td>
<td>86</td>
</tr>
<tr>
<td>II</td>
<td>(131)</td>
<td>25.7</td>
<td>10.2***</td>
<td>8.1</td>
<td>4.7***</td>
<td>74</td>
</tr>
<tr>
<td>III</td>
<td>(579)</td>
<td>6.8</td>
<td>2.7***</td>
<td>3.6</td>
<td>2.1**</td>
<td>65</td>
</tr>
<tr>
<td>IV</td>
<td>(421)</td>
<td>3.3</td>
<td>1.3(\text{ns})</td>
<td>2.5</td>
<td>1.7(\text{ns})</td>
<td>58</td>
</tr>
<tr>
<td>V</td>
<td>(2443)</td>
<td>2.5</td>
<td>1.0</td>
<td>1.7</td>
<td>1.0</td>
<td>60</td>
</tr>
<tr>
<td>All</td>
<td>(3589)</td>
<td>4.1</td>
<td></td>
<td>2.3</td>
<td></td>
<td>64</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for hypertension, hypercholesterolemia, smoking, obesity and diabetes.

\(^2\) See text for explanation.

\(\text{ns} = \) not significant, ** \(p < 0.01\), *** \(p < 0.001\).

7.4.1.2. Discussion

Many retrospective studies have consistently shown that most SCDs follow manifest CHD, often MI, and it has been stated that SCD is the first diagnosed manifestation of CHD in only about 20-25 per cent of cases (Kuller et al. 1966). In prospective studies the prevalence of earlier CHD has varied considerably, presumably because of differences in the definition of CHD and SCD and the length of the follow-up. The unexpectedness of SCD was especially stressed in the Framingham study (Kannel and Thomas 1982). However, in the Tecumseh study one-half of the SCD victims had established CHD at the beginning of the six-year follow-up (Chiang et al. 1970).

A particularly high risk group for SCD were the few post-MI men who had ectopic beats in their resting ECG. This finding is in agreement with the Coronary Drug Project (1973) and the Framingham study (Kannel and Schatzkin 1985). The rate of SCD was fairly constant over the three-year follow-up in a large group of post-MI men with ectopic beats, suggesting a long-term effect of ectopic beats (Ruberman et al. 1981).
The increased risk of SCD in this study was additionally obvious among men without past MI but with ischemic ECG changes. In contrast, the men with symptoms as the only indicator of CHD did not appear to be especially prone to SCD. An increased risk of SCD among men with ECG changes has been noted previously (Kannel and Thomas 1982; Kreger et al. 1987). Experience concerning the prognosis of symptomatic CHD without changes in ECG has been contradictory: in the Framingham study, the risk of SCD was four times greater in AF patients than in the symptomless population (Kannel and Thomas 1982), whereas some other studies showed no independent contribution to SCD by the symptoms (Reeves 1985). The results of the present study can be explained by the fact that the hierarchical group of men with ECG changes includes more men with advanced CHD than the group with AF only.

7.4.2. Hypertension, high serum cholesterol, smoking, obesity and diabetes as risk factors (Paper IV)

Relative risks were used to describe the associations of SCD and NSCD with levels or categories of risk factors. For the calculation, the exposed groups were compared with other men. Exposed men were defined as follows: Hypertensives were those whose systolic BP was 160 mmHg or above or whose diastolic BP was 95 mmHg or above. The cut-off point for hypercholesterolemia was 7.8 mmol/l and for obesity 30 kg/m². All men who reported currently smoking cigarettes, pipe or cigars were considered smokers. Diabetics were men with a history of clinical diabetes or those with new diabetes unequivocally detected at baseline examination (National Diabetes Data Group 1979).

7.4.2.1. Results

The level or prevalence of risk factors at baseline in incident cases of SCD, NSCD, and of other men according to presence (Groups I-IV) or absence (Group V) of CHD, is presented in Table 6. Men initially free of CHD who survived CHD had a lower systolic BP and smoked less than did cases of SCD. In men with indicators of CHD at baseline, but not dying of CHD, the serum cholesterol values were lower than in other groups. Smoking was less frequent in surviving men and those experiencing NSCD than in cases of SCD.
**Table 6.** Means with standard deviations (SD) and prevalences of risk factors for cases of SCD and NSCD and other men by presence of indicators for CHD at baseline examination.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No CHD</th>
<th></th>
<th></th>
<th>No CHD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCD (N = 59)</td>
<td>NSCD (N = 40)</td>
<td>Other (N = 2344)</td>
<td>SCD (N = 91)</td>
<td>NSCD (N = 44)</td>
<td>Other (N = 1011)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>143.6</td>
<td>147.0</td>
<td>138.4</td>
<td>151.1</td>
<td>146.0</td>
<td>144.6</td>
</tr>
<tr>
<td>SD</td>
<td>(21.1)</td>
<td>(29.1)</td>
<td>(19.1)</td>
<td>(26.3)</td>
<td>(25.6)</td>
<td>(22.8)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>83.0</td>
<td>85.6</td>
<td>81.9</td>
<td>86.1</td>
<td>88.4</td>
<td>84.6</td>
</tr>
<tr>
<td>SD</td>
<td>(12.3)</td>
<td>(12.9)</td>
<td>(12.2)</td>
<td>(14.7)</td>
<td>(12.7)</td>
<td>(13.9)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.77</td>
<td>6.50</td>
<td>6.60</td>
<td>7.13</td>
<td>7.41</td>
<td>6.65</td>
</tr>
<tr>
<td>SD</td>
<td>(1.40)</td>
<td>(1.32)</td>
<td>(1.28)</td>
<td>(1.41)</td>
<td>(1.72)</td>
<td>(1.26)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8</td>
<td>26.4</td>
<td>25.6</td>
<td>25.8</td>
<td>26.5</td>
<td>26.1</td>
</tr>
<tr>
<td>SD</td>
<td>(3.2)</td>
<td>(3.0)</td>
<td>(3.2)</td>
<td>(3.5)</td>
<td>(3.5)</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>70.2</td>
<td>61.8</td>
<td>52.2</td>
<td>64.7</td>
<td>51.3</td>
<td>53.9</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0.0</td>
<td>2.5</td>
<td>1.2</td>
<td>5.5</td>
<td>4.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Table 7 presents the independent contribution of SCD and NSCD risk factors as assessed by the Cox model for all men. The relative risk of SCD was highly significantly elevated in the presence of hypercholesterolemia (p < 0.01) and smoking (p < 0.001). This increased risk was particularly prominent in the age group 40-49 years. The only risk factor significantly predicting NSCD was hypercholesterolemia. Obesity did not appear to be statistically significant independent risk factor of SCD or NSCD.
Table 7. Age group specific and adjusted\(^1\) relative risks for SCD and NSCD by presence of risk factors. The reference groups are men without the risk factor.

<table>
<thead>
<tr>
<th></th>
<th>SCD</th>
<th></th>
<th>NSCD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>40-49</td>
<td>50-59</td>
<td>All</td>
</tr>
<tr>
<td>Systolic BP (\geq 160) mmHg</td>
<td>630</td>
<td>1.3</td>
<td>1.7</td>
<td>1.4(\text{ns})</td>
</tr>
<tr>
<td>Diastolic BP (\geq 95) mmHg</td>
<td>590</td>
<td>1.0</td>
<td>1.4</td>
<td>1.2(\text{ns})</td>
</tr>
<tr>
<td>Cholesterol (\geq 7.8) mmol/l</td>
<td>656</td>
<td>2.6</td>
<td>1.7</td>
<td>1.8(\text{**})</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1925</td>
<td>3.2</td>
<td>1.5</td>
<td>1.9(\text{***})</td>
</tr>
<tr>
<td>Body mass index (\geq 30) kg/m(^2)</td>
<td>394</td>
<td>1.5</td>
<td>1.1</td>
<td>1.2(\text{ns})</td>
</tr>
<tr>
<td>Diabetes(^3)</td>
<td>53</td>
<td>5.0</td>
<td>1.6</td>
<td>1.2(\text{ns})</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for age, other risk factors and the presence of any indicators of coronary heart disease.

\(^2\) Diastolic BP was not included in the model simultaneously with systolic BP.

\(^3\) Too few cases for reliable results (5 cases of SCD and 3 cases of NSCD).\(\text{ns} = \text{not significant, } * p < 0.05, \text{**} p < 0.01, \text{***} p < 0.001.\)

Among the CHD-free men, only smoking was significantly associated with SCD \((p < 0.01)\) (Table 8). Among men with CHD, both hypercholesterolemia and smoking were associated with a significant increase in the relative risk of SCD \((p < 0.001 \text{ and } < 0.05, \text{respectively})\). NSCD was significantly predicted by high BP among the CHD-free men \((p < 0.05)\), and by hypercholesterolemia among CHD men \((p < 0.001)\). Hypercholesterolemia and smoking appeared to be significant predictors of SCD even among men with past MI \((p < 0.05)\), Table V/Paper IV (p. 101).
Table 8. Age and other risk factor adjusted risk for SCD and NSCD by presence of hypertension, hypercholesterolemia and smoking in men without and with CHD initially.

<table>
<thead>
<tr>
<th></th>
<th>No CHD</th>
<th>CHD</th>
<th>SCD&lt;sup&gt;1&lt;/sup&gt;</th>
<th>No CHD</th>
<th>CHD</th>
<th>NSCD&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 160 mmHg</td>
<td>2101</td>
<td>858</td>
<td>1.0</td>
<td>3.2</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>≥ 160 mmHg</td>
<td>342</td>
<td>288</td>
<td>1.5&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>4.1&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>2.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7.8 mmol/l</td>
<td>2027</td>
<td>906</td>
<td>1.0</td>
<td>2.7</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>≥ 7.8 mmol/l</td>
<td>416</td>
<td>240</td>
<td>1.4&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>5.8&lt;sup&gt;***&lt;/sup&gt;</td>
<td>0.7&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>4.5&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Current smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1148</td>
<td>516</td>
<td>1.0</td>
<td>3.8</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1295</td>
<td>630</td>
<td>2.3&lt;sup&gt;**&lt;/sup&gt;</td>
<td>6.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.3&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>2.8&lt;sup&gt;ns&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Statistical significances were computed using the men without the risk factor but belonging to the same CHD - no CHD group as the reference group.

ns = not significant, * p < 0.05, ** p < 0.01, *** p < 0.001.

7.4.2.2. Discussion

The decision to dichotomize the level of all risk factors analysed in this report was made to simplify the presentation of the results. The cut-off point for high systolic and diastolic BP as well as that for hypercholesterolemia and obesity corresponded roughly to the lower limit of the highest quintile of the distribution of each continuous variable. Furthermore, more or less comparable results were obtained in analyses in which the risk factors were treated as continuous variables.

In this study, SCD was associated particularly with smoking among both CHD-free men and men with CHD, and this relationship was more pronounced among younger men. The exclusion of ex-smokers from the group of non-smokers should have accentuated the significance of smoking as a predictor of SCD, since the risk of SCD was appreciably higher among ex-smokers than among those who had never smoked. Furthermore, the prevalence of smoking has steadily declined among Finnish men during recent decades (Martelin 1984), causing some bias towards smaller risk among smokers. In other prospective studies, smoking appeared to be a significant predictor for SCD (Salonen 1982; Schatzkin et al. 1984). In the Framingham study, this did not apply to men with indicators of CHD
initially (Schatzkin et al. 1984). In the Tecumseh study the prevalence of smoking in future SCD cases was equal to that of the rest of the population (Chiang et al. 1970).

Hypercholesterolemia seemed to be a significant risk factor of SCD among men with CHD. This association applied even to men after MI, as in the Coronary Drug Project study (Schlant et al. 1982). In the Framingham study, a high serum cholesterol level lost its significance as a risk factor of SCD among men with prior CHD (Schatzkin et al. 1984). Unlike in some other prospective studies (Salonen 1982; Kozarevic et al. 1984), in this study hypercholesterolemic CHD-free men did not have a significantly elevated risk of SCD or NSCD. This peculiar finding - if not pure chance - has many possible explanations. One might be that hypercholesterolemia exerts its atherogenic effect on coronary arteries at a relatively early age in susceptible persons. Other men who, despite high serum cholesterol, remain CHD-free until middle age possibly have some protective factor against the atherogenic property of cholesterol.

Hypertension appeared to be a weaker risk factor of SCD than smoking and hypercholesterolemia. The results were not altered when all the men receiving antihypertensive drugs were included in the group of men with high systolic or diastolic BP. Most other prospective studies have shown that hypertension is a significant risk factor of SCD among men without CHD (Chiang et al. 1970; Hinkle 1982; Kannel and Thomas 1982; Salonen 1982; Kozarevic et al. 1984). In the present study, hypertension seemed to have very little impact on SCD among men with pre-existing CHD, and the only significant association was observed in predicting NSCD among CHD-free men. The significance of hypertension in CHD populations may be biased by the BP-lowering effect of prior MI.

Obesity was not an independent risk factor of SCD in this study. This lack of independence was also found in earlier prospective studies concerning various manifestations of CHD (Keys et al. 1972). In the Framingham study, however, relative weight appeared to be an independent risk factor of SCD among men without CHD (Schatzkin et al. 1984).

All types of manifestations of CHD, CHD mortality in particular, are increased among diabetics (Herman et al. 1977; Pyörälä and Laakso 1983), and it has been argued that more than half of all cardiovascular mortality could be attributed to the interaction of smoking and diabetes (Suarez and Barrett-Connor 1984). There is no evidence from previous prospective studies that diabetes disproportionately increases the risk of SCD (Herman et al. 1977). In our study, there were too few CHD deaths among diabetics for relevant conclusions to be drawn.

In conclusion, the results of this study confirm that pre-existing CHD and smoking habits are the risk factors which may be more important as predictors of SCD than NSCD. Other risk factors appear to have a more or less equal effect in predicting either mode of CHD death.
7.4.3. Alcohol as a risk factor (Paper V)

The association between alcohol consumption and subsequent CHD death, especially SCD, was studied prospectively in 4532 men, aged 40-64 years, who participated in the re-examination in 1973-76. The participation rate was 89 per cent. Alcohol consumption was assessed by a questionnaire method as described earlier (p. 24). The mean follow-up time was five years (range 4-7 years). The association between alcohol consumption and CHD was analysed, first, as the prevalence of clinical CHD initially and second, as the incidence of CHD death, especially SCD, during the follow-up in various consumption classes.

Twenty-one per cent of all men stated that they were abstainers. Only one in four of the men were wine drinkers, about half of the men drank beer and over 60 per cent spirits (Table 9). The distribution of calculated average monthly consumption of absolute alcohol for different age groups is shown in Table 10. The calculated average monthly consumption of absolute alcohol was 500 g or more in 19 per cent and 1000 g or more in 5 per cent of all men.

Table 9. Age-adjusted mean annual death rates (per 1000) for all causes, CHD and SCD according to consumption of wine, beer and spirits.

<table>
<thead>
<tr>
<th>Consumption category</th>
<th>Death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All causes (N = 314)</td>
</tr>
<tr>
<td></td>
<td>% (N)</td>
</tr>
<tr>
<td>Wine (bottles/month)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3390 74.8</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>943   20.8</td>
</tr>
<tr>
<td>≥ 2</td>
<td>199   4.4</td>
</tr>
<tr>
<td>Beer (bottles/week)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2362 52.1</td>
</tr>
<tr>
<td>&lt; 8</td>
<td>1861 41.1</td>
</tr>
<tr>
<td>≥ 8</td>
<td>309   6.8</td>
</tr>
<tr>
<td>Spirits (bottles/month)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1633 36.0</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>2544 56.2</td>
</tr>
<tr>
<td>≥ 3</td>
<td>355   7.8</td>
</tr>
</tbody>
</table>
7.4.3.1. Results

The prevalence of AP, unequivocal ECG signs of past MI and a history of verified MI in various consumption classes of absolute alcohol is presented in Table I/Paper V (p. 106). The prevalence of verified MI was significantly higher (p < 0.05) among abstainers than among alcohol consumers. A similar, but statistically nonsignificant, trend was observed when the prevalence was assessed for various consumption classes of spirits.

During the follow-up, 314 men died, 140 of them of CHD. Of the CHD deaths, 87 (62 per cent) were definite or probable SCDs. The mean annual death rates in various consumption classes of wine, beer and spirits are presented in Table 9. Total CHD mortality was higher among non-wine drinkers than in other consumption classes, and the incidence of SCD was highest among the men who drank two or more bottles a month. These differences were not statistically significant. Those who drank eight or more bottles of beer a week had a lower CHD mortality (p < 0.05) and a lower incidence of SCD than other consumption groups. As to spirits, the amount drunk was positively associated with CHD mortality and the incidence of SCD, but the variation did not reach statistical significance.

The association between total alcohol consumption and mortality is shown in Table 10. Both CHD mortality and the incidence of SCD were lowest among abstainers in all age groups. In all age groups combined, this variation reached statistical significance (p < 0.05). When the difference in survival rates from SCD between abstainers and consumers was tested by Cox's model (Figure 2/Paper V, p. 107), survival appeared to be equal for the first two years. Thereafter the risk of SCD was significantly higher among consumers than among abstainers (relative risk 2.5, 95 per cent confidence interval 1.1 - 5.9).

The mortality in different alcohol consumption classes was studied separately for men without and with CHD. Figure 1/Paper V (p. 107) shows that the incidence of SCD among the men without CHD was significantly (p < 0.05) lower for abstainers than for alcohol consumers. Among the men with CHD, those consuming 200 g or more alcohol a month had a significantly (p < 0.05) higher incidence of SCD than other men.

The incidence of SCD for alcohol consumers was also higher than for abstainers when smoking was added to the multivariate model (Table 11), but the difference no longer had statistical significance. To further analyse the effect of smoking on the observed association between drinking and the incidence of SCD, the men were stratified first into smokers and non-smokers, and second into abstainers and alcohol consumers. The interaction term - smoking-alcohol consumption - was included in the model (Figure 4). Among non-smoking men, alcohol consumers had a significantly higher (p < 0.05) incidence of SCD than abstainers. Among smokers this difference did not reach statistical significance.
Table 10. Mean annual age group-specific and age-adjusted death rates (per 1000) for all causes, CHD and SCD by mean total alcohol consumption.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Mean total consumption (g/month)</th>
<th>N</th>
<th>%</th>
<th>Death rate</th>
<th>% (N)</th>
<th>CHD (%)</th>
<th>% (N)</th>
<th>SCD (%)</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>&lt;200</td>
<td>752</td>
<td>34.7</td>
<td>All causes</td>
<td>6.7 (26)</td>
<td>4.1 (16)</td>
<td>2.3 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200-249</td>
<td>1036</td>
<td>47.9</td>
<td>CHD</td>
<td>6.3 (35)</td>
<td>2.4 (13)</td>
<td>1.8 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>&lt;200</td>
<td>628</td>
<td>37.7</td>
<td>SCD</td>
<td>13.1 (26)</td>
<td>5.1 (10)</td>
<td>2.5 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200-249</td>
<td>652</td>
<td>39.2</td>
<td>All causes</td>
<td>12.2 (39)</td>
<td>6.6 (21)</td>
<td>3.1 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>&lt;200</td>
<td>283</td>
<td>40.3</td>
<td>CHD</td>
<td>16.6 (57)</td>
<td>5.8 (20)</td>
<td>5.3 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200-249</td>
<td>213</td>
<td>30.3</td>
<td>SCD</td>
<td>32.6 (33)</td>
<td>11.8 (12)</td>
<td>4.9 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>&lt;200</td>
<td>1663</td>
<td>36.7</td>
<td>All causes</td>
<td>33.4 (46)</td>
<td>15.3 (21)</td>
<td>10.2 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200-249</td>
<td>1901</td>
<td>41.9</td>
<td>CHD</td>
<td>41.0 (44)</td>
<td>22.4 (24)</td>
<td>13.0 (14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 11. Age and risk factor adjusted\(^1\) relative risk (RR) with 95 per cent confidence intervals (CI) for death from any cause, for CHD death and for SCD in alcohol consumers compared with abstainers in five years.

<table>
<thead>
<tr>
<th>Death</th>
<th>CHD death</th>
<th>SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR  95% CI</td>
<td>RR  95% CI</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.2 (0.9 - 1.6)</td>
<td>1.5 (0.9 - 2.3)</td>
</tr>
<tr>
<td>Adjusted for age and smoking</td>
<td>1.1 (0.8 - 1.4)</td>
<td>1.3 (0.9 - 2.1)</td>
</tr>
<tr>
<td>Risk factor adjusted(^1)</td>
<td>1.0 (0.8 - 1.4)</td>
<td>1.3 (0.8 - 2.0)</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for age, smoking, systolic BP and cholesterol.
* \(p < 0.05\).
Figure 4. Alcohol consumption and age-adjusted total mortality and incidence of SCD among non-smokers and smokers in five years. The relative risk of death, given above each column, and the significances were tested against the non-smoker-abstainer group. Significance shown as: * p < 0.05, ** p < 0.01, *** p < 0.001, ns = not significant. The estimated death rate is based on a model which included the smoking-alcohol consumption interaction term.

7.4.3.2. Discussion

In contrast to several earlier studies, this study indicates that coronary mortality is lower for abstainers than for alcohol consumers. The result was entirely due to the lower incidence of SCD among abstainers, a tendency that was most clearcut in the oldest age group. The result was the same for men with and without pre-existing CHD. The prevalence data gave some indication that alcohol consumers may have less CHD in their clinical history than abstainers.

Although the alcohol consumption data obtained by a questionnaire method underestimate the true consumption (Simpura 1978; Cahalan 1981), the division into current abstainers and current alcohol consumers is probably
valid, and the reported consumption can be used reliably enough to classify the examinees into groups consuming, on average, different amounts of alcohol. This could be inferred, although indirectly, from the highly significant positive association between the informed consumption of alcohol and systolic BP (Table 12). This association has been confirmed in many previous studies (Gyntelberg and Meyer 1974; Myrhed 1974; Klatsky et al. 1977; Arkwright et al. 1982; Portmann et al. 1983; Salonen et al. 1983b). A change in drinking habits after the field survey is likely to detract from the importance of the observed associations.

**Table 12.** Age-adjusted mean systolic BP and prevalence of smoking in various mean total alcohol consumption classes.

<table>
<thead>
<tr>
<th>Alcohol consumption (g/month)</th>
<th>0</th>
<th>&lt; 200</th>
<th>200 - &lt; 700</th>
<th>≥ 700</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>144.05</td>
<td>144.68</td>
<td>146.70</td>
<td>149.92</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prevalence of smoking (%)</td>
<td>25.3</td>
<td>38.9</td>
<td>46.7</td>
<td>58.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

The different time trends observed in the mortality of abstainers and alcohol consumers may be explained by the heterogeneity of current abstainers, a mixed group of lifelong teetotallers and former alcohol consumers. On the other hand, some men may have stopped drinking because of manifestations of CHD.

The etiological role of CHD as a cause of death may have been overestimated among alcohol consumers, because there is evidence that alcohol per se can injure the myocardium (Vikhert et al. 1986) and cause dangerous arrhythmia (Singer and Lundberg 1972; Ettinger et al. 1978, Greenspon et al. 1979) or MI (Regan et al. 1975). There is also epidemiological evidence that alcoholic liver disease can manifest itself as sudden death without evidence of CHD (Kuller et al. 1974).

The higher prevalence of past MI among current abstainers might be because they stopped drinking after sustaining MI. The result may also reflect a higher CHD mortality among alcohol consumers. Although the data do not directly support the hypothesis that moderate drinkers have a lower incidence of NFMI, they do not rule out such an effect, either.

The finding that abstainers fared best as regards the risk of CHD death, especially SCD, is contrary to the findings of an earlier Finnish study (Salonen et al. 1983a). Both the Yugoslavian cardiovascular disease study (Kozarevic et al. 1980, 1982) and the Framingham study (Gordon and
Kannel 1983) revealed differences between SCD and other CHD which were similar to our observations: a negative association between alcohol consumption and CHD was not found for SCD. One reason for the increased risk of SCD among alcohol consumers in this study might be the aforementioned arrhythmogenic effect of alcohol, which can manifest itself as sudden death in patients with pre-existing CHD.

It has been claimed that binge drinkers have more occlusive changes in their coronaries than do regular drinkers (Gruchow et al. 1982). Thus, the rather common Finnish habit of occasional heavy drinking (Simpura 1981) might be an additional explanation for the association between alcohol consumption and increased risk of CHD death.

The apparently low CHD death rate among men drinking the largest amount of beer may be pure chance, or it may be due to an association of other factors conducive to low CHD mortality in beer drinkers.

Earlier studies have indicated a distinct positive association between smoking and drinking (Gyntelberg and Meyer 1974; Craig and Van Natta 1977; Kaprio et al. 1982; Gordon and Kannel 1983), and the result was the same in this study (Table 12). Thus smoking as an established risk factor of CHD might have explained the results. However, alcohol remained an independent risk factor of SCD when only non-smokers were examined.

As stated earlier, high BP is associated with the level of alcohol consumption. The association between drinking and SCD was not, however, altered when allowance was made for systolic BP in the multivariate analysis (Table 11).

In conclusion, the average Finnish male derives no benefit from alcohol as a preventive measure against fatal CHD. On the contrary, drinking should be added to the list of risk factors, since it is associated with an elevated risk of SCD.
8. SUMMARY AND CONCLUSIONS

The epidemiology of SCD in Finland was studied prospectively in 6510 men and 5800 women, aged 30-59 years, derived from 12 population cohorts in four different geographical areas. The objective of the study was to investigate the incidence and risk factors of SCD, to some extent also its attendant circumstances.

The study population was fairly representative of the whole middle-aged population of Finland, and thus conclusions drawn on the basis of this population can be applied to the whole country, perhaps excluding the big cities. The age distribution of the study population was rather young from the viewpoint of CHD manifestations in women, and consequently the number of SCD cases was too small for any detailed conclusions concerning women to be made.

The hierarchical distribution of CHD manifestations during six years of follow-up, when only the 'hardest' manifestation was taken into account, was rather different for men and women. Among men the proportion of fatal events was about 20 per cent, and more than half of them were SCDS. Among women, only 3 per cent of the manifestations were fatal, and the majority of them were NSCDs. This small proportion of fatal events derives in part from the apparently high prevalence of false positive AP cases among women. Among men, the distribution was similar to that noted in earlier Finnish studies, and also congruent with the findings of prospective population studies in Great Britain and the U.S.A.

Among men, the four-year age-adjusted incidence of SCD was 7.8 per 1000, that is, about ten times higher than among women. SCD was rare among men under 40, and among women of all ages. The incidence of SCD among men increased steeply by age, but its proportion in relation to all CHD fatalities remained fairly constant over the whole age distribution. The incidence of SCD was higher in non-participants than in participants, indicating a higher prevalence of CHD among non-participants.

In accordance with earlier observations, the incidence of NFMI and CHD death varied considerably by geographical area. The most striking feature was the low rate of events among men in the southwestern study area as compared with the other areas. The variation in SCD was similar to that of other 'hard criteria' manifestations of CHD. Among women, the differences by study area were insignificant.

In a study of this nature it was impossible to obtain detailed information about the sudden death event and its short-term precursors. Moreover, one in every four deaths occurred unwitnessed. Most deaths took place at home, and there were no successfully resuscitated cardiac arrests among participants before the re-examination. This result indicates that a pre-
requisite for the successful treatment of most cardiac arrests is the possibility of starting resuscitation at home. Even then, the substantial number of people dying without witnesses will continue to remain outside the reach of treatment facilities. The preponderance of forenoon-noon as the time of death gives some support to the view that activation of the sympathetic nervous system may be a factor in the genesis of SCD.

During 11 years of follow-up, about 60 per cent of the cases of SCD occurred among men with some indicator of CHD initially, and only about 10 per cent of future SCD victims were healthy at the baseline examination. In particular, typical AP and the use of nitroglycerin were more common among the subsequent SCD cases than among those with other outcomes, NSCD included. This may indicate that, on average, future SCD victims had the most advanced CHD and/or they had a special tendency to coronary spasm. It is also noteworthy that the people whose death was un witnessed seemed to be the least healthy at the baseline.

When the population at risk was hierarchically classified according to various CHD indicators, men with past MI had a ten times greater risk of SCD during the follow-up than men without CHD initially, and although very small in number the group of post MI men who had extrasystoles in their resting ECG were especially prone to SCD. Among men with ischemic ECG changes, the risk of SCD was markedly higher than among men with AP only, probably indicating more advanced CHD in the former group. The association between CHD indicators and future NSCD was less strong.

These results indicate that, in most cases, SCD is a logical end point of severe CHD rather than a random event among all people who have some evidence of CHD.

Of the so-called primary risk factors, a high serum cholesterol level was an equally significant predictor of SCD and NSCD, whereas smoking was a more powerful risk factor of SCD than NSCD. This difference may indicate that smoking could have some precipitating effect on the appearance of SCD. High BP did not appear to increase SCDs significantly, but it increased the incidence of NSCDs significantly. This result may be due partly to the BP-lowering effect of NFMI. Both smoking and high serum cholesterol were significant independent risk factors of SCD among men with prior CHD, even with past MI. This result gives some indirect support to the view that reducing primary risk factors, especially smoking and a high serum cholesterol level, is important even after manifest CHD.

Most hitherto published studies have indicated that moderate drinking provides protection against NFMI, to a lesser extent against fatal CHD, too. In the present study no relevant conclusions about the association between alcohol and NFMI could be drawn, although the prevalence of past MI was higher among abstainers than among alcohol consumers. On the contrary, it was confirmed that drinkers had a higher CHD mortality than abstainers. The result was entirely due to the higher incidence of SCD
among drinkers. One explanation for the increased risk of SCD among drinkers might be the arrhythmogenic effect of alcohol, which can manifest itself as sudden death in patients with pre-existing CHD.

To sum up, this study has given ample evidence that SCD is an essential manifestation of CHD among middle-aged Finnish males, to a much lesser extent among females of the same age. It has no specific primary risk factors, although smoking seems to be somewhat more prominent in the risk profile of SCD than in that of NSCD.

In the natural history of CHD, SCD seems to be the end result principally of long-lasting clinical CHD. It is only occasionally an early manifestation of the disease. Successful treatment of cardiac arrest is rarely possible, and thus the main option for reducing SCD in the community is to prevent CHD itself. In fact, this has been realized to an encouraging extent: since the beginning of the present study, mortality from CHD has declined by one-third in the middle-aged population of Finland and several other countries. Apparently the incidence of SCD has declined correspondingly.

Sufficient epidemiological data are thus now available to continue comprehensive primary prevention of all manifestations of CHD and SCD in particular. Future research should concentrate more on the biochemical and electrophysiological features of SCD. Such research may lead to a better understanding of the mechanism of SCD. It may also provide methods for prevention of SCD in people with severe manifestations of CHD, who have not benefitted of primary prevention.
9. YHTEENVETO


9.1. Johdanto

Sepelvaltimotausi on vuosikymmeniä ollut teollistuneissa maissa keskeinen sairastuvuuden ja ennenäikaisen kuoleman aiheuttaja. Suomalaisien työikäisten miesten sairastuvuus- ja kuolleisuusluku ovat olleet korkeimpia maailmassa. Myös naisten sepelvaltimotautudivi kuolleisuusluku ovat olleet kansainvälisesti verraten suuret.

Kansaneläkelaitoksen liikkuvaa tutkimusyksikkö autoklinikka aloitti vuonna 1966 maan eri puolilta valittuihin väestöryhmiiin kohdistuneen sepelvaltimotautitutkimuksen, jonka tavoitteena oli selvittää sepelvaltimotautudivi eri ilmenemisvuotojen esiintymistä sekä tutkia erilaisten taustatarkoituksen yhteyksiä taudin esiintymiseen. Osana tätä tutkimusta selvitettiin sepelvaltimotautudivi aiheuttaman äkkikuoleman (jäljempänä äkkikuolema) ilmaantuutuvutta ja siihen vaikuttavia tekijöitä, samoin äkkikuolemaan liittyvää piirteitä.

9.2. Tutkimusväestö ja tutkimusmenetelmät


Perustutkimuksessa selvitetettiin kyselyn mm. aikaisempaa sairastamista, lääkkeiden käyttöä ja tupakointia sekä haastattelun avulla mm. sepelvaltimotaudivi viittaavien oireiden esiintymistä. Terveystarkastuksessa mitattiin pituus, paino ja verenpaine, rekisteröitiin EKG sekä tehtiin joukko laboratoriotutkimuksia, mm. määritettiin veren glukoosi- ja kolesterolipitoisuus.

Tutkimusväestölle tehtiin keskimäärin 6 vuotta myöhemmin perustutkimuksen kaltainen uusintatutkimus. Kyselyyn selvitetettiin mm. tutkittavien sairaalahoidon sydäninfarktiksi tai sen epäilyyn takia tutkimusten välillä, vanhempiin kuolinkäyttöä ja -syyt sekä tutkittavien alkoholinkäyttöä.

Perustutkimukseen kutsutun väestön - niin osallistuneiden kuin poisjääneidenkin - kuolleisuutta ja kuolinsyitä seurattiin perustutkimusajankohdasta

9.3. Tulokset

9.3.1. Äkkikuoleman ilmaantuvuus

Eri alueiden tutkimusväestön vertailtavuuden saavuttamiseksi kuolleisuus määriteltiin kaikissa väestöryhmissä 4 vuoden aikana. Miesten ikävakiointu kuolleisuus (1 000 henkeä kohti) 4 vuodessa oli 39,2, naisten 10,7. Miesten sepelvaltimotautikuolleisuus oli 13,0, naisten 1,8. Äkkikuoleman ilmaantuvuus oli miehillä 7,8 ja naisilla 0,7. Samana seuranta-aikana oli varmoinen kuolemaan johtamattomien sydäminfarktien ilmaantuvuus miehillä 15,1 ja naisilla 2,7. Perustutkimuksesta poisjääneiden miesten ja naisten sepelvaltimotautikuolleisuus oli yli kaksinkertainen osallistuneiden kuolleisuuteen verrattuna.

Maantieteellisten alueiden vertailussa merkitseväin piirre oli miesten sepelvaltimotautikuolleisuuden ja äkkikuoleman ilmaantuvuuden vähyys Lounais-Suomessa (luvut 4,7 ja 2,5) muihin tutkimusalueisiin verrattuna (Pohjanmaa 14,4 ja 8,1, Keski-Suomi 14,3 ja 7,7, Pohjois-Karjala 17,5 ja 11,9). Naisten kuolleisuusluvut olivat kaikilla alueilla pieniä eikä merkitseviä alue-eroja voitua todeta.

9.3.2. Äkkikuolema ja äkkikuolemapistilaiden aikaisempi terveys

Äkkikuoleman tavallisissa tapahtumapaikka oli koti (43 % tapauksista). Vain 10 % äkkikuolemista sattui työpaikalla eikä ainoatakaan sattunut liikenteessä. Tavallisissa kuoleman ajankohta oli aamupäivä. Eri viikonpäivien ja vuoden aikojen välillä ei ollut merkitystä eroa. Varaa äkkikuolema sattui noin puolassa tapauksia ennalta arvaamattomasti, ja noin kolmasosassa tapauksia kuolemaa edeltä oireita, joista tavallisissa oli rintakipu.

Äkkikuolleilla oli perustutkimuksessa keskimäärin enemmän oireita ja merkkejä sydänsairauudesta kuin muilla sepelvaltimotautui kuolleilla tai kuolemaan johtamattoman sydäminfarktik in sairastaneilla. Erotyisesti tyypil-
lisen angina pectorisken ja rasitushengenhdistuksen esiintyvyyssä oli äkkikuolleilla suurempi kuin muilla ryhmillä, ja he käyttivät myös nitroglyceriiniä muita useammin. Vain 12 % tutkimusten väliaikana äkkikuoleman kohdanneista olivat alkututkimuksen perusteella täysin terveitä. Terveiden osuus oli yhtä suuri myös muilla sepolvaltimotautiin kuolleilla.

Vanhempien kuolinsyitä selvitetäessä voitiin todeta äkkikuolemapotilaiden äittien kuolleisuuden sydän- ja verisuonitauteihin olleen suurempaa kuin vastaanottavien naisväestön keskimäärin. Sama koski muidenkin sepolvaltimotautiin kuoleiden äitejä.

9.3.3. Äkkikuoleman vaaratekijät


Sepolvaltimotautikuoleman vaara osoittautui suurimmaksi sydäninfarktin aikaisemmin sairastaneilla. Tässä ryhmässä äkkikuoleman osuus kaikista sepolvaltimotautikuolemista oli selvästi suurin (76 %), ja äkkikuoleman vaara oli erityisen suuri niillä sydäninfarktin sairastaneilla, joilla todettiin lisäyöntejä perustutkimuksen EKG:ssa. Sepolvaltimotautiin viittavaat EKG-muutokset lisäivät äkkikuoleman vaaran 2,7-kertaiseksi, sen sijaan pelkkä angina pectoris -oire ei lisännyt merkitsevästi tätä vaaraa.

Kohonneeseen verenpaineeseen (systolinen verenpaine 160 mmHg tai enemmän) ei liitetty merkitsevästi kohonnutta äkkikuoleman vaaraa (vaarasuhde 1,9), joskin sekä äkkikuoleman että ei-äkillisen sepolvaltimotautikuoleman kohdanneiden miesten systolinen verenpaine oli perustutkimuksessa korkeampi kuin muiden.

Suuri seerumin kolesterolipitoisuus (7,8 mmol/l tai enemmän) lisäsi samalla tavalla sekä äkkikuoleman (vaarasuhde 1,8) että ei-äkillisen sepolvaltimotautikuoleman (vaarasuhde 1,7) vaaraa. Erittäin merkitsevästi suurentunut äkkikuoleman vaara liittyi tupakointiin (vaarasuhde 1,9), sen sijaan tupakoinnilla ei ollut merkitsevää yhteyttä ei-äkillisen sepolvaltimotautikuoleman ilmaantuutteen. Sekä suurentunut kolesterolipitoisuus että tupakointi säilyttivät vaaratekijävaikutuksensä niillä miehillä, joilla oli seurannan alkakessa viitteitä sepolvaltimotaudista. Tämä vaikutus ulottui myös sydänin farktin sairastaneisiin miehiin.

Alkoholinkäyttö korreloii sepolvaltimotautikuolemaan siten, että alkoholinkäyttäjiin sepolvaltimotautikuolleisuus oli erityisesti seurantajaksoneen loppupuolella merkitsevästi suurempi kuin raittiiden. Lisääntynyt kuolleisuus
perustui yksinomaan äkkiakuoleman ilmaantuvuuteen alkoholinkäyttäjillä. Tämä korrelatio sääli, kun sekoittavana tekijänä otettiin huomioon tutkittujen tupakointi.

9.4. Pohdintaa

Tutkimusväestöä voidaan pitää verraten edustavana otoksena koko maan työikäisestä väestöstä, joten tutkimuksen tuloksista voidaan tehdä jossakin määrin koko Suomea koskevia päätelmiä erityisesti miesten osalta. Naisen äkkiakuolemataustain luku oli liian pieni tarkempien päätelmiin tekemiseksi. Johtopäätöksiä tehtäessä on muistettava tutkimustulosten valaisevan runsaan vuosikymmenen takaista tilannetta. Sepelvaltimotautisairastuvuu- den myöhämpi pieneminen ja taudin vaikeusasteen lieveneminen työikäisessä väestössä ovat saattaneet vaikuttaa myös äkkiakuoleman asemaan sepelvaltimotaudin ilmenemismuutona.

Vain pienessä osassa äkkiakuolemia sepelvaltimotaudin diagnoosi perustui ruumiinnavaukseen. Äkkiakuolemissa saattettiin näin joskus päätä erheellisesti sepelvaltimotaudin diagnoosiin, joskin valtaosassa tapauksia hoitavan lääkärin kuolintodistusdiagnoisin valintaan lienee vaikuttanut tieto vainajan aikaisemmasta terveydentilasta.

Tutkimus osoitti äkkiakuoleman olevan työläissä miehillä yli 10 kertaa tavallisempi kuin naisilla, samoin äkkiakuoleman osuus kaikista sepelvaltimotau- tiin sairastumisista oli miehillä selvästi suurempi kuin naisilla. Nämä erot vastaavat muuta teollistuneissa maissa todettuja. Maantieteelliset erot miesten äkkiakuolemissa noudattivat sydäninfarktiin ilmaantuvuudessa nyt ja aiemmin todettua vaihtelua, joten sepelvaltimotaudin kulku näyttää olevan samanlainen suuren ja pienen ilmaantuvuuden alueilla.

Äkkiakuolema sattuu tavallisimmin kotona ja usein ilman todistajia. Tässä tutkimuksessa ei käynyt ilmi ainaotakaan tapausta, jossa elvytystoimien olisivat pelastaneet sairaalan ulkopuolella sydänpsyshyksen saaneen. Äkki- kuoleman merkityksellisimmäksi hoidoksi jää ehkäisy, johon tieto äkkiaku- leman vaaratekijöistä antaa kiinnekohtat.

Tutkimus osoitti äkkiakuoleman poimivan uhrinsa ensisijaisesti niiden joukosta, joilla oli ennestään vakava sepelvaltimotauti. Tupakoinnin selvä yhteys äkkiakuolemaan viittasi siihen, että sillä olisi ateroskleroseosia aiheuttavan vaikutuksensa ohella jokin välittömämpi yhteys äkkiakuoleman ilmaantumiseen. Tämä tutkimus ei voinut vahvistaa sitä viime vuosina runsaasti huomiota saanutta käsitystä, että alkoholinkäyttö ehkäisi sepelvaltimotautikulmia. Suomalaisten miesten verraten raju juomatapa voi olla yksi selitys sille, että alkoholi päinvastoin lisäsi äkkiakuoleman vaaraa.

Suuren kolesterolipitoisuuden, tupakoinnin ja alkoholinkäytön vaaratekijä- ominaisuus säilyi sepelvaltimotauviin sairastuneilla, mikä viittaisi siihen, että näihin vaaratekijöihin vaikuttaminen voisi parantaa taudin saaneiden ennustetta.
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