From INSTITUTE OF ENVIRONMENTAL MEDICINE
Karolinska Institutet, Stockholm, Sweden

FATALITY OF CORONARY EVENTS – EPIDEMIOLOGICAL STUDIES OF POTENTIAL DETERMINANTS

Hedley Knewjen Quintana

Karolinska Institutet

Stockholm 2017

Published by Karolinska Institutet.
Printed by E-Print AB, 2017

ISBN 978-91-7676-679-8

FATALITY OF CORONARY EVENTS – EPIDEMIOLOGICAL STUDIES OF POTENTIAL DETERMINANTS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Hedley Knewjen Quintana
M.D., M.Sc.

Principal Supervisor:
Associate professor Karin Leander
Karolinska Institutet
Institute of Environmental Medicine
Unit of Cardiovascular Epidemiology

Co-supervisor(s):
Associate professor Bruna Gigante
Karolinska Institutet
Institute of Environmental Medicine
Unit of Cardiovascular Epidemiology
Danderyd Hospital
Division of Clinical Sciences

Senior Professor Ulf de Faire
Karolinska Institutet
Institute of Environmental Medicine
Unit of Cardiovascular Epidemiology

Professor Imre Janszky
Norwegian University of Science and Technology
Department of Public Health and Nursing
Karolinska Institutet
Department of Public Health Science
Division of Public Health Epidemiology

Opponent:
Professor Grethe Seppola Tell
University of Bergen
Department of Global Public Health and Primary Care
Research Group Lifestyle epidemiology

Examination Board:
Professor Eva Swahn
Linköping Academic Research Centre (LARC)
Department of Medical and Health Sciences (IMH)
Division of Cardiovascular Medicine (KVM)
Linköping University

Associate professor Nele Brusselaers
Karolinska Institutet
Department of Molecular, Tumor and Cell Biology (MTC)
Research Group Centre for Translational Microbiome Research (CTMR)/Clinical epidemiology

Associate professor Andreas Rosenlund
Uppsala University
Centre for Clinical Research
County of Västmanland

The last four dialogues of "Romeo and Juliet"

William Shakespeare

1595

"Capulet head

O brother Montague, give me thy hand.
This is my daughter's jointure, for no more
Can I demand.

Montague head

But I can give thee more;
For I will raise her Statue in pure gold,
That whiles Verona by that name is known,
There shall no figure at such rate be set
As that of true and faithful Juliet.

Capulet head

As rich shall Romeo's by his lady's lie-
Poor sacrifices of our enmity!

Prince Escalus of Verona

A glooming peace this morning with it brings.
The sun for sorrow will not show his head.
Go hence, to have more talk of these sad things;
Some shall be pardon'd, and some punished;
For never was a story of more woe
Than this of Juliet and her Romeo."

ABSTRACT

Background

Although there has been a large number of improvements in prevention and care, coronary heart disease (CHD) was one of the main causes of death in 2010 around the world. The majority of CHD deaths are due to myocardial infarction (MI) and occur out-of-hospital. The research regarding determinants of MI fatality including out-of-hospital deaths is scant.

Aims

The overall aim of this project was to increase knowledge about the determinants of MI fatality in men and women from the Stockholm general population who suffer a first MI. Specific aims were to: 1) validate questionnaire data collected from close relatives of MI patients, 2) assess how known cardiometabolic risk factors are associated with MI fatality, 3) describe which comorbidities are the most common among fatal MI cases and to assess if they are associated to MI fatality, and 4) assess whether low-grade inflammation is associated to fatality of future coronary events.

Methods

Using material from the Stockholm Heart Epidemiology Program (SHEEP), a case-control study, the validity of questionnaire data provided by spouses/common-law spouses (proxy respondents) of non-fatal MI cases regarding 82 exposures was valuated. Using conditional logistic regression we calculated for each of the exposures, a "proxy bias", based on information collected from 1) MI cases and controls [odds ratio A] and 2) proxies and the same set of controls [odds ratio B]. Disagreement was measured by calculating the ratio between odds ratio B and odds ratio A; 95% confidence intervals (CI) were calculated using resampling bootstrap with replacement.

From the SHEEP, an inception cohort of first time MI cases was formed. Data were retrieved from questionnaires (filled in by a close relative if the case was fatal), physical examinations (for non-fatal cases), national registers and autopsy reports. Associations between selected cardiometabolic risk factors and MI fatality were assessed through calculations of risk ratios (RR) with 95% confidence intervals (CI) using binomial regression with log link. Presence of comorbidities among the fatal MI cases was mapped out and the number of previous hospitalizations was assessed. Associations between specific comorbidities, as well as number of previous hospitalizations, and MI fatality were assessed using the same modelling as for the cardiometabolic risk factors. A structured review of autopsy data was performed to identify additional indicators of comorbidities in fatal MI cases.

Using material from the AMORIS cohort, sex specific associations between low-grade inflammation (using a score of five biomarkers: C-reactive protein, haptoglobin, white blood cell count, uric acid and albumin) and a fatal outcome in subjects who subsequently experienced a first coronary event were assessed. Odds ratios were calculated with 95% CI using logistic regression.

Results

For the vast majority of the exposures considered in the validation study, there was no significant disagreement between reports from MI patients and proxies. However, leisure time physical inactivity was overestimated by proxies compared to MI patients.

Diabetes, but not hypertension and hyperlipidemia, was associated with MI fatality. Overweight, as compared to normal BMI, was inversely associated with MI fatality; the results for obesity went in the same direction. The results were adjusted for age, current smoking, parental history of premature cardiac death, number of previous hospitalizations, educational level, disposable income, and other cardiometabolic risk factors.

An increased number of previous hospitalizations was associated with MI fatality after adjustments for sex, age and disposable income. Among comorbidities identified as prevalent in fatal cases, the following were, after adjustments (where possible), associated with 7-day fatality: heart failure, stroke, diabetes, alcoholism, psychiatric diseases, cancer, kidney diseases, epilepsy, rheumatoid arthritis and asthma. Indicators of comorbidities identified from autopsy data included silent MI, severe abdominal aortic atherosclerosis, liver steatosis, and underweight.

An elevated inflammation score was after adjustments by age at the time of the coronary event, calendar year of the coronary event, diabetes, level of education, serum total cholesterol, serum triglycerides, and angina associated with increased fatality of future coronary events, both in men and in women.

Conclusions

MI patients and their spouses similarly reported data on a wide range of exposures including traditional cardiovascular risk factors, leisure time physical inactivity being an exception.

Among the cardiometabolic factors under study, diabetes and presence of a low-grade inflammation, but not hypertension and hyperlipidemia was associated with an increased MI fatality. Overweight was associated to a decreased MI fatality. Repeated prior hospitalizations and/or heart failure, diabetes, stroke, psychiatric disease, alcoholism, cancer, renal diseases, epilepsy, rheumatoid arthritis and asthma were associated with increased MI fatality.

LIST OF SCIENTIFIC STUDIES

I. **Quintana HK**, Vikström M, Andersson T, Hallqvist J, Leander K. Agreement between Myocardial Infarction Patients and Their Spouses on Reporting of Data on 82 Cardiovascular Risk Exposures. *PLoS One. July 2015;10(7):e0132601*

II. **Quintana HK**, Janszky I, Gigante B, Druid H, Ahlbom A, Hallqvist J, de Faire U, Leander K. Diabetes, hypertension, overweight and hyperlipidemia and 7-day case-fatality in first myocardial infarction. *IJC Metabolic & Endocrine, Vol 12, September 2016, Pages 30-5*

III. **Quintana HK**, Janszky I, Alkass K, Gigante B,d, Druid H, Ahlbom A, de Faire U, Hallqvist J, Leander K. Prior repeated hospitalizations and a number of comorbidities elevate the risk of death from a first myocardial infarction. *Manuscript submitted.*

IV. **Quintana HK,** Walldius G, Malmström H, Vikström M, de Faire U, Jungner I, Hammar N, Leander K. Inflammatory markers predict fatality of future coronary events in men and women in the AMORIS cohort. *Manuscript submitted.*

CONTENTS

LIST OF ABBREVIATIONS

AMORIS	Apolipoprotein-related Mortality Risk
BMI	Body mass index
CI	Confidence intervals
CALAB	Central Automation Laboratory
CDR	Cause of death register
CK	Creatinine kinase
CK-B	Creatinine kinase B
CDR	Cause of Death Register
CHD	Coronary heart disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DAMP	Damage associated molecular patterns
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HbA1C	Glycosylated hemoglobin
HR	Hazard ratio
ICD	International Classification of Diseases
LD	Lactate dehydrogenase
LISA	Longitudinal integration database for health insurance and labor market studies
MI	Myocardial infarction
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
NPR	National patient register
OR	Odds ratio
RDW	Red distribution width
RR	Risk ratio
SD	Standard deviation
SHEEP	Stockholm Heart Epidemiology Program
WBC	White blood cells count

1 BACKGROUND

1.1 GLOBAL PERSPECTIVE OF CORONARY HEART DISEASE

Cardiovascular disease (CVD) includes diseases of the heart, blood vessels in the brain and blood vessels of the heart, such as coronary heart disease (CHD), stroke and heart failure. CVD killed about 17 million persons in 2010 and it is estimated that 23 million persons will die in 2030 due to CVD (1). Cardiovascular disease (CVD) is a serious global health problem. Among CVD, CHD was responsible for about 7 million deaths worldwide during 2010 (2). The highest rates of CHD mortality occur in Surinam, Russia, Central Asia, the Middle East, North Africa, India and Eastern Europe, while the lowest occur in the high income regions of Asia Pacific and sub-Saharan Africa (2). The world distribution of CHD mortality is shown in Figure 1.

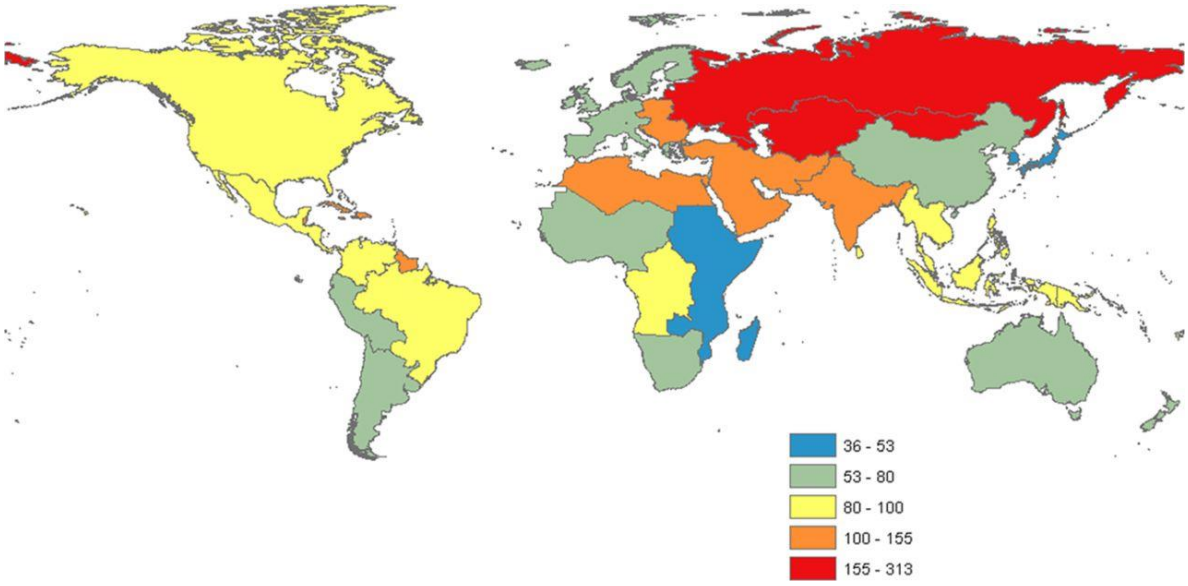

Figure 1. Map of age-standardized CHD mortality rate per 100 000 persons in 21 world regions. Source: Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study (2). Published with permission of the journal.

Survival of the acute phase after a myocardial infarction (MI) or a CHD event varies over countries (3-7) although for many countries such statistics are not available. Papers describing the survival after a MI/CHD in United States, Australia, Sweden, the Netherlands and some European cities show that between 15% and 43% of individuals who suffer a fatal MI/CHD event die shortly after the event (3-8). The majority of these fatal events occur in individuals that were not admitted to hospital (3, 6-8). A recent publication from the National Board of Health and Welfare in Sweden shows a decrease in the fatality of the first MI from 1987 to 2015 in Sweden (4). The publication also shows that about half of deaths during the first year after coronary event symptoms occurs within 24 hours regardless in which year the event happened, as shown in Figure 2 (4).

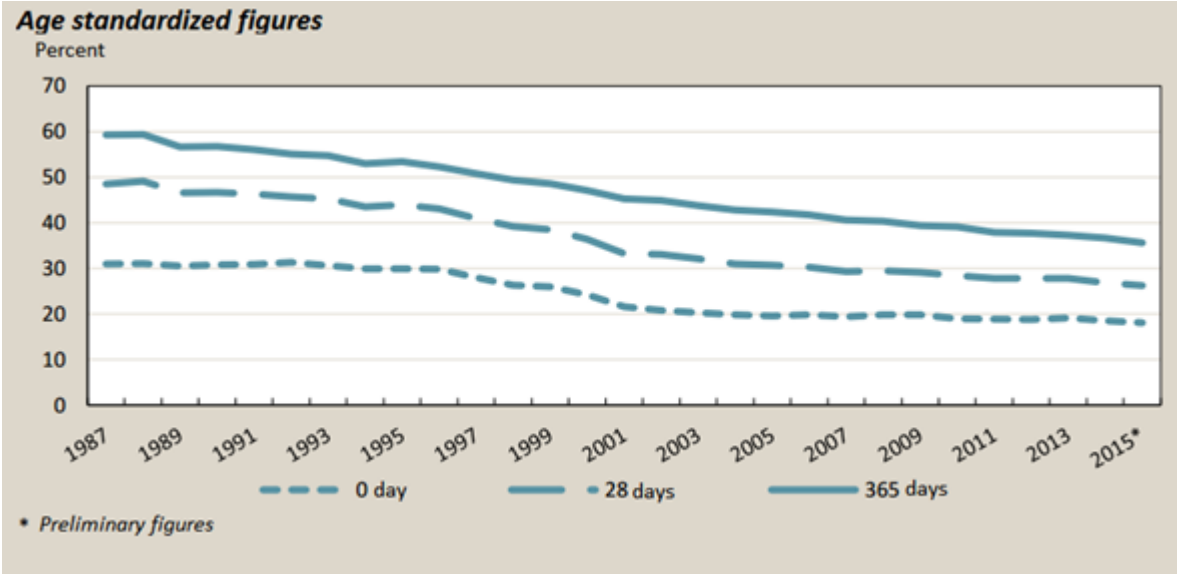

Figure 2. Proportion of deaths occurring within 0, 28 and 365 days among Swedish men and women older than 20 years old who suffered a first MI. Source: Socialstyrelsen, Statistik om hjärtinfarkter 2016 (Statistics on Myocardial Infarction 2016 In Swedish language) (4).

1.2 POSSIBLE DETERMINANTS OF MI FATALITY

The natural history of disease is defined as the course of a disease from pathological onset to resolution (9). The natural histories of several diseases are rather well known and often taught as part of basic medical training. The knowledge of the natural history of a given disease is important in order to better understand the mechanisms behind the disease. Such knowledge may enhance prevention of undesirable outcomes, for example death. Risk factors may increase the risk of developing a disease, but these risk factors may also act at different stages of a disease, determining its progress and prognosis. In MI, for example, the risk factors contributing to its onset may not necessarily be the same as those acting in the acute phase affecting the short-term outcome. In animal models, biomarkers with potential influence on survival in the acute phase of an MI have been identified (10-12) but research is scant. Epidemiological studies aiming at increasing knowledge about determinants of MI fatality are rather limited, in particular studies that consider out-of-hospital deaths (13-15). The presence of low-grade inflammation is one of the specific factors hypothesized to have a role (16, 17).

1.3 CHD, MI AND SUDDEN DEATH

CHD is an unbalanced supply/demand of oxygen to the heart muscle. CHD is mainly related to insufficiency of the function of coronary arteries that leads to localized myocyte ischemia (18) which leads to several symptoms, most commonly chest pain. If the clinician finds evidence that the ischemia leads to death of myocytes it is referred to as an MI, otherwise it is called angina (18). Angina is classified as stable when symptoms (usually chest pain) do not appear at rest, otherwise it is unstable.

In MI, there is a leakage of intracellular contents that leads to detection of cardiac enzymes in blood and a local release of several damage associated molecular patterns (DAMP) leading to a severe sterile inflammation (19). In addition, there is also lateralization of gap junctions that

might lead to electrocardiographic changes and arrhythmias (20). There have been changes over time in the MI diagnostic criteria. These changes reflect improvements in the technology to better detect small amounts of leakage of intracellular matter (21).

The dysfunction of the coronary vessels leading to MI is often related to a sudden change in atherosclerosis plaques (18). But there are other rare causes: the spasm of large coronary artery (22) and "bridging" of cardiac tissue over the large coronary arteries (23). An acute MI can be associated with acute heart failure, arrhythmias, or mechanical complications (24).

MI can be ascertained as a cause of death using the same criteria as for diagnosing it in a living person, if these criteria are applied when the case is alive. However, due to the suddenness of the event, the lack of time to take samples and to assess the anamnesis of the patient, MI as a cause of death can be asserted observing autopsy findings as those described in detail by Kumar et al. (25), as well as by Knight et al. (26). These autopsy changes reflect how long the person suffered MI symptoms before death. According to Kumar et al., findings of an MI can be detected using electron microscopy if the onset of symptoms started at least half an hour before the death (25). If light microscopy is used, pathological findings can be detected if death takes place after at least 4 hours of the onset of symptoms (25, 26). An MI can also be detected if there are signs of coronary occlusion regardless the myocardial findings (25, 26). When the clinician in charge of the death investigation suspects an MI as a cause of death but the autopsy is lacking or it is not clear for ascertaining it as cause of death, then the case will usually be considered a "fatal CHD".

Sudden death is defined by a sudden loss of pulse in a person who was apparently healthy 24 hours before death (23, 27), although some authors use a shorter period of time in their definition (26). Sudden death is commonly caused by heart diseases, which include CHD (27). However, there are several non-cardiac diseases that might cause this syndrome and each forensic pathology book dedicates a whole chapter to describe all its possible causes (23, 26, 28).

1.4 POSSIBLE DETERMINANTS OF MI FATALITY

1.4.1 Main exposures assessed in this thesis

1.4.1.1 Cardiometabolic risk factors

1.4.1.1.1 Diabetes

Diabetes has consistently been identified as a relevant risk factor of in-hospital MI fatality (15, 29-33). However; studies that also consider out-of-hospital MI/CHD do not show so clear picture; some of these studies agree with studies based solely on hospitalized MI patients (15, 32) and others show no association (13, 14).

1.4.1.1.2 Hypertension

Whether hypertension associates with MI/CHD fatality is not clear from the literature. Among studies where out-of-hospital CHD cases are included, some studies show no association (13, 15), whereas other ones show an increased MI/CHD fatality (14, 34).

Studies including hospitalized MI cases also show mixed results, some of them show no association (30, 35-38) but other studies show decreased MI/CHD fatality (29, 39).

1.4.1.1.3 Overweight, obesity and BMI

Overweight and obesity have been studied in relation to fatality of first time MI in hospital settings and in meta-analysis, showing an inverse association (40).

Overweight and obesity have not been thoroughly assessed in studies that include out-of-hospital CHD deaths. However, a previous paper shows similar body mass index (BMI) measurements for fatal CHD and non-fatal MI (14).

1.4.1.1.4 Hyperlipidemia

Serum cholesterol levels were not found associated with fatality of future CHD events in previous literature (13, 14).

1.4.1.2 Comorbidities

Comorbidity may be defined as a medical condition or a set of them existing simultaneously with, and independent of, another medical condition (41). Comorbidity has been associated to increased 30-day fatality of events in a coronary ward in Spain using the Charlson scale (42). Dudas et al. have shown a list of selected comorbidities with different associations to 28-day MI fatality according to data from Swedish national registers; the results show that most of those comorbidities increase MI fatality (5).

Most of the previous studies assessing the role of selected comorbidities in relation to MI fatality were performed using an in-hospital setting. Elixhauser et al. state that 12 comorbidity groups, out of 30 they defined, increase the risk of dying in-hospital after having been admitted with an MI diagnosis, while seven of these groups decrease the risk of dying; the study was performed in California, USA (43).

1.4.1.3 Inflammation

Inflammation represents a set of events that happens when the immune system is triggered due to tissue damage. Inflammation assessed using a set of acute phase proteins has been associated with increased fatality of future coronary events in a population-based cohort from Malmö, Sweden (17).

Other literature on this topic involves the assessment of individual biomarkers of inflammation, with diverse results regarding associations to fatality of coronary events (44-47).

1.4.2 Other exposures

1.4.2.1 Age

Age at MI has been associated with increased MI/CHD fatality (3, 13, 15, 17).

1.4.2.2 Calendar year & early treatment

The chain of survival is a series of steps performed shortly after a cardiac arrest (which includes CHD) occurring in order to increase the chances of survival of the person suffering such catastrophic event. These 4 steps are: 1) Early access; 2) Early cardiopulmonary resuscitation; 3) Early defibrillation and 4) Early advanced cardiac life support (48, 49). There are improvements over time regarding these steps in the last 10 years (48). The chain of survival was not considered in this thesis, because information about these steps is lacking for most of the subjects in our data. However, the chain of survival improves as the calendar years increase (48). Therefore, adjustment for calendar year is done in Study IV, but not for Studies II-III.

1.4.2.3 Other factors

A number of other factors have been studied in relation to MI/CHD fatality in population-based studies. Physical inactivity has been associated with increased MI fatality (13). Lung volumes were studied in relation to MI fatality (13, 50): the forced expiratory volume in one second (FEV1) was inversely associated to CHD fatality in one study (50), but not in the another (13), and the forced vital capacity (FVC) was inversely associated with CHD fatality (50).

Socioeconomic deprivation has been associated with increase fatality of MI events (51).

Red distribution width (RDW) was associated with increased CHD fatality (52). Resting heart frequency had a tendency to be associated with increased CHD fatality (13).

Birth weight has a U-shaped association with MI fatality in men, but not in women (53).

1.5 METHODOLOGICAL CONSIDERATIONS

1.5.1 Perspective I: MI/CHD fatality

In what will be referred to as "perspective I" in this thesis, MI/CHD fatality is assessed in an inception cohort (9) of MI/CHD. Case fatality rate is defined as the proportion of cases that are fatal within a specified time (9). In Perspective I, we compare the case fatality rate among cases exposed to the variable of interest to the case fatality rate among the unexposed.

This perspective, used in some population-based studies (13, 15, 17, 46), is shown in the top panel of Figure 3.

This perspective is used in Studies II-IV.

1.5.2 Perspective II: Risk of non-fatal MI and fatal CHD

In what will be referred to as "perspective II", the hazard ratio of non-fatal MI and fatal CHD, respectively, associated with the exposure of interest are assessed. If the point estimate for developing a fatal CHD is higher than the point estimate for developing a non-fatal MI, then it is inferred that the exposure of interest is associated to increased fatality of coronary events. This perspective has been used in several cohorts (44, 45, 54). The concept is illustrated in the bottom panel of Figure 3.

This perspective is used in Study IV, in parallel with Perspective I.

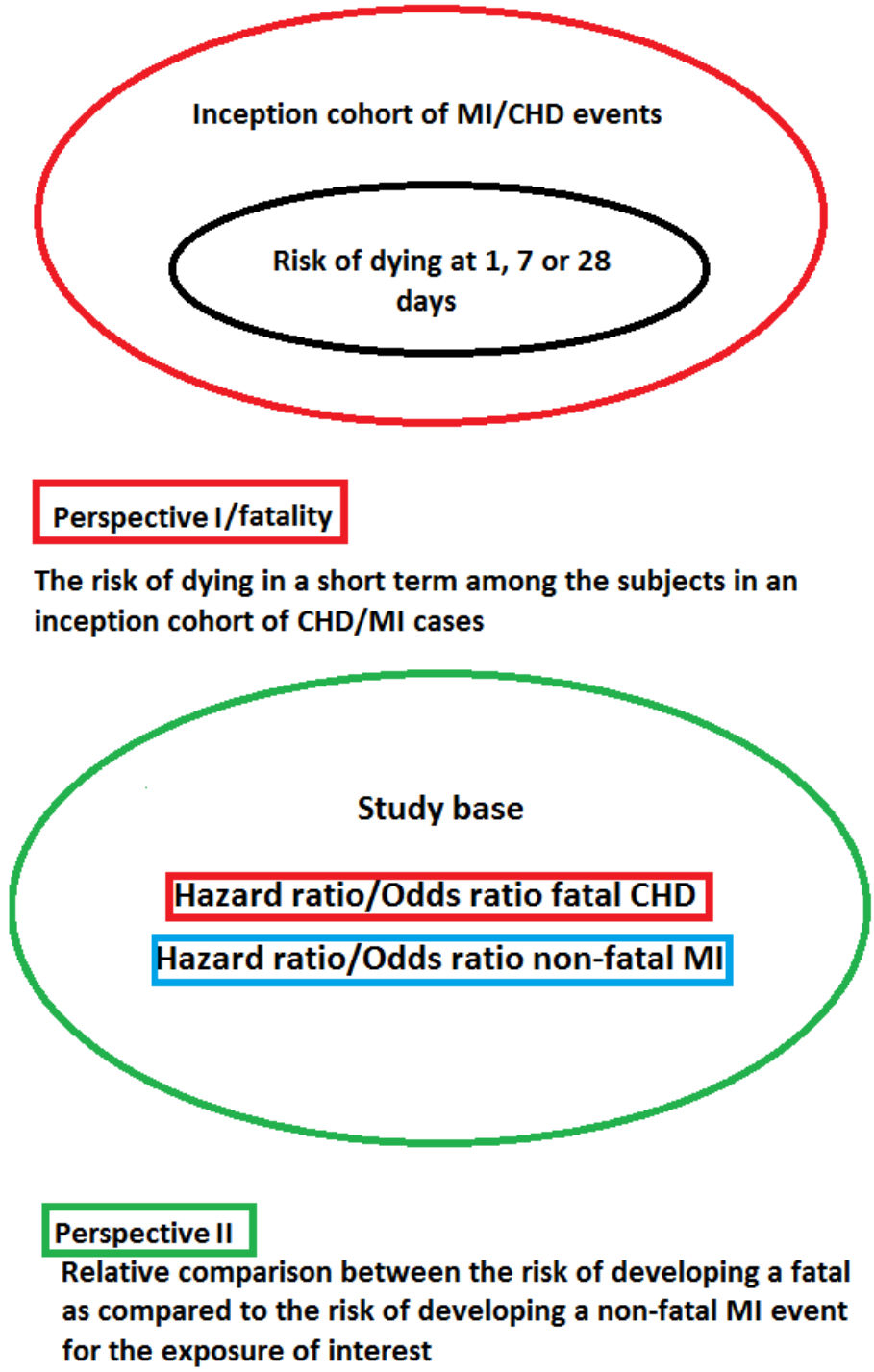

Figure 3. Two different perspectives for assessing death shortly after an MI/CHD event.

1.5.3 Validation of proxy-based information in MI cases

In case-control studies of MI, fatal cases dying outside the hospital are usually not considered. Therefore, results generated from these studies can only be generalized to MI cases who survive long enough to be hospitalized. This is a disadvantage and the possibility to contact close relatives of the fatal cases, as "proxy respondents" may therefore be considered. One way to assess the validity of the information provided by "proxies", used in

the present thesis (Study I) is to compare the odds ratios generated from a case-control study material when they are based on reports from the cases themselves (non-fatal cases) and when they are based on responses of proxies.

2 AIMS

The main aim of this thesis is to contribute to fill the gap in knowledge regarding determinants of the fatality of coronary events.

The specific aims of this thesis are:

1. To increase knowledge regarding the validity of data collected from proxy respondents to MI cases.

2. To assess how cardiometabolic risk factors (diabetes, hypertension, hyperlipidemia, overweight, and obesity), measured close in time to a first MI event, are associated with MI fatality.

3. To increase knowledge about how presence of comorbidities may influence fatality in first time MI in the general adult population using an explorative approach.

4. To assess sex specific associations between inflammatory markers and risk of a fatal outcome in subjects who subsequently experience a first coronary event.

3 METHODS

3.1 THE STUDY MATERIALS

3.1.1 Stockholm Heart Epidemiology Program (SHEEP) (Studies I-III)

3.1.1.1 Study base description

SHEEP is a population-based case-control study. The study base comprises all Swedish citizens living in Stockholm, aged 45-70 years old free of previous hospitalizations with MI as a main or secondary diagnoses in Stockholm since 1975. The study period started on the 13th of January, 1992, and ended on the 12th of January, 1994 in men and on the 31st of December, 1994 in women. The upper age limit from the beginning of the study period until October 1992 was 65 years. Starting from November 1992, the age limit was raised up to 70 years old.

3.1.1.1.1 MI diagnostic criteria used in SHEEP and number of cases identified

During the SHEEP study period, MI was diagnosed based on the following four diagnostic criteria stated by the "Coronary Units Care. Guidelines of treatment for Stockholm hospitals (in Swedish: Stockholm County Council. *Hjärtintesivvård. Behandling for Danderyd skujhus, Ersta sjukhus, Huddinge sjukhust, etc…*) (55):

1. Anamnesis, the patient must have any of the following:
    a. Crushing central chest pain with/without sweating in the last 24 hours before diagnosis with duration longer than 15 minutes that should not change with respiratory movements, changes in the body position or during ingestion.
    b. The previous symptom could last less than 15 minutes, if the patient was resting when it happened in the last 24 hours.
    c. Pulmonary oedema.
    d. Shock without suspicion of bleeding, hypovolemia, sepsis or intoxication.
    e. Syncope in the last 24 hours.
2. Elevated enzyme values:
    a. Creatinin kinase (CK) levels over 3,3 µkat/L in men or over 2,5 µkat/L in women with CK-B values above 0,5 µkat/L. The quotient CK-B/CK must be 3-12%. The maximum value should be measured approximately between 15 and 18 hours before the symptoms onset.
    b. Two lactate dehydrogenase (LD) levels above 0,8 µkat/L with LD1 higher than 3,3 µkat/L. The maximum value should be measured approximately between 36 and 48 hours before the symptoms onset.
3. A forthcoming pathological Q wave in at least two consecutive leads.
4. Myocardial necrosis identified in an autopsy which an age that corresponds to the lapse between the onset of symptoms and the death.

Individuals that had two out the first three criteria had an MI diagnosis. Individuals with the fourth criterion also had MI as a cause of death. These criteria were stated in 1990 and they did not change during the SHEEP study period.

From the study base, 2246 MI cases were identified from any of the following sources:

1. Coronary units and internal medicine wards for acute care in Stockholm county.
2. National Patient Registry: Cases with main or secondary diagnosis corresponding to MI (-International Classification of Diseases- ICD-9 410).
3. Death certificates: Cases with ICD-9 codes 410 as a main or contributory cause of death were also identified.

3.1.1.1.2 Definition of fatal MI and number of events identified (Studies II-III)

MI cases who were hospitalized and died within 7 days after symptoms started or died without being hospitalized were classified as 7-day fatal MI (n=524). An alternative classification of fatal MI was used: 28-day fatal MI (n=603).

3.1.1.1.3 Definition of non-fatal MI and number of cases identified.

Study I included 243 participating 28-day non-fatal cases living with a spouse/common law spouse who received a questionnaire between 5th April, 1993 and 31st December, 1993.

Cases who survived at least 28 days and filled in the questionnaire were included in Studies II and III as non-fatal MI cases (n= 1,381). In Study III cases who survived 7 days but died within 28 days were also considered non-fatal (n=79), while in Study II these cases were excluded from the analyses.

3.1.1.1.4 Proxy respondents (Study I)

The SHEEP secretariat sent an invitation letter to participate in a pilot validation study to a selection of the MI cases participating in SHEEP and asked for permission to contact his/her spouse/common law spouse ("proxy"). If the case agreed to participate, the SHEEP secretariat sent a similar letter to the proxy. The proxies who agreed to participate (n=243) were asked to complete a very similar questionnaire to the one sent to the MI patients. When the data collection had ended, the proxies were sent a letter where they were asked about whether some parts of the questionnaire were difficult to answer and if they received any help from their spouses. None of the proxies reported they received help from their spouses. However, 5 reported they had some difficulty giving information about work related exposures.

3.1.1.1.5 Control individuals (Study I)

Control individuals were selected continuously from the population register during the study period. Each control was matched to the respective case index by sex, age (within 5 years) and residential area. Matched controls were selected within 2 days after his/her respective index case occurrence. The first responding matched control to each selected case was included.

The extraction of participants from the SHEEP (for Studies I-III) is shown in Figure 4.

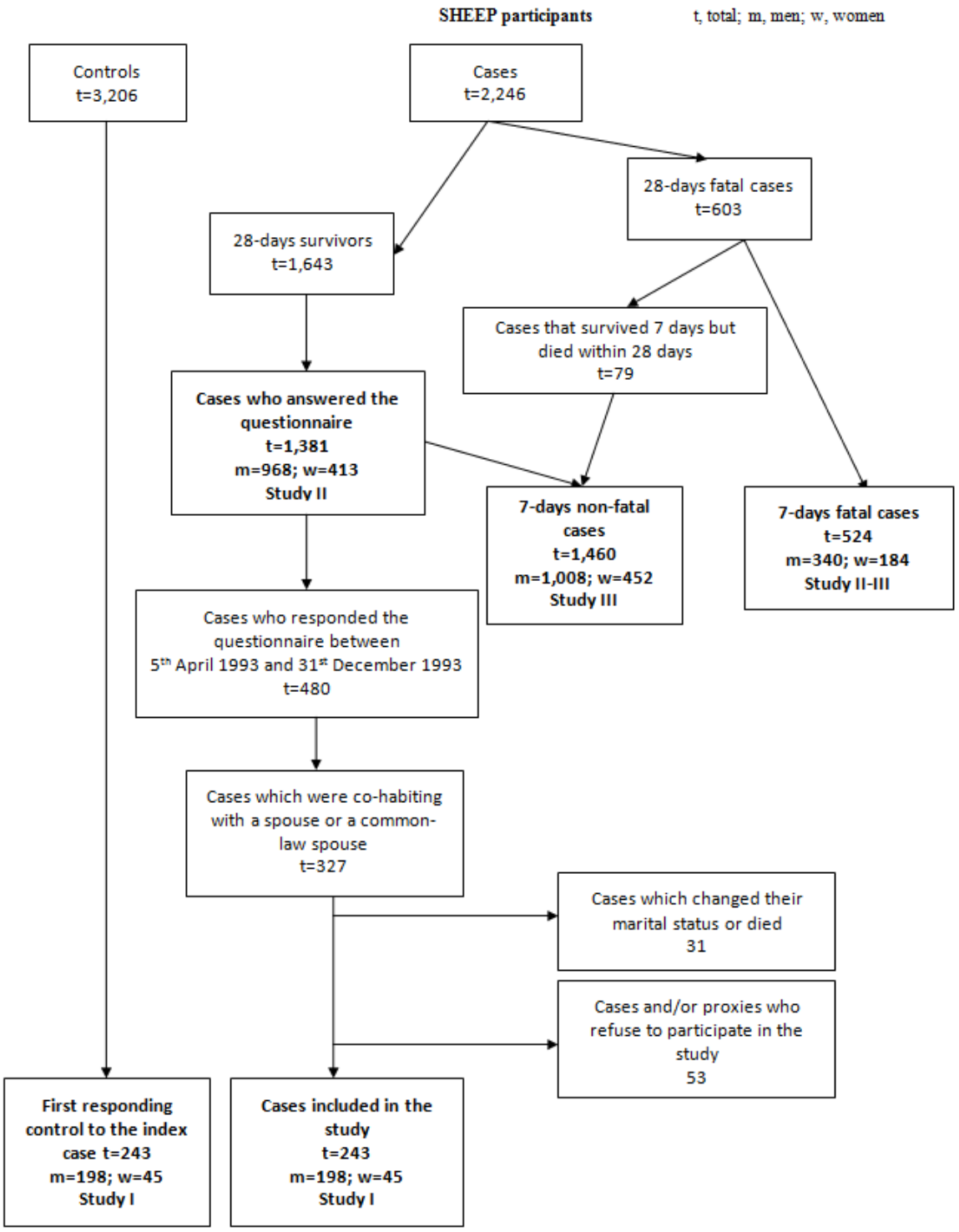

Figure 4. Participants in SHEEP (Studies I-III)

3.1.1.2 Questionnaire data

3.1.1.2.1 Use of the questionnaire data in the validation study (Study I)

The exposure assessment in Study I was exclusively based on questionnaire data provided by proxies, cases and controls (except for age and sex).

The participants were asked to report how often (considering the previous year) they had the following sleep-related problems: 1) Difficulties to fall asleep, 2) Difficulties to wake up, 3)

Difficulty to go back to sleep, 4) Heavy snoring, 5) Nightmares, 6) Not feeling thoroughly rested after waking up, 7) Waking up too early, 8) Restless while sleeping, 9) Feeling tired/sleepy, 10) Eyes tired/irritated, 11) Experiencing non-voluntary falling asleep at workplace, 12) Experiencing non-voluntary periods of sleep during leisure time. 13) Feeling fatigued and easily distracted.

For each sleeping problem item, there were five predefined answer alternatives: "never", "a few occasions yearly", "a few occasions monthly", "a few occasions weekly" and "on daily basis". The median frequency of sleeping problems among control individuals was determined and subjects reporting a frequency of problems at that median level or above were classified as exposed; for all sleeping-related problems except from "Experiencing non-voluntary periods of sleep during leisure time", the answer alternative "a few occasions monthly" was the median. For "Experiencing non-voluntary periods of sleep during leisure time", it was "a few occasions yearly".

The definition of "leisure time physical inactivity" was based on reports of questions regarding the level of leisure time physical activity in the previous 5 to 10 years. Respondents reporting "very little exercise" or "isolated walks only" were considered exposed. The reference category for this study includes a combination of those respondents who replied either "regular exercise" (at least once weekly) or "exercise once in a while"

The participants were also asked about other variables that include diet, alcohol consumption, work-related exposures and psychosocial factors. The validity of responses in proxies was evaluated for these variables.

3.1.1.2.2 Definition of variables (Studies I-III)

Participants were considered exposed to hypertension if they replied "yes" to the query "do you have hypertension?"/"does your close relative have hypertension?", or if they reported use of any medication against hypertension. Identification of exposure to diabetes and hyperlipidemia, respectively, was done in a similar fashion.

The questionnaire included specific questions on previous diagnoses of history of heart failure, stroke, angina or intermittent claudication. In addition, any pharmacological treatment during the week preceding the MI event was asked for and also the reason for any treatment (Studies II-III). Cases were considered "exposed" or "unexposed" to each comorbidity according to the responses to these questions. "Previous non-MI CVD" was defined from questionnaire reports by the participant/proxy of previous diagnosis of heart failure, stroke, angina or intermittent claudication (Studies I).

The body mass index (BMI) was calculated based on questionnaire information on weight and height. However, if these data were available from the physical examination (non-fatal cases) or from autopsy reports (fatal cases), they were used from these other sources instead (Studies II-III). "Overweight" was defined as a BMI $\geq$ 25 kg/m^2 and < 30 kg/m^2. "Obesity" was defined as a BMI $\geq$ 30 kg/m^2.

Individuals reporting current smoking of cigarettes, cigarillos, cigars or pipes for at least a year, or that they had quit smoking within the last two years, were classified as current

smokers (Study I-II). Stopping smoking more than two years ago was classified as former smoking (Study I). Not smoking in a regular fashion for at least a year was classified as "never-smoking" (Study I-II). The use of moist snuff or Swedish tobacco in the year preceding the survey was classified as use of "smokeless tobacco" (contrary to "non-use") (Study I).

Based on replies to questions with preset options about cardiovascular diagnoses and causes of death (whether relevant) in either a parent and/or a sibling of the index participant before they turned 65 years old, participants were classified as exposed or non-exposed to maternal, paternal and sibling history of CHD and CVD, respectively (Studies I-II). In these classifications, CHD comprised "sudden death", "MI" and "angina" whereas CVD comprised CHD and stroke. A "Don't know" reply was included as a predefined answer choice. Our analyses used two distinct methods: A) Using individuals who provided complete data about history of disease and cause of death (if relevant) in parents and potential siblings. B) Considering individuals who provided any information about history of disease or cause of death (if relevant) in parents or potential siblings. In approach B, "don't know" answers were set to "no" (Study I).

3.1.1.3 Register based data on comorbidities (Studies II-III)

Data from questionnaires were used to assess presence of cardiometabolic risk factors (usually comorbidities) and comorbidities in Studies II and III. However, the comorbidities of interest were also considered present if they were registered in any of the following: the Swedish National Patient Register (NPR), the Cause of Death Register (CDR) (Study II-III) and the autopsy reports (Study III).

3.1.1.3.1 The Swedish National Patient Register (NPR) (Studies II-III)

The NPR contains data on the date of admission, the date of discharge and the main and secondary diagnoses of each hospitalization occurring in Swedish hospitals. Data from the NPR, complete in Stockholm County since 1975 and nationwide since 1987, were available for all MI cases included in the SHEEP (56). Both main and secondary diagnoses (up to 7 secondary diagnoses) were considered to assess the presence of cardiometabolic risk factors (Study II) and comorbidities (Study III).

For each individual, the number of hospitalizations during the ten years preceding the MI event was counted using the NPR, but hospitalizations due to normal child delivery were not considered. Individuals were divided in 4 categories: not hospitalized (reference category), one hospitalization, two hospitalizations, and three or more hospitalizations (Study III).

For the study period, the NPR contains information on the 8th (1969-1986) and the 9th (1987-1996) revisions of the ICD. The ICD revisions contained in the NPR used for Study IV are described in 3.1.2.2.1.

3.1.1.3.2 The Cause of Death Register (CDR) (Studies II-III)

The CDR contains a copy of the information registered in each death certificate of deaths occurring in Sweden. It covers all people holding a permanent residency in Sweden and who

died within the study period. The variables of this register include the unique personal identification number, age, sex, date of death, the main and secondary causes of death, the manner of death, the timing between the beginning of symptoms and death, and on which grounds the causes of death were ascertained.

For the study period, the CDR contains information based on the 9th (1987-1996) revision of the ICD (57). The ICD revisions contained in the CDR used for Study IV are described in 3.1.2.2.2.

3.1.1.3.3 Autopsy records (Studies II-III)

Among 7-day fatal cases identified in the inception cohort extracted from SHEEP, 72% (n=377) underwent autopsy, as documented in death certificates, and 23% (n=120) did not. The MI diagnosis in the latter group was asserted on clinical grounds.

Among the fatal cases who underwent autopsy, 49% (n=186) of the reports were retrieved from county council archives (mainly for Stockholm County) or from departments of forensic medicine (all in Stockholm, except from one autopsy that took place in Uppsala). Among the autopsies for which a report was retrieved, 37% were performed at a department of forensic pathology.

An historical summary was available in 95% of the retrieved autopsy reports, and this information was used to identify comorbidities in fatal cases for which questionnaire data were not available. In addition to the data extracted from the SHEEP questionnaire and from the NPR, data from the historical summary was used to identify comorbidities (Study III). The findings from the external and internal autopsy examinations were reviewed for indicators of additional findings indicating comorbidity in a structured manner (Study III).

3.1.1.3.4 The longitudinal integration database for health insurance and labor market studies (LISA) (Studies II-III)

Data on individual disposable income the year preceding the year of the index event was extracted from the LISA register as an indicator of socioeconomic status.

3.1.2 Apolipoprotein-related Mortality Risk (AMORIS) cohort (Study IV)

3.1.2.1 Study base description

Study IV is based on the AMORIS cohort described *in extenso* in previous publications (58-60). In brief, the cohort comprises male and female participants who previously went through a health check-up, with samples analyzed by the Central Automation Laboratory (CALAB) in Stockholm, Sweden between 1985 and 1996.

The AMORIS cohort includes 391,669 male and 412,077 female participants of all ages with varying information on a large number of biomedical factors (60). In Study IV, a minimum age at baseline was set to 18 years old.

3.1.2.2 Low-grade inflammation biomarkers

All laboratory measurements were extracted from the CALAB dataset in AMORIS.

In Study IV low-grade inflammation was evaluated using a score comprised by five biomarkers. The five biomarkers used were: C-reactive protein (CRP), haptoglobin, white blood cell counts (WBC), albumin and uric acid. Three of them are acute phase proteins (APPs; CRP, haptoglobin and albumin), whereas WBC represents inflammatory cells and uric acid is a DAMP.

Sex specific distributions of the individual biomarkers forming basis for the inflammation score were analysed. The sex specific quartile cut-off values were identified and shown in Table 1. For each biomarker value in the top quartile, a point was generated in the inflammation score, except for albumin where a point was generated if the value of this biomarker was in the bottom quartile.

Table 1. Sex specific cut-off values to generate a point in the inflammation score

	Men	Women
Serum CRP	≥ 7.0 mg /L	≥ 7.0 mg /L
Serum haptoglobin	≥ 1.3 g/L	≥ 1.2 g/L
WBC	≥ 7.5 x 10^9/L	≥ 7.6 x 10^9/L
Serum uric acid	≥ 360 mmol/L	≥ 278 mmol/L
Serum albumin	≤ 42 g/L	≤ 41 g/L

CRP: C- reactive protein; WBC: White blood cell count.

Laboratory methods for the biomarkers used in the inflammation score and additional biomarkers has been earlier described (61-64).

Only subjects with valid information on each of the biomarkers forming the score were included in Study IV (Figure 5).

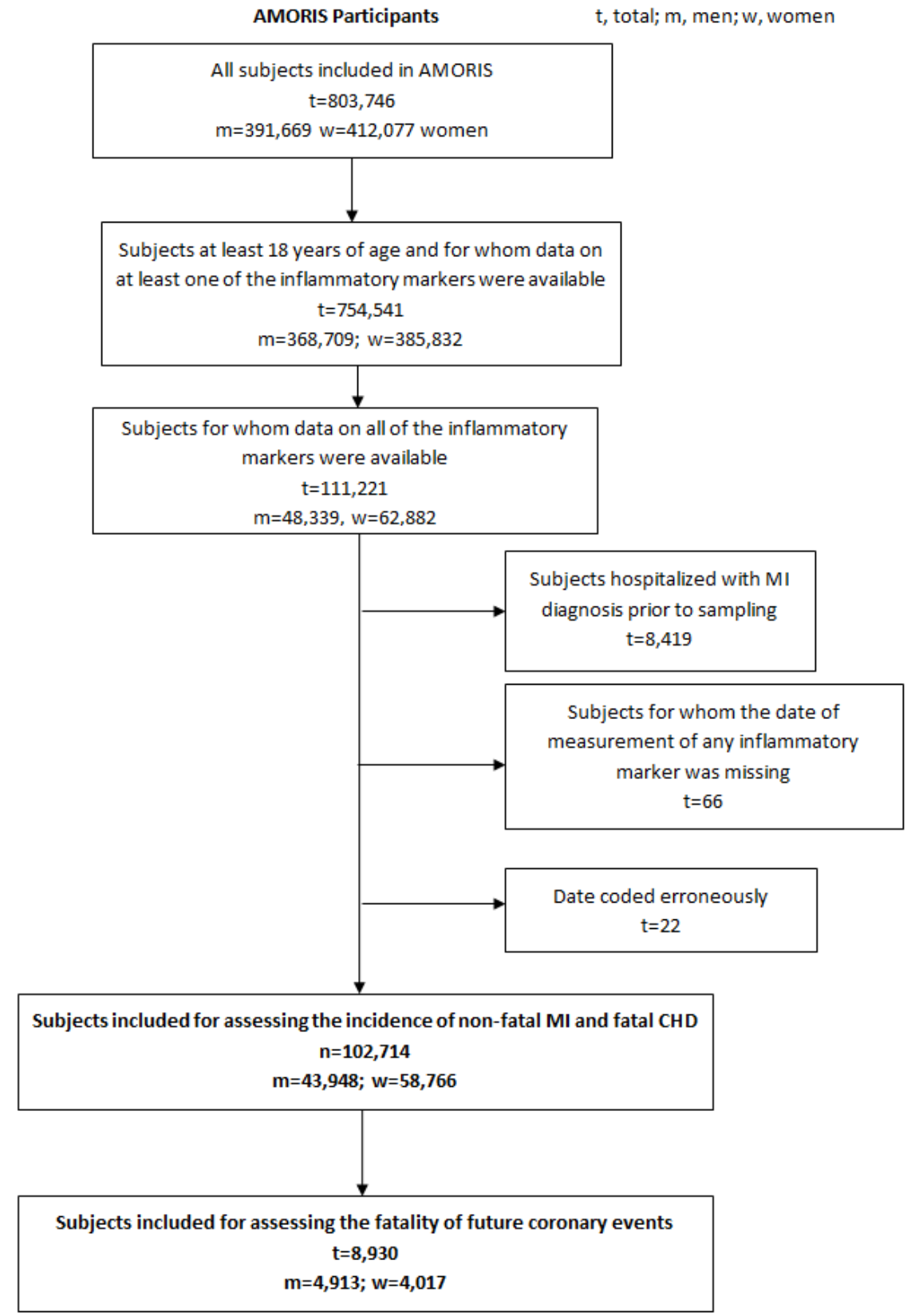

Figure 5. Selection of the study sample from the AMORIS cohort (Study IV)

3.1.2.3 Registers linked to AMORIS cohort data

3.1.2.3.1 The NPR

This register has been described in section 3.1.1.3.1.

For the study period, the NPR contains information of the 8th (1969-1986), 9th (1987-1996) and 10th (since 1997) revisions of the ICD (57).

3.1.2.3.2 The CDR

This register has been described in section 3.1.1.3.2.

For the study period, the CDR contains information of the 9th (1987-1996) and 10th (since 1997), revision of the ICD (57).

3.1.2.4 CHD case identification in AMORIS

3.1.2.4.1 CHD diagnostic criteria

The diagnostic criteria among hospitalized MI cases have changed during the AMORIS follow-up. The diagnostic criteria until 2000 are the same as those used in SHEEP, described in 3.1.1.1.1.

3.1.2.4.1.1 CRITERIA FOR DETECTING FIRST TIME MI USED SINCE 2000 (18):

1. Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one of the following:
    - ○ Symptoms of ischemia.
    - ○ New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block.
    - ○ Development of pathological Q waves in the ECG.
    - ○ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
    - ○ Identification of an intracoronary thrombus by angiography or autopsy.
2. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block, but death occurred before cardiac biomarkers were obtained, or before biomarker values would be increased.

3.1.2.4.2 Non-fatal MI

Non-fatal cases were identified from the NPR if they were hospitalized with MI (ICD-9 410 or ICD-10 I21) as a main diagnosis or secondary diagnosis during the follow-up and survived at least 1 day after being hospitalized.

Cases with MI as a main or secondary diagnosis in the NPR before the first examination in AMORIS were excluded (n=8,419). After excluding these subjects, as well as additional exclusions, the numbers of participants with complete information of all biomarkers were 43,948 men and 58,766 women (Figure 5).

3.1.2.4.3 Fatal CHD

Fatal CHD cases were defined as those who were hospitalized with MI (ICD-9 410 or ICD-10 I21) as a main diagnosis or any secondary diagnosis and died in the first day (regardless of the cause of death), and those participants who died out of hospital with CHD (ICD-9 410-4 or ICD-10 I20-5) as an underlying or cause of death without previous hospitalizations with MI. An alternative definition of fatal CHD included death up to 28 days

3.1.2.5 Possible confounders

3.1.2.5.1 Diabetes

Subjects were classified as suffering diabetes if any of four conditions occur before the index examination: 1) fasting serum glucose level above 6.9 mmol/L, 2) glycosylated hemoglobin (HbA1C) $\geq$ 6.5%, 3) a documented hospitalization in the NPR with diabetes as main or secondary diagnosis (ICD 9 code 250; ICD10 codes E10-E13), and 4) a registration in the Swedish National Diabetes Register.

3.1.2.5.2 Angina

Diagnoses of angina prior to the index examination were identified from the NPR, diagnostic code (main or secondary diagnosis) ICD-9 code 413 or ICD-10 code I20.

3.1.2.5.3 Highest attained education

The highest attained level of education was used as an indicator of socioeconomic status. The information was extracted from LISA national register for the year 1990 if the index examination took place before 1993 and for the year 1995 if it took place 1993 or later.

The educational level was categorized into four levels: nine years or less; ten to twelve years; thirteen years or more; and missing (65).

3.1.2.5.4 Other laboratory measurements

Others biomarkers extracted from AMORIS as additional variables include fasting glucose levels, HbA1C, total cholesterol and triglycerides. Laboratory methods to assess these biomarkers were described in earlier publications (63, 64).

3.2 STATISTICAL ANALYSES

3.2.1 Assessing Proxy Bias (Study I)

The prevalence of each exposure according to data collected from cases, proxies, and controls was calculated. To assess possible bias introduced by the use of data collected from proxies instead of cases, two odds ratios (ORs) were calculated using conditional logistic regression:

1) OR-A from a model based on data collected from cases and their matched controls, and 2) OR-B from a model based on data collected from the proxies and the same set of controls. For each exposure, the quotient from dividing OR-B by OR-A was calculated ("proxy bias").

A proxy bias of 1.0 indicates that on average proxies do not systematically overestimate or underestimate the exposure assessed as compared to cases. Values below 1.0 indicate that proxies underestimate the exposure and that OR-B is underestimated, whereas values above 1.0 indicate that proxies overestimate the exposure and that OR-B is overestimated. The 95% CI limits for the "proxy bias" was calculated using resampling bootstrap based on 5000 iterations, considering the difference between the variable coefficients of the model producing OR-A and OR-B. The bootstrap is suitable because it requires very limited assumptions about the probability distribution where the data comes from. Logistic regressions and the bootstrap analyses were performed using SAS version 9.2. This method to assess disagreement between cases and proxies has not earlier been used, as far as the literature currently states.

3.2.2 Assessing MI fatality (Studies II-III)

Using the NPR and data from the SHEEP questionnaire, the prevalence of all comorbidities in the group who suffered a fatal MI was assessed (Study III). Whenever questionnaire data were not available for a fatal case, the historical summary in the autopsy report, if available, was used instead. A few of the comorbidities considered, such as asthma, were defined narrowly and identified with a single ICD-8/ICD-9 code whereas the majority, including psychiatric disease was not.

The risk of death within 7 days among cases (7-day MI fatality) was calculated in different strata of cardiometabolic risk factor status(diabetes, hypertension, hyperlipidemia, and BMI categories) (Study II), number of hospitalizations, and comorbidities with prevalence above 2% in fatal MI cases (Study III). Risk ratios with 95% CIs of 7-day MI fatality associated with the different risk factors were calculated using binomial regression with log link.

Adjustments were made for age and sex in all analyses (Studies II-III), except for alcoholism and epilepsy (Study III). In subsequent analyses, additional potential confounding factors were considered for adjustments: cardiometabolic risk factors (other than the one under study), current smoking, physical inactivity, educational level, low disposable income, family history of CVD, parental history of premature cardiac death, and number of hospitalizations (Study II). All confounding variables were dichotomized, except BMI and educational level that were divided into four and three categories, respectively (Study II). Because the results from Study I showed an overestimation of level of physical inactivity by proxies, this variable was not considered in the adjustments (Study II).

The attributable proportion (AP) of each comorbidity (AP) was calculated using the following formula:

$$\text{AP} = \frac{RR-1}{RR} * proportion\ of\ the\ 7-day\ fatal\ cases\ with\ this\ comorbidity$$

3.2.3 Low-grade inflammation in relation to risk of non-fatal MI, fatal CHD and a fatal outcome of future coronary events (Study IV)

3.2.3.1 Incidence rates of non-fatal MI and fatal CHD

Incidence rates of non-fatal MI and fatal CHD, stratified by sex and inflammation score were calculated. Sex specific hazard ratios (HR) with 95% CI of non-fatal MI and fatal CHD, respectively, associated with a one-unit increase of the inflammation score were modelled using Cox regression. Analyses using the score as a categorical variable with zero as reference were also performed. Follow up started at baseline and ended at time of the event, death from other cause or end of follow-up, whichever occurred first. Factors considered for adjustments were age at baseline, diabetes, educational level, serum total cholesterol level, serum triglyceride level and angina.

3.2.3.2 Case-fatality of future coronary events

The association between a one-unit increase of the inflammation score and 1-day and 28-day fatality of coronary events, respectively, was modelled using logistic regression. Analyses using the inflammation score as a categorical variable with zero as reference were also performed. Adjustments were made for age at the index event and calendar year of index event. In additional models, further adjustments were made for diabetes, educational level, total cholesterol, triglycerides and angina.

4 SUMMARY OF THE RESULTS

4.1 VALIDITY OF INFORMATION FROM PROXY RESPONDENTS (STUDY I)

The main finding of the validation study is the agreement between index MI cases and their respective spouses and common-law spouses for most of the exposures under study. However, as compared to their index cases, proxies had a tendency to overestimate the exposure to leisure time physical inactivity, non-voluntary falling asleep during leisure time, and heavy snoring. In the other hand, as compared to index cases, proxies had a tendency to underestimate the frequency of non-voluntary falling asleep at work, pollution at workplace, coffee consumption and intake of vitamin supplements.

4.2 RISK FACTORS ASSOCIATED TO FATALITY OF CORONARY EVENTS (STUDIES II-IV)

4.2.1 Association between cardiometabolic risk factors and MI fatality (Study II)

Diabetes was associated with an increased risk of dying within 7 days after the MI (RR 1.68, 95% CI 1.20-2.28) both in crude and multiple adjusted models.

Overweight, as compared to normal weight, was associated with a decreased risk of dying within 7 days after the MI (RR 0.68, 95% CI 0.49-0.94). For obesity, also compared to normal weight, a similar tendency was observed.

The risk ratios of 7-day MI fatality associated with hyperlipidemia and hypertension, respectively, were close to the null.

4.2.2 Comorbidities in relation to MI fatality (Study III)

4.2.2.1 Association between the number of previous hospitalizations and MI fatality

Fatal cases were more often repeatedly hospitalized prior to the MI event. As the number of hospitalizations increases, the stronger the association with MI fatality becomes.

4.2.2.2 Prevalence of specific comorbidities in fatal MI cases

The five most common comorbidities among 7-day fatal cases were all related to CVD: hyperlipidemia (36.1%), hypertension (35.3%), angina (34.7%), diabetes (23.7%) and heart failure (18.4%). The six comorbidities most strongly associated to 7-day MI fatality were epilepsy (RR 2.4, 95% CI 1.7-3.0), heart failure (RR 2.0, 95% CI 1.7-2.4), alcoholism (RR 2.0, 95% CI 1.9-3.2), stroke (RR 1.9, 95% CI 1.6-2.6), renal diseases (RR 1.8, 95% CI 1.4-2.2) and cancer (RR 1.8, 95% CI 1.4-2.2). The comorbidities found to have the highest estimated AP were: heart failure (9%), diabetes (7%), stroke (7%), psychiatric disease (other than alcoholism) (5%) and alcoholism (5%). Intermittent claudication, hyperlipidemia, hypertension, angina and obesity were not associated with 7-day fatality of MI.

Table 2 shows the findings from our structured review of the external and internal examination parts of the autopsy reports, indicative of the presence of comorbidities. The

most prevalent indicators of comorbidity in the external examination were missing teeth (considered to be an indicator of dental disease), obesity and underweight. The internal examination revealed myocardial scars (indicative of a previous silent MI), severe atherosclerosis of the abdominal aorta, and hepatic steatosis. Half of the fatal cases with moderate-severe atherosclerosis of the abdominal aorta had no previous record of CVD in any of our other sources of information. Fifty percent of those with hepatic steatosis exhibited no evidence of alcoholism, hospitalizations for alcohol psychosis or use of medications for treatment of alcohol abuse.

Table 2. Findings indicative of the presence of comorbidity in 7-day fatal MI cases based solely on the autopsy reports.

Autopsy finding	All	N
External examination, N (%)		
Missing teeth	27 (38.6)	68
Obesity	12 (13.6)	88
Underweight	6 (6.8)	88
Internal examination, N (%)		
Abdominal aortic atherosclerosis[a]		
More advanced than individuals of the same age	136 (76.4)	178
Low degree	22 (12.4)	178
Moderate degree	60 (33.7)	178
Severe degree	54 (30.3)	178
Difficult to assess by the pathologist or not described	11 (6.2)	178
Myocardial scar	68 (36.6)	186
Hepatic steatosis	51 (28.0)	185

MI: myocardial infarction; NA: Not available; obesity was defined as a body mass index of 30 kg/m2 or more; underweight was defined as a body mass index of 18 kg/m2 or less;
[a]As described by the pathologist in the autopsy protocol.

4.2.3 Low-grade inflammation and fatality of future coronary events (Study IV)

4.2.3.1 Non-fatal MI and fatal coronary events

The mean period of follow-up was 22.1 ± 5.8 years. The number of incident CHD cases identified during follow-up, forming basis for the analyses of case fatality, was 4,913 in men and 4,017 in women. Of them, 1,357 male cases (28%) and 1,347 female cases (34%) were classified as 1-day fatal. Among the fatal coronary events, 2,408 (1,218 men and 1,190 women) occurred out-of-hospital or at the hospital upon arrival (with no admission diagnosis). Of these, 47% (57% of the men and 36% of the women) were subject to autopsy; another 34% were subject to clinical investigation at the hospital prior to death; and an additional 10% to clinical investigation outside of the hospital prior to death.

Among the individuals who suffered a fatal coronary event during the follow-up, the mean age at the time of this event was 73 years for men and 81 years for women (Table 3). The corresponding ages at the time of a non-fatal coronary event were 69 years and 76 years

(Table 3). The average time that elapsed between the examination and the coronary event was 13.3 ± 6.3 years.

Table 3. Age and distribution of biomarkers conforming the inflammation score in participants in the AMORIS cohort who subsequently suffered a coronary event during follow-up.

	Men		Women	
	1-day fatal CHD (N=1,357)	Non-fatal MI (N=3,552)	1-day fatal CHD (N=1,347)	Non-fatal MI (N=2,670)
Age, years (mean ± SD)	60 ± 13	56 ± 12	68 ± 11	62 ± 12
Age at coronary event, years (mean ± SD)	73 ± 11	69 ± 11	81 ± 10	76 ± 11
Serum levels of the inflammatory markers				
CRP (mg/L), median (IQR)	4 (1-9)	4 (1-8)	4 (1-10)	4 (1-8)
Haptoglobin (g/L), mean ± SD	1.23 ± 0.44	1.18 ± 0.38	1.24 ± 0.41	1.19 ± 0.37
WBC (n x 10^9/L), median (IQR)	6.9 (5.8-8.5)	6.7 (5.6-8.2)	6.7 (5.6-8.2)	6.6 (5.4-8.0)
Uric acid (mmol/L), mean ± SD	340 ± 78	334 ± 70	290 ± 80	282 ± 74
Albumin (g/L), mean ± SD	42.0 ± 3.0	42.0 ± 3.0	41.0 ± 2.7	41.4 ± 2.6

CHD: coronary heart disease; MI: myocardial infarction; SD: Standard deviation; CPR: C-reactive protein; IQR: Interquartile range; WBC: white blood cell count.

4.2.3.2 Associations between the inflammation score and non-fatal MI, fatal CHD and fatality of future coronary events

The sex stratified incidence of fatal CHD and non-fatal MI, respectively, rose by inflammation score. A significant association with non-fatal MI and fatal CHD, respectively, was observed for each unit increase in the inflammation score in both the crude and the adjusted models. This association was somewhat more pronounced for fatal CHD (adjusted models: HR in men 1.36, 95% CI 1.30-1.42; HR in women 1.34, 95% CI 1.28-1.40) than for non-fatal MI (adjusted models: HR in men 1.23, 95% CI 1.19-1.25; HR in women 1.25, 95% CI 1.21-1.29).

In men, the crude OR for 1-day and 28-day fatality of coronary events, respectively, associated with a one-unit increase in the inflammation score were 1.17 (95% CI 1.11-1.23) and 1.18 (95% CI 1.12-1.24), respectively. These values decreased to 1.13 (95% CI 1.07-1.19) and 1.13 (95% CI 1.07-1.19) after adjustments for age at the time of the coronary event and calendar year of this event. Further adjustments for diabetes, level of education, serum levels of total cholesterol and triglycerides, and angina did not substantially alter these values. In women, the crude OR for 1-day and 28-day fatality of coronary events, respectively, associated with a one-unit increase in the inflammation score were 1.16 (95% CI 1.01-1.23) and 1.16 (95% CI 1.10-1.22), respectively. These values decreased to 1.12 (95% CI 1.06-1.19) and 1.12 (95% CI 1.06-1.18) after adjustment for age at the time of the coronary event and calendar year of this event. As for the men, further adjustment for diabetes, level of education, serum levels of total cholesterol and triglycerides, and angina had little impact in the estimates.

5 DISCUSSION OF RESULTS

5.1 VALIDITY OF INFORMATION FROM PROXY RESPONDENTS (STUDY I)

Taken together, the results of Study I suggest that information collected from close relatives of MI patients regarding their exposures prior to the MI event in general is valid. Caution must however be taken in relation to information on level of physical activity, presence of sleep-related disorders as well as some work-related exposures.

The overestimation observed for level of physical inactivity agrees with a study by Nelson et al. (66) based on index patients who suffered a stroke.

5.2 POTENTIAL DETERMINANTS OF CORONARY EVENT FATALITY (STUDIES II-IV)

The interpretations of results on associations between risk factors and fatality of coronary events are not straight-forward from a disease etiology perspective. In an inception cohort of individuals who suffered an MI, extracted from a case-control study material, as in Studies II and III, the exposures are assessed close in time to the MI event. Both the current exposure status and the duration of the exposure back in time may affect the outcome of the MI event. In an inception cohort extracted from a population-based cohort, as in Study IV and several other studies (13, 14, 34), the exposures are generally assessed distant in time from the disease onset. In neither of those study designs, it is possible to distinguish between influences from exposures during the period before the MI event from influences during the acute phase of the event. The same exposure factor may theoretically exert effects both before the MI event and during the acute phase. The pre-event influences may theoretically influence not only if the MI event will occur or not, but also the severity of the event. This is illustrated in Figure 6.

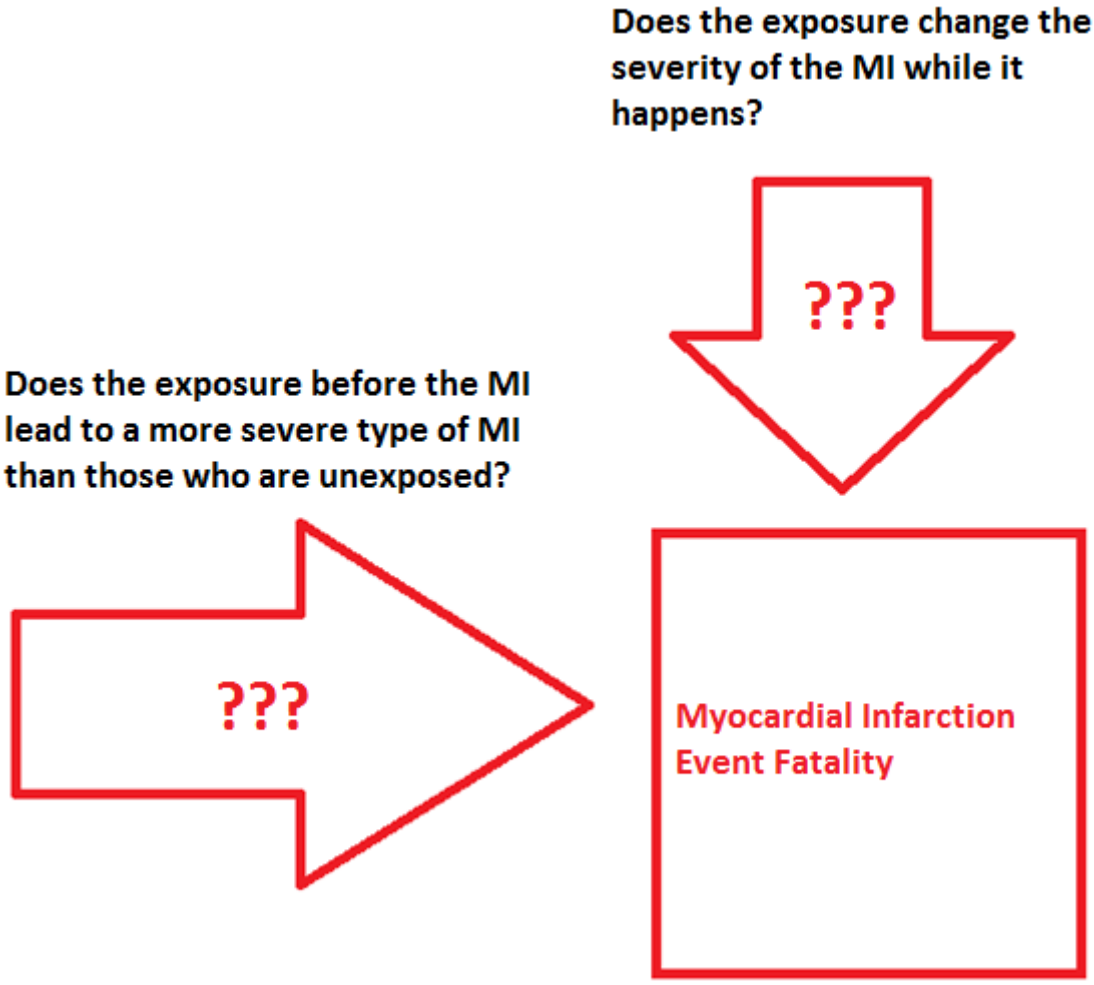

Figure 6. The timing when the exposure exerts its effect cannot be asserted regardless the study design.

5.3 POSSIBLE MECHANISMS IN RELATION TO CARDIOMETABOLIC RISK FACTORS ASSOCIATED TO MI FATALITY (STUDY II)

5.3.1 Diabetes

Our finding of an association between diabetes and MI fatality agrees with findings from two previous publications where both hospitalized patients and out-of-hospital deaths were considered (15, 32). This finding also agrees with a large body of literature reporting such association in studies restricted to hospitalized patients (29, 30, 35, 67, 68).

Possible mechanisms explaining why diabetes increases MI fatality are related to decreased blood supply in normal and infarcted myocardial tissue as compared to persons without diabetes (69). Animal models show a decreased availability of nitric oxide in diabetic mice, leading to a fatal vasoconstriction (70). Another possible mechanism relates to a reduced consumption of glucose by the myocyte due to a decreased translocation of glucose transporter 4 (GLUT4) to the sarcoplasmic membrane (69). Yet another possible mechanism is the decreased angina perception that leads to decreased awareness of MI which may render it fatal due to a delay in seeking care. Silent MI is more common in individuals with diabetes (71) and scarred tissue in the heart may negatively influence the recovery of function of the

heart in the acute phase of an MI event. We identified signs of a previous silent MI in 36.6% of the fatal cases subjected to autopsy in SHEEP. However, because we had no possibility to assess silent MI in non-fatal cases, we could not assess the association between silent MI and MI fatality.

Future research on how diabetes may influence MI fatality may perhaps take advantage of post mortem vitreous glucose level measurements mirroring serum glucose levels just before death (72).

5.3.2 Overweight, obesity, hypertension and hyperlipidemia

Results regarding overweight and obesity, showing an inverse relation with MI fatality agree with previous studies of hospitalized MI cases (40, 73). However, a study where out-of-hospital deaths are included showed no association (14). A possible reason for this discrepancy is that BMI were categorized while the compared study assessed BMI as continuous. Since there is no clear understanding about possible biological mechanisms, our results must be interpreted with caution.

Our results are coherent with the "obesity paradox", a hypothesis stating that individuals with a high BMI have a better prognosis after a CVD (74, 75). From a biological perspective, our observed low 7-day MI fatality in overweight and obese individuals, as compared to normal BMI, could be attributed to larger fat storages than in thinner peers which lead to more energy available to engage the demands after an MI event takes place. Another explanation of our findings might be that individuals with normal weight may have comorbidities that made them lose weight rendering them vulnerable after an MI occurs (76). Despite adjustments for comorbidities in the final models, there is a possibility that residual confounding effects exist. For instance, insulin resistance as well as complicated diabetes may involve weight loss and may be associated with MI fatality.

Hypertension and hyperlipidemia for example are known to be associated with an increased incidence of MI, but in Studies II and III, they were not associated with MI fatality. These results could however also potentially be explained by presence of the so called "index event bias". An author states that "Index event bias is an unwelcome consequence of selecting a study population on the basis of a prior event. The possibility of index event bias should be a reason for caution in the causal interpretation of (null) associations, because it can conceal the effect of risk factors" (77). This explanation is not widely accepted, for example, in an editorial from the European Heart Journal, it is stated that the effect of obesity and overweight on patient suffering CVD is real, because some comorbidities can decrease the weight and increase death in these patients (76).

5.4 POSSIBLE MECHANISMS BEHIND THE ASSOCIATIONS BETWEEN FATALITY OF CORONARY EVENTS AND INFLAMMATION AND VARIOUS COMORBIDITIES (STUDIES III-IV)

5.4.1 Inflammation

Inflammation is a non-specific immune response to any kind of injury (78). Low-grade inflammation could be considered as an inflammatory response in absence of inflammation

cardinal focal symptoms and signs, known as the Celsus tetrad (warmth, pain, redness and swelling). As our results point out, low-level inflammation might increase fatality after a future coronary event. Possible mechanisms proposed include a decreased buffering capacity to engage the coronary event due to a more diffuse necrosis (16) or an increased possibility of developing a fatal arrhythmia (16, 17, 79).

It is not difficult to speculate that chronic symptomatic inflammation will also favor a deadly outcome after a coronary event with similar mechanisms. All of the diseases identified in Study III to be associated to increased MI fatality have a symptomatic inflammatory component, with the exception of psychiatric disease and epilepsy. However, low-grade inflammation seems to be associated to psychiatric disease (80) unless it is related to an organic component, for example, drug abuse or some dementias when a symptomatic inflammation might occur.

Regardless the clinical presentation of inflammation, the timing of its effect on the MI/CHD event cannot be easily assessed as we mentioned above in 5.2.

5.4.2 Number of hospitalizations

In the inception cohort of MI cases extracted from SHEEP, the number of previous hospitalizations was associated with increased MI fatality after adjustment for age, sex and low disposable income (Study III). Such association was previously not analyzed. The number of hospitalizations might reflect multiple co-morbidities, severe comorbidity or the amount of damage to organs which in turn may affect survival in the acute phase of a MI through an increased fragility (unspecified). Another possibility is that the number of hospitalizations reflect, potential deleterious effects of various treatments hampering the chances of survival in the event of an MI. The number of hospitalizations may also perhaps reflect the level of anxiety related to deteriorating well-being and/or stress from being absent from work and not being able to take care of private matters, which might influence MI fatality via mechanisms that are as yet unknown.

5.5 GENERALIZABILITY OF RESULTS (STUDY II-IV)

The results based on the SHEEP material, collected between 1992 and 1994 could be difficult to be generalized to more recent settings, considering that the criteria for MI diagnosis has changed (18, 55) and that treatments for specific diseases and exposures have improved over time.

AMORIS is a very large cohort of men and women living in Stockholm county comprising almost a half of the population in this county (60). However, the generalizability of results to the general population may be somewhat compromised due to a potential “healthy worker” effect (a selection of individuals healthier than the general population, the underlying reason being that they are employed and thus not too sick to be in the working force) (81). The mortality rate in this cohort is somewhat lower than the mortality rate in general Stockholm population (standardized mortality rate: 0.86) (60).

6 DISCUSSION OF METHODS

6.1 DESIGN LIMITATIONS OF THE VALIDATION STUDY (STUDY I)

The main limitation of this study design is a potential misclassification of the exposure in either the case or the control or in both. Because the design builds upon a "true" odds ratio based on reports from cases and controls, the assessment of proxy data will not be correct if the compared odds ratio is not "true". The study design of Study I cannot address the occurrence of such misclassification. A comparison to objective measures in the cases would have been preferable but for most exposures considered such data would not be possible to get.

6.2 POSTMORTEM MI ASSESSMENT

An advantage of the SHEEP study is the thorough assessments of MI as a cause of death performed by clinicians based on data from death certificates. The relatively high rate of autopsies during the 1990's when the study was performed contributes to a high validity of postmortem MI assessment. Problems to distinguish between MI death and other cardiac related death may however still have been present.

It is for example not possible to ascertain MI if the death occurs too early for signs of MI to be detected using light microscopy or the naked eye as described in 1.3. The Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) consortium refers to these cases as F2 (82), and White et al. called them "MI type 2" in their updated MI criteria (18).

Due to the problems to distinguish MI death from other cardiac related death, most studies use the broader "CHD death" definition instead of MI death. In Study IV, we chose to do so because we had no access to autopsy records. Further, the declining rate of autopsies since the 1990's may have led to an attenuated validity of post mortem MI assessment.

Because the proportion of autopsies has decreased over time in Sweden as shown in Figure 8, it might be intuitive to think that the proportion of autopsies in CHD suspected cases has also decreased. Although this could be true, our data show that a relatively high proportion of cases with identified MI/CHD undergo an autopsy both in SHEEP and in AMORIS. Information about the autopsy proportion among individuals classified as dead from CHD is not to be found in national statistics. The MONICA study has a relatively large documentation on autopsies in CHD cases between 1980 and 1995. Among the participating centers, the highest proportion of autopsy were found in Toulouse in France, New Zealand, the former Yugoslavia, US, Switzerland, Russia and Gothenburg in Sweden (110). The autopsy proportions in MI cases in SHEEP are quite similar as the ones found in Gothenburg city when the MONICA study took place.

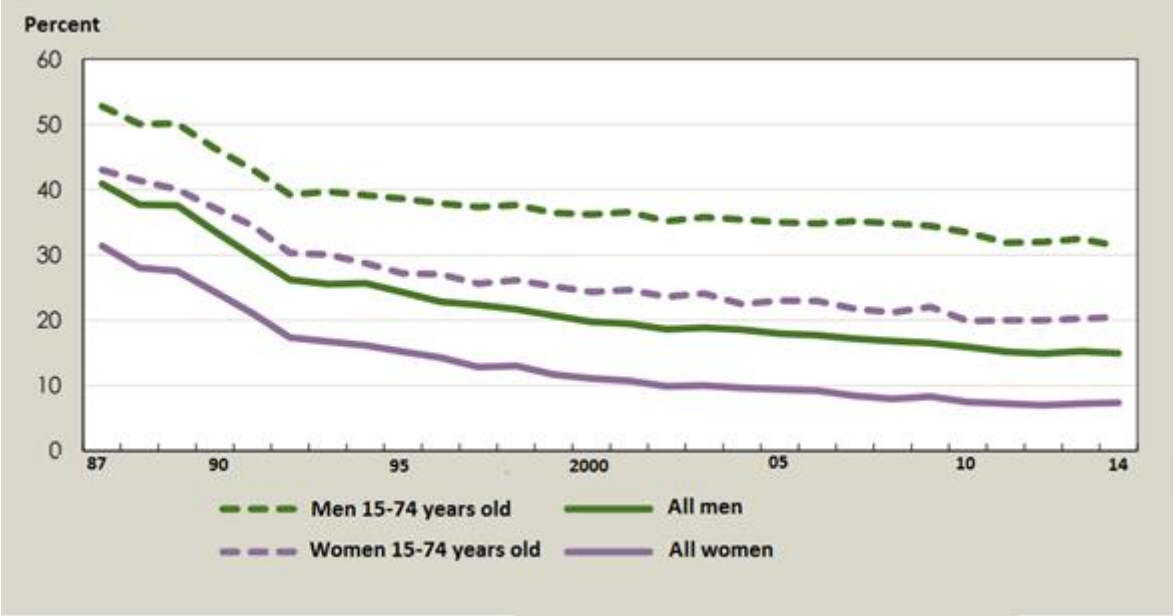

Figure 7. Proportion of autopsies from 1987 to 2014, among all fatal events men and women, as well as in those aged 15-74 years in Sweden. Legends were translated from Swedish and the time scale was reformatted in order to reflect the calendar year. Source: Dodsorsaker 2014 (Causes of Death 2014- In Swedish language) (83).

6.3 REGISTER-BASED DATABASES (STUDIES I-IV)

The studies included in this thesis are all to some extent based on data from national registers. The use of a unique 10-digit personal identification number in Sweden has made it possible to extract information about diagnoses at hospitalizations and causes of death during a follow-up period with virtually no loss to follow-up. It also provided the possibility to extract data on socioeconomic indicators.

6.4 CONFOUNDING (STUDIES II-IV)

Considering the relatively limited knowledge about determinants of MI fatality, it is not evident what potential confounders to adjust for in the analyses of various potential risk factors considered in this thesis. Further, it may be difficult to distinguish between confounding factors and factors that have a role in the causal chain of mechanisms behind a fatal outcome. The possibility of uncontrolled confounding should be considered when interpreting the results from this thesis.

7 CONCLUSIONS

This PhD thesis contributes to fill a void of knowledge regarding determinants of MI fatality. It also contributes to the limited scientific knowledge about validity of information collected from proxy respondents.

Among the cardiometabolic factors considered in this thesis, diabetes and presence of a low-grade inflammation were observed to associate with fatality of coronary events. No such associations were observed for hypertension, and hyperlipidemia. Further, our results seem to favor the "obesity paradox", since individuals with overweight and obese individuals had lower fatality than those with a normal BMI.

Our explorative approach to identify comorbidities in fatal MI cases revealed that the following were prevalent and also associated with increased MI fatality: heart failure, diabetes, stroke, alcoholism, psychiatric disease, rheumatoid arthritis, asthma and epilepsy

Our explorative approach to identify indicators of additional comorbidities in fatal MI, based on autopsy records, revealed presence of partial or total edentulism (data available only from forensic autopsy records), advanced atherosclerosis in the abdominal aorta, and hepatic steatosis.

Low-grade inflammation was associated with an increased fatality of future coronary events of a cohort of healthy individuals at baseline.

8 FUTURE RESEARCH

Time to treatment is the most important factor influencing MI fatality. To lower rates of MI fatality, efforts to shorten time to treatment in the acute phase are important. However, an improved understanding of other determinants of MI fatality is also needed. This thesis addresses the potential influences from cardiometabolic risk factors including a low-grade inflammation and from comorbidities. Several interesting associations were observed and possible avenues for future research include investigating whether treatments of low-grade inflammation will lower fatality of future MI events. The components of inflammation should also be better characterized. Future research may also address other potential risk factors of MI fatality. Future research may take advantage of novel imaging techniques in non-fatal MI cases which will allow comparisons to pathological findings in fatal cases.

9 SUMMARY IN SWEDISH

Bakgrund

Trots ett stort antal förbättringar i förebyggande och vård av kranskärlssjukdom (CHD) under senare år, var denna sjukdomsgrupp en av de främsta dödsorsakerna år 2010 runt om i världen. Majoriteten av dödsfallen i CHD inträffar utanför sjukhus och forskning kring riskfaktorer för död i samband med CHD-insjuknande, där dödsfallen utanför sjukhus beaktas, är begränsad.

Mål

Det övergripande syftet med projektet var att öka kunskapen om faktorer som bidrar till risken att avlida i samband med insjuknande i en förstagångs hjärtinfarkt i Stockholms allmänna befolkning. Specifika syften var att: 1) validera enkätuppgifter som samlats in från nära släktingar till hjärtinfarktpatienter, 2) bedöma hur kända kardiometabola riskfaktorer är förknippade med risken att avlida i samband med en hjärtinfarkt, 3) beskriva vilka andra sjukdomar som vanligen förekom hos individer som avled i samband med hjärtinfarkt samt bedöma om dessa sjukdomar är associerade till en fatal utgång av hjärtinfarkt, 4) bedöma om låggradig inflammation är associerad till död i samband med framtida insjuknande i koronarsjukdom.

Metoder

Utnyttjande studiematerial från Stockholm Heart Epidemiology Program (SHEEP), en fall-kontrollstudie, värderades giltigheten av enkätuppgifter (82 variabler) som makar/sambor (proxy-respondenter) tillpatienter med icke-fatal hjärtinfarkt rapporterat. Med användning av villkorlig logistisk regression beräknade vi för var och en av exponeringarna, en ”proxy bias”, baserat på information som samlats in från 1) hjärtinfarkt-fall och kontroller [oddskvot A] och 2) ”proxies” och samma uppsättning kontroller [oddskvot B]. Oenighet mättes genom beräkning av förhållandet mellan oddskvot B och oddskvot A; 95% konfidensintervall (Cl) beräknades med s.k. resampling bootstrap with replacement.

Från SHEEP extraherades en kohort av alla förstagångs-fall av hjärtinfarkt. Data om exponeringar inhämtades från frågeformulär (ifyllda av en nära släkting om fallet hade haft dödlig utgång), kroppsundersökningar (för icke-dödliga fall), nationella register och obduktionsrapporter. Associationer mellan utvalda kardiometabola riskfaktorer och hjärtinfarkt-fatalitetanalyserades genom beräkningar av riskkvoter (RR) med 95% konfidensintervall (Cl) under användning av binomial-regression med log link. Förekomst av andra sjukdomar, s.k. co-morbiditeter, bland de fatala hjärtinfarkt-fallen kartlades och antalet tidigare sjukhusinläggningar räknades. Samband mellan specifika sjukdomsdiagnoser samt antal tidigare sjukhusinläggningar och hjärtinfarkt-fatalitet analyseradesmed samma metod förmodellering som för kardiometabola riskfaktorer. En strukturerad genomgång av obduktionsuppgifter utfördes för att identifiera ytterligare indikatorer på sjukdomstillstånd hos fatala hjärtinfarkt-fall.

Utnyttjande material från AMORIS-kohorten, analyserades könsspecifika associationer mellan låg-gradig inflammation (identifierad genom en poängskala byggd på mätningar i

blod av fem olika biomarkörer: C-reaktivt protein, haptoglobin, antalet vita blodkroppar, urinsyra och albumin) och en dödlig utgång hos individer som under uppföljningstiden i AMORIS drabbades av en första koronar-händelse. Associationerna fastställdes genom beräkning av oddskvoter med 95% Cl under användning av logistisk regression.

Resultat

För de allra flesta av de exponeringar som beaktades i valideringsstudien fanns ingen statistiskt signifikant oenighet mellan rapporter från ”proxies” och hjärtinfarktpatienter. Emellertid överskattades fysisk inaktivitet på fritiden av ”proxies” jämfört med hjärtinfarktpatienter.

Diabetes, men inte hypertoni och hyperlipidemi, var associerad med hjärtinfarkt-fatalitet. Övervikt, jämfört med normal BMI, var omvänt associerat med hjärtinfarkt-fatalitet; resultaten för fetma gick i samma riktning. Resultaten justerades för ålder, aktuell rökning, förtida hjärtdöd hos föräldrar, antal tidigare sjukhusinläggningar, utbildningsnivå, disponibel inkomst, och andra kardiometabola riskfaktorer.

Antalet tidigare sjukhusinläggningar var associerat med hjärtinfarkt-fatalitet efter justering för kön, ålder och disponibel inkomst. Bland de co-morbiditetersom befanns relativt vanligt förekommande hos fatala fall och som efter justeringar (om möjliga) var associerade med 7-dagars hjärtinfarkt-fatalitet var: hjärtsvikt, stroke, diabetes, alkoholism, psykiatriska sjukdomar, cancer, njursjukdomar, epilepsi, reumatoid artrit och astma. Indikatorer för sjukdomstillstånd utifrån obduktionsuppgifter var s.k. tyst hjärtinfarkt, grav åderförkalkning av bukaorta och lever-steatos.

En låg-gradig inflammation var, efter justeringar (för ålder vid tidpunkten för den koronara händelsen, kalenderår för den koronara händelsen, diabetes, utbildningsnivå, serumnivå av totalkolesterol, serumnivå av triglycerider och angina) associerad med ökad dödlighet i samband med en framtida koronar händelse, hos både män och kvinnor.

Slutsatser

Hjärtinfarkt-patienter och deras makar/sambor rapporterade samstämmiga uppgifter om ett stort antal exponeringar som föregick insjuknandet hos patienten. Detta exponeringar innefattade traditionella kardiovaskulära riskfaktorer. Dock observerades oenighet beträffande rapporter om fysisk inaktivitet på fritiden.

Bland de kardiometabola faktorer som studerades, befanns diabetes och förekomst av en låggradig inflammation, men inte hypertoni och hyperlipidemi, vara associerade med en ökad hjärtinfarkt-fatalitet. Övervikt var associerad med en minskad hjärtinfarkt-fatalitet. Upprepade tidigare sjukhusvistelser och/eller hjärtsvikt, diabetes, stroke, psykiatrisk sjukdom, alkoholism, cancer, njursjukdomar, epilepsi, reumatoid artrit och astma var associerade med ökad hjärtinfarkt-fatalitet.

10 SUMMARY IN SPANISH

Antecedentes

Aunque ha habido un gran número de mejoras en la prevención y atención de las enfermedades coronarias (EC), ésta fue una de las principales causas de muerte en el 2010 en todo el mundo. La mayoría de las muertes por EC se producen fuera del hospital y la investigación sobre los determinantes de la letalidad por EC donde se consideran tales muertes es escasa.

Objetivos

El objetivo general de este proyecto fue aumentar el conocimiento sobre los determinantes de la letalidad por EC en la población general de Estocolmo. Los objetivos específicos fueron: 1) validar los datos recopilados por parte de parientes cercanos de pacientes con infarto de miocardio (IM) en un cuestionario; 2) evaluar cómo los factores de riesgo cardiometabólico conocidos se asocian con la letalidad del IM; 3) describir qué comorbilidades son las más frecuentes entre los casos de IM fatal y evaluar si éstas están asociadas a la letalidad de IM, y 4) evaluar si la inflamación de bajo grado se asocia con la fatalidad de futuros eventos coronarios.

Métodos

Utilizando material del Programa de Epidemiología del Corazón de Estocolmo (SHEEP, por sus siglas en inglés: "*Stockholm Heart Epidemiology Program*", un estudio de casos y controles), se evaluó la validez de los datos de su cuestionario proporcionados por cónyuges/cónyuges de derecho consuetudinario (proxies) en casos de IM no fatales en 82 variables. Utilizando regresión logística condicional, se calculó para cada una de las variables un "sesgo del proxy", basado en información recogida de 1) casos de IM y controles [odds ratio A] y 2) la de los proxies y el mismo conjunto de controles [odds ratio B]. El desacuerdo se midió calculando el cociente del odds ratio B dividido entre el odds ratio A; Los intervalos de confianza (IC) del 95% se calcularon utilizando el *bootstrap* de reemplazo con remuestreo.

Del SHEEP, se formó una cohorte de casos incidentes con IM. Los datos se obtuvieron de los cuestionarios (rellenados por un familiar cercano si el caso era fatal), exámenes físicos (para casos no mortales), registros nacionales e informes de autopsias. Las asociaciones entre los factores de riesgo cardiometabólico seleccionados y la letalidad de IM se evaluaron mediante cálculos de las razones de riesgo (RR) con intervalos de confianza (IC) del 95% mediante regresión binomial con enlace logarítmico. Se determinó la presencia de comorbilidades entre los casos fatales de IM y se evaluó el número de hospitalizaciones previas. Las asociaciones entre comorbilidades específicas, así como el número de hospitalizaciones previas y la letalidad por IM fueron evaluadas utilizando el mismo modelo que para los factores de riesgo cardiometabólico. Se realizó una revisión estructurada de los datos de las autopsias para identificar indicadores adicionales de comorbilidades en casos de IM fatal.

Utilizando material de la cohorte AMORIS, se valoraron las asociaciones entre la inflamación de bajo grado (usando una puntuación basada en cinco biomarcadores: los niveles séricos de la proteína C reactiva, los niveles séricos de haptoglobina, el recuento de

leucocitos, los niveles séricos de ácido úrico y los niveles séricos de albúmina) y la letalidad en sujetos que posteriormente experimentaron su primer evento coronario. Los odds ratios se calcularon con IC del 95% usando la regresión logística.

Resultados

Para la gran mayoría de las variables consideradas en el estudio de validación, no hubo desacuerdo estadísticamente significativo entre los informes de pacientes con IM y proxies. Sin embargo, la actividad física en el tiempo libre fue subestimada por los *proxies* en comparación con los pacientes con IM.

La diabetes, mas no la hipertensión ni la hiperlipidemia, se asoció con la letalidad del MI. El sobrepeso, en comparación con el índice de masa corporal normal, se asoció inversamente con la letalidad de IMI. Los resultados para la obesidad apuntaron en la misma dirección de los del sobrepeso. Los resultados se ajustaron en función de la edad, el tabaquismo, la historia paterna de muerte cardiaca prematura, el número de hospitalizaciones previas, el nivel educativo, el ingreso disponible y otros factores de riesgo cardiometabólicos.

Un número mayor de hospitalizaciones precediendo el infarto se asoció con un aumento en la letalidad por IM después de ajustes por sexo, edad e ingreso disponible. Entre las comorbilidades identificadas como prevalentes en los casos de IM fatales, las siguientes fueron asociadas con un aumento de la letalidad a los 7 días: la insuficiencia cardíaca, el accidente cerebrovascular, la diabetes, el alcoholismo, la enfermedad psiquiátrica, el cáncer, las enfermedades renales, la epilepsia, la artritis reumatoide y el asma. Los indicadores de comorbilidades identificados a partir de datos de autopsia incluyeron el IM silencioso, la aterosclerosis aórtica abdominal severa, la esteatosis hepática y el bajo peso.

Un puntaje de inflamación elevado después de los ajustar por edad en el momento del evento coronario, el año calendario del evento coronario, la diabetes, el nivel de educación, el colesterol total sérico, los triglicéridos séricos y la angina, se asoció con un aumento de la letalidad de futuros eventos coronarios, tanto en hombres como en mujeres.

Conclusiones

Tanto los pacientes con IM como sus cónyuges informaron de manera similar acerca de una amplia gama de variables, incluidas los tradicionales factores de riesgo cardiovascular, siendo la inactividad física durante el tiempo libre una excepción.

Entre los factores cardiometabólicos en estudio, la diabetes y la presencia de la inflamación de bajo grado, pero no la hipertensión ni la hiperlipidemia, se asociaron con un aumento de la letalidad del IM. El exceso de peso se asoció con una disminución de la letalidad del IM. Las hospitalizaciones previas repetidas y/o la insuficiencia cardiaca, la diabetes, el accidente cerebrovascular, la enfermedad psiquiátrica, el alcoholismo, el cáncer, las enfermedades renales, la epilepsia, la artritis reumatoide y el asma se asociaron a un aumento en la letalidad del IM.

11 ACKNOWLEDGEMENTS

Karin Leander, my main supervisor for her kindness and patience that had made this project possible!

Anita Berglund, Catherine (Cattis) Böllo and **Karin** (once again) as the Swedish representatives of the ERACOL program: Such program allowed me to participate in this ambitious project.

SENACYT: partially gave funding for this project.

Ulf de Faire, **Imre Janszky** and **Bruna Gigante**, as co-supervisors

Annika Gustavsson, SHEEP database manager.

Claes-Göran Linden and co-workers at Journal Service, Karolinska Universitetssjukhuset-Huddinge.

Prof. Johan Hallqvist, **prof. Henrik Druid**, **prof. Anders Alhbom**, **Dr. Alkass Kanar**, **prof. Göran Walldius**, **prof. Niklas Hammar**, **Håkan Malmström, Tomas Andersson** and **Max Vikström**, coauthors of the papers who took a very relevant role in this project.

My colleagues in the corridor who gave me a lot of support and developed a friendly environment: **Max, Ilais, Hozan, Mohammad, Xia, Reza, Zhara, Dashti, Dong, Qory, Federica, Cecilia, Ashwini, Erik, Maria, David, Mats Talbäck, Annika, Lena, Boel, Bahare** and **Alice.**

My mother **Eris Quintana**, my aunt **Mirella Molina** and my grandmother **Eleuteria Quintana** RIP; my uncles: **Rubén Chavarría** and **Mario Molina**; my aunts: **Marta** and **Martha**.

My wife, **Rosa Orellana**, and her family for supporting me.

12 REFERENCES

1. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. Int J Cardiol. 2015 Dec;201 Suppl 1:S1-7.

2. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. Circulation. 2014 Apr 08;129(14):1483-92.

3. Grey C, Jackson R, Schmidt M, Ezzati M, Asaria P, Exeter DJ, et al. One in four major ischaemic heart disease events are fatal and 60% are pre-hospital deaths: a national data-linkage study (ANZACS-QI 8). Eur Heart J. 2017 Jan 14;38(3):172-80.

4. (Socialstyrelsen) SMoHaW. Statistik om hjärtinfarkter 2015 (Statistics on Myocardial Infarction-In Swedish). 2016.

5. Dudas K, Lappas G, Stewart S, Rosengren A. Trends in out-of-hospital deaths due to coronary heart disease in Sweden (1991 to 2006). Circulation. 2011 Jan 4;123(1):46-52.

6. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011 Feb 01;123(4):e18-e209.

7. Degano IR, Salomaa V, Veronesi G, Ferrieres J, Kirchberger I, Laks T, et al. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. Heart. 2015 Sep;101(17):1413-21.

8. Koopman C, Bots ML, van Oeffelen AA, van Dis I, Verschuren WM, Engelfriet PM, et al. Population trends and inequalities in incidence and short-term outcome of acute myocardial infarction between 1998 and 2007. Int J Cardiol. 2013 Sep 30;168(2):993-8.

9. Porta M, Greenland S, Hernán M, dos Santos Silva I, Last JM, Burón A. A Dictionary of Epidemiology. 6th ed: Oxford University Press; 2014.

10. Kempf T, Zarbock A, Widera C, Butz S, Stadtmann A, Rossaint J, et al. GDF-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. Nat Med. 2011 May;17(5):581-8.

11. Xiao J, Sun B, Li M, Wu Y, Sun XB. A novel adipocytokine visfatin protects against H(2) O(2) -induced myocardial apoptosis: A missing link between obesity and cardiovascular disease. J Cell Physiol. 2012 Oct 12.

12. Smithline H, Rivers E, Appleton T, Nowak R. Corticosteroid supplementation during cardiac arrest in rats. Resuscitation. 1993 Jun;25(3):257-64.

13. Wannamethee G, Whincup PH, Shaper AG, Walker M, MacFarlane PW. Factors determining case fatality in myocardial infarction "who dies in a heart attack"? Br Heart J. 1995 Sep;74(3):324-31.

14. Njolstad I, Arnesen E. Preinfarction blood pressure and smoking are determinants for a fatal outcome of myocardial infarction: a prospective analysis from the Finnmark Study. Arch Intern Med. 1998 Jun 22;158(12):1326-32.

15. Chun BY, Dobson AJ, Heller RF. The impact of diabetes on survival among patients with first myocardial infarction. Diabetes Care. 1997 May;20(5):704-8.

16. Sattar N, Murray HM, Welsh P, Blauw GJ, Buckley BM, Cobbe S, et al. Are markers of inflammation more strongly associated with risk for fatal than for nonfatal vascular events? PLoS Med. 2009 Jun 23;6(6):e1000099.

17. Engstrom G, Hedblad B, Stavenow L, Tyden P, Lind P, Janzon L, et al. Fatality of future coronary events is related to inflammation-sensitive plasma proteins: a population-based prospective cohort study. Circulation. 2004 Jul 6;110(1):27-31.

18. White H, Thygesen K, Alpert JS, Jaffe A. Universal MI definition update for cardiovascular disease. Curr Cardiol Rep. 2014;16(6):492.

19. Fang L, Moore XL, Dart AM, Wang LM. Systemic inflammatory response following acute myocardial infarction. J Geriatr Cardiol. 2015 May;12(3):305-12.

20. Severs NJ, Bruce AF, Dupont E, Rothery S. Remodelling of gap junctions and connexin expression in diseased myocardium. Cardiovasc Res. 2008 Oct 01;80(1):9-19.

21. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? Circulation. 2013 Jun 18;127(24):2452-7.

22. Hung MJ, Hu P, Hung MY. Coronary artery spasm: review and update. Int J Med Sci. 2014;11(11):1161-71.

23. DiMaio D, DiMaio VJM. Forensic Pathology, Second Edition: CRC Press; 2001.

24. Makki N, Brennan TM, Girotra S. Acute coronary syndrome. J Intensive Care Med. 2015 May;30(4):186-200.

25. Kumar V, Abbas AK, Aster JC, Robbins SL. Robbins basic pathology. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013.

26. Knight B, Saukko PJ. Knight's Forensic pathology. 3rd ed: Oxford University Press; 2004.

27. Bayes de Luna A, Elosua R. Sudden death. Rev Esp Cardiol (Engl Ed). 2012 Nov;65(11):1039-52.

28. Kaikkonen KS, Kortelainen ML, Huikuri HV. Comparison of risk profiles between survivors and victims of sudden cardiac death from an acute coronary event. Ann Med. 2009;41(2):120-7.

29. Ahmed B, Davis HT, Laskey WK. In-hospital mortality among patients with type 2 diabetes mellitus and acute myocardial infarction: results from the national inpatient sample, 2000-2010. J Am Heart Assoc. 2014 Aug;3(4).

30. Capewell S, Livingston BM, MacIntyre K, Chalmers JW, Boyd J, Finlayson A, et al. Trends in case-fatality in 117 718 patients admitted with acute myocardial infarction in Scotland. Eur Heart J. 2000 Nov;21(22):1833-40.

31. Alvarez-Leon EE, Elosua R, Zamora A, Aldasoro E, Galcera J, Vanaclocha H, et al. [Hospital resources and myocardial infarction case fatality. The IBERICA study]. Rev Esp Cardiol. 2004 Jun;57(6):514-23.

32. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care. 1998 Jan;21(1):69-75.

33. Reina A, Colmenero M, de Hoyos EA, Aros F, Marti H, Claramonte R, et al. Gender differences in management and outcome of patients with acute myocardial infarction. International Journal of Cardiology. [Article]. 2007 Apr;116(3):389-95.

34. Engstrom G, Hedblad B, Janzon L, Lindgarde F. Fatality of acute coronary events in relation to hypertension and low-grade inflammation: a population-based cohort study. J Hum Hypertens. 2006 Aug;20(8):581-6.

35. Canto JG, Kiefe CI, Rogers WJ, Peterson ED, Frederick PD, French WJ, et al. Atherosclerotic risk factors and their association with hospital mortality among patients with first myocardial infarction (from the National Registry of Myocardial Infarction). Am J Cardiol. 2012 Nov 1;110(9):1256-61.

36. Pedersen F, Butrymovich V, Kelbaek H, Wachtell K, Helqvist S, Kastrup J, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol. 2014 Nov 18-25;64(20):2101-8.

37. Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL, Jr., et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation. 2007 May 29;115(21):2761-88.

38. Chang WC, Boersma E, Granger CB, Harrington RA, Califf RM, Simoons ML, et al. Dynamic prognostication in non-ST-elevation acute coronary syndromes: insights from GUSTO-IIb and PURSUIT. Am Heart J. 2004 Jul;148(1):62-71.

39. Abrignani MG, Dominguez LJ, Biondo G, Di Girolamo A, Novo G, Barbagallo M, et al. In-hospital complications of acute myocardial infarction in hypertensive subjects. Am J Hypertens. 2005 Feb;18(2 Pt 1):165-70.

40. Wang L, Liu W, He X, Chen Y, Lu J, Liu K, et al. Association of overweight and obesity with patient mortality after acute myocardial infarction: a meta-analysis of prospective studies. Int J Obes (Lond). 2016 Feb;40(2):220-8.

41. Buck HG, Akbar JA, Zhang SJ, Bettger JA. Measuring comorbidity in cardiovascular research: a systematic review. Nurs Res Pract. 2013;2013:563246.

42. Nunez JE, Nunez E, Facila L, Bertomeu V, Llacer A, Bodi V, et al. [Prognostic value of Charlson comorbidity index at 30 days and 1 year after acute myocardial infarction]. Rev Esp Cardiol. 2004 Sep;57(9):842-9.

43. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998 Jan;36(1):8-27.

44. Kuller LH, Eichner JE, Orchard TJ, Grandits GA, McCallum L, Tracy RP. The relation between serum albumin levels and risk of coronary heart disease in the Multiple Risk Factor Intervention Trial. Am J Epidemiol. 1991 Dec 1;134(11):1266-77.

45. Kucharska-Newton AM, Couper DJ, Pankow JS, Prineas RJ, Rea TD, Sotoodehnia N, et al. Hemostasis, inflammation, and fatal and nonfatal coronary heart disease: long-term follow-up of the atherosclerosis risk in communities (ARIC) cohort. Arterioscler Thromb Vasc Biol. 2009 Dec;29(12):2182-90.

46. Adamsson Eryd S, Smith JG, Melander O, Hedblad B, Engstrom G. Incidence of coronary events and case fatality rate in relation to blood lymphocyte and neutrophil counts. Arterioscler Thromb Vasc Biol. 2012 Feb;32(2):533-9.

47. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol. 1996 Sep 15;144(6):537-47.

48. Hollenberg J, Svensson L, Rosenqvist M. Out-of-hospital cardiac arrest: 10 years of progress in research and treatment. J Intern Med. 2013 Jun;273(6):572-83.

49. Nolan JP, Perkins GD, Soar J. Improving survival after out-of-hospital cardiac arrest. BMJ. 2015 Sep 21;351:h4989.

50. Engstrom G, Hedblad B, Janzon L. Reduced lung function predicts increased fatality in future cardiac events. A population-based study. J Intern Med. 2006 Dec;260(6):560-7.

51. Davies CA, Leyland AH. Trends and inequalities in short-term acute myocardial infarction case fatality in Scotland, 1988-2004. Population Health Metrics. [Article]. 2010;8:8.

52. Borne Y, Smith JG, Melander O, Engstrom G. Red cell distribution width in relation to incidence of coronary events and case fatality rates: a population-based cohort study. Heart. 2014 Jul;100(14):1119-24.

53. Rajaleid K, Hallqvist J, Koupil I. The effect of early life factors on 28 day case fatality after acute myocardial infarction. Scand J Public Health. 2009 Sep;37(7):720-7.

54. Holme I, Aastveit AH, Jungner I, Walldius G. Relationships between lipoprotein components and risk of myocardial infarction: age, gender and short versus longer follow-up periods in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med. 2008 Jul;264(1):30-8.

55. Stockholm County Council. Hjärtintensivvård. Behandingsprogram for Danderyd sjukhus, Ersta sjukhus, Huddinge sjukhus, Karolinska skjuhuset, Löwenströmska sjukhuset, Nacka sjukhus, Nortälje skjuhus, Sabbatsbergs sjukhus, S:t Görans sjukhus, Söderskujhuset, Södertälje sjukhus, Stockholms läns landinsting. Heart intensive care. Guidelines for treatment in Danderyd sjukhus, Ersta sjukhus, etc.: Stockholm County Council (in Swedish). 1990.

56. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

57. National Board of Health and Welfare. Historiska klassifikationer (ICD) - Previous versions of ICD used in Swedish registers (in Swedish language). Available from: http://www.socialstyrelsen.se/klassificeringochkoder/diagnoskodericd-10/historiska-klassifikationer.

58. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet. 2001 Dec 15;358(9298):2026-33.

59. Walldius G, Jungner I, Kolar W, Holme I, Steiner E. High cholesterol and triglyceride values in Swedish males and females: increased risk of fatal myocardial infarction. First report from the AMORIS (Apolipoprotein related MOrtality RISk) study. Blood Press Suppl. 1992;4:35-42.

60. Walldius G, Malmstrom H, Jungner I, de Faire U, Lambe M, Van Hemelrijck M, et al. The AMORIS cohort. Int J Epidemiol. 2017 Feb 02.

61. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Inflammatory markers, lipoprotein components and risk of major cardiovascular events in 65,005 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). Atherosclerosis. 2010 Nov;213(1):299-305.

62. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Haptoglobin and risk of myocardial infarction, stroke, and congestive heart failure in 342,125 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). Ann Med. 2009;41(7):522-32.

63. Jungner I, Marcovina SM, Walldius G, Holme I, Kolar W, Steiner E. Apolipoprotein B and A-I values in 147576 Swedish males and females, standardized according to the World Health Organization-International Federation of Clinical Chemistry First International Reference Materials. Clin Chem. 1998 Aug;44(8 Pt 1):1641-9.

64. Malmstrom H, Walldius G, Grill V, Jungner I, Gudbjornsdottir S, Hammar N. Fructosamine is a useful indicator of hyperglycaemia and glucose control in clinical and epidemiological studies--cross-sectional and longitudinal experience from the AMORIS cohort. PLoS One. 2014;9(10):e111463.

65. Abdoli G, Bottai M, Moradi T. Cancer mortality by country of birth, sex, and socioeconomic position in Sweden, 1961-2009. PLoS One. 2014;9(3):e93174.

66. Nelson LM, Longstreth WT, Jr., Koepsell TD, Checkoway H, van Belle G. Completeness and accuracy of interview data from proxy respondents: demographic, medical, and life-style factors. Epidemiology. 1994 Mar;5(2):204-17.

67. Capewell S, Murphy NF, MacIntyre K, Frame S, Stewart S, Chalmers JWT, et al. Short-term and long-term outcomes in 133 429 emergency patients admitted with angina or myocardial infarction in Scotland, 1990-2000: population-based cohort study. Heart. [Article]. 2006 Nov;92(11):1563-70.

68. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002 May 15;287(19):2570-81.

69. Aronson D, Rayfield EJ, Chesebro JH. Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. Ann Intern Med. 1997 Feb 15;126(4):296-306.

70. Gronros J, Jung C, Lundberg JO, Cerrato R, Ostenson CG, Pernow J. Arginase inhibition restores in vivo coronary microvascular function in type 2 diabetic rats. Am J Physiol Heart Circ Physiol. 2011 Apr;300(4):H1174-81.

71. DeLuca AJ, Kaplan S, Aronow WS, Sandhu R, Butt A, Akoybyan A, et al. Comparison of prevalence of unrecognized myocardial infarction and of silent myocardial ischemia detected by a treadmill exercise sestamibi stress test in patients with versus without diabetes mellitus. Am J Cardiol. 2006 Oct 15;98(8):1045-6.

72. Zilg B, Alkass K, Berg S, Druid H. Postmortem identification of hyperglycemia. Forensic Sci Int. 2009 Mar 10;185(1-3):89-95.

73. Gurm HS, Brennan DM, Booth J, Tcheng JE, Lincoff AM, Topol EJ. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). Am J Cardiol. 2002 Jul 1;90(1):42-5.

74. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. J Am Coll Cardiol. 2014 Apr 15;63(14):1345-54.

75. Hansel B, Roussel R, Elbez Y, Marre M, Krempf M, Ikeda Y, et al. Cardiovascular risk in relation to body mass index and use of evidence-based preventive medications in patients with or at risk of atherothrombosis. Eur Heart J. 2015 Oct 21;36(40):2716-28.

76. Doehner W, von Haehling S, Anker SD. Protective overweight in cardiovascular disease: moving from 'paradox' to 'paradigm'. Eur Heart J. 2015 Oct 21;36(40):2729-32.

77. Sep SJ, van Kuijk SM, Smits LJ. Index event bias: problems with eliminating the paradox. J Stroke Cerebrovasc Dis. 2014 Oct;23(9):2464.

78. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. Clin Exp Immunol. 2007 Feb;147(2):227-35.

79. Bonaccio M, Di Castelnuovo A, Rago L, de Curtis A, Assanelli D, Badilini F, et al. T-wave axis deviation is associated with biomarkers of low-grade inflammation. Findings from the MOLI-SANI study. Thromb Haemost. 2015 Nov 25;114(6):1199-206.

80. Lowry CA, Smith DG, Siebler PH, Schmidt D, Stamper CE, Hassell JE, Jr., et al. The Microbiota, Immunoregulation, and Mental Health: Implications for Public Health. Curr Environ Health Rep. 2016 Sep;3(3):270-86.

81. Baillargeon J. Characteristics of the healthy worker effect. Occup Med. 2001 Apr-Jun;16(2):359-66.

82. Mähönen M, Tolonen M, Kuulasmaa K, Tunstall-Pedoe H, P A. Quality Assessment of Coronary Event Registration Data in the WHO MONICA Project. World Health Organization (WHO) and the WHO MONICA Project investigators. 1999.

83. National Board of Health and Welfare (Socialstyrelsen). Myocardial Infarctions in Sweden 1990–2013. Sweden. 2014. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19595/2014-11-13.pdf.