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When every minute counts

From symptoms to admission for acute myocardial infarction with special emphasis on gender differences

Thesis for the degree of Doctor Philosophiae

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Norwegian University of Science and Technology
Faculty of Medicine
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Når hvert minutt teller.

Fra symptomer til innleggelse ved akutt hjerteinfarkt, med fokus på kjønnsforskjeller

Den tidligste fasen av et akutt hjerteinfarkt er mest kritisk, ettersom det er en tydelig sammenheng mellom rask behandling og redusert dødelighet. Mange pasienter med et akutt hjerteinfarkt søker ikke medisinsk hjelp straks og denne utsettelsen fra pasientenes side bidrar i størst grad til forsinket behandling. Selv om færre yngre kvinner enn menn blir rammet av et hjerteinfarkt er disse kvinnene spesielt sårbare på grunn av høyere dødelighet.

Målsetningen med studien var å frembringe kunnskap om faktorer knyttet til kjønn som kan bidra til en tidlig diagnose av kvinner og menn med hjertesykdom og til å redusere tiden mellom symptomer og innleggelse hos pasienter med et akutt hjerteinfarkt.

Studien inkluderte 149 kvinner og 384 menn med førstegangs akutt hjerteinfarkt.

Over halvparten av kvinnene og mennene ventet mer enn en time før de søkte medisinsk hjelp, og ingen forskjell ble funnet mellom kvinner og menn. Det var derimot kjønnsforskjeller i forhold til hva som påvirket tiden mellom symptomdebut og innleggelse. Hvordan den enkelte handlet i den akutte situasjon hadde stor innflytelse på hvor lang tid det tok før de kom på sykehuset blant både kvinner og menn.
Færre kvinner enn menn erfarte brystsmerter samtidig som kvinnene i større grad enn menn erfarte andre symptomer.
Flere kvinner enn menn erfarte symptomer som kan relateres til hjertesykdom det siste året før det akutte hjerteinfarktet, og vi fant en sammenheng mellom disse tidlige varselsymptomene og symptomene i den akutte fasen.

Oppsummert viser studien at mange kvinner og menn venter for lenge før de søker hjelp ved et akutt hjerteinfarkt, og at faktorer som medvirket til denne utsettelse var ulike hos kvinner og menn. Kjønnsforskjeller ble også funnet i forhold til symptomer.

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Contents

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Paper I

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Are There Gender Differences Related To Symptoms of Acute Myocardial Infarction? A Norwegian Perspective.
Progress in Cardiovascular Nursing 2006;21:14-19.

Paper II

Løvlien Mona, Schei Berit, Hole Torstein.
Women with myocardial infarction are less likely than men to experience chest symptoms.
Scandinavian Cardiovascular Journal 2006;40:342-347.

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European Journal of Cardiovascular Nursing 2007;6:308-313.

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Journal of Advanced Nursing 2008;63:148-154.

Paper V

Løvlien Mona, Johansson Ingela, Hole Torstein, Schei Berit.
Early warning signs of an acute myocardial infarction and their influence on symptoms during the acute phase, with comparisons by gender.
Gender Medicine 2009;6:444-453.

Abstract

Background

Acute myocardial infarction is a major cause of death and morbidity worldwide, both in women and in men. Up to the age of 70 the incidence of acute myocardial infarction is higher in men than in women. Although the incidence is lower in young women than in young men, young women are particularly vulnerable due to higher fatality rates. The lower incidence in women compared to men might underestimate women's risk. Women might also be less likely to identify themselves as possible sufferers and to take cardio-protective actions.

The treatment of acute myocardial infarction has changed dramatically the last decades and reperfusion therapy has great impact on myocardial damage. The most critical time of an acute myocardial infarction is the very early phase, as rapid treatment is significantly associated with reduced mortality. Time has therefore become an important issue regarding the patients' prognosis. These patients often delay in seeking medical assistance, and this "patient delay" accounts for most of the total prehospital delay. Several aspects are reported to influence prehospital delay but knowledge about gender specific aspects is limited.

Aims

The overall aim was to generate knowledge about gender- specific aspects that might contribute to an early diagnosis of women and men with ischaemic heart disease and to decrease prehospital delay in patients with acute myocardial infarction.

Material and methods

This is a multicentre cross- sectional study including 149 women and 384 men with a first acute myocardial infarction. Respondents were consecutively recruited from the coronary units in 5 Norwegian hospitals. A self- administered questionnaire was mailed to eligible patients after hospital discharge. The respondents were asked about symptom experience, symptom assessment and illness behaviour. A pilot study including 82 patients with a first acute myocardial infarction was conducted prior to the main study.

Results

There were no statistically significant gender differences in patient delay or total prehospital delay. More than half of both women and men waited more than an hour before they called for medical assistance and a total prehospital delay exceeding two hours was reported by half the study population. How symptoms were experienced and interpreted had a greater impact on men's delay compared to women's. Consulting a partner increased patient delay in both genders; however, having a partner with low education level increased patient delay in men and not in women. More than half of both women and men reported that their acute symptoms were not in accordance with their expectations and this increased delay in both genders. Illness behaviour had a vital influence on prehospital delay in both women and men.

Women were less likely than men to experience chest symptoms and more likely to report atypical symptoms in the acute phase. Hypertensive women were also less likely than women who were not hypertensive to experience acute chest symptoms, but this association was not found in men. Though gender differences were found in the frequency of symptoms the top four reported acute symptoms (symptoms from chest, left arm, sweating and dyspnoea) were the same in women and men. Symptom experience more likely influenced a cardiac attribution in women than in men, while medical history had a greater impact in men than in women. Younger men (<55 years) were more likely than older men to report musculoskeletal symptoms in the acute phase, to report a higher number of acute symptoms and to attribute their symptoms as non-cardiac. These associations were not found in women.

During the year before the acute myocardial infarction women were more likely than men to report symptoms that might be related to a cardiac disease, and these early warning symptoms were associated with symptoms experienced in the acute phase. Women experiencing chest symptoms the year before had five times higher risk of experiencing acute chest symptoms, and this risk was nearly tripled in men. One in three women and one in four men had consulted a physician for their chest symptoms the year before the acute myocardial infarction. Younger men (<66 years) were less likely than older men to contact a physician for these chest symptoms.

Conclusions

There were no statistically significant gender differences in prehospital delay; however, factors associated with delay differed between women and men. Women and men differed in symptom presentation and how these influenced the interpretation of the situation. Early warning symptoms might be a tool to early diagnoses of coronary heart disease, and a greater awareness of these symptoms might be vital. Younger men differed from older men regarding acute symptoms and cardiac attribution.

Keywords

Ischaemic heart disease, acute coronary syndrome, acute myocardial infarction, prodromal symptoms, gender (sex) differences, prehospital delay, decision-making.

Abbreviations

ACS: Acute coronary syndrome

AMI: Acute myocardial infarction

CAD: Coronary artery disease

CVD: Cardiovascular disease

CI : Confidence interval

EMS: Emergency medical System

GP : General practitioner

IHD: Ischemic heart disease

MI: Myocardial infarction

NSTEMI: Non ST-elevation myocardial infarction

OR : Odds ratio

PCI: Percutaneous coronary intervention

SD: Standard deviation

STEMI: ST-elevation myocardial infarction

1.0 INTRODUCTION

1.1 Ischaemic heart disease

Ischaemic heart disease (IHD) is a major cause of death and disability worldwide, both in women and men (1). In 2007, 1814 Norwegian women and 1961 men died of a first acute myocardial infarction (AMI) (2). Young women are particularly vulnerable, as several studies have reported higher fatality rates among younger women compared with men (3-6). In younger age groups the incidence of AMI is lower in women compared with men, but in the seventh decade of life women and men approach equal prevalence rates (7). However, with multiple risk factors the incidence in women is equal to men (8).

Acute coronary syndrome (ACS) is the acute manifestation of IHD, which includes AMI and unstable angina pectoris. IHD is usually caused by obstructive atherosclerosis of one or more coronary arteries, whereas an AMI reflects myocardial cell death due to prolonged ischemia. This is most often caused by acute thrombosis on an unstable atheromatous plaque. An AMI may be the first manifestation of IHD, or it may occur in patients with an established coronary disease (1).

The most critical time of an AMI is the very early phase; hence delay from symptom onset to reperfusion therapy has a vital impact on myocardial damage and further prognosis regarding the patients' health outcome (9). The period between the onset of symptom and the decision to call for medical assistance (patient delay) remains by far the most significant cause of prehospital delay (10, 11). As fatality rates are highest within the first two hours (9), it is crucial for patients with an AMI to call for medical assistance rapidly, as every minute counts.

1.2 Acute myocardial infarction in a gender perspective

Traditionally, medical science has presupposed that gender differences are non- existent or irrelevant, except for reproduction (12). When gender becomes neutral, however, specific aspects concerning men and women might be concealed (13). AMI has for

many years been viewed as a male disease (7). Until the last decades, women were not included in most funded biomedical trials and the rationale for this might have been that findings generated from men could be generalized to women (14). It has been indicated that this "add women and stir" approach in cardiac research has resulted in limited gender- specific knowledge and an image of AMI as a phenomenon affecting mainly middle-aged white men (15). Some of the large clinical studies have included patients from Veterans' Hospitals with only men hospitalized (12). A Norwegian example of this exclusion of women is the "Oslo I Study" in 1972-1973 (16) which included only men. In 1993 "The Established Guidelines on Inclusion of Women in Clinical Trials" was published by the American Food and Drug Administration (FDA) with a recommendation to include sufficient number of women in clinical trials (17). And in 2005 the Women at Heart initiative was launched by the European Society of Cardiology (ESC). This was initiated to highlight to medical professionals the growing burden and under-appreciation of women's heart disease, and to promote improved handling of women at risk of cardiovascular disease in clinical practice. One of the aims was to promote basic and clinical research on gender issues (17). And the research focus on women and cardiac disease has increased the last years. But still the number of women included in clinical trials is sometimes too small to achieve adequate statistical power, and uncertain knowledge about women might be the results (18).
It has been suggested that the incidence of AMI in women might increase due to the increasing stressful demands in the modern women's lives (12). It has also been suggested that the risk of AMI in women is underestimated because of the perception that women are "protected" against this disease (17) and that women are less likely to identify themselves as possible sufferers and to take cardio-protective action (19). Another problem is that an appropriate diagnosis might be delayed or neglected due to health professionals' knowledge about the low incidence in younger women (20). Women being less likely than men to experience chest symptoms in the acute situation have been reported (21, 22, 23, 24, 25, 26). As patients presenting with non- chest symptoms are frequently misdiagnosed and undertreated (27), women's symptoms need special attention. It has also been reported that primary care physicians asked fewer questions to women than to men with symptoms of IHD (28).

1.3 Incidence of ischaemic heart disease (IHD)

U.S. national trend data reveals an increase in IHD incidence among younger women and men, probably contributed by the rising rates of cigarette smoking, physical inactivity, obesity, hypertension and the metabolic syndrome (7).

In younger age groups (<70 years) the incidence of AMI is lower in women compared with men, and women experience their first AMI about 10 years later than men (29). Why women during the fertile age have a lower incidence of cardiac events is not fully understood (17), but it has been suggested that the difference in age of first AMI largely might be explained by the higher risk factor levels in younger men compared with younger women (30).

It has been suggested that up to 44 % of cardiac events are unrecognized or "silent", and the Rotterdam study (31) reported that the proportion of unrecognized AMI was 54 % in women and 33 % in men, independent of age.

In 2000, 4368 Norwegian women and 7448 men were hospitalized with an AMI (32). The average number of hospital discharges for IHD in the European population is 8.7 per 1.000 inhabitants (33).

The population in Europe is aging rapidly, and the European population aged 65 years and older is expected to increase from 13.7 % in 2004 to about 30 % in 2050 (33). This aging population will probably have an impact on the incidence of AMI, also due to increasing prevalence of diabetes and obesity.

1.4 Case fatality

Several studies have shown higher fatality rates in younger women with AMI compared with younger men (3- 6). In recent years, however, in- hospital fatality rates has decreased in women younger than 55 years (34). It has also been reported that women were more likely than men to die of a prehospital cardiac arrest (7), to have a higher in-hospital fatality (35) as well as higher fatality rates in STEMI (36, 37). In a Norwegian study however, there were no gender differences in age adjusted early and long-term fatality (8).

Overall the fatality rates have declined since the 1980's in most western countries (38-

42), and faster in men than in women. However, prehospital fatality rates have not been reduced over the last years (9). Among Norwegian women and men the seven days fatality rate decreased from 17.9% in the eighties to 11.4 % in the nineties (40). However, from 2003 the fatality rates among Norwegian women and men between 45 and 64 years are no longer declining (43). The Swedish MONICA study also reported the same development in fatality among women with first AMI (38).

1.5 Prehospital delay; longer in women than in men?

There are conflicting data concerning whether there are gender differences in prehospital delay. Some investigators (19, 44- 47) have found that women delayed longer than men, while others (21, 48- 51) have documented no significant gender difference. Prehospital delay times has remained essentially unchanged during the last 20 years (21, 52, 53), but among patients with ST-elevation myocardial infarction (STEMI) the time between symptom onset and arrival at the emergency room for percutaneous coronary intervention (PCI) has decreased (33).

The most critical time in an AMI is the very early phase, as the earlier the treatment is given, the greater the beneficial effect. International guidelines advise people to call the Emergency Medical Service (EMS) if symptoms are unimproved or worsening after five minutes, despite feeling uncertainty about the symptoms and fear of potential embarrassment (54). Reduced mortality has been demonstrated in patients treated within the first two hours after symptom onset compared to those treated later ("time is muscle") (9).

Prehospital delay, defined as the time from symptom onset to hospital admission consists of two components. The first phase concerns the time between symptom onset and the patients' call for medical assistance, and this "patient delay" accounts for most of the total prehospital delay (10, 11). It has been reported that patient delay exceeded 1.5 hours for more than 50% of the patients (46, 53, 55) and in a Norwegian study median patient delay was 59 minutes (11). Patient delay varies internationally, and Japanese are more likely than other nationalities to delay seeking medical assistance (56, 57).

Only a minority of AMI patients receive optimally-timed treatment because of this patient delay (55) and it has been reported that only a minority of AMI patients are aware

of the significance of early treatment (10).

The Self-Regulatory Model of illness behaviour presented by Leventhal et al.(58) has been applied (59, 60) as a framework to understand the patients' decision process (patient delay). This model proposes that internal and environmental stimuli affect the patients' response to a health threat and how they behave (59). Internal stimuli include personal characteristics, such as gender, age, socioeconomic status, ethnicity and medical history. Environmental stimuli concern attitudes and messages from significant others, such as family members or physicians. In the first step, the patients cognitively and emotionally identify the symptoms as a sign of illness. This phase is strongly influenced by the individuals' knowledge, attitudes and beliefs regarding their symptoms, perceived control and anxiety. Then they identify potential causes and consequences of this illness. In the second phase a plan of action is initiated. This process is influenced by several individual factors, such as symptom appraisal and prior expectations. This is primarily the patients' decision process, but other people also may have an impact on this evaluation; typically spouse, children/ parents etc. An individual may choose to ignore the symptoms, self medicate, consult family or friends, visit their general practitioner or attend an emergency Medical Service (EMS).

Another theoretical model that has been used in understanding the patients' decision process (61) emphasizes that the course of action taken in a specific situation involves cognitive, social and behavioural skills.

The next phase in prehospital delay concerns the time between the patients' call for medical assistance and hospital admission (physician delay or "call-to-door" time). Few studies have recorded the time of this delay, but some have reported increased delay in women (10, 62), of these a Danish study (10) reporting 69 minutes delay in women and 16 minutes in men. A Norwegian study reported a median physician delay of 32 minutes, with no gender comparisons (11).

1.6 Factors associated with prehospital delay

A review of the literature indicates that the following factors contribute to prehospital delay: socio demographics, medical history, symptom interpretation and illness

behaviour.

However, knowledge about gender differences is limited. Socio demographic aspects such as old age, low education, low socioeconomic status and black race are associated with increased prehospital delay (45, 51, 53, 55, 57, 63, 64). It has, however, been reported that the age factor concerns older women and not men (5, 21 48). Patients with diabetes, angina and hypertension being more likely than other individuals to have a longer prehospital delay has also been reported (45, 52, 63, 65). The reported prevalence of silent ischemia, or AMI with atypical symptoms, is 10-20 % in diabetics, compared with 1-4 % in non- diabetic populations. Prolonged prehospital delay, as well as delayed diagnosis, thereby reducing the opportunity to administer adequate treatment is also reported among diabetics (66). It has been reported that women with a combination of older age, Hispanic or black race and with diabetes mellitus have a particularly long delay, and that the total prehospital delay may be 60 minutes longer than groups without those characteristics (53).

Cognitive factors, or interpretations and assessments of situations might also contribute to delay, especially when a discrepancy exists between the patients' expectation and what they actually experience (51, 67, 68). Patients attributing their symptoms to a non-cardiac condition also tended to have increased delay (10, 48, 56, 69, 70) as did those who reported not knowing the symptoms of an AMI (48). Not wanting to trouble others has been reported to contribute to delay in women only (48).

There is conflicting evidence as to whether the occurrence of chest pain influence prehospital delay (46, 63), but increased delay in patients with NSTEMI and patients experiencing diaphoresis, back pain and dyspnoea has been reported (63, 69). A gradual symptom progression also might increase prehospital delay (48, 56, 69).

Other aspects influencing the delay process that have been reported are self-medication (11, 48, 49, 51, 68, 70), when patients consult their family members (particularly spouses) (55) and patients calling a GP (46, 51, 68, 71). It has been reported that half the patients calling for a GP were delayed by wrong advice or misinterpretation (10) and that patients think that calling a GP was the proper action (72). Calling the EMS reduces the prehospital delay (45, 46, 51. 63, 71, 73, 74). It has been reported that the use of EMS has increased the last years (45) but that this positive development differs between countries (57).

1.7 Acute treatment

There are conflicting opinions as to whether gender differences in management of AMI still exist (8). Some studies have reported that women were less likely than men to be referred to diagnostic procedures, and less likely to be revascularized or to get other medical treatment (6, 33, 69, 75, 76, 77). Further, a large American study found that medical and interventional strategies according to guidelines recommendations were used significantly less frequently in women than in men (77). A European study reported that women with newly diagnosed angina pectoris were less likely than men to be further examined and treated for their cardiac condition (78). One aspect regarding these gender differences concerns women's smaller coronary arteries which make revascularization more difficult than in men (79). However, the success rate for percutaneous coronary intervention (PCI) is reported to be similar in both genders (80). It is also reported that women and elderly patients particularly benefit from PCI versus fibrinolytic therapy (81). Another suggestion is that the gender differences in coronary treatment represent an overuse in men rather than an underuse in women (82). There is an opinion that gender- related differences in responses to therapy should be addresses in a more systematic fashion and that gender-specific diagnostic and therapeutic options may be necessary (17). An example of this is that a normal exercise ECG effectively excludes IHD as the cause of chest pain in low risk women, due to a high negative predictive value (83).

Rapid diagnosis and early risk stratification of patients presenting with symptoms of an AMI are important in order to identify patients for whom early interventions can improve their outcome (9). This intervention usually starts in the prehospital setting. The medical treatment aims at relieving pain, breathlessness and anxiety, and further to restore coronary flow (9). In the early phase of an AMI this includes morphine, oxygen, nitrates and aspirin (MONA). Further treatment depends on whether the diagnosis is a ST-elevation myocardial infarction (STEMI) or a non ST-elevation myocardial infarction (NSTEMI). Fibrinolytic therapy has a great impact on myocardial damage and thus on the prognosis regarding death and functional capacity in STEMI patients. The success of this reperfusion therapy is time dependent, and is most effective if it is given soon after the onset of symptoms (9). A Norwegian study reported that

fibrinolytic therapy administered by a GP reduced the time from symptom onset to treatment by 82 minutes compared with in-hospital fibrinolytic administration (84). Further medical treatment of the AMI includes percutaneous coronary intervention (PCI), anti-ischemic agents, anticoagulants, anti-platelet agents and coronary by-pass surgery (9, 29). In patients presenting with an evolving AMI, primary PCI is considered the best treatment option as it is more effective and safer than fibrinolysis (33). It is recommended to perform primary PCI within two hours after first medical contact in patients with STEMI, (9) and within 72 hours in patients with NSTEMI (29). The superiority of primary PCI over fibrinolysis in STEMI seems to be especially relevant for the time interval between 3 and 12 hours after symptom onset. Within the first 3 hours after symptom onset both reperfusion therapies seem equally effective in reducing infarct size and mortality (81). The choice of one reperfusion strategy over the other depends on the availability of prehospital fibrinolysis and high volume PCI facilities, transfer times to and between hospitals in addition to patient characteristics. It is recommended that patients presenting within 12 hours after symptom onset, in hospitals without PCI facilities and where fibrinolysis is contra-indicated, should be immediately transferred for coronary angiography and, if applicable, primary PCI in another hospital (81). A Norwegian study reported that after 12 months, patients with STEMI transported to a hospital with PCI facilities were less likely than patients treated in hospitals without PCI facilities to have a new AMI, stroke or fatal outcome (85). Of all PCI procedures in the Euro Heart Survey (33) 25% were conducted in STEMI patients, 14% in NSTEMI, 16% in unstable angina and 43% in a stable angina.

1.8 Gender and risk factors

In general, risk factors are less often evaluated in women than in men (86). Risk factors for developing IHD are similar for women and men, but diabetes, hypertension, alcohol use, physical inactivity and smoking are reported to be more strongly associated with AMI in women than in men (30). Diabetes, hypertension, smoking and abnormal lipids are also are more strongly associated with AMI in women younger than 60 years compared with older women (30). A clustering of several risk factors is more common in women than in men (8).

It has been suggested that family history of AMI might be a useful risk assessment tool in young women as young women with a family history of AMI demonstrated less risk awareness and worse lifestyle choices than young men (87). In a qualitative study of women with AMI none of these women had seen themselves at risk of developing IHD, despite a strong family history (88).

Diabetes

Diabetes is probably the most important risk factor for IHD in women (8). A large epidemiological study reported a 3.3-fold risk of deaths from IHD among women with diabetes and 1.9-fold risk among men, compared with non-diabetics. The reason for the higher risk of IHD in diabetic women than diabetic men is still unclear (66). Young adults with diabetes also have 12-40 times higher rates of IHD than those without diabetes (89). As the prevalence of diabetes is rising, this is a risk factor that requires great attention. The 2003 prevalence rate of 7.8% in the European Region is expected to increase to 9.1% in 2025 (33). In multinational registers the prevalence of diabetes ranges from 19 to 23 % in AMI patients (66).

Hypertension

Hypertension is associated with a two- to threefold increased risk of coronary events in women (83). Increased risk of IHD in individuals with hypertension is present in all age groups ranging from 40 to 89 years old (86). And data from the Framingham Heart Study indicated that BP values in the 130-139/85-89 mmHg range are associated with more than a two-fold increase in relative risk from CVD compared with those with BP levels below 120/80 mmHg (86).

Obesity

In most countries, obesity is more prevalent in women than in men. However, for younger age-groups the prevalence is higher in men. Obesity (BMI $\geq$ 30) contributes to hypertension, hypercholesterolaemia, low HDL cholesterol and hyperglycaemia, and is associated with higher cardiac risk (66). If the prevalence of obesity continues to increase at the same rate as in the 1990s, it is estimated that about 26% of the population in the European Region will be obese by 2010 (33). It has however been

suggested that obesity itself is not an independent risk factor but that the metabolic syndrome is one link between obesity and IHD (7).

Dyslipidemia

There is a strong positive association between total as well as LDL-cholesterol and the risk of IHD in women and men (7). IHD is rare in populations with total cholesterol less than 3-4 mmol/l, but inevitable in untreated patients with the most severe forms of familial hypercholesterolaemia (86). It has been reported that hypertriglyceridemia is a more potent risk factor for IHD in women as compared with men (7).

Smoking

Results from prospective studies have demonstrated that mortality is higher in female smokers than in male smokers. The impact of smoking on atherosclerosis progression is also greater for patients with diabetes and hypertension (86).

2.0 AIMS

2.1 Overall aim

To generate knowledge about gender specific aspects that might contribute to an early diagnosis of women and men with ischaemic heart disease (IHD) and to decrease prehospital delay in patients with acute myocardial infarction (AMI).

Primary hypothesis

Women with an AMI have a longer prehospital delay compared with men

Secondary hypotheses

- Women are less likely than men to experience chest symptoms.
- Women are more likely than men to experience AMI symptoms located to shoulders, back and between the scapulae.
- Experiencing AMI symptoms located to shoulders, back and between the scapulae (musculoskeletal symptoms) increases patient delay in women and men.
- Psycho-social aspects influence patient delay in women and men.
- Women are more likely than men to experience early warning symptoms the year before the AMI.

3.0 MATERIAL AND METHODS

3.1 Development of study design

In the 1980's, while as a hospital nurse in an acute medical unit, I often experienced that nurses and physicians assessed AMI symptoms more seriously in men than in women. An increasing interest in how women experienced an AMI and how they interpreted their symptoms evolved. Due to these experiences, the subject for my Master degree assignment was women and cardiology. I conducted a qualitative study of women with a first time AMI (90), which demonstrated the complexity of the women's decision process before hospital admission. These women experienced atypical AMI symptoms and delayed calling for medical assistance. The results from this study aroused my curiosity regarding this decision process (patient delay) as well as the women's symptom experience, and in particular whether there were gender differences regarding these aspects.

To investigate whether women and men differed in their AMI symptoms and aspects associated with prehospital delay a pilot study including 82 women and men was conducted. After the completion of this study hypothesises regarding gender differences were elaborated and tested in a main study. A self-administered questionnaire was developed, based on extensive literature on the topic in addition to experiences from the two previous studies. In the main study 149 women and 384 men with a first-time AMI were included.

3.2 The pilot study

The study was conducted among 38 hospitalized women and 44 men. Inclusion criteria were women and men 65 years or younger, diagnosed with a first-time AMI and physically and mentally able to answer a questionnaire. The patients should also be haemodynamically stable and pain-free when they were asked to participate. Exclusion criteria were patients hospitalized or staying in another health institution at symptom onset.

All university and regional hospitals in the Norwegian health regions were invited to participate. In addition, some of the smaller hospitals in all regions were included, all

with acute medical function for the surrounding urban and rural areas. An invitation letter was sent to the head of the Medical department in 25 hospitals, of these 13 hospitals gave their consent. These covered all the four health regions in Norway (Table 1).

The twelve non-participating hospitals included two hospitals in the North region, two in the West region, three in the Central region and five hospitals in the South Eastern region.

Table 1. Study sites in the pilot study

Health regions	Population	Hospitals
Northern	460.000	Hammerfest Hospital Kirkenes Hospital
Central	640.000	St.Olavs University Hospital Levanger Hospital Namsos Hospital Kristiansund Hospital
South eastern	2.600.000	Ulleval University Hosptal Aker University Hospital Gjøvik Hospital Lillehammer Hospital Buskerud Hospital Telemark Hospital Sørlandet Hospital

The respondents were consecutively recruited from the coronary units in 13 Norwegian hospitals, and information was collected by self- administered questionnaires. During the study period (March- October 1999) 98 patients were invited to participate, and of these 82 (84%) responded to the questionnaire (38 women and 44 men).

A nurse at each coronary unit was employed as a research assistant responsible for the identification of eligible patients. These research assistants gave eligible patients a letter with information and invitation between three and four days after hospital admittance.

Consenting patients were given the questionnaire, which was completed while in

hospital, collected by the research assistants and returned to the researcher at the end of data collection. Female respondents were included the whole study period and male respondents for two months.

The questionnaire was developed by the researcher, based upon literature review and a qualitative study using in-depth interviews of women with first-time AMI (90). To test the user- friendliness of the questionnaire, ten healthy women and men below 65 years of age with varying demographic background were asked to comment on the questionnaire before data collection.

The questionnaire consisted of 32 items including demographic and lifestyle characteristics (Paper I, Table I), medical history and reported physical symptoms in the past year (Paper I, table II) and the respondents' symptom presentation and illness behaviour prior to hospitalization (Paper I, Table III). Additionally the respondents were asked whether or not they attributed these acute symptoms to a cardiac condition. Illness behaviour included whether the patients consulted family or friends about their acute symptoms and how they arranged for medical assistance. In a separate question they were asked whether they had to ask for assistance repeatedly.

Prehospital delay included two phases: the time between the onset of symptoms and first call for medical assistance (patient decision time or patient delay) and the time between the first call for medical assistance and arrival at the emergency department (health care confirmation time or physician delay).

All analyses were conducted with SPSS version 11.5 (91). Twin tailed chi-square tests were used to compare women's and men's demographic and lifestyle characteristics and clinical presentations. Logistic regression analyses were used to assess the relationship between symptom presentation, attribution of symptoms, illness behaviour and prehospital delay (Paper I, Table IV and V).

3.3.0 The main study

Based on experiences from the pilot study the main study was developed to assess hypothesises about gender differences. Power calculation was conducted and the number of study sites reduced in order to ensure continuity in recruitment.

Women and men diagnosed with a first time AMI were consecutively recruited from the

coronary units in five Norwegian hospitals. All eligible patients were registered while in hospital, and the questionnaires mailed to the respondents after hospital discharge. A gender comparison of patient characteristics and the relationship between various variables was explored in all papers.

Paper II focused on the patients' symptom experience in the acute prehospital phase. In paper III and IV the main focus was to assess various patient characteristics contributing to prehospital delay. Paper V concerns the patients' early warning symptoms during the year prior to the AMI.

3.3.1. Study design

The design of the study was descriptive and analytic, testing specific hypotheses on gender differences. The study aimed to obtain the respondents' own description of their symptom experiences, how these were assessed and interpreted and how they responded to these symptoms.

3.3.2 Inclusion criteria

Women and men 75 years and younger admitted and diagnosed with a first-time ST-elevation AMI (STEMI) or non ST-elevation AMI (NSTEMI) were invited.

Patients admitted with a tentative AMI diagnose were excluded if the diagnosis was not confirmed. In 2000 a "consensus document" between the European Society of Cardiology and the American College of Cardiology was published (92) regarding a new uniform definition of AMI. These new criteria were adapted by the Norwegian Society of Cardiology the same year, and presented in "Hjerteforum" nr 1, 2001. During the carrying out of the study, the 2000 uniform ESC/ACC definition of AMI was the definition in use, and all hospitals participating in the study used troponins as cardiac markers.

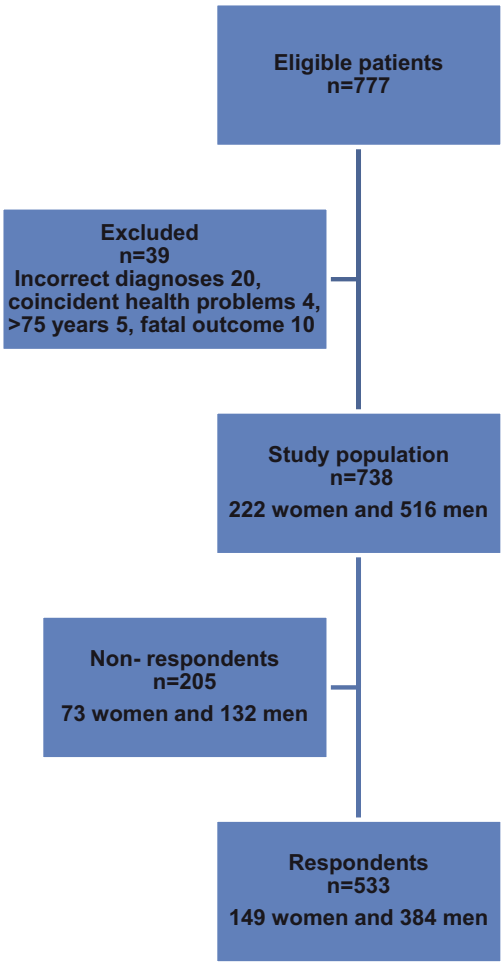
The diagnoses of patients with AMI were based on serum cardiac troponin activity above accepted cut-off values, ischemic electrocardiographic (ECG) changes with ST-segment elevation, ST-segment depression or T wave abnormalities, and/or the presence of clinically appropriate symptoms. First-time AMI was diagnosed

according to the stated definition and without any indication of previous AMI from the patient history, medical record or ECG findings. ST- segment elevation (STEMI) was based on ST- elevation ≥ 1 mm in at least two standard leads or ≥ 2 mm. in at least two contiguous precordial leads or the presence of a new left bundle branch block. Non-ST-segment elevation (NSTEMI) was those with confirmed AMI but not fulfilling criteria for STEMI (29). Location of the AMI was classified into anterior, posterior and other location, based on ECG-criteria.
Information about STEMI/ NSTEMI and infarct location was collected from the respondents' discharge reports. STEMI/NSTEMI was included in some of the logistic regression analyses when the relationship between chest symptoms and other aspects was analyzed.

3.3.3 Recruitment

All eligible women and men admitted to the coronary units in five hospitals were consecutively registered and invited to participate. Between February 2003 and March 2004, 777 women and men were invited. Of them 39 were later excluded due to information in the questionnaire, the medical records, information from the patients' relatives and the National Death Register (fig.1). The study population consisted of 738 respondents, and of these 149 women and 384 men were included. The response rate for the total number of patients was 72% (67% for the women and 74% for the men).

Fig.1. Flow chart over recruitment



3.3.4 Study sites

Five hospitals were invited to participate, and the aim was to include institutions of various sizes. The two university hospitals had emergency medical function for two health regions and the three other hospitals had emergency medical function for the surrounding urban and rural areas (Table 2).

Table 2. Study sites.

Regional health authorities	Hospitals
Central	St.Olavs University hospital
	Ålesund hospital
	Molde hospital
	Kristiansund hospital
South Eastern	Ullevål University hospital

3.3.5 Procedure

After exploring potential study sites a cover letter with invitation and information about the study was sent to the Head of the Medical departments. The study was approved by the Head of the Medical departments who appointed one of the hospital staff as research assistance (RA). A folder with information about the study was developed by the principal investigator (Mona Løvlien) and distributed to the patients while in hospital. Regular contact by telephone was established between the RA and ML.

A register including all eligible patients was established and administered by the research assistance (RA) at each hospital. Only the RA had access to the patients' names in this register. The principal investigator sent envelopes including patient invitations and questionnaires to the hospitals, all marked with a study number. Before the RA posted the invitations, names of eligible patients were linked to the national death register, and those who died soon after hospital discharge were excluded. Patients consented to participate by signing the consent form including permission to obtain medical information from their medical records. The consents including the questionnaires were returned to the principal investigator, in a prepaid envelope. Patients not responding to the invitation received a reminder distributed by the RA at each hospital. When questionnaires and consent forms had been returned, discharge reports from these respondents were obtained from the hospitals. Diagnostic results, STEMI/ NSTEMI and infarct location were extracted from these records.

3.3.6 Respondents

Out of a study population of 738 (fig.1), 533 respondents (67% women and 74% men) were included (149 women and 384 men). The majority were recruited from Ullevål University Hospital and St.Olavs University Hospital (Table 3).
Mean (SD) age for women was 61.2 years (9.8) and median age 61 years (the 25 quartile 55 years and the 75% quartile 69.5 years). Mean (SD) age for men was 58.5 years (9.5) and median age 58 years (25 % quartile 51 years and the 75 % quartile 64 years).

Table 3. Number of respondents (%) and characteristics of the study population by study site

	Ullevål	St.Olavs	Ålesund	Molde	Kristiansund
Total respondents	224(42)	185(35)	58(11)	38(7)	28(5)
Women	53(24)	52(28)	21(36)	12(32)	11(39)
Men	171(76)	133(72)	37(64)	26(68)	17(61)
Age ≤ 55 years	95(42)	67(36)	16(28)	8(21)	8(29)
Age 56-75 years	129(58)	118(64)	42(72)	30(79)	20(71)
Married/ cohabitant	170(76)	139(75)	41(71)	31(82)	20(71)
≥ 12 years education	60(27)	32(18)	12(21)	5(14)	6(23)
< 12 years education	159(73)	146(82)	44(79)	31(86)	20(77)
Employed					
yes	141(63)	96(52)	29(50)	17(45)	17(61)
no	83(37)	89(48)	29(50)	21(55)	11(39)

Non-responders

Of the total study population, 73 women and 132 men did not respond to the questionnaire. The response rate was higher in men than in women, except for respondents recruited from Ullevål University Hospital (Table 4). Mean (SD) age for non-respondents was 59.0 (10.4) years with no significant differences between women and men.

Table 4. Response rate (%) by study site and for the total of the study population

	Women	Men	Total
Ullevål University Hospital	88	73	74
St. Olavs University Hospital	61	74	70
Ålesund Hospital	72	79	76
Molde Hospital	52	79	68
Kristiansund Hospital	73	74	74
Total	67	74	72

3.3.7.0 The questionnaire

To test the user-friendliness of the questionnaire 8 healthy women and men, between 40 and 60 years of age, were asked to give comments. Further, the questionnaire was distributed to 20 women and men with first-time AMI, and these patients were given the opportunity to comment or call the principal investigator concerning the clarity and content of the questionnaire.
The questionnaire consisted of 48 questions including socio-demographics, medical history, symptoms during the year prior to the AMI, symptom experiences in the acute phase of the AMI and illness behaviour. Items related to the acute phase of the AMI included symptoms, how these were experienced and interpreted, illness behaviour and the time from symptom onset to hospital admission (Table 5).

3.3.7.1 Socio demographics

Age was classified into four categories (Paper III, Table 1). The respondents were asked to indicate their own and their partners' highest fulfilled education (separately) in a list including seven alternatives, between "less than 7 years" and "college/ university for at least 4 years". High education was defined as "at least high school education" and low education was defined as "less than high school education". The respondents' employment status was assessed by "full time employment", "part time employment",

"full time caring at home", "sickness benefit/ pension", "in education", "on maternity leave" and "unemployed/ unpaid leave". Sickness benefit/ pension and unemployed/ unpaid leave was defined as "on social security". Marital status and whether they lived alone (separate questions) were also included (Paper III, Table 1). These questions were based on various Norwegian epidemiological studies.
The respondents' knowledge about symptoms was assessed by the following question: "were you acquainted with symptoms of an AMI before hospital admission ?" (Paper IV, Table I).

3.3.7.2 Medical history

Medical history included medical treatment for hypertension, diabetes or hypercholesterolemia, whether they were prescribed nitrates and whether or not a physician had diagnosed angina. Positive family history was defined as having parents or siblings who had suffered an AMI before 60 years of age. (Paper II, Table 1). Questions about medical history had "yes" and "no" alternatives.

3.3.7.3 Acute symptoms

The respondents were asked to report symptoms which caused their decision to arrange for medical assistance. A list of symptoms was provided (Table 5 and Paper II, Table II). Pain, discomfort, pressure or tightness located to the chest (one or several descriptions) was further defined as chest symptoms. Pain in the shoulders, back or between the scapulae was defined as musculoskeletal symptoms, as such symptoms among the public often are associated with musculoskeletal problems. Reported chest symptoms and non-musculoskeletal symptoms were classified as typical symptoms. For each symptom the respondents were asked whether it was experienced initially (the first occurring symptoms) or experienced later (Paper II, Table II). Some respondents reported symptoms occurring both "early" and "late". We therefore had to compute new variables, and symptoms reported both "early" and "late" were recoded into symptoms experienced "early".

3.3.7.4 Symptom appraisal

The respondents' appraisal of their symptoms included questions on attribution and expectations (Table 5 and Paper II, Table III). Attribution was assessed as "what did you think was the reason for your symptoms?" They were also asked whether or not their symptoms corresponded with their own expectations regarding a cardiac origin (Paper II, Table III). The respondents reporting a mismatch between their expectation and experience of the acute symptoms were asked why these symptoms did not correspond, alternatives being "weaker than expected", "stronger than expected" and "expected other symptoms".

Table 5. Symptom experience in the acute phase (Paper II)

The acute situation prior to hospital admission:	**Dimensions**
Symptoms located to: the chest, right or left arm (separately), jaw/ throat, shoulders, between scapulae, back, abdomen or head. Nausea, dyspnoea, fatigue, sweating, dizziness, hot flashes or fainting	 Pain, discomfort, pressure or tightness. Pain or discomfort pain or numbness pain pain
Symptom progression Symptom intensity	Slow or quickly. Not very strong, moderate or unbearable
Symptom appraisal	Attribution as cardiac, stress, abdominal, musculoskeletal or flu. Expectation and in accordance with experience.

3.3.7.5 Illness behaviour

Illness behaviour was defined as various types of self-care interventions, whether they consulted other lay persons about their symptoms before calling for medical assistance and how they arranged for medical assistance (Table 6). The alternatives "called a general practitioner" (GP) and "self-transportation to a health centre" were combined into "called a GP". Some respondents had used several options when they arranged for medical assistance, and in the analyses the number of patients using exclusively one method was included.

Prehospital delay was assessed by two questions; time from symptom onset to the decision to arrange for medical assistance (patient delay) and time from symptom onset to hospital arrival (total prehospital delay) (paper III, Table 2). Patient delay consisted of 13 time categories between ½ hour and more than 24 hours and in the analyses patient delay was dichotomized into < one hour and ≥ one hour. The rationale was to distinguish between those who called rapidly for assistance and those who delayed. Total prehospital delay was classified into 14 categories between < one hour and > 24 hours, and later dichotomized into < two hours and ≥ two hours. The distance to the hospital was classified into six categories between "< 10 km" and ">50 km". This variable was included in all regression analyses regarding total prehospital delay.

Table 6. Illness behaviour

Items	Dimensions	Papers
Self-care interventions	Taking pain killers, tranquilizers or nitrates	III
Consulting lay persons	Partner, other family members or friends/colleagues.	III & IV
Arrangements for medical assistance	Called a GP (public/ private), called EMS, self-transport to the hospital/ health centre.	III
Patient delay	13 time categories between < ½ hour and > 24 hours	III & IV

3.3.7.6 Symptoms the year before the AMI

The respondents were asked whether they had experienced any physical or psycho-somatic symptoms during the year before the AMI. Physical symptoms included pain or discomfort in chest, pain in back/ shoulders, pain /numbness in arms, fatigue and dyspnoea. Response options were "none", "some", "rather much" and "very much". Physical symptoms are later in this thesis defined as "early warning symptoms", and in Paper V also defined as "early warning signs" and "prodromal symptoms". The respondents were asked to describe their level of activity when physical symptoms occurred (triggering activity) (Paper V, Table 2). Whether they contacted a physician for these symptoms was also included (Paper V, Table 2).

Further, the respondents were asked about symptoms of depression, anxiety, nervousness and sleep disturbances. Retrospective accounts of depressive symptoms were assessed using the short form of the Symptom Check List (SCL 25) developed by Tambs and Moum (93) who found that a weighted sum of three questions from the SCL correlated at r = 0.89 with the global 15-item SCL-25 score with alpha reliability 0.80 (Chronbach's alpha). The questions "feeling hopeless about the future", "feeling blue" and "worrying too much about the future" were defined as symptoms of depression. A sum score of these symptoms was computed and divided by the number of items. The upper 10th percentile was defined as symptoms of major depression (Paper IV, Table1). Two other questions from this short form about anxiety and nervousness were also included (Paper V, Table 1).

Further, the respondents were asked about perceived stress, stressful demands and major life events. To measure stress the year prior to the AMI, the respondents were asked whether they had experienced stress and nagging at work or in their family situation (separately). To test the internal consistency of the questions measuring stress, a reliability test was conducted (Chronbach's alpha) and the alpha score was 0.742. Additionally they were also asked whether they experienced demands from other people perceived as difficult to cope with, at work or in their family situations (separately). These questions about perceived stress and stressful demands have previously been used in the "Nord Trøndelag health survey" (94). Response options for these questions were "never", "some periods", "several periods" and "almost permanently". High family

stress (vs. high work stress) was defined as several periods of or almost permanent stress coincident with several periods of or almost permanent demands in family situation (vs. work situation). The frequency (%) of high work stress was based on the number of respondents employed during the year prior to the AMI. High general stress was defined as either high family stress or high work stress (Paper IV, Table 1).
The presence of life events were assessed by applying a list used in the Norwegian Mother and Child study, and the same items were also used in the INTERHEART study (122) (Paper IV, Table 2). If they responded positively to any items in this list, they were requested to grade their experience into "not so painful", "painful/difficult" or "very painful/difficult".

3.3.8 Ethical issues.

The pilot study as well as the main study was approved by the Regional Ethics Committee for Medical Research in Norway and conformed to the principles of the Declaration of Helsinki. Eligible patients responding positively to the invitation gave their written consent to participation. They were informed that participation was voluntary and that they at any moment could withdraw from the study. In the main study this information was included in the letter sent to the eligible patients, while in the pilot study the coronary nurses informed the patients while in hospital. In the main study the principal investigator had no access to the respondents' medical record before the respondents gave their written consent. The names of the registered patients were also controlled against the National Death Register to reduce the chance of sending the invitations to patients who had died immediately after hospital discharge.
They were also given the opportunity to call the principal investigator if items in the questionnaire were difficult to understand. Several respondents used this opportunity to describe their experiences after hospitalization. Some relatives also informed about problems in responding to the questionnaire due to coincident health problems.

3.4.0 Statistics

3.4.1 Calculation of sample size

When this study was planned few studies included a gender comparison of prehospital delay. Some had reported a longer delay in women than in men (72, 95). Gender difference in prehospital delay was the main hypothesis in the study. Previously reported median prehospital delay was 3.25 hours in women and 2.50 hours in men (95). In my pilot study mean (SD) patient delay was 2.05 (1.9) for the women and 1.80 (1.5) for the men. We decided that a prehospital delay of 3.5 hours vs. 3.0 hours was appropriate to use in the calculation.
The sample size was calculated with the statistic program nQuery (96). We chose a two sample t-test (two-sided), power 0.80, SD 1.7 and p -value < 0.05. It was included in the model that the male population would be approximately 2.5 larger than the female population. This calculation indicated that the total sample size required was a minimum of 448 respondents.

3.4.2 Statistical analyses

All analyses were conducted with SPSS for Windows (91) version 11.5. – 16.0. Continuous variables are presented as mean (SD). The median and quartiles were used to compare women and men's age. Chi square tests and Man Whitney tests were used to compare patient characteristics and clinical presentation. A sum score for three symptoms of depression was computed, and the upper 10^{th} percentile was defined as major depression (Paper IV). A sum score for psychosocial stressors was also conducted, in order to assess a possible dose- response association (Paper IV). Logistic regression analyses were used to assess the association between clinical characteristics and patient delay /total prehospital delay (paper III and IV), the effect of gender on acute symptoms (Paper II), the association between acute and prodromal symptoms (Paper V) and the association between medical history and prodromal symptoms (Paper V). These analyses estimated odds ratios and their 95% Confidence Intervals (CI). Odds ratios provide an estimation of the relative risk, and were adjusted for any confounding variables. Factors included in the

regression analyses were those which were statistically significant in the univariate analyses.

Power analyses were included to minimize the possibility of type II error when an association was statistically significant only in men. As the study population included fewer women than men, a non-significant result might be related to the female sample size. P-values < 0.05 or a 95% CI that excluded the null value were considered statistically significant.

4.0 RESULTS- REVIEWS OF PAPER I - V

4.1 Review of Paper I

Are there gender differences related to symptoms of acute myocardial infarction? A Norwegian perspective.

Aims

To compare symptom presentation and illness behaviour among women and men with a first-time acute myocardial infarction (AMI) and assess aspects that influence prehospital delay.

Methods

A pilot study including 38 women and 44 men with first-time AMI, consecutively recruited from the coronary unit in 13 Norwegian hospitals. The respondents completed a questionnaire while in hospital.

Results

Women were more likely than men to report pain located in the arms (61% vs. 32%, $p< 0.01$), back (40% vs. 16%, $p= 0.02$), jaw/throat (50% vs. 25%, $p= 0.02$) as well as nausea (66% vs. 34%, $p<0.01$) in the acute phase. Women attributing their symptoms as non- cardiac were more likely than men to experience typical AMI symptoms (66% vs. 0 %, $p< 0.01$). None of these women reported that they were well informed about AMI symptoms.

No statistically significant gender differences were found in prehospital delay. Respondents who interpreted their symptoms as cardiac or being diagnosed with hypercholesterolemia called for medical assistance more rapidly than other respondents. Calling a GP increased prehospital delay. When calling for medical assistance, more women than men had to call repeatedly (26% vs. 5%, $p<0.01$).

During the year prior to the AMI women were more likely than men to experience fatigue (52% vs. 20%, $p<0.01$).

Conclusions

Women experienced a greater diversity of symptoms than men in the acute phase as well as the year prior to the AMI.

4.2 Review of Paper II

Women with myocardial infarction are less likely than men to experience chest symptoms.

Aims

To investigate whether women and men experienced different symptoms with an AMI, and whether they differed in their interpretation of these.

Methods

A retrospective, cross-sectional study including 149 women and 384 men consecutively recruited from the coronary unit in 5 Norwegian hospitals. A questionnaire was distributed to the respondents after hospital discharge.

Results

Women were less likely than men to experience chest symptoms in the acute phase (86 % vs. 92 %, OR 0.53, 95 % CI. 0.29-0.97).

Women were also more likely than men to report pain in the back, shoulders or between the scapulae (musculoskeletal symptoms) (54 % vs. 38 %, OR. 2.1, 95 % CI. 1.39-3.1). These analyses were adjusted for age.

Proportionally more women than men reported dyspnoea, nausea, palpitations, hot flushes, pain in the jaw/throat and right arm, dizziness and fainting. The four most frequently reported acute symptoms (symptoms from the chest, left arm, sweating and dyspnoea) were the same among women and men.

Young men (<55 years) were more likely than older men to experience musculoskeletal symptoms (47 % vs. 33 %, OR. 1.81, 95 % CI. 1.20 – 2.76), to report a higher number of symptoms (mean 8.41, SD 3.83, vs. mean 5.30, SD 3,70, p= 0.03) and to attribute their symptoms as non-cardiac (55 % vs. 41 %, OR 1.81, 95 % CI. 1.20-2.74). Age did not impact on these symptoms among women.

Symptoms were attributed as exclusively cardiac among 42 % of both women and men. Among women, chest symptoms experienced in an early phase of the AMI contributed to a cardiac attribution (45 % vs. 35 %, p <0.01). Among men, there was a weak association between chest symptoms experienced initially and a cardiac attribution (49

% vs. 39 %, p= 0.04).

Symptoms contributing to a non-cardiac attribution in women were late onset of chest symptoms (9 % vs. 0 %, p <0.01), fatigue (28 % vs. 17 %, p =0.016) and hot flushes (19 % vs. 9 %, p =0.01). Abdominal pain influenced a non-cardiac attribution in men only (9 % vs. 5 %, p <0.01).

Men who had been prescribed nitrates (9 % vs. 2 %, p < 0.01) and diagnosed with hypercholesterolemia (10 % vs. 4 %, p < 0.01) were more likely than other men to attribute their symptoms as cardiac. These factors did not contribute to a cardiac attribution among women.

Other aspects contributing to a cardiac attribution in both genders were being familiar with AMI symptoms, symptoms corresponding with expectations and previously diagnosed angina pectoris.

More than half of both women (58 %) and men (57%) reported that their symptom experiences did not match their expectations.

Conclusions

Women were less likely than men to report chest symptoms and more likely to experience atypical AMI symptoms. Younger men differed from older men in symptom experience and symptom appraisal. Attribution of symptoms as non-cardiac was influenced by cognitive aspects in both women and men. Women and men differed in how medical history and symptom characteristics influenced a non-cardiac attribution.

There is an error in Table II in this article. The proportions of “late” presentation for “pain”, “discomfort”, “pressure” and “tightness” presented in this table includes respondents that reported these symptoms both “early” and “late”. The proportion of respondents reporting “early” and “late” “chest symptoms” (totally) is correct, and only these proportions were used in the analyses.

4.3 Review of Paper III

Prehospital delay, contributing aspects and responses to symptoms among Norwegian women and men with first-time acute myocardial infarction.

Aims

To assess gender differences in prehospital delay among women and men, their responses to acute symptoms and the aspects influencing prehospital delay.

Methods

A retrospective, cross-sectional study including 149 women and 384 men consecutively recruited from the coronary unit in 5 Norwegian hospitals. A questionnaire was distributed to the respondents after hospital discharge.

Results

Women did not report a longer prehospital delay than men. More than half of both women (56 %) and men (57 %) waited one hour or more before they called for medical assistance and 11 % of the women and 10 % of the men more than 24 hours. Total prehospital delay was two hours or more for 52 % of the women and 51 % of the men. Gender differences were only found among respondents with a patient delay between 2 and 6 hours (Table 7).

Consulting their spouse was reported by 52 % of the women and 66 % of the men (p=0.012). More than half of both women (53 %) and men (52 %) called exclusively a GP, while 26 % vs. 30 % called exclusively the EMS.

Aspects influencing delay in both women and men are illustrated in Table 8. Among men, experiencing AMI symptoms located to shoulders, back and between the scapulae increased both patient delay and total prehospital delay. This association was stronger when the symptoms were experienced initially. However, this was not found in women.

Experiencing chest symptoms, age and knowledge about AMI symptoms had no significant impact on delay in either gender.

Conclusions

There were no statistical significant gender differences in patient delay or total prehospital delay. How symptoms were experienced and interpreted was more likely to influence patient delay in men than in women. Illness behaviour influenced prehospital delay in both women and men.

Table 7. Patient delay, total prehospital delay and gender differences between women and men with a first-time AMI

	Patient delay			Total prehospital delay		
	Women n=140(%)	**Men** n=376(%)	**p-value**	**Women** n=142(%)	**Men** n=374(%)	**p-value**
≤ 1 h	62(44)	178(47)	0.536	29(20)	86(23)	0.531
1-2 h	16(11)	49(13)	0.626	39(27)	97(26)	0.725
2-6 h	32(23)	52(14)	0.014	42(30)	94(25)	0.306
> 6 h	30(21)	97(26)	0.306	32(22)	97(26)	0.426

Table 8. Aspects influencing patient delay and total prehospital delay in women and men with a first-time AMI.

	Increasing delay	Reducing delay
STEMI/ NSTEMI	NSTEMI (in men only)	STEMI (in men only)
Experiencing symptoms	•Musculoskeletal symptoms (in men only)	•Rapid development of symptoms • Unbearable symptoms (in men only)
Assessment and interpretation of symptoms	Mismatch between symptoms expected and experienced	•Symptoms matching expectations •Cardiac attribution (in men only)
Illness behaviour	•Consulting their spouse •Self medication (taking pain killers in particular) •Calling a GP	•Calling the EMS

4.4 Review of Paper IV

Myocardial infarction: psychosocial aspects, gender differences and impact on prehospital delay.

Aims

To explore gender differences in psychosocial aspects the year prior to a first-time AMI and the association between these aspects and prehospital delay.

Methods

A retrospective, cross-sectional study including 149 women and 384 men consecutively recruited from the coronary unit in 5 Norwegian hospitals. A questionnaire was distributed to the respondents after hospital discharge.

Results

Women were more likely than men to report major depression (19 % vs. 10 %, p< 0.01), high family stress (21 % vs. 7 %, p < 0.01), major life events (73 % vs. 59 %, p <0.01) and sleep disturbances (54 % vs.36 %, p< 0.01). Depression, high family stress and major life events were most common among women 65 years and younger. Young age (<65 years) was associated with symptoms of depression and major life event among men. Depression and other psychosocial stressors had no statistically significant impact on delay in any of the genders.

Men with low education had a longer patient delay than men with high education (OR.1.63, 95 % CI. 1.03-2.58), but this association was not found in women (OR.0.71, 95 % CI. 0.22-2.32). Having a partner with low education was also a negative factor regarding patient delay in men (OR. 2.29, 95 % CI. 1.31-4.02) as well as for total prehospital delay (OR. 2.0, 95 % CI. 1.12-3.56). No statistically significant association was found in women (OR. 0.61, 95 % CI. 0.19-1.96). When both male respondents' and their partner's education was included in regression analyses (adjusted for age), only having a partner with low education was a predictor for increased patient delay (OR. 2.29, 95 % CI. 1.31-4.01).

No knowledge about AMI symptoms was reported by 21 % of the women and 20 % of the men. This aspect had no impact on delay in any genders.

Conclusions

Women and men 65 years and younger were more likely than older respondents to report psychosocial stressors the year prior to the AMI. Our results suggest that men's partners have a more discouraging influence on the patients' decision process than women's partners.

Spouses/partners have to be included in information-giving about AMI, as significant others seem to play a vital role in the patients' decision-making process.

4.5. Review of Paper V

Early warning signs of an acute myocardial infarction and their influence on symptoms during the acute phase, with comparisons by gender.

Aims

To assess early warning signs of AMI and how individuals responded to these symptoms, with comparisons made by gender. Medical history was also reviewed to see whether it was associated with these symptoms and might be a tool for diagnosing coronary heart disease (CHD) in high-risk patients. An additional aim was to assess whether these early warning symptoms had any influence on symptoms occurring in the acute phase of an AMI.

Methods

A retrospective, cross-sectional study including 149 women and 384 men consecutively recruited from the coronary unit in 5 Norwegian hospitals. A questionnaire was distributed to the respondents after hospital discharge.

Results

Proportionally more women than men (84 % vs. 76 %, $p<0.05$) reported that they had experienced at least one early warning symptom during the year before the AMI. There were no statistically significant gender differences in the prevalence of each of these symptoms, but women were more likely than men to report a stronger degree of fatigue. Almost half the women (44 %) and the men (46 %) experienced chest symptoms. Women were most likely to contact a physician for their chest symptoms and men for their shoulder/back symptoms. Among men with chest symptoms, those ≥ 66 years were more likely than younger men to contact a physician for these problems (41 % vs. 20 %, $p< 0.01$). No such association was found in women.

Among respondents experiencing chest symptoms after minor activity, 23 % of both genders had previously been diagnosed with angina pectoris. Among women and men with a combination of chest symptoms and dyspnoea, angina was previously diagnosed in 21 %.

Women who experienced early warning symptoms were more likely than other women to report a gradual development of symptoms in the acute phase (36 % vs. 13 %, p= 0.029) and the same association was found in men (39 % vs. 9 %, p<0.01).
In regression analysis including hypertension, early chest symptoms, previously diagnosed angina, STEMI, anxiety and age, hypertension in women was significantly associated with a lower likelihood of acute chest symptoms (OR=0.29, 95 % CI. 0.10-0.82). No statistically significant association was found in men (OR=0.54, 95 % CI. 0.24-1.23).
Respondents experiencing symptoms in the chest, pain in the shoulder/ back, pain in the arms, dyspnoea and fatigue during the year before the AMI had an increased risk of experiencing similar symptoms during the acute phase of AMI. The risk of experiencing chest symptoms in the acute phase was > 5 times higher in women who had experienced symptoms in the chest the year before the AMI and nearly 3 times higher in men. The risk of experiencing shoulder/ back pain in the acute phase was almost 5 times higher in men with similar symptoms the year before and almost doubled in women. The risk of experiencing dyspnoea in the acute phase was almost 5 times higher in men with similar symptoms the year before and more than doubled in women.

Conclusions

Almost half of the study population experienced early warning symptoms, more commonly in women than in men. These symptoms were associated with symptoms that occurred during the acute stage of AMI, with some differences between the genders. Women and men differed in responses to these early symptoms and how medical history influenced their symptoms.

5.0 GENERAL DISCUSSION

5.1.0 Methodological considerations

5.1.1 Study design

This study has some limitation related to design. In a cross-sectional study the data are collected at one point in time, thus missing the information about the development of the various variables over time. With this study design it is not possible to make any causal inferences about exposures and clinical conditions. The results of these analyses can therefore only indicate associations.

5.1.2 The role of chance

When a sample of a population is examined the observed associations might be due to the element of chance. A priori power calculation of sample size was conducted to reduce the possibility of making spurious inferences. P-values below 0.05 were defined as the level for statistically significant results. This means that there is no more than a 5% probability that the results are due to chance alone. However, as p-values reflect both the magnitude of the difference between the groups and the sample size, the confidence interval (CI) is considered as an additional measure of the role of chance. A 95% CI that excluded the null value was considered statistically significant. A non-significant result with a narrow CI implies that that there most likely is no real association, whereas a wide interval suggests that the sample size was too small to have sufficient statistical power to conclude that there might be an association. In regression analyses of gender differences in patient delay (adjusted for age), the OR for delay > one hour was 1.13 (CI 0.77-1.67) in women. In addition to the non- significant result (the CI includes the 0 value), the narrow CI also implies that the findings are not due to chance alone. In regression analyses of gender differences in total prehospital delay, (adjusted for age and distance to hospital), the OR for delay > two hours was 1.02(CI 0.76-1.53) in women. This interval also makes it unlikely that our findings are due to small sample size.

Whether our findings about gender differences in acute chest symptoms are due to the role of chance has to be considered. A post-hoc power test was computed to measure

the statistical power of these gender differences, showing a power 0.66. To achieve a power 0.80 a sample size of 700 respondents was required. These findings indicate that the results are not likely to be due to the role of chance alone. As only 167 additional respondents were required for a power 0.80, the clinical and the statistical significance of these findings supports our result.

As the number of female participants was only 149, there was a probability of making a type II error, which refers to a possibility of rejecting a true association. When associations were statistically significant in men and not in women, the effect of sample size might be ascertained from the width of the CI. Musculoskeletal symptoms experienced in the acute phase increased patient delay in men and not in women. Evaluation of the CI for this association in women suggests that there most likely is no real association, due to a narrow interval (CI 0.41-1.73). However, the association between musculoskeletal symptoms and total prehospital delay in women also needs to be considered. The OR for this association was 1.92 and the CI 0.85-4.38. This interval suggests that the non statistical significant association that was found in women might be due to low sample size.

ST elevation infarction (STEMI) was associated with prehospital delay in men and not in women. As information about STEMI was missing for 49 respondents, the negative result regarding women's delay might be due to the small female sample size. In power analyses a sample size of 460 women had been required to achieve a power 0.80, which indicates that we cannot disregard an association between STEMI and patient delay in any genders.

Partner's education was associated with increased patient delay only in men. The narrow CI (0.19-1.96) for this association in women indicates that the non-significant result is probably is not due to sample size and to chance alone.

5.1.3 Validity

The items in the questionnaire used in both the main study and the pilot study were based upon a review of the literature on the topic in addition to a qualitative study with in-depth interviews of women with-first time AMI (90). The questionnaire used in the main study was also evaluated by clinical researchers specialized in cardiac care. As

the questionnaire was not formally validated, we cannot disregard the possibility that the items did not measure what was intended.
To measure depression we used a short-form questionnaire measuring mental health (93). This short version was based on a validated instrument (SCL-25) and was reported to correlate at 0.89 with the full scale instrument (93). As to external validity, the hospitals recruiting respondents were the only options for AMI patients in the various regions. There is no reason to believe that these respondents differed from patients with first time AMI in other health regions. We therefore consider that our findings are representative and generalizable to other patients with first-time AMI. As to generalizability to all AMI patients, some of the results may be more typical for patients suffering their first AMI than for patients with a previous AMI. And due to the age limit the results may not be representative for women and men older than 75 years.

5.1.4 Selection bias

An aspect that reduced the risk of selection bias in our study is the high response rate (72 %). Non- responders did not differ from responders as to age and gender, but differences regarding ethnicity and clinical conditions are unknown. As almost all the respondents had Norwegian or Scandinavian names, it is possible that non-ethnic Norwegians were more likely than ethnic Norwegians to be non-responders.
A possible selection bias is that patients who died before or immediately after hospital admission differed from the study population. There is no national registry of individuals who died prior to hospital admittance with a possible AMI, and therefore their clinical characteristics are unknown. Women being more likely than men to die of a cardiac arrest has been reported (7), and this gender difference is a potential bias.

5.1.5 Recall bias

As this study was based upon self- reported data, some errors might occur. And our results about an association between symptoms the year before the AMI and acute symptoms might be due to recall bias. As this information was recorded retrospectively it is possible that the respondents may have recalled the symptoms they experienced the

year before the AMI more easily if they also experienced the same symptoms in the acute situation. This potential bias might have contributed to an overestimation of this association. As to differences between women and men however, we have no reason to believe that there should be any gender differences in this recall.

5.1.6 Reliability

To measure stress, respondents were asked whether they experienced stress and nagging at work or in their family situation (separately). They were also asked whether they experienced demands from other people that were perceived as difficult to cope with, at work or in their family situation (separately). These questions have been previously used in a Norwegian health survey (94). To test the internal consistency of the questions measuring stress a reliability test (Chronbach's alfa) was computed. This test has values between .00 and +1.00 and higher values reflect a higher internal consistency. In our study the alpha score for questions measuring stress was considered adequate for reliability (0.742).

A reliability test had previously been conducted on the questions measuring depression, reporting an alpha score 0.80 (93). A reliability test of acute AMI symptoms was also computed, with an alpha score 0.80.

Information on diabetes was obtained by the following question: "have you been medically treated for diabetes?" Individuals with food restricted diabetes 2 might not respond positively. This potential misclassification might have influenced the results. Diabetes is known to be more common in women than in men and diabetics are less likely than non-diabetics to experience chest symptoms. It is therefore not likely that an increasing prevalence of diabetics would affect our results regarding gender differences in chest symptoms.

5.1.7 Confounding factors

To reduce the possibility of results being affected by confounding variables, analyses were adjusted for some potential confounding factors. In the analyses of gender differences in reported chest symptoms regression analyses were adjusted for

age and diabetes, as these variables are associated with both the independent and the outcome variable. The prevalence of AMI increases with age, but differs between women and men. Chest symptoms are also known to be less common in older patients. Diabetes is more common in women than in men, and diabetics are less likely than non- diabetics to report chest symptoms.
Whether any confounding factors might influence gender differences in delay also has to be assessed. A potential confounder is STEMI infarction, as some studies have indicated that this factor is associated with delay, as well as being more common in men than in women. As STEMI was not included in the previous analyses, we decided to conduct new regression analyses of gender differences in patient delay and total prehospital delay. Gender, age and STEMI were included in these analyses, but there were still no statistically significant gender differences in patient delay or total prehospital delay.

5.2 Discussion of results

5.2.1 Symptom experience and interpretation

Our findings that women were less likely than men to experience chest symptoms in the acute phase are in accordance with the MONIKA study and some others (21, 22-26). Whether there are gender differences in acute chest symptoms is debated, and no gender difference in chest symptoms has also been reported (50, 97, 98). In a review of large cohort studies between 1970 and 2005, 63 % of the women and 73 % of the men reported chest symptoms (74) which are lower than our findings (86 % vs. 92 %). The inconsistent findings might be due to different study populations, as some of these studies included recurrent AMI and angina. Our findings are however, quite similar to a Swedish study which reported chest symptoms in 88.5 % of the women and 94.8 % of the men, all with a first AMI (99). The MONIKA study (21), including only AMI patients reported chest symptoms in 81 % of the women and 86 % of the men, which is quite similar to our results. However, this study also included recurrent AMI.
Some studies also report less chest symptoms in older patients (21, 23, 100), and the age of the study population might also explain conflicting results. Patients experiencing non-

chest symptoms are particularly vulnerable, as they have a higher mortality compared with patients presenting with chest symptoms (25, 27). A higher prevalence of hypertension among respondents without chest symptoms is consistent with other reports (24, 25, 27) but whether this is an aspect concerning only women is inconclusive. This association is important regarding female patients, as women with AMI, and particularly older women, are more likely than men to be hypertensive.

Our findings that women were more likely than men to experience AMI symptoms located to back, jaw/throat, nausea, dyspnoea, palpitations and fatigue are consistent with several other reports (24. 50, 97, 99, 101, 102).

The four most frequently reported symptoms being equal among women and men (chest symptoms, sweating, left arm pain and dyspnoea) have been previously reported (50, 101).

In our study, we defined musculoskeletal symptoms as pain located between the scapulae, in the back or shoulders. A female predominance of pain located in the back and shoulders has been reported (101, 103) but whether women are more likely than men to experience pain between the scapulae is still questionable.

Our findings that younger men (55 years and younger) were more likely than older men to report a higher proportion of symptoms has been reported (104), but whether younger men are more likely to experience musculoskeletal symptoms and to attribute their symptoms as non- cardiac needs to be further investigated. It has however, been reported that chest symptoms, arm pain, dyspnoea and sweating vary by age (21, 23, 100, 105), and we therefore consider it as not unlikely that other symptoms vary between age groups.

How symptoms are interpreted is vital for recognizing the symptoms as cardiac in origin. Our findings about no gender differences in cardiac attribution are consistent with previous reports (72), but women being less likely to attribute their symptoms as cardiac has also been reported (106). The number of respondents in our study attributing their symptoms as cardiac is quite consistent with other reports (48, 57, 106) but lower than a Swedish study (70). Why these Swedish patients were more likely than the respondents in our study to interpret their symptoms as cardiac in origin is clinically interesting.

Our findings that respondents experiencing chest symptoms in the early phase of the AMI were more likely than others to attribute their symptoms as cardiac, and whether

these initial symptoms have a more significant influence in women than in men have to be further investigated. Moreover, whether fatigue and hot flushes have a more significant influence on the attribution in women than in men is not conclusive.

5.2.2 Prehospital delay

Our findings about no gender differences in prehospital delay are consistent with some reports ([5, 21, 48 - 51, 69, 70, 106]), but longer delay in women than in men has also been reported ([19, 44- 47]). There are to our knowledge no data about gender differences in prehospital delay in Norwegian populations, but the MONIKA study in addition to two other Swedish studies have reported no gender differences ([21, 69, 70]). A Danish study, however, reported longer delay in women ([10]). Conflicting results regarding delay might be influenced by culture, as geographical differences have been reported ([44]). Cultural aspects such as differences in medical insurance coverage and health systems as well as how health care providers perceive clinical symptoms might differ geographically. As some studies have reported increased delay in older women ([5, 21, 48, 70]) conflicting results also might be due to the age of the study population. Many women and men in our study waited too long before they arranged for medical assistance. According to international guidelines patient delay should not exceed 45 minutes ([54]), but more than half the respondents delayed more than 45 minutes. Patient delay and total prehospital delay in our study was similar or somewhat shorter than other reports ([21, 45, 46, 52, 53]). However, a total prehospital delay exceeding 4 hours for half the study population has been reported ([45]).

5.2.3 Aspects influencing patient delay

The decision process from symptom onset to the arrangement for medical assistance (patient delay) includes assessing and interpreting symptoms. The patients will cognitively and emotionally identify the symptoms as a sign of illness and symptom appraisal and prior expectations will influence the decision process ([58]). This is illustrated by our findings that a discrepancy between symptoms expected and experienced increases patient delay in both women and men, as several others have

reported (51, 67, 68).

That rapid development of symptoms and symptoms attributed as cardiac decrease delay is consistent with other reports (10, 48, 56, 69, 70). But our findings that a cardiac attribution decreased delay in men and not in women need to be further confirmed. These findings indicate that interpretation of symptoms has a different impact on women and men's illness behaviour. Knowledge about these aspects is limited, but it has been suggested that genetic and physiological differences combined with environment might result in gender differences in cognition and behaviour (12). Men who experienced musculoskeletal symptoms had a longer patient delay than other men, but whether these symptoms have no influence on the women's decision process is not conclusive. It has previously been reported that back pain increased patient delay (69), but in this study gender comparisons were not reported. And moreover, whether musculoskeletal symptoms are most important when they are experienced initially has to be further investigated.

Our findings about increased delay among respondents consulting their spouse/ partner as well as those taking pain killers is consistent with others (10, 41, 45, 46, 49, 51, 55, 56, 73). According to Leventhal (58) attitudes and messages from significant others may have an impact on the patients' decision process. The spouses'/partners' contribution to increased delay is not clear, but according to a qualitative study (107) the spouses shared their partners' denial and were not willing to confront their symptoms. They also organized rest or provided medication rather than quickly recommending their partners to seek medical assistance (107). Our findings that men were more likely than women to consult their spouse are in accordance with another study (108).

Our findings that low education level predicted longer prehospital delay is consistent with previous reports (65, 69). As these studies did not include gender comparisons it is still questionable whether educational level only concerns men's delay. Whether the patients' level of knowledge about AMI symptoms influence their decision to seek medical assistance is inconclusive (48, 55). Whether a partner's low education is an aspect concerning patient delay only in men is still questionable. The influence of wives' education has been investigated regarding men's CHD risk, and a Norwegian study found that wives' education was inversely correlated to men's risk factors as well

as to their risk of CHD mortality (109). A Swedish study including both women and men reported that a wife's education was more important for her husband's mortality risk than his own education. Conversely, the husband's social class and income were particular important for all-cause mortality in women (110).
Our findings that respondents with major depression did not delay longer than non-depressive respondents are inconsistent with one other report (111). These conflicting results might be due to various instruments used to measure depression as well as different study populations.

5.2.4 Illness behaviour and influence on total prehospital delay

Our findings that calling the EMS reduced and calling a GP increased prehospital delay are consistent with several reports (45, 51, 70, 73, 112). How the respondents arranged for medical assistance varied, and the number of respondents calling exclusively the EMS (26 % women and 30 %) is consistent with a French (113) and a British study (72) but lower than two Swedish studies (70, 112). The patients in one of these Swedish studies (70) being more likely than the Norwegians to call the EMS may be related to the higher number of patients attributing their symptoms as cardiac, as previously discussed. The fact that so few of the respondents in our study called the EMS needs attention. A common reason for not calling the EMS being reported is that the symptoms were not important enough (72, 112). It has also been reported that only a minority of AMI patients were aware of the significance of early treatment (10), and this might have been a contributing aspect.

5.2.5 Symptoms the year before the AMI and illness behaviour

Gender differences in symptoms the year before the AMI are scarcely investigated, but our findings that women experienced a higher frequency of symptoms than men have been reported (114). Fatigue being the most common symptoms among both women and men is consistent with other reports (115- 117). Some of the previous reports have focused on symptoms experienced the days before the AMI, but in a study including only women (115) symptoms were experienced for a mean of four to six months before the

AMI.

The prevalence of chest symptoms the year before the AMI in our study was quite similar to a review of 28 studies (118). Many respondents experiencing chest symptoms did not contact a physician, and this lack of appropriate action is consistent with some reports (117, 119). According to a qualitative study (88) many women with AMI reported reluctance to visit their GP for symptoms they experienced the year before, as they were assessed as vague and rather trivial. Whether other aspects than this reluctance contribute to this illness behaviour is not clear. An early recognition of individuals with these early warning symptoms might contribute to an early treatment and thereby affect morbidity and mortality (116, 118). Our findings indicating that women were more likely than men to contact a physician for their chest symptoms need to be further investigated.

Our findings that women were more likely than men to report depression, sleep disturbances and stressful life events is consistent with other studies (120,121). Younger women and men being more likely than older to experience depression and major life events have also been reported (122, 123).

The female predominance of depression and sleep disturbances has also been reported among healthy individuals (124), but conversely, most common in women aged 67 years and older. The fact that these symptoms were most predominant among younger women with AMI is clinically important as depression and sleep disturbances are known to predict cardiac events as well as increased mortality (121, 122, 125).

5.2.6 Early warning symptoms and influence on symptoms in the acute phase

Our findings that respondents reporting symptoms the year before the AMI were more likely than others to experience a gradual development of acute symptoms are consistent with another study (116). As a gradual progression of acute symptoms might increase prehospital delay (67) this highlights the importance of focusing on symptoms the year before the AMI. Our findings that these early warning symptoms were associated with the symptoms in the acute phase are consistent with two other reports (115, 126).

However, these studies did not include gender comparisons, and our findings that chest symptoms the year before the AMI more significantly were associated with acute chest symptoms in women than in men need further investigation.

6 CLINICAL IMPLICATIONS

Early identification of women and men at risk of developing CHD is vital to decreasing mortality and morbidity caused by an AMI. Interventions for patients with AMI have evolved from treatment of complications to preservation of myocardial muscle with reperfusion therapies, and therefore an early diagnose is essential. Knowledge about early warning symptoms is important for all clinicians, and information to high risk patients about how to recognize these symptoms should be considered. Early warning symptoms might be difficult to evaluate, especially fatigue. But these symptoms need attention in high risk patients, and the patients should be informed that these symptoms might be early warning signs of CHD. Furthermore, to acknowledge that an AMI can be prevented is vital. That very few respondents in our study consulted a GP for their chest symptoms the year before the AMI indicates that high-risk patients should be informed about how to respond to these symptoms.

Public education campaigns have so far not contributed to reduced patient delay, and the benefit of education is not definite. Intervention studies using individual education and counselling have reported increased knowledge about AMI, and increased knowledge might contribute to a cardiac attribution. As symptoms experienced being in accordance with expectations has a vital impact on attribution of symptoms as well as prehospital delay, it is important that individuals recognize potential AMI symptoms. Knowledge about the possibility of experiencing a variety of acute symptoms as well as non-chest symptoms is vital, and this must be particularly emphasized in counselling women. Women also need to be informed about the possibility of experiencing non-chest symptoms in the acute phase if they have experienced non-chest symptoms the year before. The possibility of experiencing chest pain after the onset of other symptoms as well as a slow symptom progression is important knowledge. A lower likelihood of chest symptoms in addition to a higher likelihood of atypical symptoms might mislead the patients to attribute the symptoms as musculoskeletal, gastrointestinal or neurologic in origin.

The patients' decision process is complex and knowledge is only one of several components influencing this process. Many patients are reluctant to seek medical assistance, and one of the reasons is that their symptoms are not assessed as serious

enough. Information about appropriate behaviour when experiencing possible AMI symptoms is vital for high-risk patients, as well as for the public. Our findings that a cardiac attribution did not contribute to decreased delay in women imply that they might not acknowledge the importance of early treatment. That calling the EMS is recommended in an acute situation must be emphasized. The importance of early treatment should be included in the information to high risk patients emphasizing that calling the EMS once too often might be less serious than not calling.

Spouses/partners ought to be included in information- giving about AMI, as significant others may play a vital role in the patients' decision-making process.

Though individual counselling to high risk patients is most important, some information is also necessary to the public. In such public education it has to be taken into account the possibility of causing unnecessary worries in healthy individuals.

7 CONCLUSIONS

Prehospital delay was too long for many women and men, with no statistically significant gender differences. However, aspects influencing the decision to seek medical assistance varied between the genders. Both women and men had an illness behaviour that increased prehospital delay and many respondents used other options than calling the EMS in the acute situation. Our results suggest that men's partners have a more discouraging influence on the patients' decision process than women's partners. Women were more likely than men to report atypical symptoms as well as a higher number of AMI symptoms. However, the most frequently reported symptoms were equal between the genders. Attribution of symptoms as cardiac was influenced by cognitive aspects in both genders, but acute symptoms and medical history influenced women and men differently.

Women were more likely than men to report symptoms the year before the AMI, and almost half the respondents had experienced chest symptoms. These early warning symptoms were associated with symptoms that occurred during the acute stage of AMI, with some differences between the genders. Women and men differed in responses to these early warning symptoms, and younger men differed from older men. Greater awareness of early warning symptoms might be a tool to an early diagnosis of CHD.

8 SUGGESTIONS FOR FURTHER RESEARCH

Aspects influencing the attribution of symptoms have been scarcely investigated, and more gender specific knowledge is necessary. Knowledge about the progression of symptoms and how these influence the patients' interpretation and illness behaviour is also necessary. It is vital to understand how the patients interpret their symptoms and what make them assess a situation as serious enough to seek medical assistance. Knowledge about attitudes towards using the emergency phone number in the Norwegian population is necessary to reduce prehospital delay.

Gender specific aspects are necessary and differences between younger and older men in symptom presentation and symptom attribution need to be further investigated.

Further research is necessary to better understand how symptoms the year before the AMI might be associated with symptoms in the acute phase.

New intervention strategies should be tested, targeting women and men at risk of coronary disease as well as their families.

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Prehospital delay, contributing aspects and responses to symptoms among Norwegian women and men with first time acute myocardial infarction

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Abstract

Background: In patients with acute myocardial infarction (AMI), the delay between the onset of symptoms and hospital admission is a critical factor in reducing morbidity and mortality.
Aims: To assess gender differences in prehospital delay among women and men with first time AMI, generate more knowledge about aspects influencing this delay and investigate responses to acute symptoms.
Methods and result: Of 738 eligible patients, 149 women and 384 men responded to a questionnaire (72%). Over half of both women and men waited over one hour before they called for medical assistance and more than half the patients had a total prehospital delay exceeding two hours. Rapid development of symptoms and symptoms matching expectations reduced, self medication and consulting the spouse increased patient delay in both genders. Calling the Emergency Medical Service (EMS) reduced and calling a general practitioner increased total prehospital delay in both genders.
ST-elevation: (STEMI), symptoms experienced as unbearable and attributed as cardiac reduced patient delay, and symptoms from the back, shoulders or between scapulae increased prehospital delay, only in men.
Conclusion: How patients responded to symptoms had vital impact on prehospital delay among both genders, but the experience and interpretation of symptoms had more influence in men than in women.

Keywords: Acute myocardial infarction; Prehospital delay; Gender (sex) differences

1. Introduction

The efficacy of thrombolysis and percutaneous coronary intervention (PCI) in reducing morbidity and mortality in acute myocardial infarction (AMI) is well documented [1–4]. For maximal benefit of this treatment, patients must recognize cardiac symptoms and seek prompt medical assistance. According to international guidelines, the patients' decision time should not exceed 45 min and reperfusion therapy should be performed within 90 min after the onset of symptoms [5]. The period between the onset of symptoms to the decision to call for medical assistance, patient delay, remains by far the most significant cause of total prehospital delay [6–8]. Reported median prehospital delay time from symptom onset to hospital arrival ranges from 1.6 to 4 h and more in Western countries [6–19].

There are conflicting data whether there are gender differences in prehospital delay, as well as whether there are gender differences in the associated factors. Suggestions include the possibility that older age, self medication, a mismatch between symptoms experienced and those expected, consulting a family member and calling a non-Emergency Medical System (EMS) contribute to increased prehospital delay [10,14,15,17,20–24].

Interventions to reduce prehospital delay have not been particularly successful [18], and a new approach in public

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health campaigns has been suggested [19,25]. The process from symptom onset until hospital admission is complex, and how patients make sense of their symptoms and determine whether they need urgent help, are aspects that need to be more investigated in greater detail.

The aim of the study was to assess gender differences in prehospital delay among Norwegian women and men with first time acute myocardial infarction (AMI), their responses to acute symptoms, and the aspects influencing their decision to seek medical assistance.

2. Methods

Patients under 76 years admitted to the coronary care unit with their first AMI, with ST-elevation (STEMI) and non ST-elevation (NSTEMI), between February 2003 and March 2004 were invited to participate, and questionnaires were sent by mail within two weeks after hospital discharge. The diagnoses of patients with first time AMI was based on serum cardiac troponin beyond cut off, electrocardiogram changes with ST-segment elevation, ST-segment depression or T wave abnormalities, and a history of clinically appropriate symptoms.

The patients were consecutively recruited from the coronary care units in five Norwegian hospitals, two University hospitals with 900–1200 beds and three district hospitals with 200–400 beds, with emergency medical function for the surrounding urban and rural areas. Patients being hospitalized, or staying in another health institution at symptom onset, were not invited.

The questionnaire was sent to 777 patients. Of them 39 patients were excluded due to information in the questionnaire, the medical records, information from relatives and the National Death Register. This exclusion was due to incorrect diagnosis (twenty patients), coincident serious mental health problems (four patients), age over 75 years (five patients) and death (ten patients).

The questionnaire was developed by the researcher, and the validation of the questions was based upon a previous qualitative study [26], a quantitative study [27], a pilot study on twenty AMI patients in 2002 and research published on the topic.

The questionnaire included 48 items, with patient characteristics, medical history, experiences and responses to acute symptoms prior to hospitalization and prehospital delay. Acute symptoms were classified as early when experienced initially; the first occurring symptoms, and late when experienced after the onset of other initial symptoms. This question had multiple-choice alternatives. Chest symptoms were described as pain, discomfort, pressure and tightness, several classifications permitted. Musculoskeletal symptoms were defined as pain between the scapulae, or in the back or shoulders. The incentive for this definition was that such symptoms are often associated with musculoskeletal problems. Typical symptoms were defined as experiencing chest symptoms without symptoms from back, shoulders or between scapulae. They also graded the intensity (unbearable, moderate or strong) and symptom progress, whether or not the symptoms corresponded with expectations on a cardiac origin, and finally stated whether they attributed their acute symptoms to the heart, abdomen, musculoskeletal system, flu or stress, one or more alternatives permitted. Time and day at symptom onset, place of residence and activity at symptom onset was also included. Prehospital delay comprised two questions: time from symptom onset to call for medical assistance (patient delay) and time from symptom onset to hospital arrival (total prehospital delay). Patient delay was classified into 13 categories, from under ½ h to over 24 h. Prehospital delay was classified into 14 categories, from under one hour to over 24 h, to obtain more detailed information on prolonged delay. Responses to acute symptoms included self medication with pain killers, tranquilizers or nitroglycerin. Consulting other lay persons before calling for medical assistance included spouse, other members of the family and friends/colleagues. Arrangement for medical assistance included general practitioner, Emergency medical system (EMS) and own transportation to the hospital. Some of the patients had used more than one alternative, and in the regression analysis patients using exclusively one method were analyzed. Positive family history was defined as having siblings or parents who had suffered an AMI before 60 years of age. Hypercholesterolemia, hypertension and diabetes were defined as being diagnosed by a physician and medically treated for these conditions, based upon information in the questionnaire. Distance to hospital was classified into six categories between under 10 km and over 50 km. A folder with information about the study was given to the patients while in hospital. Patients not responding to the invitation received a reminder letter. Patients who agreed to participate were asked to give their written consent about the participation and permission to obtain information from their medical records. They were requested to call the principal researcher if items in the questionnaire were difficult to understand. The calculation of sample size was based on data from a previous study on prehospital delay [27] with power 0.80, mean 3.0 vs. 3.5 h and standard deviation 1.7. The sample size required was 448 patients.

The rationale behind the analysis of the data was that symptoms associated with musculoskeletal symptoms, symptom appraisals, expectations and attributions of symptoms and self care interventions influenced patient delay, and that chest symptoms and methods for calling for medical assistance influenced further in the delay process. As we hypothesize that symptoms associated with the musculoskeletal system might have an impact on both the patients' decision process and health professionals' interpretation of symptoms, we analyzed this aspect according to both patient delay and prehospital delay.

The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the Regional Ethics Committee for Medical Research in Norway.

2.1. Data analyses

The analyses were conducted with SPSS for Windows version 11.5 (SPSS Inc. Chicago, Illinois). Twin-tailed chi

square tests were used to compare patient characteristics among women and men. Logistic regression adjusted for age (classified into four categories), education and employment was used to analyze aspects contributing to patient delay and also adjusted for distance to hospital (classified into four categories) regarding total prehospital delay. The rationale for these adjustments (the three first variables) was to avoid bias, due to gender differences in these characteristics. Variables included in the regression analysis were those who were statistically significant in the univariate tests. Musculoskeletal symptoms were also analyzed in a model in which symptoms from chest and left arm, dyspnoea and nausea, were additionally included. Power analysis was included for some of the variables (unadjusted) associated with delay. Continuous variables are presented as mean (SD). *P*-values <0.05 or 95% CI that excluded the null value were considered statistically significant.

3. Results

3.1. Characteristics of study objects

Of 738 eligible patients 533 (149 women and 384 men, 67% vs. 74%) responded. Mean age was 61.2 (9.8) years for the women and 58.5 (9.5) years for the men. Mean age for non-responders was 59.0 (10.4) years. Non-responders did not differ significantly to responders regarding gender. Hypertension and hypercholesterolemia were significantly more frequent in women than in men. There were no gender differences as to prescribed Nitroglycerin, previously diagnosed angina and positive family history (Table 1). Information about infarct location and STEMI has been previously reported [28]. Among the patients on social security, 96% of the women and 93% of the men were retired or had health related pension.

Table 1
Patient characteristics, medical history and gender differences among Norwegian women and men with first time AMI

	Women $n=149$(%)	Men $n=384$(%)	p
Age: (years)			
≤45	9(6)	44(11)	0.061
46–55	33(22)	108(28)	0.160
56–65	48(32)	150(39)	0.142
66–75	59(40)	82(21)	<0.01
Education			
≤10 years	89(60)	127(33)	<0.01
11–13	36(24)	148(39)	<0.01
≥14	13(9)	102(27)	<0.01
Employment			
Full time	29(19)	229(60)	<0.01
Part time	20(13)	23(6)	<0.01
On social security	96(64)	140(36)	<0.01
Marital status			0.04
Married/cohabitant	97(65)	304(79)	
Single	52(35)	80(21)	
Living alone	39(26)	70(18)	0.04
Medical history			
Hypertension	57(38)	113(30)	0.046
Hypercholesterolemia	39(26)	57(15)	<0.01
Diabetes	12(8)	27(7)	0.684
Prescribed Nitroglycerin	19(13)	43(11)	0.616
Previously diagnosed angina	20(13)	50(13)	0.902
Positive family history	55(37)	133(35)	0.621
Infarct location			
Anterior	50(34)	119(31)	0.598
Posterior	46(31)	152(40)	0.055
Other	52(35)	108(28)	0.136
STEMI*	75(55)	216(62)	0.162
NSTEMI *	61(45)	132(38)	0.162

* $n=136$ vs. 348.

Table 2
Patient delay, total prehospital delay and gender differences among women and men with first time myocardial infarction

	Patient delay			Total prehospital delay		
	Women	Men	p	Women	Men	p
	$n=140$(%)	$n=376$(%)		$n=142$(%)	$n=374$(%)	
≤1 h	62(44)	178(47)	0.536	29(20)	86(23)	0.531
1–2 h	16(11)	49(13)	0.626	39(27)	97(26)	0.725
2–6 h	32(23)	52(14)	0.014	42(30)	94(25)	0.306
>6 h	30(21)	97(26)	0.306	32(22)	97(26)	0.426

3.2. Patients' responses to acute symptoms

Self medication was reported among 33% of the women and 25% of the men ($p=0.066$): the use of pain killer in 19% vs. 14% ($p=0.2$), nitroglycerin in 15% vs. 12% ($p=0.34$) and tranquilizers in 1% vs. 2% ($p=0.57$). Other self-care interventions were sitting down (54% vs. 65%, $p=0.045$) and lying down (43% vs. 46%, $p=0.5$).

Consulting a lay person before calling for medical assistance was reported by 84% of all the patients; the spouse in 52% of the women and 66% of the men ($p=0.012$), other family members in 33% vs. 19% ($p<0.01$) and friends/colleagues in 19% vs. 22% ($p=0.4$).

3.3. Calling for medical assistance

More than half of both women and men called exclusively a GP (53% vs. 52%, $p=0.81$), while 26% vs. 30% called the EMS ($p=0.388$) and 7% vs. 8% ($p=0.597$) went to the hospital by own transportation. Some of the patients used more than one alternative, 9% of the women and 8% of the men called both EMS and GP and 5% vs. 2% called a GP before they went to the hospital by own transportation. Age had no significant influence on how the patients arranged for medical assistance.

3.4. Patient delay and total prehospital delay

More than half the patients waited more than an hour before they called for medical assistance, and more than half the patients had a total prehospital delay exceeding two hours. More women than men had a patient delay between 2 and 6 h (Table 2). A very short patient delay (<½ h) was

Table 3
Patient delay </> one hour and patient characteristics among women and men with first time myocardial infarction

	Patient delay among women			Patient delay among men		
	≤1 h	>1 h	OR (CI)	≤1 h	>1 h	OR (CI)
	n=62(%)	*n*=78(%)		*n*=178(%)	*n*=198(%)	
STEMI *	34(62)	35(49)	0.65(0.30–1.44)	108(69)	108(58)	0.60(0.38–0.96)
NSTEMI *	21(38)	37(51)	1.53(0.69–3.37)	48(31)	77(42)	1.66(1.04–2.65)
Symptoms						
Musculoskeletal early	30(48)	35(49)	0.84(0.41–1.73)	50(28)	80(40)	1.66(1.06–2.60)
Symptom appraisal						
Unbearable symptoms	32(52)	38(49)	0.73(0.35–1.52)	82(46)	63(32)	0.50(0.33–0.78)
Rapid development	52(84)	43(55)	0.14(0.05–0.37)	134(75)	101(51)	0.29(0.18–0.47)
Matches expectations	30(48)	26(33)	0.42(0.19–0.90)	95(53)	67(34)	0.43(0.28–0.66)
Attributed cardiac	34(55)	38(49)	0.66(0.32–1.36)	113(63)	91(46)	0.46(0.30–0.71)
Responses to symptoms						
Self medication totally	14(23)	33(42)	2.79(1.23–6.33)	30(17)	62(31)	2.42(1.45–4.03)
Taking pain killer	7(11)	21(27)	3.87(1.32–11.3)	11(6)	42(21)	4.02(1.98–8.14)
Consulting spouse	27(43)	48(61)	2.34(1.11–4.96)	103(58)	146(74)	2.06(1.31–3.23)

* *n*=55 vs. 72 in women and 156 vs. 185 in men.
Adjusted OR (95% CI) for age, education and employment.

reported among 23% of the women and 28% of the men ($p=0.271$) and a very long patient delay (>24 h) was reported among 11% vs. 10% ($p=0.84$). Age had no significant impact on delay.

Self medication and particularly the use of pain killers as well as consulting the spouse increased, and rapid development of symptoms and symptoms matching expectations reduced patient delay among both genders (Table 3). ST-elevation (STEMI), symptoms experienced as unbearable and attributed as cardiac reduced patient delay only in men.

Calling the EMS reduced and calling a GP increased total prehospital delay among both genders (Table 4). Musculoskeletal symptoms increased both patient delay and total prehospital delay only among men, and were statistically significant also in regression analyses including symptoms from chest, left arm, dyspnoea and nausea. In these analyses of patient delay and musculoskeletal symptoms experienced initially, odds ratio (OR) was 1.77 (95% CI 1.14–2.73), and in the analyses of total prehospital delay OR was 2.08 (95% CI 1.28–3.38) for initially symptoms, and 1.64 (95% CI 1.03–2.61) for musculoskeletal symptoms experienced totally. Experiencing chest symptoms as well as typical symptoms (chest without musculoskeletal symptoms) had no significant influence on patient delay and total prehospital delay, and neither had age, infarct location, diagnosed angina, prescribed nitroglycerine, positive family history, consulting other persons than the spouse, activity, place of residence, day of the week or time of day.

4. Discussion

In this patient sample less than half the patients reached the hospital within two hours, and no gender differences were found regarding prehospital delay. Musculoskeletal symptoms, as defined in the methods, increased prehospital delay only in men.

We classified prehospital delay time into 14 categories between ½ and 24 h or more, because we hypothesized that it might be difficult to recall the exact time. Both patient delay and total prehospital delay time in our study are similar or somewhat shorter than in other comparable studies [7,15,19,21,23,29]. More than half of the patients in this study had a prehospital

Table 4
Total prehospital delay </> two hours and patient characteristics among women and men with first time acute myocardial infarction

	Prehospital delay among women (*n*=142)			Prehospital delay among men (*n*=374)		
	≤2 h	>2 h	OR(CI)	≤2 h	>2 h	OR(CI)
	n=68(%)	*n*=74(%)		*n*=183(%)	*n*=191(%)	
Symptoms						
Chest totally	58(85)	66(89)	1.49(0.46–4.87)	170(93)	176(92)	1.14(0.46–2.83)
Chest-typical	32(47)	24(32)	0.68(0.29–1.57)	110(60)	98(51)	0.67(0.42–1.07)
Musculoskeletal early	27(38)	39(53)	1.37(0.62–3.04)	51(28)	78(41)	2.15(1.31–3.53)
Musculoskeletal totally	31(46)	48(65)	1.92(0.85–4.38)	62(34)	85(44)	1.71(1.06–2.76)
Calling for assistance						
General practitioner	25(38)	52(71)	4.97(2.05–12.03)	65(36)	124(65)	3.73(2.30–6.07)
Emergency call (EMS)	25(37)	11(15)	0.30(0.11–0.77)	73(40)	41(21)	0.34(0.20–0.58)

Adjusted OR (95% CI) for age, education, employment and distance to hospital.

delay that contributed to a reduced efficacy of reperfusion therapy, according to international guidelines [5]. There are conflicting data whether there are gender differences in prehospital delay. Our findings that neither gender nor age was associated with delay are consistent with others reports [10,20,21,24,30]. Others reporting prolonged delay among older patients, particularly women [9,13,15,22,23], included older patients than we did, and this might explain the different findings.

Our findings agree with other published reports that calling EMS reduces, and calling a GP increases prehospital delay [9,17,21,24,30]. According to a Danish study [6] half the patients calling a physician were delayed by wrong advice or misinterpretation.

Rapid development of symptoms, symptoms matching expectation, symptoms attributed as cardiac and self medication influencing prehospital delay is consistent with previous reports [6,9,10,14,17,20,21,24,27,30–32]. Nevertheless, no other reports have shown whether symptom attribution has less influence on women's delay. In power analysis regarding cardiac attribution among women, a sample of 2160 was required to achieve a power 0.80, which indicated that the negative result may be due to a lack of statistical power. However, with the sample size required, the clinical significance may be questioned.

Experiencing musculoskeletal symptoms as well as unbearable symptoms have not been reported so far to influence prehospital delay. Whether musculoskeletal symptoms have a more significant influence in men than in women, and whether these symptoms are most important when they are experienced initially, needs to be carefully assessed. Whether the intensity and attribution of symptoms have no influence on women's delay is of vital interest to better understand the decision process.

That most patients consulted a lay person about their symptoms, and men more likely than women consulted their spouse is in agreement with another study [19] as is increased delay by consulting the spouse [33]. Spouses that involved themselves in self medication rather than quickly recommending their partner to seek medical assistance, has been reported [34].

ST-elevation (STEMI) contributing to a reduced prehospital delay has been reported [15]. As information about STEMI was missing for some patients, the negative result regarding women's delay might be due to the sample size. In power analysis a sample of 460 women was required to achieve a power 0.80, which indicate that we cannot disregard an association between STEMI and patient delay in both genders.

Our findings demonstrated some major gender differences in patient characteristics, which demonstrate the importance of adjusting for such variables in data analysis.

4.1. Limitations

We cannot comment on aspects related to the oldest AMI patients because we imposed an age limit of 76 years. The patients' experiences of symptoms were elicited retrospectively within two weeks after hospital discharge, with the possibility of inaccuracy. However, this possibility would be similar among women and men. The patient population did not differ from non-responders as to age and gender, but any differences regarding clinical conditions which might have influenced the symptom experience are unknown. Due to the lower number of female participants, some of the difference between women and men may be due to lack of statistical strength in the female population. The strength of this study, however, is that it was a population-based sample, including public hospitals of various sizes. These hospitals were the only options for AMI patients in the acute setting in the regions in Norway we studied. All patients experienced a first time AMI, verified by the patients' medical records. The response rate was considered high (72%) which reduced selection bias.

5. Conclusions and clinical implications

Over half of both women and men waited over an hour before they called for medical assistance, and more than half the patients had a prehospital delay exceeding two hours. There were no clinical important gender differences in patient delay and total prehospital delay. Musculoskeletal symptoms, the experience of symptoms and how these were interpreted and assessed, had a stronger impact in men than in women. These gender differences are important to better understand the patients' decision process. Altering public perception of AMI and the importance of seeking early treatment is a complex undertaking which demands thorough implementation plans. Nurses who care for patients with coronary artery diseases are in a unique position to guide and inform patients and their families about interpretations of symptoms, and stress the importance of using EMS and not contact their GP if AMI is suspected.

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Paper IV

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Early Warning Signs of an Acute Myocardial Infarction and Their Influence on Symptoms During the Acute Phase, With Comparisons by Gender

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ABSTRACT

Background: Identifying early warning signs of an acute myocardial infarction (AMI) may aid in the early diagnosis of coronary artery disease.

Objectives: This study was conducted to assess early warning signs (prodromal symptoms) of AMI, with comparisons made by gender. Another aim was to determine whether these early warning signs had any influence on the patients' acute symptoms of AMI.

Methods: This was a multicenter, cross-sectional study of Norwegian patients (aged ≤75 years) hospitalized with their first AMI. A self-administered questionnaire was used to gather information on prodromal symptoms, defined as pain in the chest, pain in the shoulder or back, radiating pain or numbness in the arms, dyspnea, and fatigue. Symptoms were reported for the year before AMI and during the acute stage. Logistic regression analyses were used to examine the association between prodromal symptoms and acute symptoms and the effect of medical history (hypertension, diabetes, and hypercholesterolemia).

Results: The self-administered questionnaire had a 72% response rate; the study included 149 women and 384 men diagnosed with first-time AMI. Symptoms occurring during the year before AMI included pain in the chest in 45% (240/533), shoulder or back pain in 51% (270/533), arm pain in 38% (205/533), dyspnea in 33% (176/533), and fatigue in 62% (330/533). There were no statistically significant gender differences. The risk of experiencing chest symptoms in the acute phase was >5 times higher in women who had experienced prodromal symptoms in the chest (adjusted odds ratio [OR] = 5.11; 95% CI, 1.38–18.88) and nearly 3 times higher in men (OR = 2.80; 95% CI, 1.17–6.70). The risk of experiencing shoulder or back pain was almost 5 times higher in men with prodromal shoulder or back pain (OR = 4.96; 95% CI, 3.01–8.19), but no statistically significant association was found in women. The risk of experiencing radiating arm pain or numbness in the acute phase was more than doubled in women with prodromal arm pain (OR = 2.68; 95% CI, 1.19–6.20) and more than tripled in men with prodromal arm pain (OR = 3.11; 95% CI, 1.90–5.07). The risk of experiencing dyspnea in the acute phase was more than doubled in women with prodromal dyspnea (OR = 2.67; 95% CI, 1.25–5.71) and >5 times higher in men with prodromal dyspnea (OR = 5.73; 95% CI, 3.42–9.62). Finally, the risk of fatigue was almost tripled in women (OR = 2.97; 95% CI, 1.28–6.85) and more than doubled in men (OR = 2.51; 95% CI, 1.54–4.11). Hypertensive women, but not men, were less likely to experience chest symptoms in the acute phase (OR = 0.29; 95% CI, 0.10–0.82).

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Conclusions: Almost half of the study patients (45%) experienced prodromal chest symptoms the year before their first AMI. These prodromal symptoms predicted the symptoms that occurred during the acute stage of AMI, with some differences between the sexes. (*Gend Med.* 2009;6:444–453) © 2009 Excerpta Medica Inc.

Key words: prodromal symptoms, acute myocardial infarction, cardiac disease, gender.

INTRODUCTION

Despite several years of research on prevention and treatment, coronary artery disease (CAD) is still the leading cause of death and disability for both women and men in many countries.[1] Various prodromal symptoms have been reported among many patients with acute myocardial infarction (AMI), so focusing on patients with these symptoms might be a way to diagnose and treat CAD early, thereby preventing or impeding the progression to AMI. According to Bahr et al,[2] recognition of individuals with possible prodromal symptoms of AMI is a critical but poorly recognized and underreported issue that could result in an earlier response before a potential AMI.

In a review of 28 retrospective and prospective studies,[2] the most commonly reported prodromal symptoms in both women and men were chest pain (49%), dyspnea (25%), and fatigue (37%). In a retrospective study that included 515 women,[3] chest discomfort was reported in 30%, fatigue in 71%, dyspnea in 42%, and anxiety in 35%. Patients experienced these symptoms for a mean of 4 to 6 months before the AMI.

Knowledge about prodromal symptoms in high-risk populations, such as those with hypertension, diabetes, and hypercholesterolemia, is, however, limited. In addition, few studies have included a gender perspective, although 1 older study reported a higher prevalence of prodromal symptoms in women than in men during the last 48 hours before the AMI.[4]

Women experience their first AMI about 9 years later than men, but by the seventh decade of life, women and men approach equal prevalence rates.[5] It is not fully understood why women of childbearing age have a lower risk of cardiac events,[6] but it has been suggested that the difference in age at first AMI is largely explained by the higher risk-factor levels in younger men compared with younger women.[7] Women have poorer outcomes once they experience an AMI, however, particularly if they are aged <60 years.[8]

Angina pectoris is the most common clinical manifestation of CAD, but the management of stable angina pectoris has not been subjected to the same scrutiny in large clinical trials as that of acute coronary syndromes, including unstable angina and AMI.[9] A systematically lower utilization of treatments and diagnostic procedures in women than in men with chronic stable angina has been reported.[10] The gender differences in the management of angina might be explained by the perception that women are at lower risk than men, which may result in a lack of attention to early warning signs and symptoms.[11] Some data indicate that physicians are more likely to classify women in a lower risk category for cardiovascular disease than men.[12]

Whether prodromal symptoms have any influence on the symptoms in the acute phase of AMI has rarely been investigated. However, it has been reported that prodromal symptoms may predict the severity of AMI symptoms.[3] When an AMI occurs, patients must seek medical assistance rapidly for optimal treatment. Early interventions are necessary to reestablish blood flow to an obstructed coronary artery and to minimize the cardiac damage. Reduced mortality has been reported in patients treated within the first 2 hours after symptom onset compared with those treated later.[13] Even after decades of public-education campaigns aimed at decreasing these delay times, however, most patients still do not seek treatment in a timely manner.[14,15] Recognizing and identifying early warning signs of AMI may contribute to an early diagnosis of CAD.

The aims of this study were to investigate what types of prodromal symptoms occurred before AMI and how individuals responded to their prodromal symptoms, with comparisons made by gender. Medical history was also reviewed to see whether it was associated with these symptoms

and might be a tool for diagnosing CAD in high-risk patients. An additional aim was to assess whether these prodromal symptoms had any influence on symptoms occurring in the acute phase of an AMI.

METHODS

This was a multicenter, cross-sectional study of Norwegian patients with AMI.

Study Population

The study population consisted of patients hospitalized with their first AMI at 5 coronary care units in Norway over a 13-month period in 2003–2004. Patients were consecutively recruited and were included in the study if they were aged ≤75 years. They were excluded if they were hospitalized or staying in another health institution at symptom onset. The hospitals were chosen to provide geographic diversity and different hospital sizes, and included 2 university hospitals with 900 to 1200 beds and 3 district hospitals with 200 to 400 beds.

The sample size was calculated with the statistical program nQuery (2-sample *t* test; Statistical Solutions Ltd., Cork, Ireland) based on data from a previous study on prehospital delay,[16] with a power of 0.80, mean (SD) prehospital delay of 3.0 (1.5) hours for male patients and 3.5 (1.9) hours for female patients, and $P < 0.05$. It was predicted that the male population would be ~2.5 times larger than the female population. The calculation resulted in a total sample size of a minimum of 448 patients.

Definition of a First-Time Acute Myocardial Infarction

The diagnosis of AMI was based on serum cardiac troponin activity above accepted cutoff values; ischemic ECG changes with ST-segment elevation, ST-segment depression, or T-wave abnormalities; and/or clinically appropriate symptoms. The cutoff value in Norway when the study was conducted was 0.10 µg for troponin T, but different assays with various cutoffs were in use for troponin I at the various study sites. First-time AMI was diagnosed according to the stated definition and without any indication of previous AMI from the patient history, medical records, or ECG findings.

Definition of Prodromal Symptoms

Pain or discomfort in the chest, fatigue, and dyspnea are the most frequently reported prodromal symptoms,[2] but in our study, we included pain or discomfort in the shoulder or back and radiating pain or numbness in the arms.[17] These symptoms, experienced during the year before the AMI, were defined as prodromal symptoms.

Data Collection

All patients were informed about the study while in the hospital, and a questionnaire was mailed to the enrolled patients within 2 weeks after hospital discharge. The patients were carefully instructed to choose the alternative(s) that reflected their prehospital experiences most accurately.

The self-administered questionnaire comprised 48 standardized questions, which asked patients with AMI to describe their prodromal and acute symptoms and how they responded to these symptoms. Content validity for the questionnaire was established by a group of clinical researchers (nurses and physicians) who specialized in acute cardiac care. In addition, the items were based on extensive international literature reviews, a previous study that used in-depth interviews with women with first-time AMI,[17] and a quantitative study of both sexes.[16] A reliability test was computed (Cronbach's α score), and the correlation between symptoms experienced the year before the AMI and symptoms in the acute phase of AMI was 0.796. A pilot study (n = 20) was conducted with AMI patients in 1 university hospital in December 2002 to test the user-friendliness and content of the questionnaire, and no changes were deemed necessary.

The patients were asked to what extent they had experienced the following symptoms during the year before the AMI: pain or discomfort in the chest or shoulder/back, pain or numbness radiating to the arms, dyspnea, or fatigue. The symptoms had response options of "none," "some," "rather much," and "very much." The total of positive symptoms was used in the analyses. The patients were also asked to describe their level of activity when they

experienced these prodromal symptoms, and the response options were after "no activity," "minor activity," "major activity," and "onset at night." The level of reported activity represented the patients' own assessment of the situation. Patients were also asked whether they had contacted a physician about these symptoms. Fatigue was not included in the questions about activity or contacting a physician because we chose to focus on symptoms that the patients were able to associate with activity. In addition, the patients were asked whether they had experienced anxiety or nervousness.

Finally, the patients were asked to report the symptoms they experienced during the acute setting of the AMI that caused the hospitalization.[18] A list of acute-AMI symptoms was provided, and the patients were asked to answer "yes" or "no" to each symptom.

Baseline characteristics included medically treated hypertension, diabetes, or hypercholesterolemia, as well as angina pectoris diagnosed by a physician during the year before the AMI. Discharge reports for all the patients were obtained from the hospitals, and data from these reports were used to ensure that the participants met the inclusion criteria.

Ethical Considerations

Participants gave written informed consent and permission to obtain information from their medical records. The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the Regional Ethics Committee for Medical Research in Norway.

Data Analysis

The results are presented as the mean (SD) and range for continuous variables and percentages for proportions. Descriptive statistics were used to present the frequencies of prodromal symptoms (contingency tables), and 2-tailed χ^2 tests were used to compare patients' characteristics between women and men. Multivariate binary analyses were used to examine how medical history (hypertension, diabetes, and hypercholesterolemia) was associated with prodromal symptoms. A stepwise logistic regression was performed with medical history as the outcome variable; each prodromal symptom, age, anxiety, and previously diagnosed angina were entered into the model. The results are expressed as odds ratios (ORs) and 95% CIs. The same regression analysis was used to explore the association between prodromal and acute symptoms. The outcome variables in these analyses were acute symptoms, and each of these was entered into the model with 1 prodromal symptom in addition to age, ST-segment elevation myocardial infarction (STEMI), anxiety, hypertension, and previously diagnosed angina. Both adjusted and unadjusted (crude) ORs are presented. The data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois). $P < 0.05$ or a 95% CI that excluded the null value was considered statistically significant.

RESULTS

Patient Characteristics

In all, 777 patients were initially included in the study and received a questionnaire. However, 39 patients were excluded because of incorrect diagnosis (20 patients), coincident serious health problems (4), age >75 years (5), and death (10). Of 738 eligible patients, 533 patients responded to the questionnaire and were included in the study (response rate 72%).

The group included 149 women (28%) and 384 men (72%). Women had a mean (SD) age of 61.2 (9.8) years, and men had a mean age of 58.5 (9.5) years. Hypertension was reported in 38% (57/149) of the women and in 30% (114/384) of the men (P = NS), diabetes in 8% (12/149) and 7% (27/384) (P = NS), and hypercholesterolemia in 26% (39/149) and 15% (57/384) ($P < 0.01$), respectively. Previously diagnosed angina was reported in 13% (70/533) of both sexes combined. Mean age for the nonresponders was 59.0 (10.4) years, and these patients did not differ significantly from the responders in terms of sex distribution.

Symptoms During the Year Before Acute Myocardial Infarction

No statistically significant gender differences were found in the prevalence of the 5 prodromal

symptoms (**Table I**). Women were more likely than men to report a stronger degree of fatigue, however; 38% (56/149) of the women versus 19% (73/384) of the men reported "rather much" or "very much" fatigue ($P < 0.01$). A combination of symptoms in the chest and dyspnea was reported in 21% (113/533) of women and men combined. Most of the patients reported that they had experienced at least 1 prodromal symptom; this was significantly more common in the women (84% [125/149]) than in the men (76% [292/384]) ($P < 0.05$). Women were significantly more likely than men to report being anxious or nervous (both, $P < 0.01$; **Table I**).

Table I. Reported symptoms the year before the acute event among women and men with first-time acute myocardial infarction, and differences between the sexes. Data are no. (%) of patients.

Symptoms	Women (n = 149)	Men (n = 384)	Total (N = 533)	*P**
Chest	65 (44)	175 (46)	240 (45)	0.685
Shoulder, back	85 (57)	185 (48)	270 (51)	0.066
Arms	67 (45)	138 (36)	205 (38)	0.066
Dyspnea	56 (38)	120 (31)	176 (33)	0.159
Fatigue	101 (68)	229 (60)	330 (62)	0.082
Anxiety	52 (35)	65 (17)	117 (22)	<0.01
Nervousness	71 (48)	121 (32)	192 (36)	<0.01

*χ^2 test.

Chest symptoms, pain in the shoulder or back, and radiating pain or numbness in the arm(s) most commonly occurred after minor activity (**Table II**). Among patients who reported chest symptoms after minor activity, 23% (22/96) of both sexes combined had previously diagnosed angina. Men were significantly more likely than women to experience dyspnea after major activity ($P < 0.01$). No other significant gender differences were found regarding the activity that triggered other prodromal symptoms or the proportions of patients who contacted a physician about these symptoms. Women were most likely to contact a physician for chest symptoms, and men for shoulder or back symptoms (**Table II**). Among men with chest symptoms, those aged ≥66 years (41% [15/37]) were significantly more likely than younger men (20% [27/136]) to contact a physician for these problems ($P < 0.01$). Age had no statistically significant influence in women, and education had no effect in either sex regarding physician contact for these chest symptoms. Both women and men who experienced anxiety and nervousness were significantly more likely than patients without these symptoms to report chest symptoms (for anxiety, 59% [69/117] vs 41% [48/117]; $P < 0.01$; for nervousness, 55% [105/192] vs 45% [87/192]; $P < 0.01$).

Prodromal Symptoms and Influence on Acute Symptoms

In general, patients who experienced symptoms in the chest, pain in the shoulder/back, pain or numbness in the arms, dyspnea, and fatigue during the year before the AMI had an increased risk of experiencing similar symptoms during the acute phase of AMI (**Table III**). The risk of experiencing chest symptoms in the acute phase was >5 times higher in women who had experienced prodromal symptoms in the chest (adjusted OR = 5.11; 95% CI, 1.38–18.88) and nearly 3 times higher in men with similar prodromal symptoms (OR = 2.80; 95% CI, 1.17–6.70). The risk of experiencing shoulder or back pain was almost 5 times higher in men with prodromal shoulder or back pain (OR = 4.96; 95% CI, 3.01–8.19), but no statistically significant association was found in women. The risk of experiencing radiating arm pain or numbness in the acute phase was more than doubled in women with prodromal arm pain (OR = 2.68; 95% CI, 1.19–6.20) and more than tripled in men (OR = 3.11; 95% CI, 1.90–5.07). The risk of experiencing dyspnea in the acute phase was more than doubled in women with prodromal dyspnea (OR = 2.67; 95% CI, 1.25–5.71) and >5 times higher in men with prodromal dyspnea (OR = 5.73; 95% CI, 3.42–9.62). Finally, the risk of fatigue was almost tripled in women (OR = 2.97; 95% CI, 1.28–6.85) and more than doubled in men (OR = 2.51; 95% CI, 1.54–4.11). Among women who experienced at least 1 prodromal symptom, 36% (45/125) reported that the symptoms in the acute phase developed gradually, compared with 13% (3/24) among those who had no prodromal symptoms ($P = 0.029$). The same

Table II. Prodromal symptoms, triggering activity, and contact with a physician among patients the year before a first-time acute myocardial infarction, and differences between the sexes.* Data are no. (%) of patients.

	Chest Symptoms			Shoulder, Back Pain			Arm Pain			Dyspnea		
Trigger	Women (n = 65)	Men (n = 172)	$P^{\dagger}$	Women (n = 85)	Men (n = 185)	$P^{\dagger}$	Women (n = 66)	Men (n = 137)	$P^{\dagger}$	Women (n = 56)	Men (n = 119)	$P^{\dagger}$
Minor activity	26 (40)	70 (41)	0.828	32 (38)	76 (41)	0.569	25 (38)	55 (40)	0.787	20 (36)	32 (27)	0.265
Major activity	15 (23)	52 (30)	0.264	12 (14)	41 (22)	0.118	10 (15)	32 (23)	0.176	14 (25)	57 (48)	<0.01
Onset at night	8 (12)	12 (7)	0.192	10 (12)	21 (11)	0.933	12 (18)	15 (11)	0.161	5 (9)	5 (4)	0.220
Contacted a physician	20 (31)	42 (24)	0.309	23 (27)	64 (35)	0.208	16 (24)	27 (20)	0.459	11 (20)	26 (22)	0.739

*Some respondents did not answer the questions about triggering activity; therefore the numbers for chest symptoms, arm pain, and dyspnea are smaller than in the other tables. Fatigue was not included in the questions about activity or contacting a physician.
$^{\dagger}\chi^2$ test.

Table III. Prodromal symptoms and the risk of experiencing similar symptoms during the acute phase among women and men with first-time acute myocardial infarction.* Data are no. (%) of patients, except as indicated.

	Similar Acute Symptoms			
Prodromal Symptoms	Yes	No	Crude OR (95% CI)	Adjusted OR (95% CI)
Women				
Chest symptoms (n = 65)	62 (95)	3 (5)	5.64 (1.58–20.08)	5.11 (1.38–18.88)
Shoulder, back pain (n = 85)	45 (53)	40 (47)	2.30 (1.17–4.52)	1.90 (0.94–3.83)
Arm pain (n = 67)	44 (66)	23 (34)	1.91 (1.19–6.20)	2.68 (1.19–6.20)
Dyspnea (n = 56)	38 (68)	18 (32)	4.02 (1.99–8.15)	2.67 (1.25–5.71)
Fatigue (n = 101)	56 (55)	45 (45)	3.73 (1.74–8.00)	2.97 (1.28–6.85)
Men				
Chest symptoms (n = 175)	168 (96)	7 (4)	2.97 (1.24–7.09)	2.80 (1.17–6.70)
Shoulder, back pain (n = 185)	96 (52)	89 (48)	5.63 (3.50–9.06)	4.96 (3.01–8.19)
Arm pain (n = 138)	95 (69)	43 (31)	2.92 (1.88–4.53)	3.11 (1.90–5.07)
Dyspnea (n = 120)	74 (62)	46 (38)	4.46 (2.82–7.05)	5.73 (3.42–9.62)
Fatigue (n = 229)	109 (48)	120 (52)	2.90 (1.84–4.55)	2.51 (1.54–4.11)

OR = odds ratio.
*Logistic regression analyses adjusted for age, anxiety, hypertension, angina, and ST-segment elevation myocardial infarction.

association was found in men (39% [113/292] vs 9% [8/92], respectively; $P < 0.01$).

High-Risk Status and Influence on Symptoms

Twenty-four percent of both women and men who reported prodromal chest symptoms and 31% of each sex with a combination of prodromal chest symptoms and dyspnea had been previously diagnosed with angina pectoris. Among the patients with diagnosed angina, 90% (18/20) of the women and 100% (50/50) of the men reported chest symptoms during the acute phase of AMI.

In the logistic regression analyses, hypertensive patients were significantly more likely than nonhypertensive patients to experience prodromal dyspnea (OR = 1.55; 95% CI, 1.03–2.31) and fatigue (OR = 1.60; 95% CI, 1.06–2.43) (**Table IV**). In gender-based analyses, however, dyspnea was asso-

Table IV. Medical history and the risk of experiencing prodromal symptoms among patients with a first-time acute myocardial infarction.* Data are no. (%) of patients, except as indicated.

	Hypertension			Diabetes			Hypercholesterolemia		
Prodromal Symptoms	Yes (n = 171)	No (n = 362)	OR (95% CI)	Yes (n = 39)	No (n = 494)	OR (95% CI)	Yes (n = 96)	No (n = 437)	OR (95% CI)
Chest symptoms	87 (51)	153 (42)	1.08 (0.72–1.62)	22 (56)	218 (44)	1.36 (0.66–2.72)	62 (65)	178 (41)	1.45 (0.86–2.44)
Shoulder, back pain	95 (56)	175 (48)	1.32 (0.90–1.93)	24 (62)	246 (50)	1.48 (0.75–2.92)	56 (58)	214 (49)	1.23 (0.76–2.01)
Arm pain	76 (44)	129 (36)	1.38 (0.93–2.05)	18 (46)	187 (38)	1.21 (0.61–2.38)	41 (43)	164 (38)	0.94 (0.57–1.58)
Dyspnea	73 (43)	103 (28)	1.55 (1.03–2.31)	21 (54)	155 (31)	2.55 (1.32–4.93)	49 (51)	127 (29)	1.79 (1.09–2.95)
Fatigue	121 (71)	209 (58)	1.60 (1.06–2.43)	26 (67)	304 (62)	1.00 (0.48–2.07)	65 (68)	265 (61)	1.04 (0.61–1.76)
None	22 (13)	94 (26)	0.53 (0.29–0.95)	5 (13)	111 (22)	0.27 (0.06–1.13)	9 (9)	107 (24)	0.68 (0.31–1.48)

OR = odds ratio.
*Logistic regression analyses adjusted for age, anxiety, and previously diagnosed angina.

ciated with hypertension in men (OR = 1.91; 95% CI, 1.19–3.07) but not in women (OR = 1.04; 95% CI, 0.49–2.18). Fatigue was not significantly associated with hypertension in gender-based analyses for either women (OR = 1.69; 95% CI, 0.75–3.80) or men (OR = 1.58; 95% CI, 0.97–2.57)

In regression analyses including hypertension, prodromal chest symptoms, previously diagnosed angina, STEMI, anxiety, and age, hypertension was significantly associated with a lower likelihood of acute chest symptoms in women (OR = 0.29; 95% CI, 0.10–0.82). No statistically significant association was found in men (OR = 0.54; 95% CI, 0.24–1.23).

Patients with known diabetes were also significantly more likely to experience prodromal dyspnea compared with patients without diabetes (OR = 2.55; 95% CI, 1.32–4.93) (**Table IV**). No differences were found between the sexes.

There were no significant associations between hypercholesterolemia and prodromal symptoms in the total group of patients with the exception of a weak association between hypercholesterolemia and dyspnea (OR = 1.79; 95% CI, 1.09–2.95). In gender-based analyses, however, hypercholesterolemia was associated with less fatigue in women (OR = 0.32; 95% CI, 0.12–0.83) but not in men (OR = 1.83; 95% CI, 0.92–3.66).

DISCUSSION

AMI-related symptoms occurring the year before the acute event were reported in 84% (125/149) of the women and 76% (292/384) of the men, and these symptoms were found to predict symptoms that occurred in the acute phase.

Limitations of our study include the upper age limit of 75 years; we cannot comment on possible findings in older patients. Including older patients might have revealed more gender differences because AMI develops after the age of 75 years in a substantial number of women. Patients' experiences of AMI symptoms were elicited retrospectively within 2 weeks of hospital discharge, raising the possibility of recall bias. However, according to a qualitative study that included 40 women,[19] the participants indicated that they needed time after the AMI to accurately recall prodromal symptoms. Study participants did not differ from the nonresponders in terms of age or sex, but any differences regarding clinical conditions are unknown.

The strength of this study was the population-based sample including public hospitals of various sizes; public hospitals are the only options for AMI patients in Norway. All patients experienced a first-time AMI, verified by their medical records. Selection bias was reduced by the high response rate (72%).

Our finding that prodromal symptoms increased the risk of experiencing similar symptoms in the acute situation must be assessed carefully because of the limited knowledge about this topic. However, a correlation between prodromal and acute symptoms was reported in a retrospective study that included 515 women.[3] Because prodromal symptoms in this study were defined as symptoms experienced during the year before the AMI—as opposed to symptoms that occurred immediately before the AMI—we believe that the patients were able to distinguish between prodromal and acute symptoms. A qualitative study including 40 women reported that patients with prodromal symptoms were more likely than other patients to experience a gradual progression of symptoms in the acute phase.[19] A gradual progression of AMI symptoms might delay the patients' decision to seek medical help,[20] and this highlights the importance of focusing on prodromal symptoms. Our finding that prodromal chest symptoms predicted acute chest symptoms more significantly in women than in men has not been reported previously and needs further investigation. The gender differences regarding this association suggest the importance of gender-based analyses. Because clinical studies of cardiac patients usually include smaller numbers of women than men, analyses that include the total number of patients typically mask specific findings in women.

The overall prevalence of prodromal chest symptoms in our study (45%) was approximately the same as previously reported (49%), but the prevalence of prodromal dyspnea was higher in our study (33%) than in others (25%).[2] However, the prevalence of prodromal dyspnea in women was almost the same (38%) as reported previously in a study that included only women (42%)[3]; prevalence rates were also similar between the studies for fatigue (68% vs 71%) and anxiety (35% vs 36%). Fatigue is probably the most difficult symptom to evaluate because it may be associated with various conditions. However, fatigue was the most frequently reported prodromal symptom in our study as well as in previous reports,[3,16,19] so this symptom requires greater awareness from the public and from health care providers.

We might expect that all individuals who experience chest symptoms after minor activity would contact their physician. That this decision was not made by all the patients indicates that they did not consider the symptoms a threat to their health. Not recognizing prodromal symptoms as a threat to health might be due to a lack of knowledge, in addition to the fact that these symptoms often evolve slowly.[19] Men were more likely to contact their physician for shoulder or back pain than for chest symptoms, which suggests that chest symptoms were not taken seriously. Younger men were less likely than older men to seek help, and this finding shows that more attention should be paid to the youngest age group. We found that among patients who experienced prodromal chest symptoms after minor activity, only ~1 in 4 (23%) in both sexes had diagnosed angina; this is probably because they were not medically examined.

Further, our study found that high-risk patients must be informed about early warning symptoms of an AMI and must take these symptoms seriously. When these high-risk patients do contact their physician for various symptoms, they must be examined thoroughly for CAD. The lower cardiac risk in women must not result in poor recognition and undertreatment.[8] In a qualitative study of 40 women by McSweeney et al,[21] the women denied their initial symptoms, but later sought medical evaluation of these symptoms. The duration of denial varied, usually depending on the severity and frequency of the symptoms. Only a few of these women reported having any cardiovascular testing before the AMI occurred.

Educating people about their potential risk might also facilitate proper action if an AMI occurs. This information might increase the awareness of symptoms among high-risk patients and reduce delays in obtaining treatment. Because highlighting chest-pain awareness might lead to chest-pain hysteria and a saturation of such patients in emergency departments, all risk factors must be included in the assessment of cardiac risk, and education must be based on these risk factors. According to Bahr,[22] a fundamental change occurs when prevention is the focus of management for individuals with chest symptoms and when these individu-

als are divided into those at high and low risk of AMI. High-risk patients, in particular, may be counseled about acting quickly in response to prodromal symptoms. The association between prodromal and acute symptoms might also be a valuable diagnostic tool for the physician, especially regarding patients who experience nonchest symptoms during the acute phase of AMI.

Finally, we found that women with hypertension were significantly less likely to report chest pain in the acute phase, as reported by others.[23] This finding indicates the importance of informing hypertensive women about the possibility of experiencing an AMI with nonchest symptoms.

CONCLUSIONS

Almost half of the study patients experienced prodromal chest symptoms during the year before their first AMI. These prodromal symptoms predicted the symptoms that occurred during the acute stage of AMI, with some differences between the sexes. Focusing on individuals who experience prodromal symptoms, in particular high-risk populations, might be an effective strategy for the early diagnosis of CAD and prevention of AMI. Health care providers and the public must be educated about early recognition of risk factors and the need for prompt intervention, and studies should include a gender perspective. Further prospective research is necessary to highlight the importance of early warning symptoms of CAD.

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Hjerteinfarkt og kjønn

FORESPØRSEL OM Å DELTA I EN VITENSKAPELIG UNDERSØKELSE.

I forbindelse med doktorgradsstudier ved Universitetet i Trondheim ønsker jeg å stille noen spørsmål til menn og kvinner under 75 år, som i løpet av de siste månedene har vært innlagt på sykehuset med et hjerteinfarkt. 700 menn og kvinner vil bli forespurt om å delta i undersøkelsen.

Denne forespørselen er sendt ut i samarbeid med avdelingsoverlege/ seksjonsoverlege ved det sykehuset du var innlagt. Det er også innhentet tillatelse fra Regional Komite for Medisinsk Forskningsetikk i Trondheim.

Med bakgrunn fra helsesektoren har jeg erfart at det er mye vi som helsepersonell kan lære av pasientenes egne erfaringer ved sykdom. For å bli bedre i stand til å møte hver enkelt pasients behov trenger helsepersonell kunnskaper om hvordan mennesker opplever å bli syke, og hvordan de opplever å bli møtt av helsevesenet.

Hensikten med denne undersøkelsen er å få kunnskaper som kan bidra til at de som får et hjerteinfarkt, får nødvendig behandling så raskt som mulig. Det er i denne sammenheng behov for mer kunnskap om sykdomsutviklingen ved et hjerteinfarkt, hvordan den enkelte reagerer på symptomene samt hvordan den enkelte opplever å bli møtt av helsevesenet. Det er også behov for mer kunnskap om hva som er ulikt mellom kvinner og menn.

I tillegg til spørreskjemaet kan det bli nødvendig å hente ut noen opplysninger fra journalen din på sykehuset. Dette gjelder opplysninger om tidspunkt i forhold til innleggelsen på sykehuset.

Innsamlede data fra undersøkelsen vil bli behandlet konfidensielt, og lagret i en database for bearbeidelse. All informasjon blir avidentifisert, og resultatene vil ikke kunne føres tilbake til deg personlig, eller det sykehuset du har vært innlagt i.

Undersøkelsen er frivillig. Hvis du ønsker å delta, ber jeg deg om å fylle ut samtykkeerklæringen, som også omfatter innsyn i journalen din. Hvis du derimot ikke ønsker å delta er det fint hvis du likevel returnerer samtykkeerkæringen. Årsaken til dette er behov for en oversikt over antallet som ikke ønsker å være med i studien.

De som ønsker å delta fyller ut spørreskjemaet som følger med. Jeg gjør oppmerksom på at du ikke trenger å svare på alle spørsmål. Spørreskjemaet legges i den ferdig utfylte og frankerte konvolutten, sammen med samtykkeerklæringen. Dette sendes til undertegnede, gjerne så snart som mulig.

Vennlig hilsen

Mona Løvlien
Høgskolelektor/ sykepleier

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Takk for at du vil delta i denne undersøkelsen !
Der det ikke står noe annet, er det meningen at du skal krysse for kun ett svaralternativ. Dette kommer fram i skjemaet. Enkelte spørsmål gir også mulighet til at du kan komme med dine egne kommentarer.

Jeg vil også gjøre oppmerksom på at dette spørreskjemaet gjelder de som ble innlagt i sykehuset som øyeblikkelig hjelp, og ikke de som var innlagt på forhånd. Hvis du ikke ble innlagt som øyeblikkelig hjelp, kan du se bort fra denne henvendelsen.

Når du har fylt ut skjemaet legger du det i konvolutten som følger med. Konvolutten er ferdig utfylt og frankert, og kan legges rett i postkassen. Ring meg gjerne hvis det er noe du lurer på !

Vennlig hilsen

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Først vil jeg gjerne ha litt bakgrunnsopplysninger om deg.

Spørsmål 1 : Kjønn?

mann ☐ **kvinne** ☐

Spørsmål 2: Alder ?

Antall år ☐☐

Spørsmål 3: Nåværende sivilstand ?

ugift ☐ **skilt /separert** ☐ **samboer** ☐

gift ☐ **enke/enkemann** ☐

Spørsmål 4: Hvor mange barn har du?

Antall ☐☐

Spørsmål 5: Hvem bor du sammen med til daglig?

Ingen ☐
andre voksne ☐
barn under 18 år ☐ **antall** ☐☐
barn over 18 år ☐ **antall** ☐☐

Spørsmål 6: Hva er den <u>høyeste</u> utdanningen du og eventuelt ektefelle/samboer har gjennomført?

	Egen utdanning	ektefelle/samboers utdanning
mindre enn 7 års grunnskole……	☐	……☐
7-10 årig grunnskole, framhaldsskole, folkehøgskole……..	☐	……☐
realskole eller middelskole……	☐	……☐
yrkesskole eller 1-2 årig videregående skole…	☐	……☐
3 årig videregående skole……...	☐	……☐
høgskole/ universitet, mindre enn 4 år……..	☐	……☐
høgskole/ universitet, 4 år eller mer…….	☐	……☐

Spørsmål 7: Hvilket yrke har du og eventuelt din ektefelle/samboer?

(sett eventuelt opp ditt tidligere yrke)

eget yrke: ……
ektefelles/samboers yrke……

Spørsmål 8 : Hva slags arbeidssituasjon hadde du <u>før</u> innleggelsen?

lønnet arbeid, heltid…. ☐
lønnet arbeid, deltid…. ☐ **stillingsstørrelse:…….**
heltids omsorgsarbeid ☐
pensjon eller trygd…… ☐
under utdanning ……. ☐
omsorgspermisjon…… ☐
arbeidsledig, permittert ☐

Det neste spørsmålet gjelder bare de som var i lønnet arbeid før innleggelsen.

Spørsmål 9: Kunne du selv bestemme hvordan arbeidet ditt skulle legges opp?

nei, ikke i det hele tatt ☐
i liten grad …… ☐
ja, stort sett …….. ☐
ja, det bestemte jeg selv ☐

De neste spørsmålene dreier seg om hvordan du opplevde livet ditt,
det siste året før innleggelsen.

Spørsmål 10: Opplevde du mye stress og mas på arbeidet ditt eller hjemme det siste året?

De som hadde lønnet arbeid setter kryss under både arbeidssituasjonen og hjemmesituasjonen. De andre krysser kun for hjemmesituasjonen.

	I arbeidssituasjon	I hjemmesituasjonen
nei, ikke i det hele tatt	☐	☐
sjelden	☐	☐
ja, en god del	☐	☐
ja, nesten hele tida	☐	☐

Spørsmål 11: Opplevde du noe av det følgende det siste året? Hvis ja, hvor vondt eller vanskelig var dette for deg?

Vennligst kryss av for alle spørsmålene, enten ja eller nei. Hvis du har krysset ja, krysser du også for den beskrivelsen du mener passer best.

			HVIS JA:		
			ikke så ille	vondt/ vanskelig	veldig vondt/ vanskelig
	nei	**ja**			
Har du hatt problemer på arbeidsplassen eller der du utdanner deg?	☐	☐→	☐	☐	☐
Har du hatt økonomiske problemer?.....	☐	☐→	☐	☐	☐
Ble du skilt, separert eller avbrøt du forholdet?.....	☐	☐→	☐	☐	☐
Har du hatt problemer eller konflikter med familie, venner eller naboer?.....	☐	☐→	☐	☐	☐
Har du vært alvorlig syk eller skadet?....	☐	☐→	☐	☐	☐
Har en av dine nærmeste vært alvorlig syk eller skadet?.....	☐	☐→	☐	☐	☐
Har du vært utsatt for alvorlig trafikkulykke, boligbrann eller tyveri?...	☐	☐→	☐	☐	☐
Har du mistet en som sto deg nær?.....	☐	☐→	☐	☐	☐

Eventuelt annet .....

Spørsmål 12: Opplevde du andre menneskers forventninger til deg som belastende?

Hvis du ikke var i arbeid, krysser du kun av for hjemmesituasjonen.

	I arbeidssituasjonen	I hjemmesituasjonen
nei, ikke i det hele tatt	☐	☐
sjelden	☐	☐
ja, en god del	☐	☐
ja, nesten hele tida	☐	☐

Spørsmål 13: Hvordan opplevde du din egen helse, det siste året før innleggelsen?

svært god ☐
god ☐
ikke helt god ☐
dårlig ☐

Nå kommer noen spørsmål som dreier seg om eventuelle sykdommer eller plager du hadde før innleggelsen.

Spørsmål 14: Hadde du noen av de følgende plagene det siste året før innleggelsen?

Vennligst kryss av for den / de beskrivelsene som passet best for deg.
Sett evt. flere kryss.

	ikke plaget	**litt plaget**	**ganske mye plaget**	**veldig plaget**
trett om dagen……..	☐	☐	☐	☐
fort sliten ……..	☐	☐	☐	☐
redd eller engstelig……	☐	☐	☐	☐
nervøsitet, indre uro ……	☐	☐	☐	☐
følelse av håpløshet med hensyn til fremtiden	☐	☐	☐	☐
nedtrykt, tungsindig ……	☐	☐	☐	☐
for mye bekymret eller urolig ……	☐	☐	☐	☐
søvnproblemer ……	☐	☐	☐	☐
smerter/ubehag i brystet ……	☐	☐	☐	☐
smerter i skuldre/rygg ……	☐	☐	☐	☐
smerter / nummenhet i armene ……..	☐	☐	☐	☐
åndenød / pustebesvær ……	☐	☐	☐	☐

annet:.....

Spørsmål 15: I hvilken forbindelse fikk du disse plagene ? Var du eventuelt hos lege for disse?

Dette spørsmålet gjelder noen av plagene som er beskrevet i spørsmål 14. Sett eventuelt flere kryss. Hvis du ikke hadde slike plager, går du videre til spørsmål 16.

	ved lite eller ingen aktivitet	ved store anstrengelser	om natten	var hos lege
smerter/ubehag i brystet	☐	☐	☐	☐
smerter i skuldre/rygg	☐	☐	☐	☐
smerter /nummenhet i armene	☐	☐	☐	☐
åndenød / pustebesvær	☐	☐	☐	☐

Spørsmål 16: Fikk du resept på noen av disse medisinene før innleggelsen? Hvor lenge har du eventuelt brukt disse?

Sett eventuelt flere kryss.

	ja	nei	**Hvis ja:** hvor mange år har du brukt disse?
medisiner for høyt blodtrykk	☐	☐	**antall år** ☐☐
medisiner for sukkersyke (diabetes)	☐	☐	**antall år** ☐☐
medisiner for høyt Kolesterol	☐	☐	**antall år** ☐☐

Spørsmål 17: Fikk du resept på Nitroglycerin i løpet av det siste året før innleggelsen?

ja ☐ **nei** ☐ **vet ikke** ☐

Spørsmål 18: Fikk du diagnosen hjertekrampe (angina pectoris) før denne innleggelsen ?

ja ☐ **nei** ☐ **vet ikke** ☐

Spørsmål 19: Har du tidligere hatt hjerteoperasjon eller utblokking av blodårer?

Sett eventuelt flere kryss.

	ja	nei
hjerteoperasjon ……	☐	☐
utblokking av blodårer	☐	☐

Spørsmål 20: Hvor lenge er det eventuelt siden denne hjerteoperasjonen/ utblokkingen?

antall år ☐☐ **antall måneder** ☐☐

Nå vil jeg gjerne stille noen spørsmål om det som skjedde kort tid før innleggelsen på sykehuset.

Spørsmål 21 : Da du ble innlagt med hjerteinfarkt, hvilke plager hadde du som medførte at du kontaktet helsevesenet?

Hvis plagene endret seg etter hvert, vil jeg gjerne vite hvilke plager du merket i starten, og hvilke som kom senere. Det skal altså krysses for når de ulike plagene startet. Vennligst kryss ja eller nei for hvert alternativ.

	Plager i starten			**Plager senere**	
	ja	**nei**		**ja**	**nei**
slapp og kraftløs ……..	☐	☐	**……**	☐	☐
ubehag i brystet ……..	☐	☐	**……**	☐	☐
smerter i brystet ……..	☐	☐	**……**	☐	☐
trang i brystet ……..	☐	☐	**……**	☐	☐
press i brystet …….	☐	☐	**……..**	☐	☐
smerter/ ubehag i venstre arm ….	☐	☐	**……..**	☐	☐
smerter/ ubehag i høyre arm …..	☐	☐	**……..**	☐	☐
smerter/ nummenhet i kjeven/halsen	☐	☐	**……...**	☐	☐
smerter i skuldre ……..	☐	☐	**……..**	☐	☐
smerter mellom skulderbladene	☐	☐	**……**	☐	☐
smerter i rygg ……..	☐	☐	**……**	☐	☐
åndenød / pustebesvær ……...	☐	☐	**……**	☐	☐
hjertebank ……	☐	☐	**……**	☐	☐
kvalme/ oppkast ……..	☐	☐	**……**	☐	☐
magesmerter ……	☐	☐	**……**	☐	☐
svette ……	☐	☐	**……**	☐	☐
varmefølelse ……	☐	☐	**……**	☐	☐
svimmelhet ……..	☐	☐	**……**	☐	☐
besvimelse ……	☐	☐	**……**	☐	☐
hodepine ……..	☐	☐	**……**	☐	☐

annet:.....

Spørsmål 22 : Hvordan utviklet disse plagene seg?

plagene kom brått ☐
plagene utviklet seg gradvis ☐

kommentarer:……..

Spørsmål 23: Hvordan opplevde du disse plagene?

plagene var ikke så sterke ☐
plagene var moderate ☐
plagene var uutholdelige ☐

Spørsmål 24 : Var plagene slik du forventet ved et hjerteinfarkt?

ja ☐ ⇒ gå videre til spørsmål 26.
nei ☐

Spørsmål 25: **På hvilken måte var de ikke slik du forventet ?**

plagene var svakere enn forventet …… ☐
plagene var sterkere enn forventet …… ☐
jeg forventet andre plager …… ☐ **eventuelt hvilke?……..**

…….

Spørsmål 26 : Hva tenkte du at årsaken til disse plagene kunne være?
Sett flere kryss hvis du tenkte på flere årsaker.

hjerteproblemer …… ☐
mageproblemer …… ☐
muskel eller leddproblemer …. ☐
stress …….. ☐
influensa …… ☐

annet…….

Spørsmål 27: Hvor oppholdt du deg da du fikk disse plagene?

hjemme ……. ☐
på arbeid …….. ☐
på besøk hos venner/ familie ☐
andre steder …… ☐

Spørsmål 28: Hva holdt du på med da du fikk disse plagene?

satt i ro …….. ☐
lå i sengen …… ☐
gikk/ beveget meg …… ☐
holdt på med lett arbeid ☐
holdt på med tungt arbeid ☐

Spørsmål 29: Hvilken ukedag begynte plagene?

mandag ☐
tirsdag ☐
onsdag ☐
torsdag ☐
fredag ☐
lørdag ☐
søndag ☐

Spørsmål 30: Hvilken tid på døgnet begynte plagene?

mellom klokka 06.00 og 12.00 ☐
mellom klokka 12.00 og 18.00 ☐
mellom klokka 18.00 og 24.00 ☐
mellom klokka 24.00 og 06.00 ☐

Spørsmål 31: Gjorde du noe selv for å lindre disse plagene?

Vennligst kryss ja eller nei for hvert alternativ.

	ja	**nei**
la meg ned ……..	☐	☐
satte meg ned ……..	☐	☐
tok smertestillende medisiner	☐	☐
tok avslappende medisiner	☐	☐
tok Nitroglycerin ……	☐	☐

annet…….

Spørsmål 32 : Snakket du med noen om disse plagene før du kontaktet helsevesenet, og i tilfellet hvem?

Vennligst kryss ja eller nei for hvert alternativ.

	ja	nei
snakket med ektefelle ……..	☐	☐
snakket med andre i familien	☐	☐
snakket med venner/kollegaer	☐	☐

Spørsmål 33: Når snakket du eventuelt med noen?

Med dette menes første gangen du snakket med noen om plagene dine.
Hvis du ikke snakket med noen, går du videre til spørsmål 35.

straks jeg begynte å få plager …… ☐
innen 1 time etter at jeg fikk plager ……. ☐
mellom 1 og 3 timer etter at jeg fikk plager ☐
mellom 3 og 5 timer etter at jeg fikk plager ☐
mellom 5 og 7 timer etter at jeg fikk plager ☐
mellom 7 og 9 timer etter at jeg fikk plager ☐
mellom 9 og 11 timer etter at jeg fikk plager ☐
mer enn 11 timer etter at jeg fikk plager ☐

Spørsmål 34: Hvis du snakket med noen, mener du at dette virket inn på hvor raskt det ble tatt kontakt med helsevesenet?

Vennligst kryss ja eller nei for hvert alternativ.

	ja	nei
det førte til at jeg utsatte å ta kontakt med helsevesenet	☐	☐
det førte til at jeg bestemte meg for å ta kontakt med helsevesenet	☐	☐

Spørsmål 35: Hvor lang tid gikk det fra du begynte å få disse plagene, til helsevesenet ble kontaktet ?

- **mindre enn ½ time** ☐
- **mellom ½ og 1 time** ☐
- **mellom 1 og 2 timer** ☐
- **mellom 2 og 3 timer** ☐
- **mellom 3 og 4 timer** ☐
- **mellom 4 og 5 timer** ☐
- **mellom 5 og 6 timer** ☐
- **mellom 6 og 7 timer** ☐
- **mellom 7 og 8 timer** ☐
- **mellom 8 og 9 timer** ☐
- **mellom 9 og 12timer** ☐
- **mellom 12 og 24 timer** ☐
- **mer enn 24 timer** ☐

Spørsmål 36 : Hvordan ble det tatt kontakt med helsevesenet?

- **ringte til fastlege/ primærlege** ☐
- **ringte til privat legesenter …** ☐
- **ringte til legevakt ……..** ☐
- **ringte til AMK sentral/ nødtlf.113** ☐
- **ringte etter sykebil ……** ☐
- **dro direkte til sykehus ……..** ☐ ⇒ gå videre til spørsmål 39
- **dro direkte til legevakt ……..** ☐ ⇒ gå videre til spørsmål 39

Spørsmål 37: Hvem ringte til helsevesenet?

Vennligst kryss ja eller nei for hvert alternativ.

	ja	**nei**
jeg selv ……	☐	☐
ektefelle/samboer	☐	☐
andre i familien	☐	☐
venner/kollegaer	☐	☐
andre ……..	☐	☐

Spørsmål 38: Ble det ringt mer enn en gang før du fikk hjelp ?

ja ☐ **nei** ☐

Spørsmål 39 : Hvor lang tid tok det fra du begynte å få disse plagene, til du ankom sykehuset ?

mindre enn 1 time ☐
mellom 1 og 2 timer ☐
mellom 2 og 3 timer ☐
mellom 3 og 4 timer ☐
mellom 4 og 5 timer ☐
mellom 5 og 6 timer ☐
mellom 6 og 7 timer ☐
mellom 7 og 8 timer ☐
mellom 8 og 9 timer ☐
mellom 9 og 10 timer ☐
mellom 10 og 11 timer ☐
mellom 11 og 12 timer ☐
mellom 12 og 24 timer ☐
mer enn 24 timer ☐

Spørsmål 40: Hvor langt er det til nærmeste sykehus, fra det stedet du oppholdt deg da du fikk plagene?

mindre enn 10 km. ☐
mellom 10 og 20 km. ☐
mellom 20 og 30 km. ☐
mellom 30 og 40 km. ☐
mellom 40 og 50 km. ☐
mer enn 50 km. ☐

Spørsmål 41 : Var dette ditt første hjerteinfarkt ?

Ja ☐ **nei** ☐

Litt mer om deg selv, og hvordan du har det nå.

Spørsmål 42: Har du noen (utenom ektefelle/ samboer) som du kan snakke med om det meste?

nei …….. ☐
ja, 1 - 2 personer……. ☐
ja, flere enn 2 personer ☐

Spørsmål 43: Hvor ofte treffer du eller snakker du i telefonen med nære venner eller familie (utenom husstandsmedlemmer) ?

en gang i måneden eller sjeldnere ☐
2 - 8 ganger i måneden ☐
mer enn 2 ganger pr. uke ☐

Til slutt har jeg noen spørsmål om hvordan du tenkte på denne sykdommen før innleggelsen.

Spørsmål 44: Har du søsken eller foreldre som har hatt hjerteinfarkt <u>før</u> de var 60 år?

ja ☐
nei ☐ ⇒ gå videre til spørsmål 46.
vet ikke ☐ ⇒ gå videre til spørsmål 46.

Spørsmål 45: Hadde du tenkt på at du kunne være arvelig disponert for å få hjerteinfarkt, før du ble innlagt ?

ja ☐ **nei** ☐

Spørsmål 46: Var du kjent med hvilke plager en kan få ved et hjerteinfarkt, før du ble innlagt på sykehuset ?

nei, ikke i det hele tatt ☐
jeg var litt kjent med disse ☐
jeg var godt kjent med disse ☐

Spørsmål 47: Hvilke av disse plagene var du kjent med at en kunne få ved et hjerteinfarkt?

Sett eventuelt flere kryss.

slapphet og kraftløshet …… ☐
smerter/ ubehag i armene ……..….. ☐
smerter/ nummenhet i kjeven/halsen ☐
smerter i skuldre …….. ☐
smerter mellom skulderbladene ☐
smerter i rygg …….. ☐
smerter i brystet …….. ☐
åndenød / pustebesvær ……... ☐
hjertebank …… ☐
kvalme/ oppkast …….. ☐
svette …… ☐
varmefølelse …… ☐
svimmelhet …….. ☐
besvimelse …… ☐
hodepine …….. ☐

Spørsmål 48: Hvordan hadde du eventuelt fått kjennskap til disse plagene ?

gjennom radio/tv …….. ☐
gjennom aviser /ukeblad …….. ☐
gjennom internett …… ☐
gjennom fagtidsskrift / fagbøker…….. ☐
gjennom bedriftshelsetjenesten …… ☐
gjennom besøk hos lege …… ☐
gjennom helsepersonell jeg kjenner …… ☐
gjennom andre som har hatt hjerteinfarkt ☐
annet …….. ☐

Hjertelig takk for at du tok deg tid til å svare på disse spørsmålene !

Hvis noen av spørsmålene er uklare, er det fint om du sier noe om dette.
Kommentarer for øvrig tas også imot med takk!

……
……
……

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36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.

133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
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