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Epidemiological studies on socioeconomic inequalities and cardiovascular disease: prevention, progression and prognosis

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Where there is a will there is a way

To

Dad, my past

Aziz, Liam and Noah, my future

FOREWORD

Cardiovascular disease is defined as a disease that occurs in the heart, vascular of the brain, or blood vessels. However, for me, cardiovascular disease changed my life. I was 9 years old when my family moved to Sweden, with my father unable to join us initially. When we were reconnected in Sweden almost 6 months later, he had a myocardial infarction at the age of 46. I grew up in fear of this disease and with knowledge of associated medications and surgery. My degree project in high school was about myocardial infarction and bypass surgery, which my father had in 1994. In 2000 I lost my dear brother, aged 27 years. He was given the unspecified diagnosis cardiac arrest without further reason. Two years later, I also lost my father, whose heart could no longer manage.

Ten years later, I was given the opportunity to fulfil mine - and my father's - dream when I was offered to do research. I knew at that time that research in the area of cervical cancer would have been a more straight forward path, but it didn't feel right. If I was going to do research, then I wanted it to be on a disease that has been a big part of my life since I was a child - cardiovascular disease.

Initially, I had hoped to do research on cardiovascular disease for both younger people and immigrants. In particular, second-generation immigrants. Unfortunately, the data available was not sufficient to investigate this. This is a pity, since I know first-hand how incomprehensible the consequences can be for young people and families affected by this disease.

I am not a medical doctor. I have a Masters degree in computer science and mathematics, so I will never be able to directly help patients with cardiovascular disease or their concerned families. However, I hope my research can bring a tiny little piece to the puzzle of bridging the gap between the most and least advantaged groups in cardiovascular disease.

ABSTRACT

Cardiovascular disease (CVD) accounts for 30% of global mortality and is the most common cause of death in the world. Population-wide prevention strategies as well as healthcare interventions have led to a decrease in CVD incidence and mortality. Socioeconomic position (SEP) is associated with almost the entire developmental course of CVD, from modifiable risk factors and atherosclerosis to incidence, survival, and mortality.

The purpose of this thesis was to investigate how absolute and relative SEP inequalities in myocardial infarction (MI) and ischemic stroke (IS) have developed over time in Sweden, and additionally, to investigate the association between SEP and subclinical biomarkers for atherosclerosis, as well as with prescription of CVD preventive drugs.

In **Study I** and **II,** record linkage of Swedish population register data and time-to-event analysis was used to estimate absolute and relative SEP inequalities in both MI/IS incidence as well as short-term and long-term case-fatality. Swedish Censuses were used to classify SEP into five different groups. Incidence and case-fatality of MI and IS have decreased over time in Sweden across all SEP groups. However, in women the reduction in incidence of MI and IS have been lower than for men. Over time, SEP inequalities persist between the lowest and highest SEP groups in MI and IS incidence and in short-term as well as long-term case-fatality in MI. Regarding IS, SEP inequalities in short-term case-fatality have decreased over time, but seem to be stable in long-term case-fatality.

In **Study III**, we investigated educational differences in several subclinical biomarkers for atherosclerosis in the cohort "Prospective Investigation of Vasculature in Uppsala Seniors" (PIVUS), which includes a range of vascular- and cardiac biomarkers. By using regression analysis, we found associations between longer education and two vascular biomarkers as well as five cardiac biomarkers. Additionally we were able to demonstrate that body mass index mediated the associations between educational level and subclinical biomarkers for atherosclerosis.

Given the overall SEP differences in CVD, it is plausible that those in disadvantaged SEP groups are in greater need of preventive drugs for CVD. In **Study IV**, we investigated whether there are SEP differences in the prescription of CVD preventive drugs according to need. In particular, we wanted to investigate SEP differences in lipid lowering drugs statins and two antihypertensive drugs, ACE-inhibitors and angiotensin receptor blockers (ARBs). According to Swedish guidelines, ACE-inhibitors are the recommended antihypertensive drugs, while

ARBs are given as second-line treatment and have fewer side effects. We used a record linkage of Swedish population register data with the Swedish Drug Prescription Register. Statins, ACE-inhibitors and ARBs were prescribed largely to socioeconomically disadvantaged groups, this did still not meet their needs. When accounting for need, we were able to report that socioeconomically advantaged groups were prescribed statins and ARBs to larger extend than disadvantaged groups, while almost equally prescription distributions were noted among SEP groups for ACE-inhibitors.

In this thesis, we conclude that SEP differences in CVD incidence and case-fatality persist over time in Sweden. SEP is associated with subclinical biomarkers of atherosclerosis as well as CVD preventive drugs. The small inequalities in ACE-inhibitors drugs prescription across SEP may have contributed to the decreased SEP difference in IS short-term case-fatality, which suggest that SEP inequalities may be reduced by targeted guidelines.

SAMMANFATTNING PÅ SVENSKA

Hjärt- och kärlsjukdomar står för 30% av den globala dödligheten och är därmed den vanligaste dödsorsaken i världen. Både befolkningsomfattande preventionsåtgärder och interventionsstrategier inom hälso- och sjukvården har bidragit till minskad förekomst och dödlighet i hjärt- och kärlsjukdomar. Socioekonomiska position (SEP) är sammankopplad med nästan hela utvecklingsförloppet av hjärt- och kärlsjukdomar, alltifrån riskfaktorer, åderförkalkning, till insjuknande, överlevnad och dödlighet.

Syftet med denna avhandling var att undersöka hur de absoluta och relativa socioekonomiska skillnaderna i hjärtinfarkt och ischemisk stroke har utvecklats över tid i Sverige. Dessutom undersöktes socioekonomiska skillnader i subkliniska biomarkörer för åderförkalkning samt i läkemedelsförskrivning för förebyggande av hjärt-och kärlsjukdomar.

I **studie I** och **II** har vi använt oss av registerutdrag baserad på hela svenska befolkningen och överlevnadsanalys för att presentera de absoluta och relativa socioekonomiska skillnaderna dels i förekomst av hjärtinfarkt och ischemisk stroke såväl som korttids- och långtidsdödlighet. Folk- och bostadsräkningar har använts för att klassificera fem socioekonomiska grupper. Resultatet visar bland annat att förekomsten och dödligheten i hjärt- och kärlsjukdomar har minskat över tid i Sverige inom alla socioekonomiska grupper. Emellertid har minskningen i förekomsten av hjärtinfarkt och ischemisk stroke bland kvinnor varit lägre än bland män. Det framgår även i resultaten att de socioekonomiska skillnaderna mellan den lägsta och högsta gruppen kvarstår över tid för insjuknanden i hjärtinfarkt och ischemisk stroke samt i både den kortsiktiga och den långsiktiga dödligheten i hjärtinfarkt. Angående ischemisk stroke så har de socioekonomiska skillnaderna minskat över tid för den kortsiktiga dödligheten men har varit stabil för den långsiktiga.

I **studie III** undersöktes utbildningsskillnader i olika subkliniska mått för åderförkalkning i en kohort ”Prospective Investigation of Vasculature in Uppsala Seniors” (PIVUS) innehåller flera kärl- och hjärtmarkörer. Med hjälp av regressionsanalys påvisas i resultaten att det finns utbildningsskillnader i kärlmarkörer och i flera hjärtmarkörer, med en effektstorlek som varierar mellan -0.2 till 0.1 per ökad utbildningsnivå. I analyserna konstaterades även att BMI (kroppsmasseindex) medierar 15-66% av förhållandet mellan utbildningsnivå och de subkliniska biomarkörer för åderförkalkning.

Eftersom det finns socioekonomiska skillnader i insjuknande av hjärt- och kärlsjukdomar så är det mer troligt att de missgynnade socioekonomiska grupperna är i större behov av förebyggande läkemedelsinsatser för hjärt- och kärlsjukdomar. I **studie IV** undersöktes om det finns socioekonomiska skillnader i läkemedelsförskrivning för förebyggande av hjärt- och kärlsjukdomar i förhållande till behovet. I synnerhet undersöktes socioekonomiska skillnader i blodfettssänkande mediciner statiner och två olika högt blodtrycksmediciner ACE-hämmare och angiotensin receptor blockerare (ARB). ACE-hämmare är den rekommenderade högt blodtrycksmedicinen enligt sjukvårdsriktlinjer medan ARB medicinen ges som ett andra handsval och är dyrare medicin med färre biverkningar. Registerdata med totala svenska befolkningen användes och läkemedelsförskrivningen identifierades från läkemedelsregistret. Statiner, ACE-hämmare och ARB förskrevs i större utsträckning för socioekonomiska missgynnade grupper, men detta mötte inte behovet. När medicinbehovet tas med i beräkningen visas det att det finns socioekonomiska skillnader i läkemedelsförskrivning, speciellt för statiner och ARB men däremot så var socioekonomiska skillnaderna för ACE-hämmare små.

Avhandlingen visar på att socioekonomiska skillnader i insjuknande och dödlighet i hjärt- och kärlsjukdomar kvarstår över tid i Sverige och att skillnaderna kan observeras i de subkliniska markörerna för åderförkalkning men även i läkemedelsförskrivning i syfte att förebygga hjärt- och kärlsjukdomar. Den jämlika högt blodtryck läkemedelsanvändning kan ha varit en bidragande orsak för den minskade socioekonomiska skillnaden i kortsiktig dödlighet, vilket ger en indikation på att socioekonomiska skillnader kan minska med målriktade riktlinjer.

LIST OF SCIENTIFIC PAPERS

I. **Malki N,** Koupil I, Eloranta S, Weibull C, Tiikkaja S, Ingelsson E, Sparén P
Temporal trends in incidence of myocardial infarction and ischemic stroke by socioeconomic position in Sweden 1987-2010. *PLoS One*. 2014; 9(8): e105279

II. **Malki N,** Hägg S, Tiikkaja S, Koupil I, Sparén P, Ploner A
Short-term and long-term case-fatality rates for myocardial infarction and ischaemic stroke by socioeconomic position and sex: a population-based cohort study in Sweden, 1990-1994 and 2005-2009. *BMJ Open* 2019, 9:e, 026192

III. **Malki N,** Ploner A, Sparén P, Koupil I, Lind L. Hägg S
Associations between socioeconomic position and subclinical biomarkers for atherosclerosis are mostly mediated via body mass index in a cohort of old Swedish adults. (Manuscript submitted)

IV. **Malki N,** Ploner A, Hägg S, Larsson H, Koupil I, Sparén P, Johnell K
Inequalities in preventive treatment of cardiovascular disease according to need – A nationwide population-based cohort study in Sweden 2006-2013. (Manuscript)

CONTENTS

LIST OF ABBREVIATIONS

ACE-inhibitors	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers
ATC	Anatomical Therapeutic Chemical Classification system
BMI	Body Mass Index
CCA	Common carotid artery
CDR	Swedish Cause of Death Register
CFR	Case-fatality rate
CFRD	Case-fatality rate difference
CHD	Coronary heart disease
CVD	Cardiovascular disease
E/A ratio	The ratio between (E wave) and (A wave)
ECG	Electrocardiogram
EDV	Endothelium-dependent vasodilation
EF	Ejection fraction
EIDV	Endothelium-independent vasodilation
FBF	Forearm blood flow
FMD	Flow-mediated vasodilation
FPM	Flexible parametric survival models
HM	High manual
HN-M	High non-manual
ICD	International Statistical Classification of Diseases and Related Health Problems
IHD	Ischemic heart disease
IM	Intima-media
IM-GSM	Intima-media grey scale median
IMT	Intima-media thickness

IR	Incidence rate
IRR	Incidence rate ratio
IS	Ischemic stroke
IVRT	Left ventricular isovolumic relaxation time
LA	Left atrial dimension
LM	Low manual
LN-M	Low non-manual
LV	Left ventricular
LVEDD	Left ventricular diameter at end diastole
LVMI	Left ventricular mass index
MI	Myocardial infarction
NPR	Swedish National Patient Register
PIN	Person identity number
PIVUS	Prospective Investigation of Vasculature in Uppsala Seniors
RWT	Left ventricular relative wall thickness
SE	Self-employed
SEI	Socioeconomic index
SEP	Socioeconomic position
SPDR	Swedish Prescribed Drug Register
SV/PP	Ratio between stroke volume and pulse pressure ratio
TPR	Total Population Register
WHO	World Health Organization

1 INTRODUCTION

Every human has the right to a normal standard of living that is adequate for health and well-being, in accordance with both human rights and dignity. Nevertheless, there are differences in life chances within and between countries. New-born children have over 20 years difference in life expectancy when comparing Sweden to many African countries.[1,2] Over many decades, the World Health Organization (WHO) has struggled to close the gap in health inequalities both within and between countries.[1] Many countries have established commissions and ministries with an equivalent aim. Reports from different parts of the world have structured and analysed the inequalities in health.[3,4] In 2015, the Swedish Government established a commission for equity in health, with the aim "*Avoidable health gaps must be closed within a generation*".[5] Despite this, the health gap still exists; in Sweden, the life expectancy at 30 years of age is 9 to 10 years greater for highly educated individuals, compared to those without any formal education.[6]

Cardiovascular disease (CVD) accounts for 30% of global mortality and is the most common cause of death in the world.[7] There has been a dramatic improvement in the prevention and treatment of CVD over the years, resulting in a substantial decrease in CVD incidence, survival and mortality.[8-10] Therefore, it is also important to ask whether we have managed to succeed in closing the gap in CVD inequalities, in a country like Sweden with universal healthcare.

This thesis investigates whether the gap in CVD inequalities has been reduced over time in Sweden, and highlights inequalities in subclinical biomarkers of CVD and in preventing CVD through the use of medications.

2 BACKGROUND

2.1 CARDIOVASCULAR DISEASE

The heart pumps blood that supply the body with oxygen and nutrients. The heart muscle receives its own blood supply from the coronary arteries. While the brain controls intellectual function and other organ systems. Two large vessels supply blood from the heart to the brain. Cardiovascular disease (CVD) is defined as heart diseases and vascular diseases both in the brain, and other blood vessels.[7] CVD include coronary heart disease (CHD) such as MI, stroke and heart failure. Figure 1 shows the proportion of different forms of CVD in Sweden. CVD is the leading cause of death in Sweden and worldwide.[7] Around 2 million deaths in Europe are due to CVD, accounting for 33 percent of all mortality. CVD mortality rates increase with age and men has higher rates than women. Several other factors may influence CVD mortality, such as social class or birth county.[11] CVD mortality has declined sharply in high-income countries,[12-14] and by nearly 70 percent in Sweden since 1987.[15] Healthcare intervention strategies and primary preventions have contributed to the improvements in CVD mortality as well as CVD incidence rates and survival.[8] The main underlying pathological process that leads to CVD is atherosclerosis.

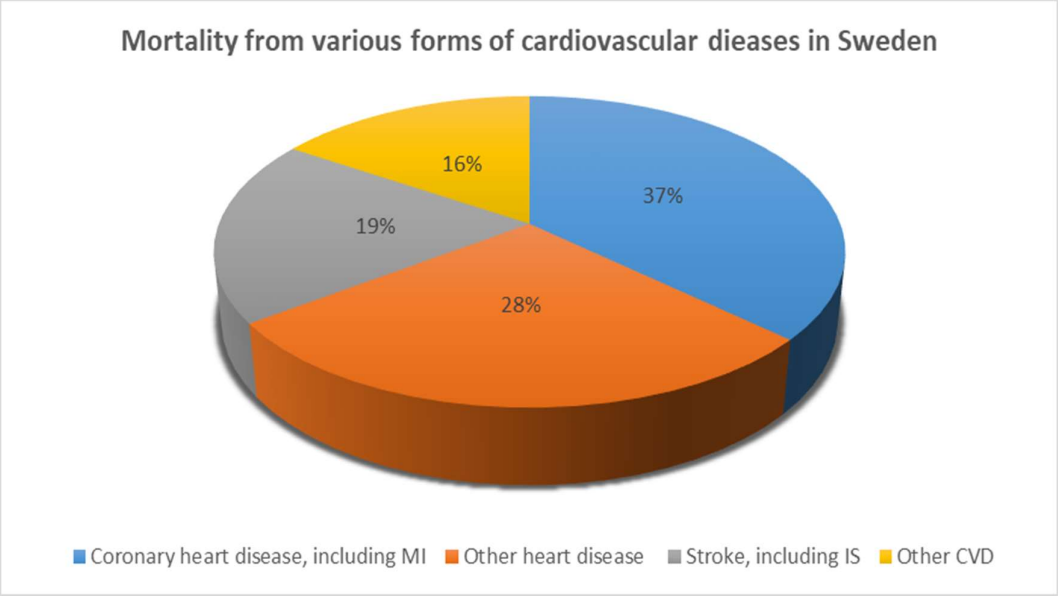


Figure 1. Proportion of deaths from cardiovascular diseases in Sweden [Source: Eurostat database][16]

2.1.1 Atherosclerosis

Atherosclerosis, which develops over many years is an inflammatory process in the walls of blood vessels.[17] Atherosclerosis is the primary cause of CVD and involves the pathological

deposition of lipoproteins.[18] The inside of an artery narrows due to plaque forming on the wall of arterial blood vessels. This narrowing limits the flow of oxygen-rich blood to all parts of the body, which can lead to calcification, inflammation, and eventual thrombosis (Figure 2).[19,20] Atherosclerosis generally starts when a person is young, though usually without symptoms.[21] It tends to worsen with age, and almost all people have some atherosclerosis by the age of 65.[22] Ageing also affects arterial stiffness, which in turn accelerates the arteriosclerosis process.[23]

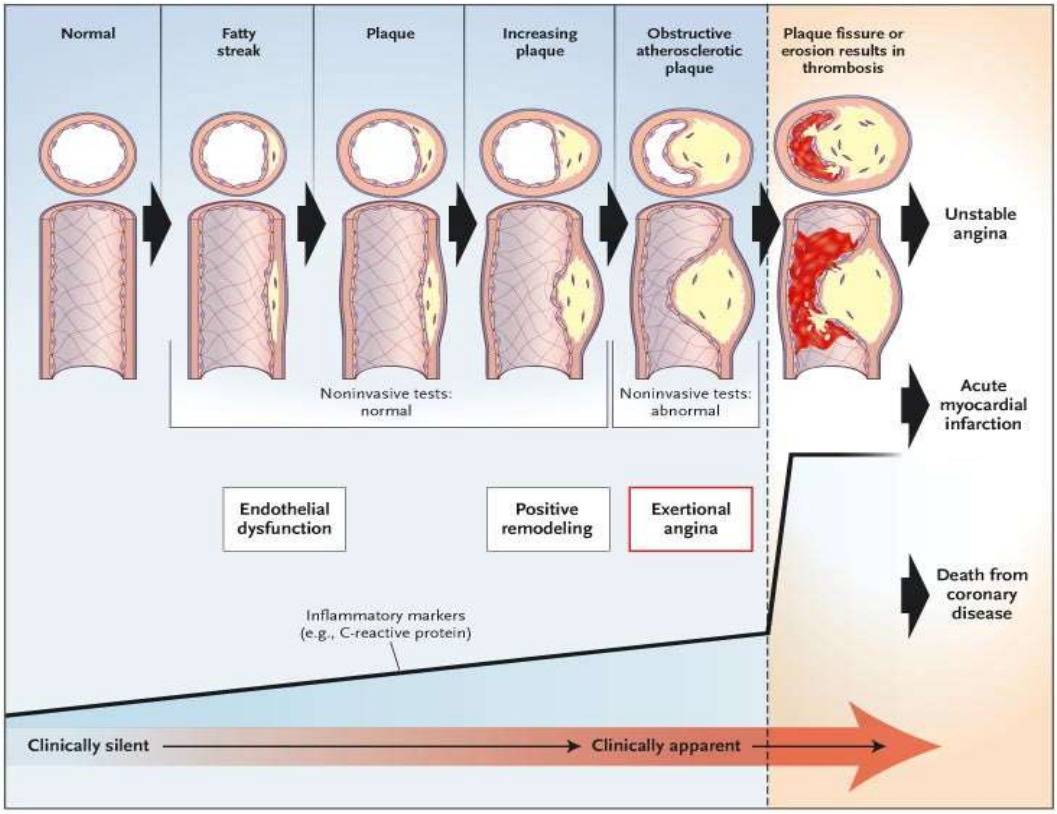


Figure 2. Progression of atherosclerosis [Reproduced with permission from Abrams[24], Copyright Massachusetts Medical Society]

Atherosclerosis can affect various arteries in the body, and so different diseases may develop depending on the arteries affected, for example arteries in the heart, common carotid arteries (CCA), brain, arms or legs.

A diagnosis of atherosclerosis or CVD is based on a blood test, physical examination, electrocardiogram (ECG), Doppler ultrasound, or stress test exercise, among others. Great efforts have been made to identify useful atherosclerosis biomarkers,[17,25-27] including endothelial dysfunction (reduce blood flow in the arteries),[28] plaque rupture in the carotids, and left ventricular (LV) geometry.

2.1.2 Myocardial infarction

Myocardial infarction (MI), occurs when part of the heart is damaged due to blood supply decreases or even stops.[7] MI usually is caused by a rupture of plaque in the atherosclerosis process, which lead to closure of an artery, due to clots. Angina or chest pain is the most common symptom, but also pain in the back, or shoulder are also common.[29] However those symptoms are more usually common among men, where women may have other symptoms such as fatigue or pain in the neck or arm.[30-34]

The mean age for MI in Sweden is 70 years for men and 76 years for women. The incidence of MI has decreased substantially in Sweden over the last two decades. In 2017, over 26,000 MI events occurred in Sweden, corresponding to about 340 events per 100,000 inhabitants. The incidence increases with age, with a greater incidence among men than women.

Overall, MI mortality has decreased by over 70% from 1987 to 2017 in Sweden. Among people aged 70-79, MI mortality has decreased by over 80% from 1987 to 2017 among both men and women.[35] The largest mortality decrease was due to both improvements in the prevention of MI incidence and better survival after MI.[8] Figure 3 illustrate trends in incidence and mortality rates of MI in Sweden.

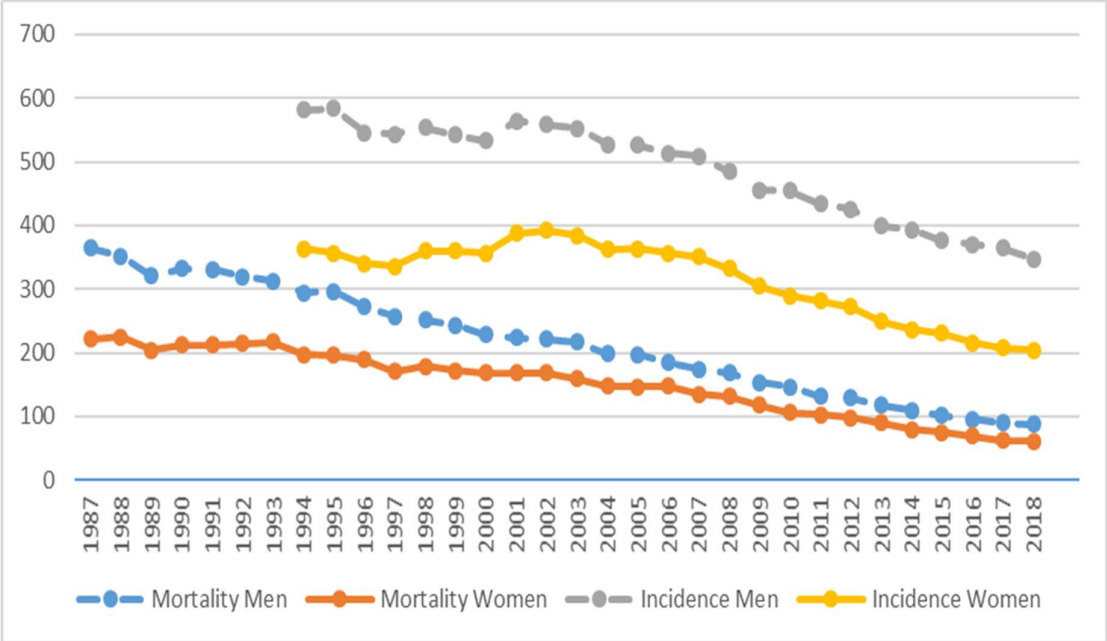


Figure 3. MI incidence and mortality rates per 100,000 inhabitants, 20 years and older by sex from 1987 to 2018 [Data source: Swedish National Patient register (NPR) and Swedish Cause of death register (CDR) from National Board of Health and Welfare].[36]

Case-fatality rate (CFR), defined as the proportion of individuals that died after a MI event, has been used as a proxy measure of hospital performance and quality of care for comparison within and between countries.[37,38] On average, a quarter of all MI events are fatal,[36] although the definition of fatal and non-fatal varies between studies. A fatal MI is often seen as death within one day, although some studies define fatal as death within 28 days. Fatal and non-fatal MIs refer to different proxies of care. A fatal MI event indicates limited possibilities of healthcare and therefore can be used as a proxy for severity of care, access to ambulatory care and time delay to hospital care.[39] On the other hand, non-fatal MI events have the opportunity to undergo treatment and access hospital care.[39] There has been a sharp decrease in MI case-fatality, both short-term and long-term, over time in Sweden (Figure 4).[15,40]

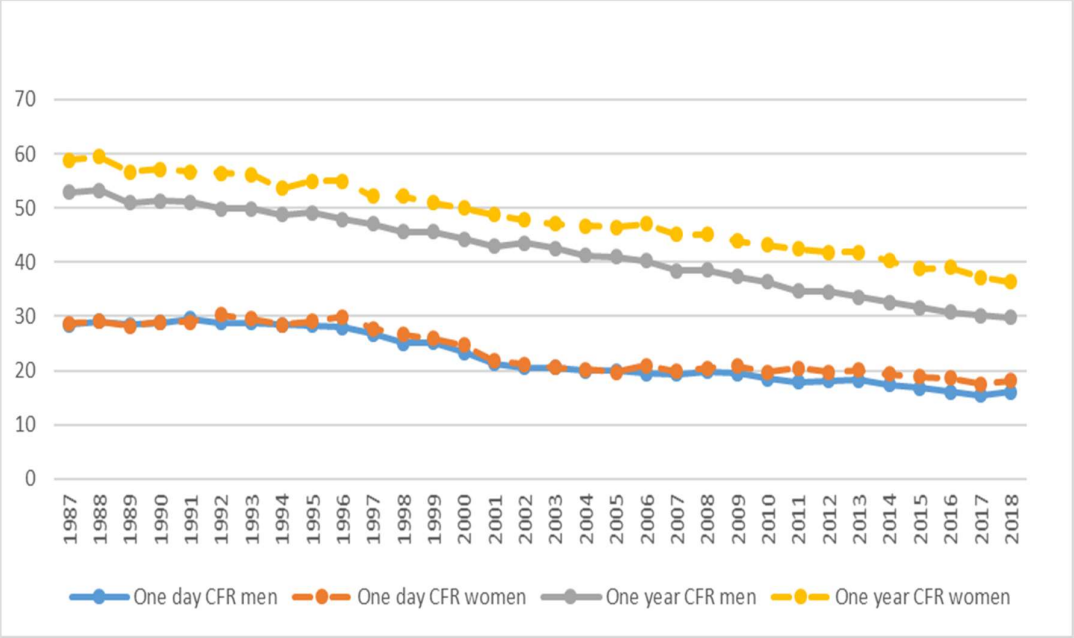


Figure 4. One-day and one-year case-fatality rates (CFRs) in MI, for individuals ages 20 years and older by sex from 1987 to 2018 [Data source: NPR and CDR from National Board of Health and Welfare].[36]

2.1.3 Stroke

Stroke is the third most common cause of death in western populations, after CHD and cancer. Stroke occurs when blood flow to the brain is decreasing. The two main types of stroke are: ischemic stroke (IS) and hemorrhagic stroke, the latter occurs due to bleeding. IS accounts for around 87% of all strokes, and occurs when the cerebral artery supplying blood to the brain is blocked. Usually the plaque in CCA ruptured and clots blocks the CCA of the neck or blocks the blood vessel that feeds the brain. An interruption of blood flow for more than some minutes may results in brain damage.

The symptoms of IS vary greatly and depend on the brain region affected. Common symptoms include blindness, weakness in some parts of the body, dizziness, double vision or difficulty in speaking.[41] The severity of IS range from mild to severe and may be permanent.

The risk of IS increases with age, and is higher for individuals with a personal or family history of stroke. The mean age for IS is 73 years in men and 77 years in women. Men are also more likely to develop and die of IS than women.[42,43]

Stroke mortality rates have been declining in Sweden and worldwide.[44] About two thirds of the decrease in stroke mortality is due to improvements in case-fatality, with the remainder being due to reduced incidence.[45]

Rapid decrease in IS incidence, by up to 30%, has been reported in Europe and Sweden. [46-51] However, decrease in IS incidence has mainly been among the elderly, and remains unchanged or possibly increasing among younger people. [48-50] Figure 5 illustrate trends in incidence and mortality rates of IS in Sweden.

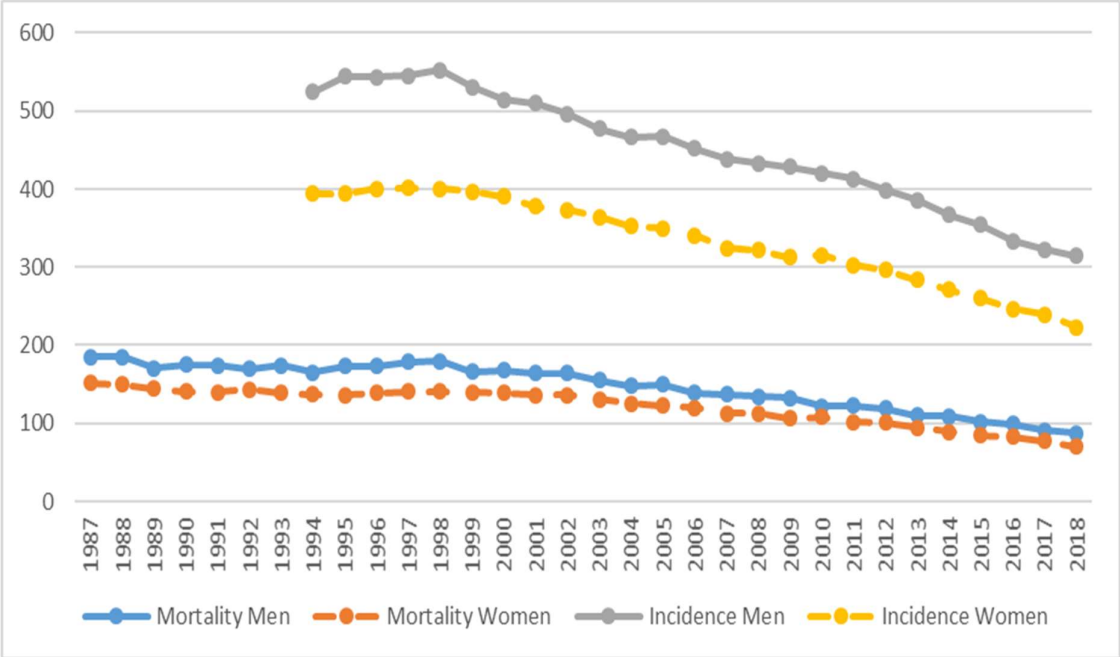


Figure 5. IS incidence and mortality rates per 100,000 inhabitants, 20 years and older by sex from 1987 to 2018 [Data source: NPR and CDR from National Board of Health and Welfare].[36]

Decline in case-fatality of IS has also been reported in recent decades.[46,52] Both short-term case-fatality and long-term case-fatality have improved in Sweden (Figure 6). On average, one-year case-fatality rates have decreased by 25% in Sweden in the last two decades.[51]

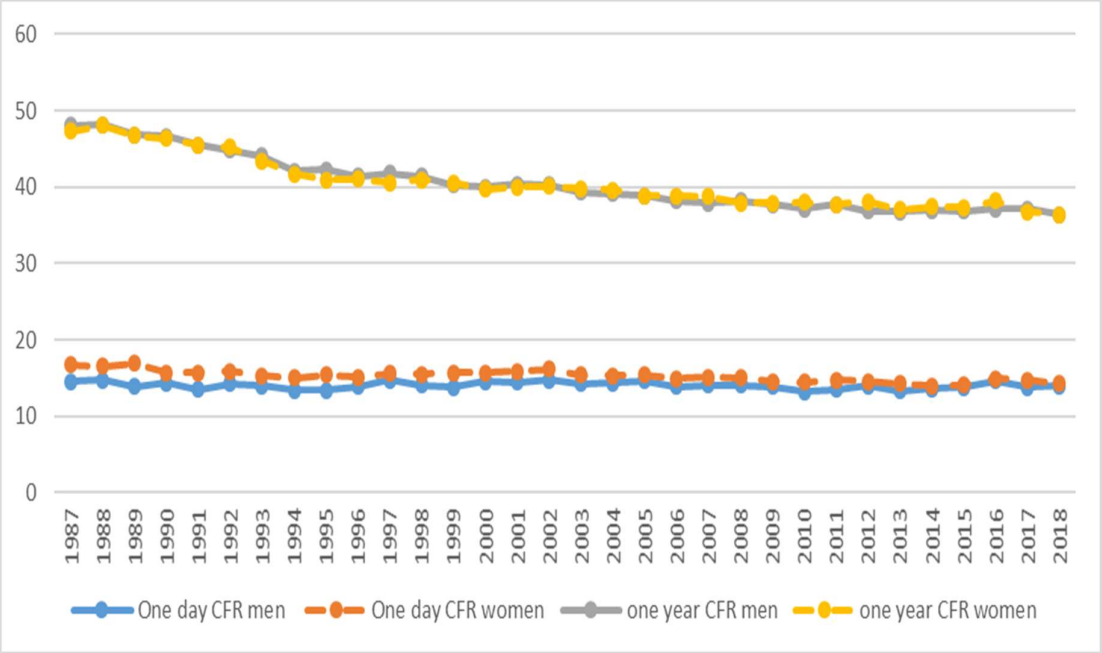


Figure 6. One-day and one-year case-fatality rates (CFRs) in IS, 20-85+ years by sex from 1987 to 2018 [Data source: NPR and CDR from National Board of Health and Welfare].[36]

2.1.4 Risk factors

Risk factors for atherosclerosis can be classified into unmodifiable and modifiable risk factors.[11] Age, sex and family history are seen as unmodifiable risk factors. About 90% of CVD burden is attributable to modifiable risk factors.[47] Smoking, heavy alcohol consumption, obesity and physical inactivity are some of the common modifiable risk factors for atherosclerosis.[11,18,53-61] Smokers have twice the risk of developing atherosclerosis compared to non-smokers.[62,63] Heavy alcohol consumption has also been associated with IS, although moderate alcohol consumption is often suggested to be protective.[64]

Over time, poor modifiable risk factors may results in high blood pressure (hypertension), obesity, diabetes or higher blood lipids (dyslipidemia), which all lead to atherosclerosis and CVD.[59,61,65-68] Other risk factors that have been associated with atherosclerosis and CVD are socioeconomic position, oral contraceptives, inflammation and infections.[17,69,70]

Risk factors for MI and IS are generally similar to those for atherosclerosis.[71] However, hypertension causes about 50% of all IS, making it the single most important risk factor for IS.[61,72,73] In fact, high blood pressure is more important for IS than for other CVD, independent of other risk factors.[74-76] Although lipoproteins are also associated with IS,[61,65] those associations are more modest for IS than for other CVD.[77]

Reductions in modifiable risk factors, such as cigarette smoking [78] account for almost half of the decreased mortality, while the other half of the mortality decrease is attributed to improvements in medical treatment and surgery, for example, treatments to better control hypertension and cholesterol, improved healthcare development and timely use of thrombolysis in the acute phase.[8,78,79]

Decreasing trends in several of modifiable risk factors for atherosclerosis such as hypertension, lipoproteins and smoking, have been noted both in Sweden and in many European countries. However, other modifiable risk factors for atherosclerosis have increased such as obesity and diabetes.[80]

2.1.5 Drug use and pharmacoepidemiology

Reducing high blood pressure and high blood cholesterol, both risk factors for CVD events, are important goals in medical treatment.

Statins are the first-line drug treatment for high blood cholesterol. Statins have been widely used in treatment after CVD event (secondary prevention). However later, statins have been found to benefit individuals without any CVD event, and therefore even prescribed as primary prevention.[81-84] Statins have been found to reduce the risk of all-cause mortality by 13% and CVD by 25% in individuals without prevalent CVD.[85]

Hypertension is the most important risk factor for CVD and death worldwide. Overall, antihypertensive therapy is associated with a 25% reduction in the incidence of CVD and a 38% reduction in the incidence of stroke.[86-89] These reductions are substantial and generally remain constant across all groups of patients, regardless of age, sex and smoking habits.[90] A recent systematic review showed that antihypertensive drugs reduced the risk of all-cause mortality by 14%, CHD by 16% and stroke by 36% among individuals without prevalent CVD.[85] Additionally, small reduction in systolic blood pressure may reduce the risk of CVD by a quarter.[91]

2.2 SOCIAL EPIDEMIOLOGY

The term socioeconomic position (SEP) refers to individual's position in the social structure of society, where some individuals have more resources and better life chances than others. Social epidemiology examines the relationship between social factors and different diseases.[92] SEP can be measured on a group level - for example neighborhood deprivation, - or on an individual level – such as achieved education, income, occupation, or a combination of several of these

measures.[93] While the various indicators of SEP are often used interchangeably, they each have a different theoretical explanation and underlying mechanism.[93-95] Despite the differences, all these measures of SEP see lower levels being linked to poorer material and immaterial resources, poorer lifestyle behaviors, worse health and higher mortality.

2.2.1 Educational level

One of the oldest and most used proxies for social class is highest achieved level of education, which has the advantage of a naturally ordered scaling. Educational level is usually fixed in early adult life, and thus reduces some of the risk of selection bias.[93] Education remains constant, even when poor health in mid-life may result in loss of job or income. In Sweden, education is compulsory from age 6 to 15, and is tax-financed for all permanent residents. Attained level of education is relevant as a mechanism in occupational advancement and is highly predictive of income and wealth.[92] Education has been strongly associated to health and to health determinants, such as health behaviors and preventative service use. Despite this, trends in educational attainment have changed over time, due to changes in educational system in Sweden. Large educational reformers were implemented in Sweden in the 50's and 60's, which resulted in larger part of the population had access to higher education.[96] Among older cohorts, fewer people, in particular women, had the opportunity to achieve a higher level of education. Therefore, comparisons between age cohorts, between sexes and across geographical regions can be difficult.[97]

2.2.2 Occupational class

An important indicator of social class is employment status or occupation.[98] These measures indicate social prestige and connections, as well as reflecting economic situation, such as income.[93,99] In addition, occupation can also reflect different aspects of the labor market, such as activities and circumstances of a job, hierarchical position, technical and social skills.[100] Furthermore, occupation has a direct impact on circumstances relevant for health, through the physical and psychological environment of the workplace itself.[93] There have been substantial changes in class differences over time, where women, for example, have nowadays more access to the labor market. The household's highest level of occupation has occasionally been used instead of individual measures as an indication of a family's SEP.[101] Unlike education which is usually fixed in early adult life, occupational class may vary over time, which may be a reason why occupational class is considered a better predictor than education, when measuring the inequalities over time.[97,102] Different classification systems can be used for SEP; it can be measured as individuals own occupation or household's highest level of occupation, but also

as a composite measure, e.g. occupation and education.[101] Among others, the Erikson and Goldthorpe's class schema[103] combines occupational class with educational requirements to generate a summary of socioeconomic index (SEI), which we will use in Study I, II and IV and will be explained in more detail in section 4.1.

2.3 SOCIAL DETERMINANTS

The conditions and circumstances such as childhood circumstances, school, work conditions, the healthcare system and the distribution of money in society (welfare) are known as social determinants (Figure 7).[1] All these conditions shape our opportunities for obtaining and maintaining good health. There are three main pathways between socioeconomic inequalities and health.[104-106] Firstly, social causation defines the process whereby SEP affects health conditions. Secondly, health selection defines the process that health conditions can lead to differences in SEP. Thirdly, indirect selection, which indicates the case in which certain factors influence both SEP and health. This thesis focuses on the health social causation pathway.

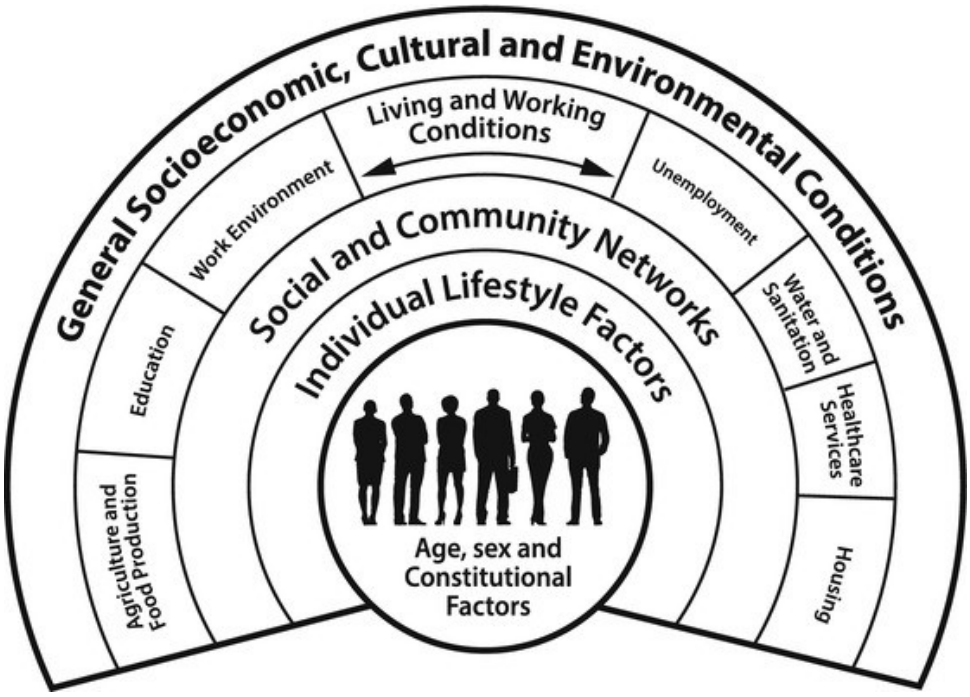


Figure 7. Social determinants of health reflecting the social structure of health [Source: Dahlgren and whitehead, 1991].[107]

2.4 SWEDISH HEALTHCARE SYSTEM

In Sweden, the state has the responsibility for establishing health policies, while the funding and provision of services is determined at the county and municipality levels. The Swedish healthcare system is largely tax-financed and aims to ensure everyone has equal access to healthcare services. Horizontal equity mean that individuals with the same level of need should have same level of healthcare access.[108,109] Access to healthcare should be equal irrespective of individuals' age, sex, country of birth, religion, SEP and other social factors. The Swedish healthcare act[110] is based on horizontal equity and has two main goals: 1) "*Healthcare shall be provided with respect for the equal value of all humans, and for the dignity of individual human beings. Those who have the greatest need of health and medical care shall be given precedence to care"; and* 2) *"health and medical care shall work to prevent ill health.*"

2.5 SOCIOECONOMIC INEQUALITIES IN CARDIOVASCULAR DISEASE

There is vast evidence of SEP inequalities in CVD, both in Sweden and worldwide. SEP gradients have been found during the process of CVD development, for almost all modifiable risk factors, such as smoking and higher body mass index (BMI),[111,112] but also for SEP and clinical conditions such as hypertension, high blood lipids and atherosclerosis.[40,113-117]. In addition, CVD morbidity, survival after a CVD event and CVD mortality differs by SEP.[40,117-123] Furthermore, inequalities in access to coronary procedures before and after a CVD event, such as revascularization and coronary angiography, have been reported[124-126] and this is also the case for recurrence of a CVD event.[127]

As mentioned previously in sections (2.1.22.1.3) there have been large reductions in CVD mortality and incidence over time as well as improvements in CVD case-fatality. Contradictory findings on how those improvements are distributed across SEP have been reported. Some studies have found that inequalities in CVD have increased,[120,128-130] while recent data from Swedish National Board of Health and Welfare (Socialstyrelsen) show that educational inequality in MI incidence has been stable over time in Sweden see Figure 8.

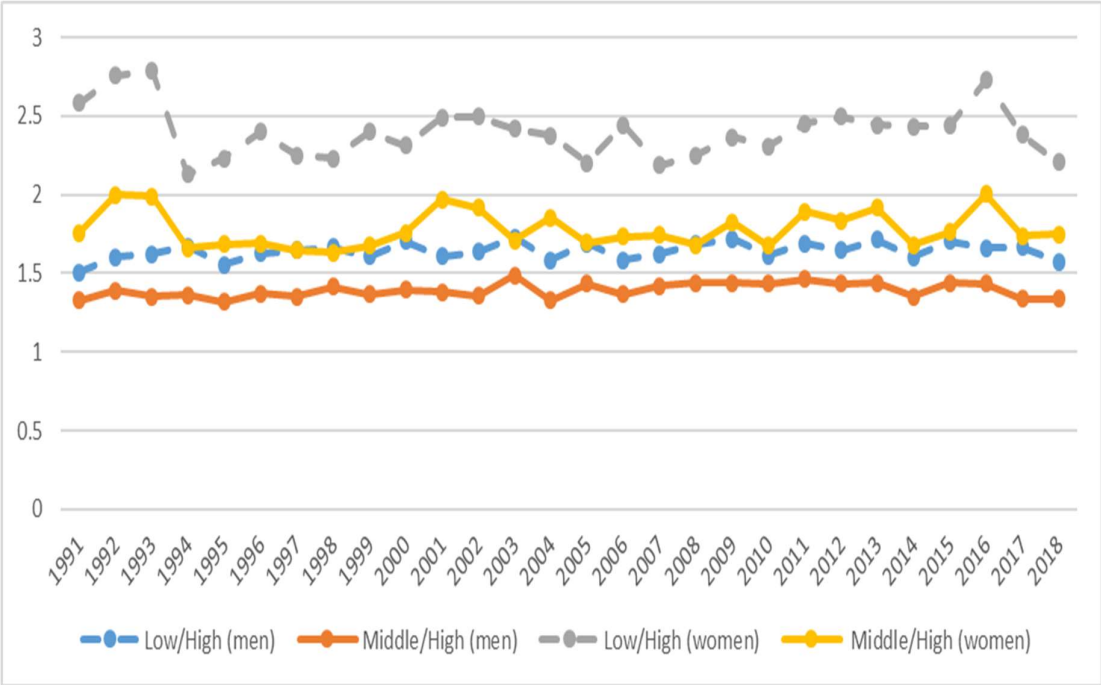


Figure 8. Relative differences by educational level in age standardized (45─74 years) MI incidence, among men and women from 1991 to 2018. Primary school (Low), Secondary school (Middle) and University or College (High) [Data source: NPR and CDR from National Board of Health and Welfare, Educational Register from Statistical Sweden].[131]

How to measure inequalities in health has been debated since long. Mackenbach et.al reported that relative inequalities in overall mortality are largest in Sweden and Norway among western European contries.[132,133] Vågerö et.al. argue that reporting only relative measures of inequality is misleading, absolute levels of inequality indicators need to be considered as well.[134] Changes in small absolute differences give higher relative differences than stable high absolute differences. A decrease in the gap between different SEP groups is not always a positive trend, because it could be due to an increase in unhealthy behaviors in all SEP groups, as has been found for overweight.[97] Whether health inequalities are increasing or decreasing is an important question for public health policies.

In this thesis we will report both absolute and relative measures of SEP inequalities in CVD incidence and case-fatality.

2.5.1 Socioeconomic inequalities in drug use

Several studies have report an association between SEP and CVD drug use in Sweden and elsewhere.[135,136] Most studies find either equal drug use by SEP, or that low SEP groups tend to use more CVD drugs than higher SEP groups. Importantly, high drug use among low SEP groups is most likely due to differences in health needs between SEP groups. Individuals in disadvantaged SEP groups have increased exposure to more unhealthy behaviors and therefore have a higher risk of developing conditions that require prescribed drugs, for example, hypertension, higher cholesterol, MI or IS.[137] A Swedish study found that, for the general population and for most drug types, there was a social gradient in drug prescription.[138]

3 AIMS

This thesis examines whether SEP inequalities in CVD have changed over time in Sweden, and whether there is a social gradient in distribution of subclinical biomarkers and in prevention treatment of CVD. The following specific aims were addressed within the framework of this thesis.

Study I: To investigate whether socioeconomic inequalities in MI and IS incidence have changed over two decades in Sweden.

Study II: To investigate whether socioeconomic inequalities in case-fatality rates of MI and IS have changed over two decades in Sweden.

Study III: To investigate the association between educational level and vascular- as well as cardiac biomarkers.

Study IV: To investigate whether CVD preventive drugs are equally prescribed to individuals across different SEP groups, while accounting for treatment needs.

4 MATERIALS AND METHODS

4.1 SWEDISH NATIONAL REGISTERS

Study I, II and IV in this thesis used record linkage data from several Swedish national and population register. The National Board of Health and Welfare (Socialstyrelsen) holds the Swedish national health registers and Statistics Sweden (Statistika centralbyrån) holds the Swedish national population register and the national Censuses. Individuals are identified through a unique personal identity number (PIN), which has been assigned to all Swedish residents since 1947.[139] Each individual is given an ID alias within the system that allows the authorities to link data from different registers, while ensuring the PIN and identity of all individuals remains protected. Study I and II, use the same linked data for individuals born up to 2002 (Figure 8). Study IV, used another data linkage, including individuals born up to 2013 (Figure 8).

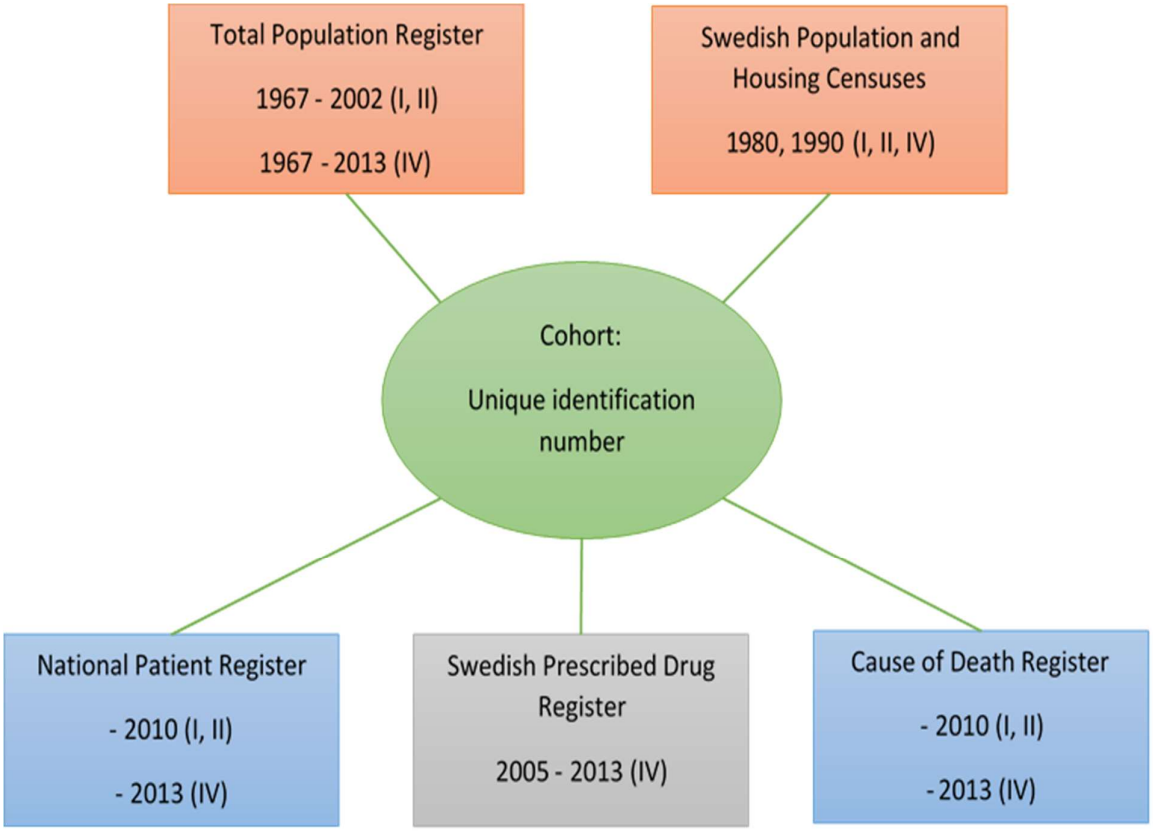


Figure 8. Swedish national registers used in Study I, II and IV

The Total Population Register (TPR) includes demographic information such as date of birth, sex, country of birth, county of birth, emigration date, migration date and death date. The TPR is hosted by Statistics Sweden and includes all living individuals since 1968.

Swedish Population and Housing Censuses: The Censuses were performed every 5 years from 1960 to 1990.[140] The questionnaire were sent to all nationally registered Swedish residents (aged 16 years and older) and were mandatory. In cases of illness, individuals unable to complete the questionnaire were permitted to have a relative to complete it on their behalf. The response rate has been very high, 99% in 1980 and 98% in 1990.[141,142]

The Censuses include detailed information on education, income, occupation, social class, housing information, and civil status.[141,142] For occupation, individuals were asked "To which occupation do you want to count your job: Enter the occupation that describe your job as accurately as possible."

Occupations were then verified with the Labor market register.[143] Socioeconomic index (SEI) was then derived for all individuals in the labor force, and based on Erikson, Goldthorpe, Portocarrero's (EGP) class schema.[144] Distinguishing between self-employed and employees, employees were then further classified into working in manual or non-manual occupations. Within both the manual and non-manual groups, individuals were also classified into low or high, based on the educational requirement for each occupation (see section 2.2.2).[144]

In Study I, II and IV in this thesis, we selected SEI from the 1990 Census. For individuals with missing information, SEI was retrieved from the 1980 Census. In Study I, II and IV, SEP was the main exposure and was classified into five groups, from the most advantaged to disadvantaged: high non-manual (HN-M), low non-manual (LN-M), self-employed including the farmers (SE), high manual (HM), and low manual (LM) see Table 1.

Table 1. Socioeconomic Index according to EGP class schema and SEP category.

SEP	SEI group	Delineations	Example of occupation
HN-M	46, 56, 57	Non-manual employees normally requiring university/collage education	Physician, teacher
LN-M	33, 36	Assistant non-manual employees normally requiring two years of secondary school education	Nursing assistant
SE	60, 79, 89	Self-employed with and without employees, small-scale and large scale farmers	Self-employed IT-consultant, craftsman
HM	21, 22	Production employees normally requiring at least two years of secondary school education	Construction workers
LM	11, 12	Production employees normally requiring less than two years of secondary school education	Cashier

The Swedish National Patient register (NPR) was established regionally in 1964 but became nationwide in 1987. Since it was initiated, the register has contained information of all inpatient care in Sweden, and by 1983 had achieved 88% coverage for inpatient care[145] Later, the NPR has also included day surgery since 1997 and outpatient care since 2001. Data from primary care is not included in the register. Within the register, diagnosis upon discharge is classified according to the Swedish International Classification of Diseases (SE-ICD) which is adapted from the WHO ICD code classification, ICD 8 (years 1968-1986), ICD 9 (years 1987-1997), ICD-10 (years 1997- on going), for Skåne county ICD-10 started in 1998 instead of 1997.[145] For Study I and II, the main diagnosis were identified as the first occasion of incidence of MI and IS. In Study IV, both main and all secondary diagnoses were used to classify the CVD diagnosis. The ICD codes used for each study in this thesis are presented in Table 2. The

validity of the NPR is high, with the overall positive predictive values of inpatient-care diagnoses being 85-100%, and 98-100% for MI and IS, respectively.[145]

Table 2. List of diagnosis used in the thesis by different ICD codes versions.

Diagnosis	**ICD-8 (years 1987 – 1996)**	**ICD-9 (years 1987 – 1996)**	**ICD-10 (years 1997 – 2010)**
Myocardial infarction	410	410	I21 – I22
Ischemic heart disease	410 – 411	410 – 411	I200, I21 – I22
Ischemic stroke	432 – 434	433 – 434	I63
Stroke	432 – 437	433 – 436	I63 – I66, G45, G46
Diabetes	250	250	E10 – E14

Swedish Cause of death register (CDR) The cause of death register is hosted by the Swedish National Board of Health and Welfare, and updated annually. And includes all deaths in Sweden, excluding stillbirths.[146] The CDR contains data from 1961, although there is also historical data for 1952–1960.[147] For each death in Sweden, a cause of death certificate must be completed by a doctor and sent to the National Board of Health and Welfare.

The causes of death reported follow the international classification of Diseases ICD-codes and include both the main cause of death and several secondary death diagnoses.

The quality of the cause of death register is affected by a variety of factors, such as how cause of death is determined, the processing method, and what cause of death classification is used. Missing cause of death data in CDR has been at around 2% in recent years.[146,148]

The Swedish Prescribed Drug Register (SPDR) was established in June 2005 and contains information on all prescribed drugs that has been dispensed in Sweden.[149] However, SPDR do not include drugs that were prescribed but not collected. The SPDR is hosted by the National Board of Health and Welfare and includes more than 100 million records per year, which makes it one of the largest pharmacoepidemiological databases in the world. All drugs in SPDR are classified according to Anatomical Therapeutic Chemical Classification system (ATC), the drugs used in this thesis is presented in Table 3. The SPDR contains information on, among other things, ATC, drug name, dose, package size, cost, defined daily dose, prescription date, and dispense date. Swedish prescriptions should be for a maximum 3-month supply and be valid for no more than a year.

Table 3. ATC codes used in the thesis

Drugs	**ATC**
Statins	C10AA
Angiotensin-converting enzyme (ACE) inhibitors	C09A
Angiotensin II receptor blockers (ARBs)	C09C
Diabetes	A10A, A10B

4.2 PROSPECTIVE INVESTIGATION OF VASCULATURE IN UPPSALA SENIORS (PIVUS)

Study III was based on the PIVUS study, hosted by Uppsala University. A detailed description of PIVUS can be found elsewhere.[150-153] In 2001, a random sample of 2,025 men and women aged 70 living in Uppsala were invited to participate, with 1,016 individuals (50.1%) agreeing to participate. Participants were asked to fill in a questionnaire including questions about their education, medical history, medication use, smoking habits and alcohol consumption. They also collected anthropometrical measures, and a seven day food diary. In Study III, the exposure of interest was highest achieved educational level, which was based on the question read as follows: "*What is the highest educational level you have completed?*" (1=Primary school; 2=Secondary school; and 3= University or College).

Several physical tests were also performed to evaluate several atherosclerosis biomarkers, for a total of four hours. There was at least 30 minutes rest between different tests. The tests included endothelial function, arterial compliance, echocardiographic test, and ultrasound of the CCA. In addition, blood samples were taken to measure the lipids and blood glucose variables with standard laboratory techniques, and blood pressure was measured, and a mean of three measurements was used.

We divided the evaluated atherosclerosis biomarkers from the PIVUS study in two groups; vascular- and cardiac biomarkers. In total we used eight vascular biomarkers and seven cardiac biomarkers.

The seven cardiac biomarkers were obtained by using a two-dimensional echocardiography Doppler examination, and was performed approximately one week after the main examination. The echocardiography, one of the most widely used diagnostic test of CVD, show the heart structure with the blood flow. The measures include left ventricular (LV) geometry and function, which are used to define LV dysfunction that is associated with atherosclerosis and CVD.[154] Additional measurements of the LV are left atrial dimension (LA), as well as LV

diameter at end diastole (LVEDD). Calculation of LV relative wall thickness (RWT) was obtained as (interventricular septal thickness + posterior wall thickness) divided by LVEDD, and LV mass index was obtained by indexing LV mass divided by height to the power of 2.7 ($LVMI/m^{2.7}$).[155,156] Ejection fraction (EF) was calculated from LV volumes according to the Teichholz formula.[157] Additionally, the LV isovolumic relaxation time (IVRT) was measured as time between aortic valve closure and the start of mitral flow. The ratio between the peak velocity blood flow from LV relaxation in early diastole (E wave) and the peak velocity of atrial filling (A wave) (E/A ratio) was calculated, which is a marker of the function of the LV. All of these biomarkers have been associated to atherosclerosis and CVD.[158-164]

The eight vascular biomarkers were obtained by four different tests: 1) The invasive forearm technique, 2) The brachial artery ultrasound technique, 3) CCA ultrasound technique and 4) Arterial compliance by pulse wave analysis.

Both the invasive forearm test and the brachial artery ultrasound were performed to assess the endothelial dysfunction. Endothelial dysfunction, which is the process of damaging the arterial wall, has been considered as an early marker for atherosclerosis.[165] The invasive forearm test was performed by venous occlusion plethysmography, as an arterial cannula was placed in the brachial artery to measure forearm blood flow (FBF). Resting FBF was measured as well as FBF after infusions of two drugs (Acetylcholine and Sodium nitroprusside) to define endothelium-dependent vasodilation (EDV) and endothelium-independent vasodilation (EIDV), more details can be found elsewhere.[151] The second technique, the brachial artery ultrasound was assessed by external B-mode ultrasound to measure the non-invasive endothelial dysfunction, flow-mediated vasodilation (FMD).[166] FMD was defined as the brachial artery maximum diameter after a cuff release minus diameter at rest divided by diameter at rest. The third technique was also assessed by external B-mode ultrasound imaging of the CCA, which has been described in more detailed previously.[153] As described before (section 2.1.3), plaque in the CCA is a marker for atherosclerosis and one key for developing IS.[167] Both sides of the CCA were visualized to search for occurrence of plaque and number of plaques in CCA was noted. The CCA far wall was evaluated 1-2 cm to the bulb and intima-media (IM) thickness (IMT) were estimated, which is widely accepted as a marker for atherosclerosis and a predictor of CVD.[168-170] A region of interest (ROI) was manually placed around the IM and a program evaluated the grey scale median (IM-GSM),[153] which has been found to be an easy measurement of the CCA wall.[153] From the fourth technique, the pulse pressure ratio (PP) was evaluated to enable the calculation of CCA distensibility as the percentage change of CCA diameter from maximum to minimum divided by PP. The CCA

distensibility, which has been linked to several factors that lead to atherosclerosis and CVD,[171,172] is a measure of the ability of the artery to expand and contract in the process of pulsation and relaxation.[173] The ratio of stroke volume (measured from ECG) divided by PP (SV/PP) was also calculated, which is a an index of large artery elasticity,[174,175] and has been found to be a marker for atherosclerosis and CVD.[176]

While the PIVUS study includes a follow-up both at age 75 and 80, Study III in this thesis uses only baseline data at age 70 years.

4.3 STATISTICAL METHODS

4.3.1 Linear regression and multiple regression

Linear regression is used to model the association between a dependent variable/outcome Y and an independent variable/exposure X. A model with two or more independent variables (X_1, X_2 etc.) is called a multiple regression model. Conventionally, regression models are based on several assumptions: fundamentally, the outcome variable needs to be on a continuous scale, and the relationship between outcome and predictors needs to be linear. Additionally, we usually assume that the observed data includes an error term that is on average zero, with constant variance and normal distribution. This is usually written as

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \varepsilon$$

where β_0 is the excepted outcome value when all predictors are set to zero (*intercept*), β_1 and β_2 are *slopes* measuring the expected change in outcome associated with a +1 change in the corresponding predictor variables, and ε is a normally distributed error term with mean zero and fixed variance.

Multiple linear regression was used in Study III to model the association between educational level and continuous atherosclerosis biomarkers.

4.3.2 Logistic regression

Logistic regression generalizes the linear regression model for a binary variable outcome variable Y, usually coded as 0 (no event) and 1 (event). The logistic regression model connects the transformed event probability P with the given predictor variables (X_1, X_2, etc.) The transformation that defines the logistic regression is the *log-odds*, or *logit* function, where the *odds* of an event is defined as the ratio of the event probability divided by the probability of that the event not occurring:

$$logit(P) = log\left(\frac{P}{1-P}\right)$$

The logistic regression model assumes that the underlying events follow a Bernoulli distribution with event probability P, and that the corresponding log-odds are a linear function of predictor variables:

$$logit(P) = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

In analogy to the linear regression model above, β_0 is the intercept, and β_1 and β_2 are slopes that describe level and change of the logit as function of the predictor variables. Exponentiating this linear equation to get a multiplicative equation for the odds

$$Odds = \frac{P}{1-P} = e^{\beta_0+\beta_1 x_1+\beta_2 x_2}$$

can be used to show that $exp(\beta_1)$ and $exp(\beta_2)$ are the *odds ratios* associated with a +1 change in the corresponding predictor variables.

This model can be generalized to situations where the discrete outcome variable Y has more k>2 categories: the multinomial logistic regression model uses k-1 parameters for each predictor variable, corresponding to one odds ratios each for k-1 outcome classes relative to a freely chosen reference outcome class. However, if the k outcome categories are ordered, this model can often be simplified again to an ordinal logistic regression model, which uses one parameter per predictor variable. Same as for the binary logistic regression model: the necessary assumption here is that of proportional odds ratios, i.e. that the odds ratio for an outcome class relative to the next-smaller class is the same for all classes.

Logistic regression was used in Study II to model the odds ratio of the binary outcome short-term case-fatality (death within one day) of MI and IS. Ordinal logistic regression was used in Study III for the association between educational level and the ordinal categorical outcome *number of plaques in CCA*.

4.3.3 Survival analysis

Survival analysis is a statistical technique for modelling the time until an event occurs. Individuals are followed from a certain point in time – such as birth or diagnosis – until an event occurs, e.g. CVD diagnosis or death. Sometimes, when individuals cannot be followed

until the event occurs, e.g. due to migration or end of study, we only know that the event time is greater than the end of follow-up, when we say that there is *right censoring*.

Survival analysis is able to account for this loss of information and individual data can still be included in the models calculations: each individual i is followed until time t_i on some underlying timescale (e.g. time since birth), until either the event of interest occurs or censoring takes place. To distinguish between event times and censoring times, all individuals have an *event indicator* d_i that takes the value one if the individual experienced the event or zero if the individual was censored.

If the probability density function for the survival time T is *f(t)*, the cumulative distribution function *F(t)* is then

$$F(t) = \int_0^t f(t)$$

Models for survival data are generally based on two related functions, the *survival function S(t)* and the *hazard function h(t)*. The survival function is simply the probability of survival beyond time t, or in other words, the probability that the survival time is greater than time *t*:

$$S(t) = P(T > t) = 1 - F(t)$$

The hazard function *h(t)* is the instantaneous event rate at time *t,* conditional on surviving up to time t:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(T < t + \Delta t \mid T \geq t)}{\Delta t}$$

A related measure of event risk is the *cumulative hazard function*, which aggregates the instantaneous hazard over time:

$$H(t) = \int_0^t h(y)dy$$

A common assumption for survival models is that of *proportional hazards*: this refers to a situation where the ratio of two hazard functions for different values of the predictor variables in the model is constant over time. In a simple example, the hazard ratios for exposed and unexposed subjects $h_e(t)$ and $h_u(t)$ are both functions of time *t*, but under the proportional hazard assumption, their ratio $\lambda = h_e(t)/h_u(t)$ is constant over time.

This simple assumption has important implications for the survival model: practically, it allows us to summarize the relative risk of an event between exposed and unexposed subjects simply by one number λ, the *hazard ratio*. Theoretically, it implies that the hazard function can be split into the product of two components, one that only depends on the observed times, and one that only depends on the predictor variables in the model; this corresponds to a sum of two components for the log-hazard function, e.g.:

$$\log[\, h(t, x_1, x_2)\,] = s(t) + g(x_1, x_2)$$

Here, the function $s(t)$ is referred to as (log-) *baseline hazard*.

4.3.4 Flexible parametric model

In its basic form, a *flexible parametric survival model* (FPM),[177-180] is a proportional hazard model that fits the log cumulative hazard as a smooth function of the observed time at risk,[181] without explicit parametric assumptions about the underlying survival function *S(t)*, and assuming linear effects of the predictor variables on the chosen scale:

$$\log[\, H(t, x_1, x_2)\,] = s(\log(t)|k) + \beta_1 x_1 + \beta_2 x_2$$

Here, $s(\cdot\,|k)$ is the baseline hazard of the survival model, which is fitted as a *restricted cubic spline* function. A cubic spline is a smoothing function consisting of pieces of cubic polynomials, joined together through a set of control points, called *knots* (*k* in the equation); to ensure the smoothness of the resulting function, the splines are forced to have the same first and second derivative at both sides of a knot; the *restriction* is the requirement that the smoothing function continuous linear outside of the range of the observed data (here: observed times), which stabilizes estimation at the edges. In the proportional hazard setting, the parameters β_1 and β_2 are the log-hazard ratios associated with a change of +1 in the corresponding predictor variables X_1 and X_2.

The FPM can be seen as an extension of the parametric Weibull model that replaces the simple linear baseline hazard of the Weibull model with a flexible, data-driven smoothing function that does not correspond to any specific distribution function for the event times. The FPM can also be extended to non-proportional hazards, by including interactions with the (log-) timescale via additional spline functions.

In practice, the FPM combines convenient estimation of smooth hazard- and survival functions (as for parametric survival models) with the absence of strict parametric assumptions (as for the Cox model). However, the FPM is only as flexible as the underlying splines, and may have

problems with situations where many events happen in a short interval of time, corresponding to a spike in the hazard function.

We used the FPM in Study I to estimate the incidence rates (IR) and incidence rate ratios (IRR) of MI and IS by SEP, with calendar year as the underlying timescale. In Study II, we used the FPM to estimate case-fatality rates (CFR) and CFR differences (CFRD) for long-term case-fatality after an MI/IS event, with time since disease event as the underlying timescale.

4.3.5 Poisson model

Like the logistic regression model, the Poisson model is a generalization of the linear regression model; it relates Poisson-distributed count data to a linear function of the predictor variables via the log-transform (instead of the logit). However, the model can also be used to describe survival data. Instead of the instantaneous hazard, it models the IR of an event of interest in a fixed time interval: if d is the number events of interest in the interval, and y is the length of the interval, this is simply

$$IR = \frac{d}{y}$$

The Poisson model for survival data assumes that the log incidence rate is a linear function of the predictor variables:

$$\log(IR) = \log(d) - \log(y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

By bringing the log-time at risk to the right hand side, we get the equation

$$\log(d) = \log(y) + \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

Here, $\log(y)$ is a constant offset term with fixed weight one that calibrates the observed event count for the time at risk, β_0 is the offset for the log-counts when both predictor variables are zero, and β_1 and β_2 are log IRR corresponding to a +1 change in the corresponding predictor variables.

For a simple survival model with constant hazard rate $h(t) = h$, the estimated hazard rate is just the IR, and the hazard ratio is estimated by the IRR above. By splitting follow-up time into suitably small intervals where hazard is approximately constant, Poisson regression can approximate any kind of hazard function with a piecewise constant step function. In practice, this often leads to very similar results as for classic survival models like Cox regression.

In Study IV, we used Poisson regression to estimate IRs of MI/IS and CVD preventive drug prescriptions (statins, ACE-inhibitors, ARBs), and estimate corresponding IRRs between SEP levels.

4.3.6 Bootstrapping

To deal with the uncertainty in the error distribution in the log-linear model for Poisson model used in Study IV,[182,183] bootstrap resampling was used.[184,185] Bootstrapping generated and analyzed a pre-defined sets of data from the original data in order to determine standard errors and confidence interval.

4.3.7 Causal mediation analysis

Causal mediation analysis[186] identify and process the underling relationship between the exposure of interest and the outcome, through a covariate, known as mediator variable (Figure 9). In study III causal mediation analysis was performed to evaluate and estimate possible mediation path in the association between educational level and atherosclerosis biomarkers. Causal mediation require some assumptions,[187] which we have tried to deal with in Study III.

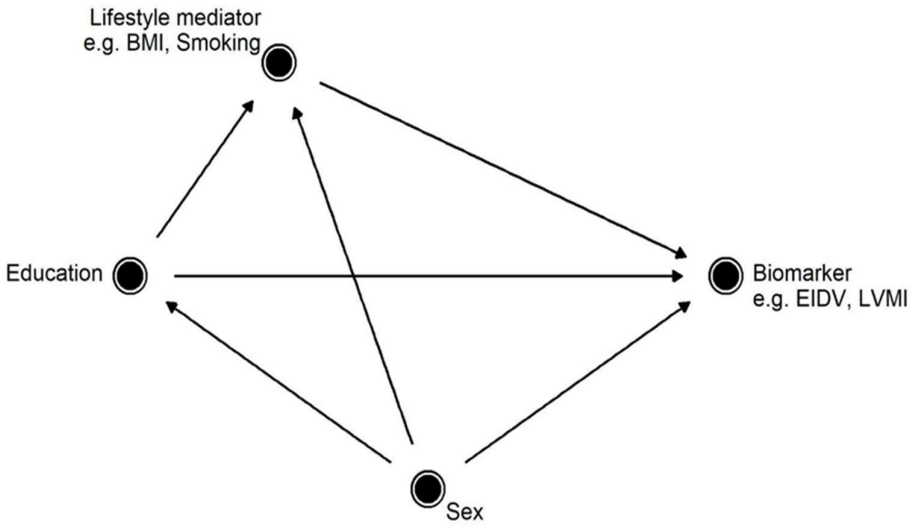


Figure 9. DAG of causal relationship of the association between educational level and atherosclerosis biomarkers mediated throw lifestyle factors.

5 STUDY SUMMARY

5.1 STUDY I

5.1.1 Objective

We analyzed absolute and relative temporal trends in incidence of MI and IS across different SEP strata from 1987 to 2010 for the entire Swedish population stratified by sex and age.

5.1.2 Method

Age is the main risk factor for MI and IS, therefore a natural timescale for a time-to-event analysis should be attained age. However we aimed to investigate the trends in IRs over time by SEP, therefore a more interesting timescale was the calendar year. Age was instead treated as second timescale grouped in 5-year intervals.

A population-based cohort study was establish using Swedish national registers (see section 4.1). All individuals resident in Sweden and born between 1932 and 1960, free from MI or IS in 1987 and who had information on SEP in the 1990 or 1980 Censuses were followed from 1987 to 2010. The first primary incident cases upon discharge of MI and IS were retrieved from NPR (non-fatal) or primary cause of death from CDR (fatal). The exposure was derived from SEI and categorized in five SEP groups (Table 1, section 4.1). The most advantaged SEP group was HN-M and intermediate SEP groups included LN-M, SE, HM, and the most disadvantaged SEP group was LM. The TPR was used to link information on sex, birthdate and country of birth, see Figure 10 for cohort selection. Almost 3 million individuals were included in time-to-event analysis (see section4.3.3) and followed from 1987 to occurrence of an event of MI/IS or censoring (migration, death) whichever came first. FPM (see section 4.3.4) was used with calendar year as primary timescale, and attained age as a secondary timescale (via stratification in four different age groups). Regression models were stratified by sex and attained age, and adjusted for birth country. IR per 100,000 person-years and IRR across SEP was estimated and presented in tables and graphically.

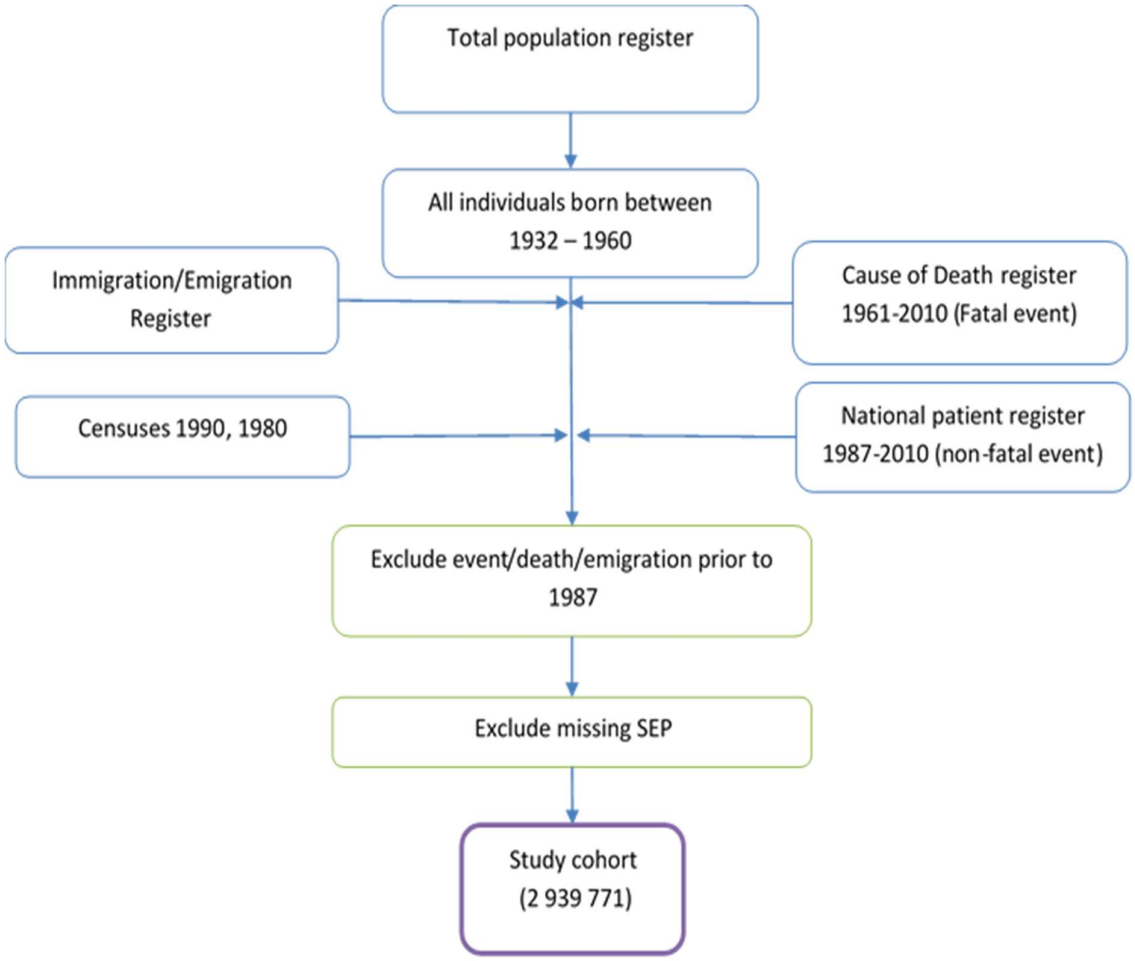


Figure 10. Cohort selection for Study I from Swedish national registers.

5.1.3 Results

Over the follow-up period, 121,496 MI cases (83% non-fatal, 17% fatal) and 61,421 IS cases (96% non-fatal, 4% fatal) were registered. There were large SEP inequalities in the incidence of MI/IS for both men and women, across all age groups (Figure 11, Figure 12). In men, the incidence in MI decreased over time for all SEP groups. While in women, the IRs in MI were stable over time (Figure 11).

Table 4 presents result summary of IRR comparing (LM, HM, SE, LN-M) with HN-M over time. Regarding MI, the IRRs comparing LM to HN-M were stable among men and women (Table 4).

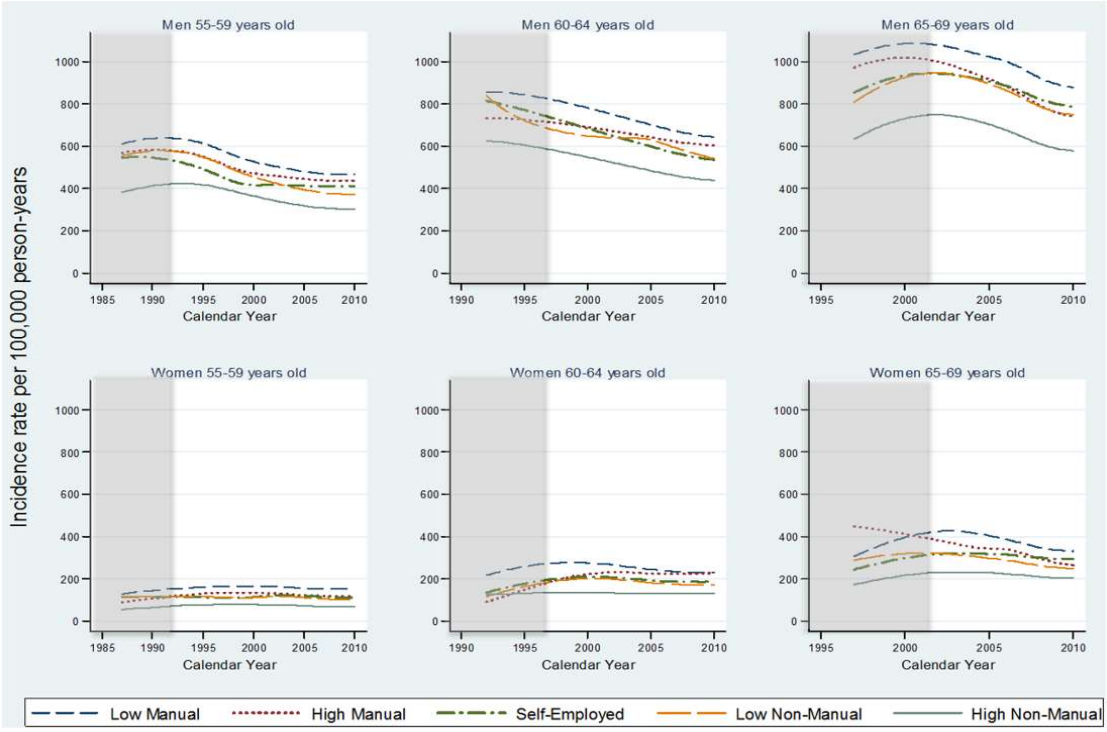


Figure 11. IR of MI by SEP among Swedish men and women in three age groups.

Table 4. Result summary, changes in IRR of MI and IS by SEP compared to HN-M from 1987 to 2010.

		Myocardial infarction		Ischemic stroke	
SEP	**Age**	**Men**	**Women**	**Men**	**Women**
LM/HN-M	**55-59**	—	—	↑	↑
	60-64	—	—	—	↑
	65-69	—	—	↑	↑
HM/HN-M	**55-59**	—	—	↑	↑
	60-64	↑	↑	—	—
	65-69	—	↓	—	↑
SE/HN-M	**55-59**	—	—	↑	↑
	60-64	—	—	—	—
	65-69	—	—	—	—
LN-M/HN-M	**55-59**	↓	—	↑	↑
	60-64	—	—	—	—
	65-69	—	—	—	—

Note: ↓ Decreasing SEP differences; — stable SEP differences; ↑ increasing SEP differences

For IS, the IRs decreased over time among men, whereas IRs were more stable over time for women. There were large SEP inequalities in IS incidence among both men and women (Figure 12). The IRR comparing LM to HN-M increased over time, particularly in women (Table 4). For the intermediate SEP groups the IRRs increased in the youngest age group (55-59), while in older age groups (60-65 and 65-69), the IRRs were stable over time (Table 4).

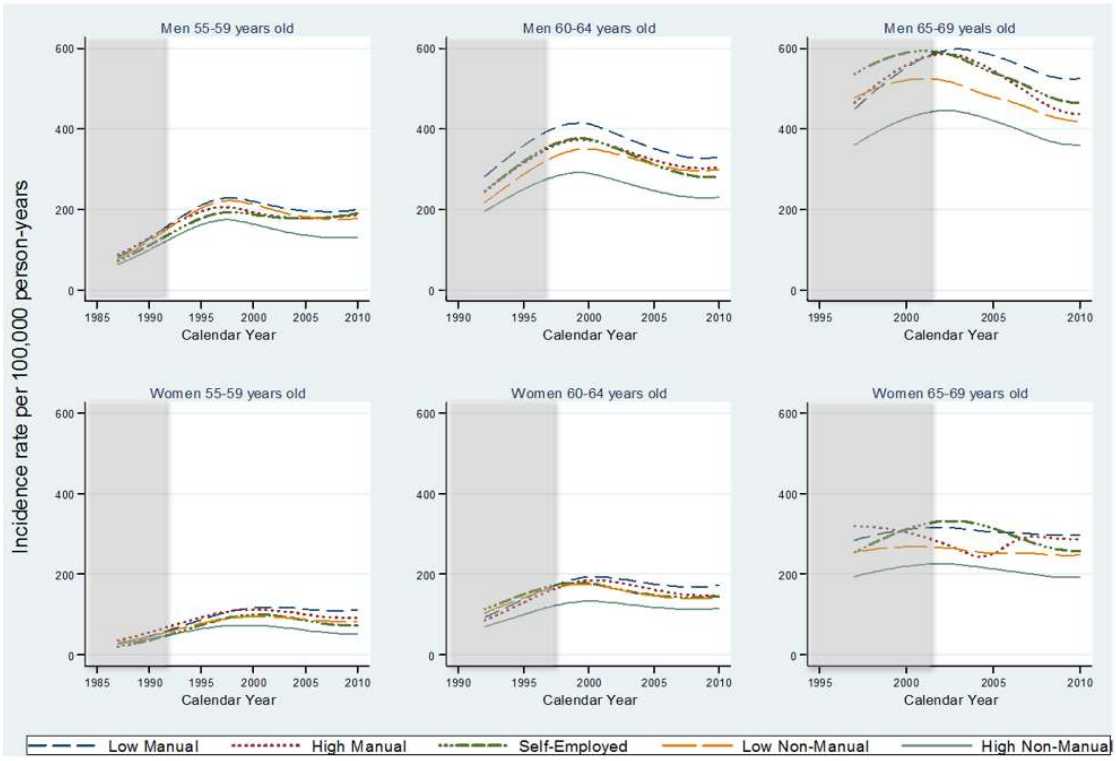


Figure 12. IR of IS by SEP among Swedish men and women in three age groups.

5.2 STUDY II

5.2.1 Objectives

We analyzed changes in short-term and long-term CFRs in MI and IS across SEP between the periods 1990-1994 and 2005-2009 by age and sex for the entire Swedish population.

5.2.2 Method

We aimed to study case-fatality over time from 1987 to 2010. Initially we aimed for a model with a four-way interaction with SEP, time-period (continuous 1987-2010), age and sex. Because this model would not converge, we had to simplify it. We analyzed changes over time, by selecting two time-periods, one at the beginning of the study period 1990-1994 and the

second at the end 2005-2009. We stratified our model between the two study periods and analyzed the case-fatality in each study period.

Since the mortality rate from IS and in particularly from MI is very high within the first day after an event, it was not meaningful to analyze the whole follow-up period. In order to deal with the fact that almost one third of all MI events deceased within one day, we divided the follow-up period in short-term case-fatality (death within one day) and long-term case-fatality (survived first day).

To identify the study population we used Swedish national registers (see section 4.1). NPR and CDR were used to identify all cases of first primary MI and IS in the two study periods, 1990-1994 and 2005-2009. The main exposure of interest, SEP, was identified from Censuses 1990 or 1980 and was categorized in five SEP groups as explained above in (Table 1, section 4.1). All Swedish born individuals were then followed from date of MI/IS diagnosis until death, emigration, end of follow-up (that is, 1 year after the diseases event) whichever came first (see Figure 13 for study flowchart). Short-term CFR, defined as death within one day after event, was estimated using logistic regression (see section 4.3.2). Subjects who survived the first day were included in time-to-event analysis (see section 4.3.3) using FPM (see section 4.3.4) and followed for one year, with time since disease event as underlying timescale. Age was included as a spline term for modelling the association between continuous age and mortality. Short-term and long-term CFRs and CFRD per 1000 subjects were estimated in both study periods and presented at three pre-specified ages (55, 65 and 75 years) in tables and graphically.

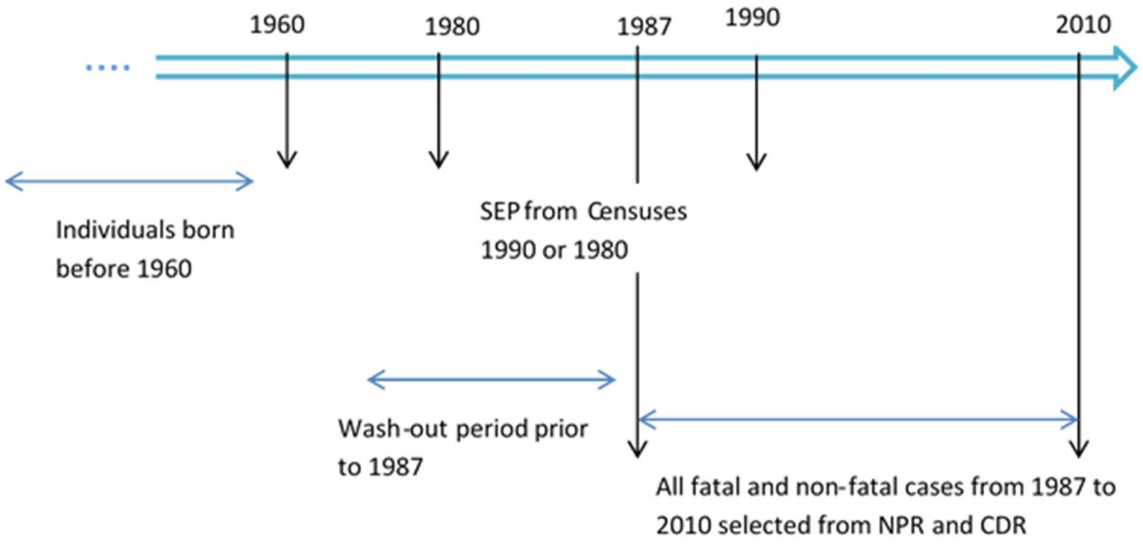


Figure 13. Flow chart for Study II.

5.2.3 Results

In 1990-1994 almost 28% of all MI events were fatal, while in 2005-2009 21% of all MI events were fatal. See Table 5 for crude numbers.

Table 5. Number of fatal and non-fatal events of MI and IS in two periods 1990-1994 and 2005-2009.

	Myocardial infarction		**Ischemic stroke**	
	1990-1994	**2005-2009**	**1990-1994**	**2005-2009**
Total events	55,456	72,883	24,046	53,213
Short-term events	15,726 (28%)	15,425 (21%)	2,152 (9%)	3,562 (7%)
Long-term events	2,834 (7%)	4,847 (8%)	1,822 (8%)	4,844 (10%)

For all SEP groups short-term CFR for MI and IS deceased over time from 1990-1994 to 2005-2009 among both men and women (Figure 14 for MI, Figure 15 for IS). In the latest study period the most disadvantaged LM group had lower short-term CFR both in MI and IS than the most advantaged (HN-M) group had at the beginning of the follow-up period.

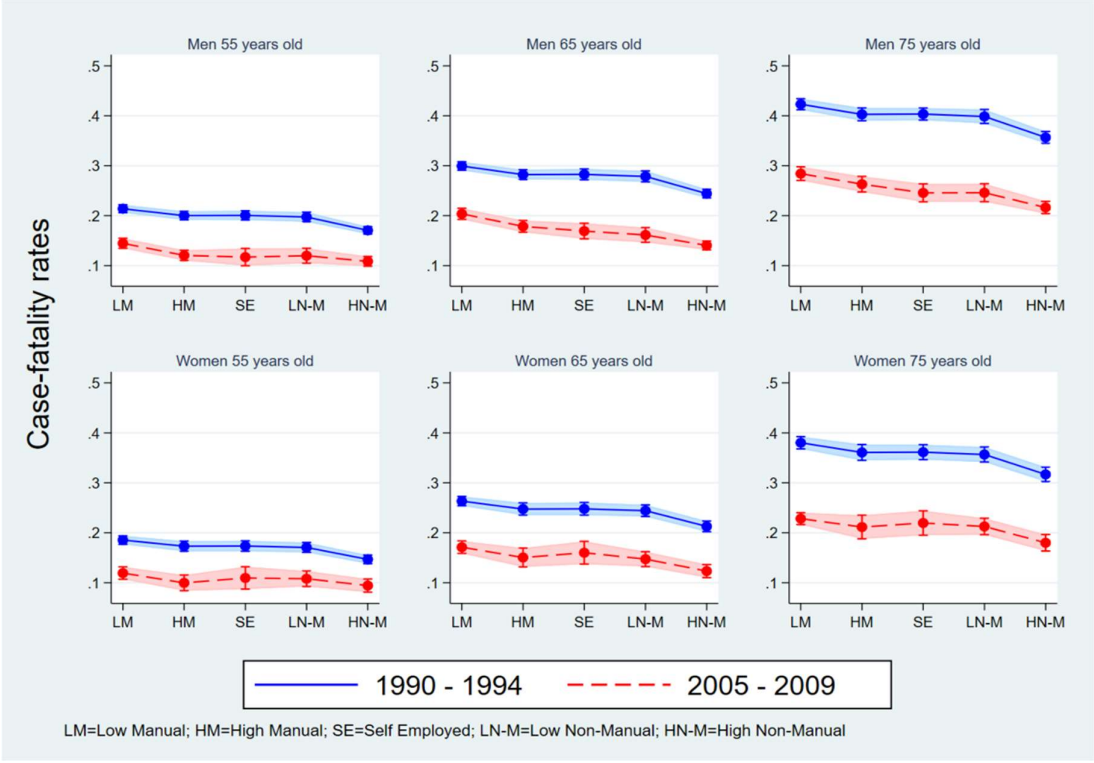


Figure 14. Short-term CFR in MI by SEP among men and women at ages 55, 65 and 75 years in 1990-1994 and 2005-2009.

Result summary of CFRDs between study periods from 1990-1994 to 2005-2009 for short- and long-term in MI and IS among men and women is presented in Table 6.

CFRD for both short-term and long-term MI between the lowest and the highest SEP group remained stable over the study period among both men and women. While the intermediate SEP groups (HM, SE, LN-M) manage to catch-up with similar CFRs as HN-M (Table 6). For IS the short-term CFRD decreased for all SEP groups compared to HN-M in all ages among both men and women, except for women 55 years. While long-term CFRD in IS remained fairly stable over time (Table 6).

Table 6. Result summary, changes in short-term and long-term CFRD of MI and IS by SEP compared to HN-M from 1990-1994 to 2005-2009.

		Myocardial infarction				Ischemic stroke			
		Short-term		Long-term		Short-term		Long-term	
SEP	Age	Men	Women	Men	Women	Men	Women	Men	Women
LM/HN-M	55	—	—	—	↑	↓	—	↑	↑
	65	—	—	—	↑	↓	—	↑	↑
	75	—	—	—	↑	↓	—	↑	↑
HM/HN-M	55	↓	↓	↓	↓	↓	↓	—	—
	65	—	↓	↓	↓	↓	↓	—	↑
	75	—	—	↓	↓	↓	↓	↑	↑
SE/HN-M	55	↓	↓	↓	↓	↓	↓	—	—
	65	—	↓	↓	↓	↓	↓	—	—
	75	—	—	—	—	↓	↓	↑	↑
LN-M/HN-M	55	↓	↓	—	↑	↓	↓	—	—
	65	↓	↓	—	↑	↓	↓	—	—
	75	↓	—	—	↑	↓	↓	↑	↑

Note: ↓ Decreasing SEP differences; — stable SEP differences; ↑ increasing SEP differences

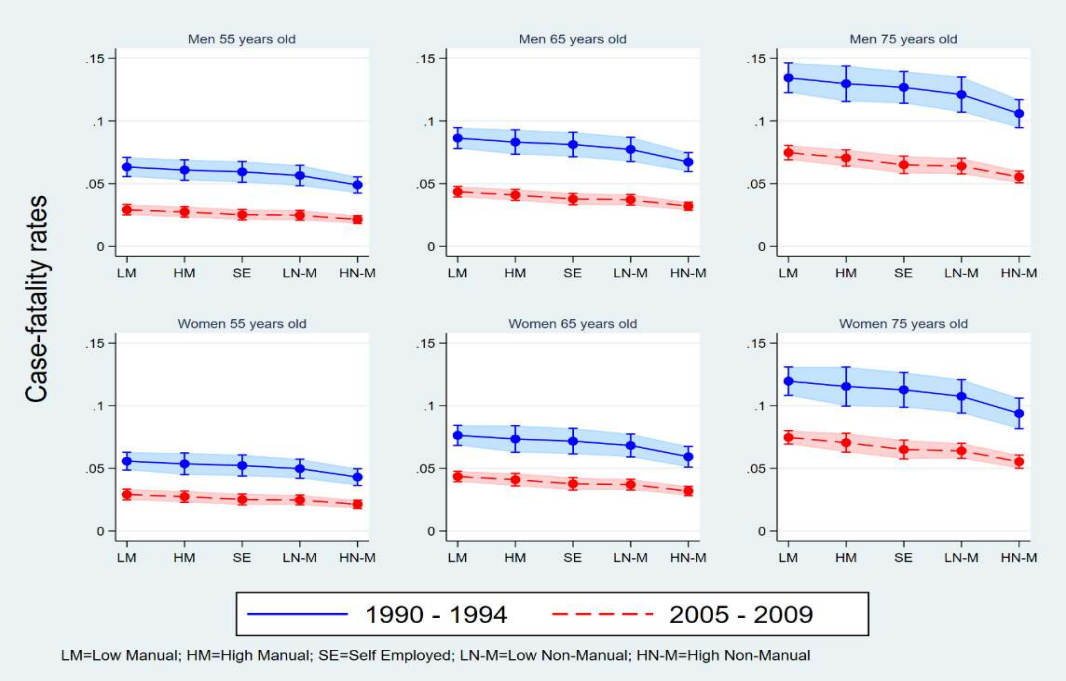


Figure 15. Short-term CFR in IS by SEP among men and women at ages 55, 65 and 75 years in 1990-1994 and 2005-2009.

5.3 STUDY III

5.3.1 Objectives

We assessed the association between educational level and vascular- as well as cardiac biomarkers. Potential impact of body mass index (BMI), smoking and alcohol intake as mediators were investigated.

5.3.2 Method

Data from the PIVUS (see section 4.2), with atherosclerosis biomarkers, collected at age 70 was used. The outcomes were defined as atherosclerosis biomarkers and were divided into eight vascular biomarkers including EDV and EIDV measured via the invasive forearm test as forearm blood flow to define the endothelial dysfunction. FMD was recorded by ultrasound of the brachial artery. IMT and number of plaques in CCA (carotid plaques) were detected by ultrasound of the CCA, CCA distensibility and (IM-GSM) were measured and SV/PP ratio was calculated. To assess the cardiac biomarkers (seven biomarkers), a Doppler echocardiography was performed to measure LA, LVEDD, RWT and calculate LVMI, E/A ratio, IVRT and EF; for further explanation of the outcomes see section 4.2. Main exposure of interest was measured as educational level, which was used as a proxy for SEP. The association between educational level (treated as a continuous variable) and the continuous outcomes where performed using

linear regression adjusted for sex (see section 4.3.1). For the association between educational level and the carotid plaques (treated as ordinal categorical variable with three category) ordinal logistic regression was used (see section 4.3.2). Possible role of modifiable lifestyle factors, including BMI, smoking and alcohol intake as potential mediators were evaluated via mediation analysis (see section 4.3.7).

5.3.3 Results

In total, 1,005 individuals were included in the analysis. We found an association between educational level and two of the vascular biomarkers, EIDV and carotid plaques (Figure 16 upper panel A). Regarding the cardiac biomarkers, we found an association between educational level and LVMI, IVRT, LVEDD, LA and EF (Figure 16 lower panel B)

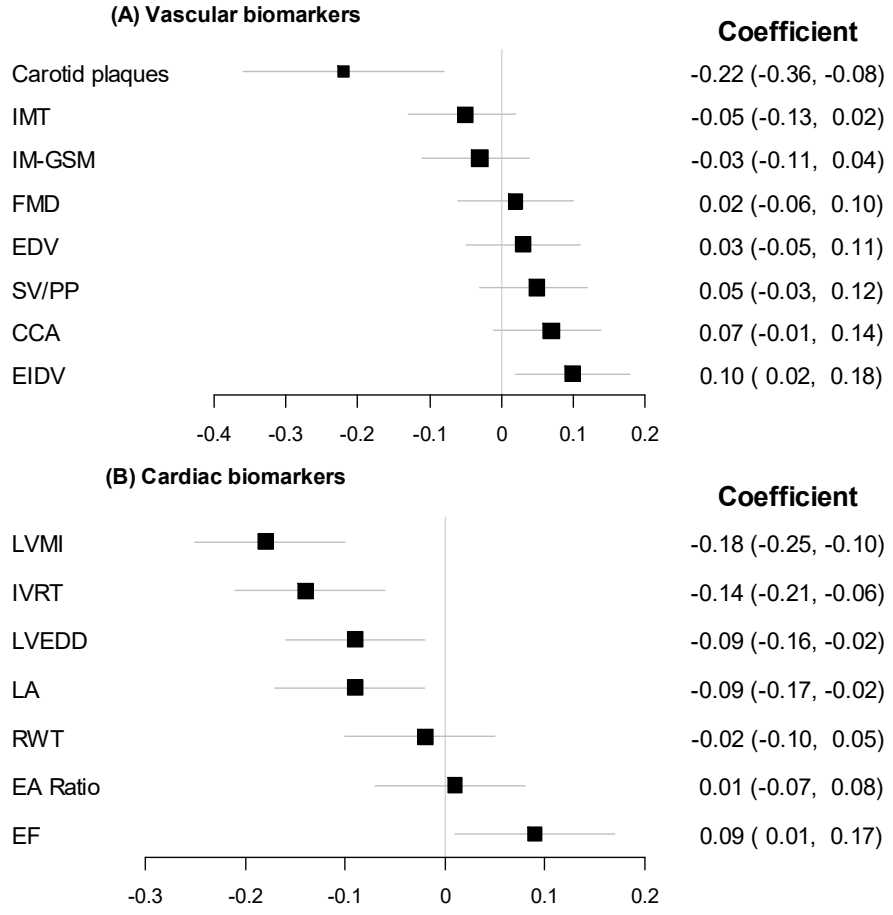


Figure 16. Forest plot for the association between educational level and vascular-, cardiac biomarkers in PIVUS study adjusted for sex (mean and 95% CI)

We further found that BMI mediated the pathways between educational level and EIDV by 33% and most of the cardiac biomarkers by 15%-66% (see Table 7), while smoking or alcohol intake did not mediate the association.

Table 7. Mediation analysis of BMI, smoking and alcohol intake in the association between educational level and vascular-, cardiac biomarkers.

		Body Mass Index [a.]	**Smoking** [b.]	**Alcohol intake** [c.]
Carotid plaques	**NID**	0.01 (-0.003; 0.03)	-0.02 (-0.04; 0.004)	-0.0001 (-0.001; 0.001)
	NDE	-0.2 (-0.3; -0.1)	-0.2 (-0.3; -0.1)	-0.2 (-0.3; -0.1)
	ME(%)	-7	10	0
EIDV	**NID**	12.1 (4.4; 19.8)	2.3 (-1.3; 5.9)	-0.03 (-0.7; 0.6)
	NDE	24.2 (-8.7; 57.2)	35.0 (1.6; 68.5)	36.6 (3.2; 70.0)
	ME(%)	**33***	6	0
LVMI	**NID**	-1.7 (-2.7; -0.8)	0.2 (-0.1; 0.5)	-0.0004 (-0.01; 0.01)
	NDE	-3.1 (-4.8; -1.3)	-4.9 (-6.9; -3.0)	-4.7 (-6.7; -2.7)
	ME(%)	**36***	-5	0
IVRT	**NID**	-1.1 (-1.8; -0.4)	0.1 (-0.2; 0.3)	0.01 (-0.2; 0.2)
	NDE	-4.8 (-8.0; -1.6)	-6.0 (-9.2; -2.7)	-5.8 (-9.1; -2.6)
	ME(%)	**19***	-1	0
LA	**NID**	-0.8 (-1.3; -0.4)	0.1 (-0.03; 0.3)	-0.001 (-0.01; 0.01)
	NDE	-0.4 (-1.2; 0.4)	-1.4 (-2.3; -0.5)	-1.3 (-2.2; -0.3)
	ME(%)	**66***	-11	0
LVEDD	**NID**	-0.4 (-0.7; -0.2)	0.1 (-0.03; 0.2)	-0.001 (-0.02; 0.02)
	NDE	-0.7 (-1.4; 0.1)	-1.1 (-1.9; -0.3)	-1.0 (-1.8; -0.3)
	ME(%)	**39***	-7	0
EF	**NID**	0.002 (0.0003; 0.004)	0.0004 (-0.001; 0.001)	0.00004 (-0.001; 0.001)
	NDE	0.01 (-0.00001; 0.03)	0.01 (0,002; 0.03)	0.01 (0.002; 0.03)
	ME(%)	**15***	2	0

Note: **Abbreviations: NID:** Natural indirect effect; **NDE**: Natural direct effect; **ME**: Mediated effect in percent

Carotid plaques, number of arteries with plaques; **EIDV**, endothelium-independent vasodilation; **LVMI**, left ventricular mass index; **IVRT**, left ventricular isovolumic relaxation time; **LA**, left atrial dimension; **LVEDD**, left ventricular diameter in end diastole; **EF**, ejection fraction.

a. **Body mass index** was used as continues mediator.

b. **Smoking** was grouped in (0 = "never smoker" or "former smoker"; 1 = "current smoker")

c. **Alcohol intake** was grouped in (0 = "Less than 24 grams per week for female" or "Less than 36 grams per week for male"; 1 = At least 24 grams per week for female" or "At least 36 grams per week for male")

5.4 STUDY IV

5.4.1 Objectives

We studied the association between SEP and CVD preventive drugs according to needs. Further we investigate the differences in prescription of lipid lowering drugs statins and two antihypertensive drugs, first line treatment ACE-inhibitors and second line treatment ARBs.

5.4.2 Method

Because disadvantaged SEP groups are more likely to suffer from CVD, they are in more need of CVD preventive drugs. In order to measure the need for medication in each SEP group, we selected two proxies for need: the ratio in MI/IS incidence in a "healthy" population (that is, free from CVD), and its comorbidities (diabetes, high blood pressure and high lipids level). This approach has been used previously in a Danish study.[188]

Based on Swedish national registers (see section 4.1), a population-based cohort study was established. We included all Swedish individuals born before 1960, with information on SEP, free from ischemic heart disease (IHD) including MI, stroke (including IS), diabetes, and not having received a prescription of statins, ACE-inhibitors or ARBs before start of follow-up. Information on CVD diagnosis was included from NPR and CDR both as primary and secondary diagnosis (for ICD-codes see Table 2, section 4.1). Prescription information was retrieved from SPDR (for ATC- codes see Table 3, section 4.1). Individuals were followed from July 1, 2006 until registration of first occurrence of IHD, stroke, diabetes, a CVD preventive treatment (statins, ACE-inhibitors, ARBs), diabetes treatment, death, migration, or end of study (December 31, 2013), whichever came first.

Time-to-event analysis was performed (see section 4.3.3), following each individual from July 1, 2006 until outcome (first prescription of statins, ACE-inhibitors or ARBS) or censoring. Need-standardized IRs of combined CVD drug treatment (statins, ACE-inhibitors, ARBs) were calculated, IRRs in MI/IS were used as need proxies to adjust for unequal needs across SEP groups (five groups see Table 1, section 4.1). Moreover, need-standardized IRs of each of the drugs statins, ACE-inhibitors and ARBs were also calculated applying MI and IS IRR as two need proxies.

To quantify the inequity in CVD preventive treatment, Poisson regression (see section 4.3.5) was used to calculate IRRs of need-standardized treatment across SEP with lowest SEP (LM) as reference group. To account for the additional uncertainty introduced in the Poisson regression bootstrapping was used to calculate the 95% CI for the IRRs (see section 4.3.5). Horizontal inequity (see section 2.4) for a SEP group relative to lowest SEP was noticed in case of a IRR>1.

5.4.3 Results

In total 2,357,351 individuals were included in the follow-up. The main results on need-standardized incidence of the combined CVD treatment applying MI/IS IRR as need proxies

are presented in Table 8. We found that statins, ACE-inhibitors and ARBs to a larger extent were prescribed to individuals in disadvantaged SEP groups, but this did not always meet the needs. We found that the typically first-line recommended antihypertensive treatment (ACE-inhibitors) almost reached horizontal equity across SEP groups, particularly when using IS incidence as need proxy (Figure 17). However, for lipid lowering statin drugs and for second-line antihypertensive treatment ARBs, which have less side effects, larger SEP inequalities were found (Figure 16 & Figure 17).

Figure 16. Horizontal inequity in need-standardized incidence treatment in statins, ACE-inhibitors and ARBs, by age, sex and SEP: applying MI IRR as need proxy.

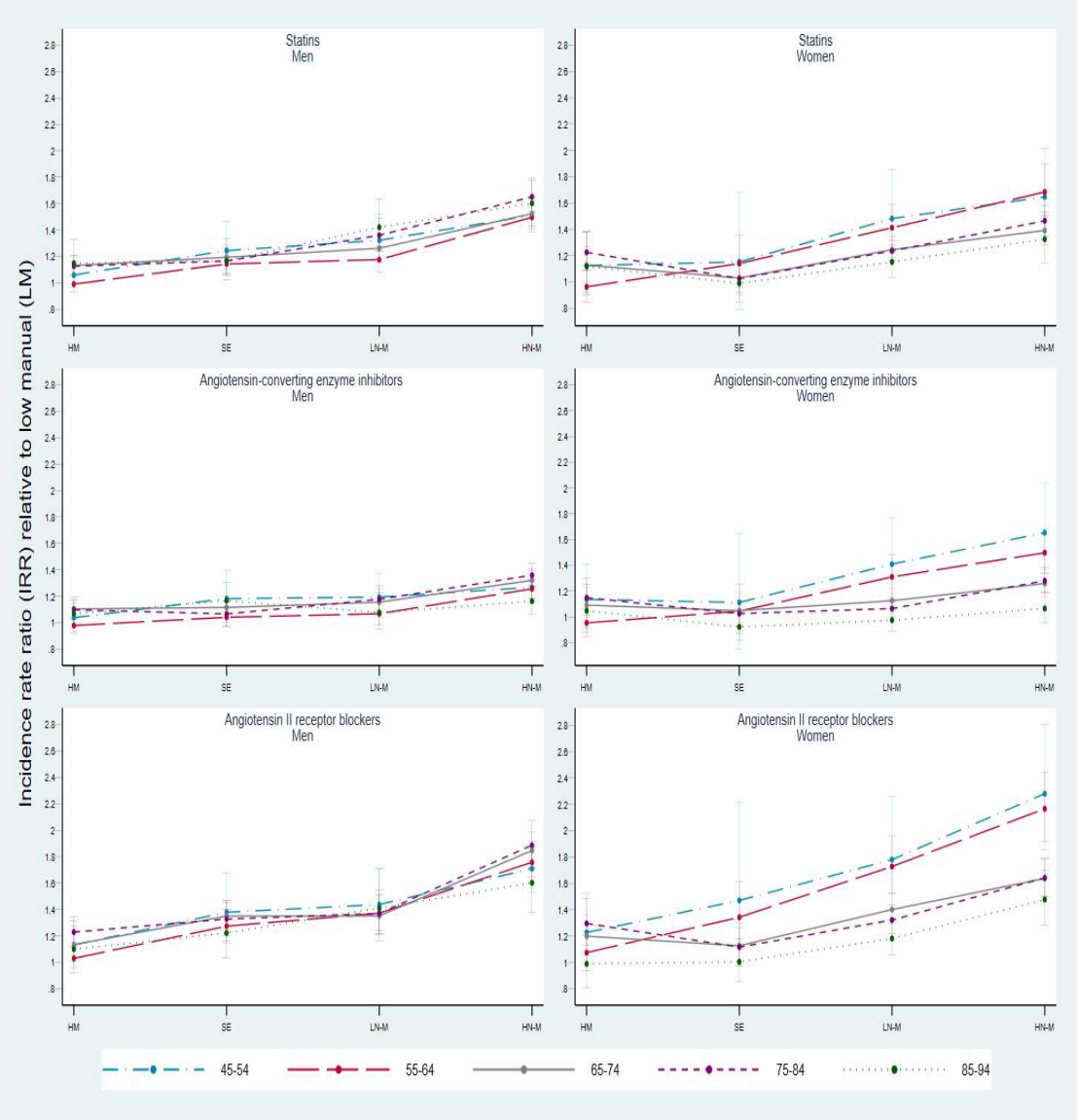
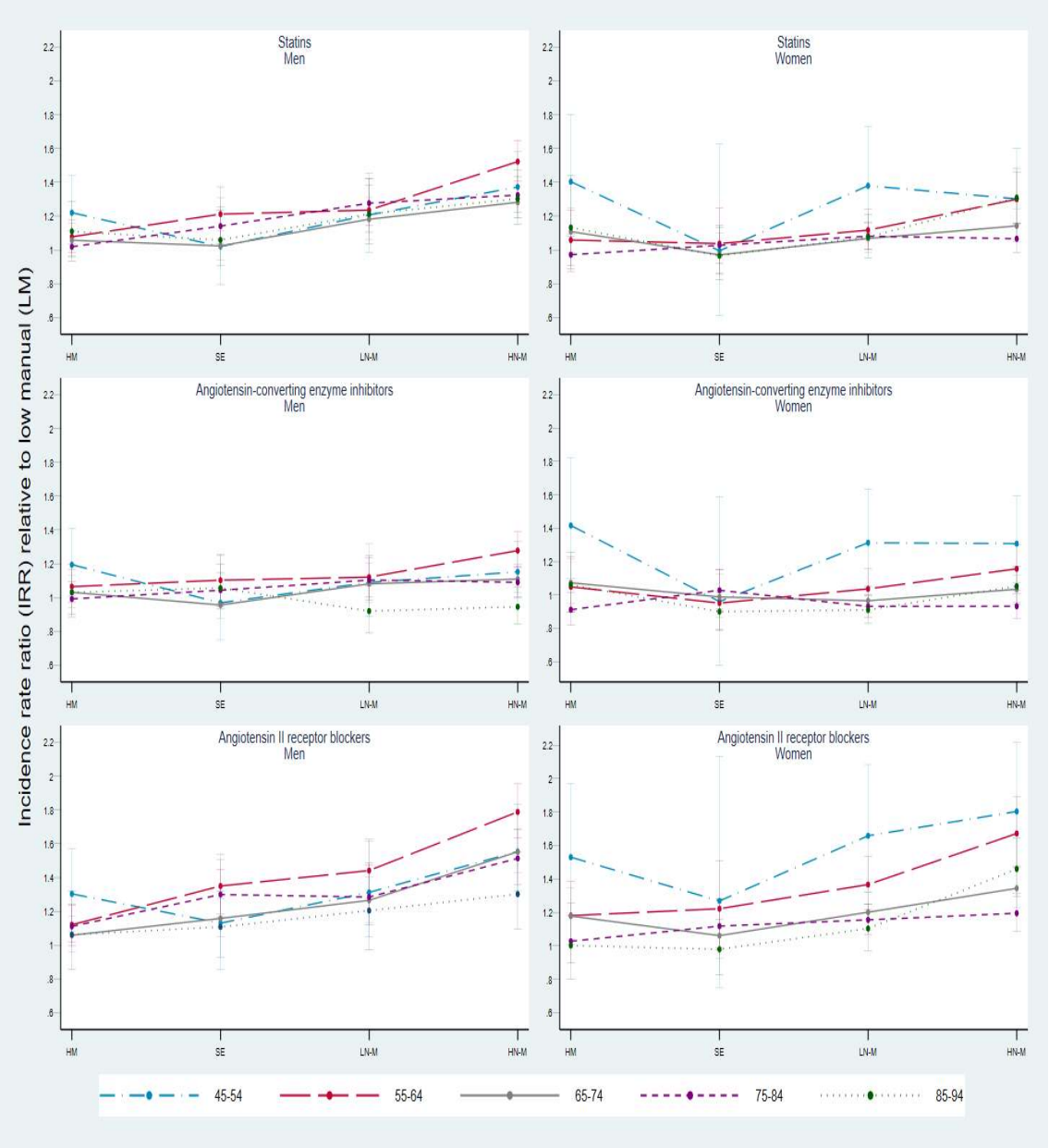


Table 8: Observed and need-standardized incidence of combined CVD drug treatment (statins, ACE-inhibitors, ARBs) by attained age groups, sex and SEP, applying incidence of MI and IS as two alternative need proxies.

Sex	SEP	45-54			55-64			65-74			75-84			85-94		
		Need-weight	Combined drug incidence [c]		Need-weight	Combined drug incidence [c]		Need-weight	Combined drug incidence [c]		Need-weight	Combined drug incidence [c]		Need-weight	Combined drug incidence [c]	
			Observed	st.dized		Observed	st.dized		Observed	st.dized		Observed	st.dized		Observed	st.dized
Myocardial infarction as need-weight for treatment [a]																
Male	LM	1.00	36.47	36.47	1.00	56.70	56.70	1.00	82.04	82.04	1.00	97.55	97.55	1.00	74.23	74.23
	HM	0.93	36.37	38.92	1.01	56.82	56.44	0.88	81.32	91.98	0.89	97.87	110.48	0.94	75.52	80.66
	SE	0.76	34.38	45.11	0.89	56.47	63.14	0.85	82.26	97.01	0.89	98.78	111.07	0.92	80.53	87.79
	LNM	0.76	35.60	46.92	0.91	59.66	65.40	0.85	85.45	100.49	0.81	100.47	123.52	0.90	79.92	88.53
	HNM	0.64	33.26	52.17	0.70	56.60	80.73	0.63	76.37	121.02	0.64	95.51	149.67	0.77	74.29	96.04
Female	LM	1.00	29.22	29.22	1.00	51.68	51.68	1.00	85.00	85.00	1.00	101.31	101.31	1.00	74.23	74.23
	HM	0.78	26.33	33.71	0.94	47.41	50.56	0.83	79.00	95.48	0.82	99.52	121.67	1.02	80.14	78.70
	SE	0.75	25.91	34.66	0.79	46.55	58.70	0.85	76.62	90.10	0.93	98.32	105.96	1.04	73.24	70.44
	LNM	0.62	27.12	43.77	0.66	48.85	73.47	0.72	75.08	104.01	0.81	96.02	118.74	0.91	70.31	77.02
	HNM	0.44	22.69	51.40	0.47	40.95	87.15	0.55	64.26	117.51	0.61	87.06	142.91	0.79	69.25	87.59
Ischemic stroke as need-weight for treatment [b]																
Male	LM	1.00	36.47	36.47	1.00	56.70	56.70	1.00	82.04	82.04	1.00	97.55	97.55	1.00	74.23	74.23
	HM	0.81	36.37	44.81	0.93	56.82	61.40	0.95	81.32	85.90	0.98	97.87	99.89	0.97	75.52	77.87
	SE	0.93	34.38	36.98	0.84	56.47	66.92	0.99	82.26	83.17	0.91	98.78	108.73	1.01	80.53	79.56
	LNM	0.83	35.60	42.82	0.87	59.66	68.68	0.91	85.45	94.07	0.87	100.47	115.87	1.06	79.92	75.59
	HNM	0.70	33.26	47.41	0.69	56.60	82.15	0.75	76.37	101.74	0.80	95.51	120.04	0.95	74.29	78.07
Female	LM	1.00	29.22	29.22	1.00	51.68	51.68	1.00	85.00	85.00	1.00	101.31	101.31	1.00	74.23	74.23
	HM	0.63	26.33	42.03	0.85	47.41	55.57	0.84	79.00	93.84	1.03	99.52	96.45	1.01	80.14	79.69
	SE	0.87	25.91	29.91	0.87	46.55	53.42	0.90	76.62	84.85	0.93	98.32	106.11	1.07	73.24	68.70
	LNM	0.67	27.12	40.76	0.84	48.85	58.10	0.84	75.08	89.17	0.92	96.02	103.83	0.98	70.31	71.91
	HNM	0.56	22.69	40.66	0.61	40.95	67.27	0.67	64.26	96.46	0.84	87.06	104.02	0.80	69.25	86.54

Incidence rate ratio (IRR) MI with LM as reference group within each strata of sex and attained age-group. b) Incidence rate ratio (IRR) of with LM as reference group within each strata of sex and attained age-group **c)** Incidence of combined drug treatment **d)** Need-standardized incidence of combined drug treatment ("st.dized").

Figure 17. Horizontal inequity in need-standardized incidence treatment in statins, ACE-inhibitors and ARBs, by age, sex and SEP: applying IS IRR as need proxy.



6 METHOD CONSIDERATION

6.1 STUDY DESIGN

The epidemiological study design in Study I, II and IV in this thesis was population-based cohort studies. In this type of studies, a defined population is followed longitudinally to assess the association between the exposure and outcome.[92,189] The advantage of population-based cohort studies in Sweden is the ability to link information from several population-based registries, enabling longitudinal follow-up of a study cohort over time and also that the results can be applied to a wide range of the population gives the opportunity to study unselected population with high precisions. On the other hand, one has to rely on existing information because register data is restricted to few variables. Unfortunately, we did not have information, on for example, personal characteristics or on modifiable lifestyles factors (e.g. smoking, physical activity, BMI). However, these factors have been considered as mediating factors and not as confounders. In this thesis, SEP is considered to involve all modifiable lifestyle factors.

6.2 VALIDITY IN EPIDEMIOLOGICAL STUDIES

In epidemiological studies, errors in estimations can be either random or systematic. Systematic errors may bias the results and interpretations of studies. The validity of a study reflects whether the results are trustworthy and meaningful, and can be divided into internal and external validity. While internal validity relates to how reliable the estimates are in supporting the findings of the study, external validity relates to how generalizable these findings are. The largest threat to internal validity is bias due to selection, information and confounding.[92]

Selection bias: Selection bias in Study I, II and IV was minimized, given that we used the total population register that includes all individuals and has no loss to follow-up. In the third study, 50% of those invited to join the study had participated. To try to evaluate this bias, we examined the characteristics of CVD and medication use in a sample of 100 non-participants. On average, non-participants had a similar prevalence of MI, revascularization, as well as antihypertensive, statins and insulin treatment, but had a higher prevalence of diabetes, heart failure and stroke. While poorer participation rates are often seen among individuals with a low education, as well as those with higher smoking and alcohol intake,[190-192] unfortunately this data was unavailable for this sample. It is possible that our limited findings of a mediating effect of smoking and alcohol intake on the association between SEP and CVD is due to underestimation caused by selection bias. Additionally, for the association between vascular and cardiac biomarkers, the association may be attenuated due to selection bias.

Information bias: In Study I, II and IV, information bias of exposure could be due to missing information on SEP from the Censuses. Individuals with an unclassifiable occupation are usually those outside the labor market, who also tend to have the highest CVD mortality.[193] This group is heterogeneous and can include individuals who are on long-term sick leave, retired, maternity leave, or students, therefore determining their SEP is difficult. For other SEP groups, the SEI occupation was based on self-reported occupation, and was additionally confirmed through information from the employer in the Labor market register (see section 4.1). A proportion of the unclassified group had occupational information (as confirmed from employer), but because this information was missing in the self-reported questionnaire or was illegible, SEI could not be assigned. Another challenge is related to the multiple birth cohorts in Study I, II and IV; we selected all individuals born before 1960 and measure their SEP in 1990. At this point, some individuals may have been too young to achieved their highest SEP, while others may have been too old on the labor market. To minimize this bias (for the elderly), we retrieved SEP from 1980 (if available) for those individuals with missing SEP information. However, for the youngest individuals, we did not have any information on SEP after 1990.

In the third study, only 11 individuals were excluded from the analysis due to missing information on education. We cannot rule out possible exposure information bias due to the misclassification of self-reported education due to recall bias. Unfortunately it were not possible to validate these self-reports with other data.

Regarding, possible information bias of the outcomes, MI and IS, were retrieved from NPR and CDR (Study I), fatal MI or IS from CDR (Study II short-term mortality), all-cause mortality from CDR (Study II long-term mortality) and first prescription of CVD preventive drugs (statins, ACE-inhibitors and ARBs) from SPDR (Study IV). The largest source of error would be the misclassification of MI and IS as causes of death from CDR (Study I and II short-term mortality), due to uncertainty of doctor's determination and reporting of the cause of death. Autopsies are one way to minimize such bias, however the rate of autopsy in Sweden has decreased substantially over time, especially for the elderly.[194] Additionally, older individuals often suffer from multi-morbidities, which may make it difficult for the physician to determine which conditions were crucial for the death. Given this, cause of death is usually more valid for younger than for older individuals. However, the overall validity in CDR is high[146] and the agreement for IHD between the underlying cause of death in the death certificate (on which the CDR is based) and the assessment of case summaries is as high as 87%.[195] Despite this, it is difficult to know to which degree this misclassification is differential based on SEP groups.

Information bias for outcomes based on the NPR are probably minor, with the positive predictive values of MI and IS diagnoses being 85-100% (see section 4.1).[145]

The SPDR includes prescribed and dispensed drugs, therefore information bias for outcomes in this register may be due to non-dispensed drugs. Additionally, drugs given in hospitals and nursing homes are not included in the SPDR. To limit this misclassification, we delayed study entry by one year to allow for issuing a prescription. Despite this, we cannot rule out the possibility of having misclassified some treated individuals as untreated in our analysis. While these patients would only contribute to an untreated risk-time until a prescription was issued. Still this bias can be differential between SEP groups, although it is not clear to what extent. Information from The National Board of Health and Welfare and Swedish eHealth Agency show that >99% of all the prescribed drugs statins, ACE-inhibitors and ARBs are included in the SPRD (personal communication).

Confounding: If a factor is associated with both the exposure and outcome, and is not in the causal pathway between the exposure and the outcome, it may act as a confounder if not taken into account. The association between an exposure and outcome can be underestimated, overestimated or reversed due to confounding, and this may lead to misleading findings.[92] There are several strategies to deal with confounding in cohort studies, including restrictions during the study design stage, stratification, and adjustment (through data modelling).[196]

In Study II and IV, we restricted to include only those born in Sweden, to remove confounding by indication through country of birth; while in the first study we adjusted for country of birth.

To deal with the confounding effects of age and sex, we stratified for both these variables in Study I; while in Study II and IV we adjusted for age and sex.

Birth county from the TPR and civil status from the Censuses where tested as other unmeasured confounders, however information was missing on current county of residence and current civil status.

Confounding by indication is most notable in pharmacoepidemiology. In Study IV, the greatest challenge in considering the association between SEP and CVD drug use is that the prevalence of CVD varies by SEP. This means that prescription of CVD preventive drugs could also differ by SEP due to comorbidity. Stratification at the design stage was done to account for this sort of confounding, by excluding all individuals with prior CVD morbidity (including only those who were free from CVD, diabetes, and who had not received a prescription of statins, ACE-inhibitors or ARBs). Additionally, our approach in calculating a need proxy as the IRR of MI/IS

was another step to account for the confounding effect of CVD preventive drugs across SEP groups.

6.3 ETHICAL CONSIDERATIONS

Study I, II and IV, included in this thesis is based on data from record linkage of Swedish registers. According to the Swedish Personal Data Act (PUL) and the European General Data Protection Regulation (GDPR), the data included in the national registers are considered as personal data. The data used in those three studies was unidentifiable and protected in database servers at the department. The national registers are governed by law and individuals included are not able to drop out from the registers. Study III is based on questionnaire and clinical test, which required that participants provided written informed consent. All studies based on personal data have to be approval by regional ethical review board. Which judge weather the potential benefits from the studies are greater than the potential harm. Ethical approval for Study I, II and IV were obtained from Regional ethical Review Board in Stockholm with diary numbers: 03-466, 2008/1482-32, 2009/1084-32 (Study I,II) and diary numbers: 2013/862-31/5, 2016/1214-32, amendment 2018/2035-32 (Study IV). In addition, Regional Ethical Review Board in Uppsala obtained ethical approval for Study III, with diary number: 2015/252.

7 DISCUSSION

7.1 MAIN FINDINGS

7.1.1 Trends in SEP inequalities in CVD (Study I and II)

In Study I and II we investigated absolute and relative SEP inequalities in incidence and case-fatality in MI and IS over two decades. We aimed to explore how the decrease in CVD incidence and case-fatality have been distributed between SEP groups and if the gap in SEP inequalities for CVD is closing.

We found there are large SEP inequalities in incidence and case-fatality in MI and IS. Overall incidence rates and case-fatality rates in MI have declined substantially over time in Sweden across all SEP groups. Particularly in short-term CFR in MI and IS where socioeconomic disadvantaged group had smaller short-term mortality in 2005-2009 than the most advantaged group had in 1990-1994. However among women, the incidence in MI and IS has not improved at similar extent.

Regarding trends in SEP inequalities, we found that inequalities in incidence of MI and IS did not decrease over time, particularly between the most and least disadvantaged LM and HN-M groups. In addition, absolute differences in case-fatality for MI have mostly remained stable over time, but increased for long-term CFR among women. However, we found decreasing SEP inequalities in short-term CFR for IS.

Previously, it has been found that SEP inequalities in MI incidence were stable over time,[40,117] or even increasing.[128,197,198] A more updated study from northern Sweden, has shown a stable trend in educational inequalities of CVD morbidity and widening income inequalities.[129] Also, data downloaded from The National Board of Health and Welfare show stable educational inequalities in MI incidence over time in Sweden (see Figure 8 in section 2.5).

Comparatively few studies have investigated the trends in SEP inequalities in CVD case-fatality, both in Sweden and Europe. Previous studies have found persistent SEP inequalities in short-term case-fatality in MI among men and women.[119,199] However, previous studies have mostly excluded death outside the hospitals or have reported an average of short-term and long-term case-fatality, which could be biased by improvements in short-term CFR. A strength in our case-fatality study, was that we reported trends in inequalities for both short-term case-fatality (including death outside the hospital) and long-term case-fatality.

Several factors may influence the observed persistent SEP inequalities in incidence of MI and IS, such as remaining inequalities in CVD risk factors.[128] Recent studies, have found that SEP inequalities in smoking and alcohol intake have been stable among men but increased over time among women.[200,201] In addition, SEP inequalities in obesity and cholesterol levels have remained stable over time.[202] However, high blood pressure have decreased across SEP over time.[203-205]

Short-term case-fatality is a proxy for disease severity, awareness of early symptoms, the emergency transport system and emergency care. The large decrease in case-fatality in MI and IS across all SEP might largely be explained by improvements in modifiable lifestyle factors and in emergency care, irrespectively of SEP. As mention previously in section 2.1.4, hypertension is the main risk factor for IS. We therefore speculate that the decreasing SEP inequalities in short-term case-fatality in IS may be due to decreasing SEP inequalities in hypertension control.

Long-term case-fatality, on other hand, is affected by both the severity of the disease and the clinical treatment following the event, such as revascularization. SEP inequalities have been found in treatment at coronary care units after first MI, as well as access to cardiac procedures and revascularization procedures [124,125,206] Contradictive results have been reported regarding, inequalities and medication after a CVD event.[207-209]

Our studies contributes to the knowledge showing that SEP inequalities in incidence and case-fatality of MI and IS have remained stable over time and even increased in some groups such as women and younger persons. Importantly, even if we can report that there have been major improvements in incidence and case-fatality of MI and IS, we are far from closing the gap in inequalities related to these disorders.

7.1.2 SEP inequalities in atherosclerosis biomarkers.

In Study III we found associations between educational level (as proxy for SEP) and vascular biomarkers (carotid plaques, EIDV) as well as most of the cardiac biomarkers (LVMI, IVRT, LA, LVEDD and EF), with higher SEP corresponding to more beneficial biomarker levels. In addition, BMI was found to mediate the associations between SEP and a majority of these biomarkers, explaining up to 66% of the association. However, we found no evidence for mediation effects of smoking or alcohol intake in the association of educational level and atherosclerosis biomarkers.

Regarding the vascular biomarkers, our results have been in line with previous studies that have found associations between SEP and carotid plaques.[210,211] Contradictory results were reported previously in association between IMT and SEP,[210,212] and we did not find an association between SEP and IMT.

There has been less investigation of the association between SEP and cardiac biomarkers. Our findings confirm the previously reported results for the association between SEP and LVMI as well as for RWT, and E/A ratio.[213,214] Inconsistent results were reported in the relationship between SEP and LA, EF,[213,214] whereas an association was found in our study.

From the mediation analysis we concluded that BMI was an important potential mediator of the association between SEP and vascular (EIDV) as well as cardiac (LVMI, EF, IVRT, LVEDD and LA) biomarkers. It has been reported that individuals with a higher BMI have increased cardiac preload and afterload, leading to high levels of peripheral resistance and high chronic volume overload.[215,216] Another important role in the atherosclerotic process is that adipose tissue contributes to increased pro-inflammatory cytokine secretion.[217] We did not find any evidence for mediation of smoking or alcohol intake in our data. This could be due to the small differences in smoking and alcohol intake prevalence across SEP, which does not allow the mediation effect to be captured.

This study contributed to the evidence that SEP gradients are associated with subclinical biomarkers of atherosclerosis and that BMI is a mediator of the association between SEP and most of the those biomarkers.

7.1.3 SEP inequalities in preventive treatment of CVD according to need

In Study IV, we found that CVD preventive drugs such as statins, ACE-inhibitors and ARBs were prescribed to a larger extent to individuals in socioeconomically disadvantaged groups. However, due to an overall increasing need with decreasing SEP among men and women, the prescription pattern still did not meet the needs. Moreover, we demonstrated small SEP inequalities in first line recommended antihypertensive treatment (ACE-inhibitors) and large SEP inequalities in second line antihypertensive treatment ARBs and in lipid lowering statin drugs.

Previous findings have demonstrated equity in prescription of CVD primary preventive treatment, or even that disadvantaged SEP groups were more often prescribed statins, ACE-inhibitors, and ARBs compared to more advantaged SEP groups.[135,136,138] This was confirmed in our study; however, it is not correct to conclude that there are no inequalities in CVD primary

preventive treatment. In fact, socioeconomically disadvantaged groups have higher risk of hypertension and high blood lipid levels due to poorer health and health-related behaviors (see section 2.1.4) and are probably in more need for medication. The horizontal equity, which the Swedish healthcare system is based on, requires access to healthcare based on need. Therefore, studies that do not consider the needs may result in biased and misleading findings. To deal with this, we used indirect standardization of MI/IS incidence as a proxy for need, in individuals free from CVD, diabetes and not receiving a prescription of CVD preventive treatments. This approach has been tested previously in a study that found education and income inequality in statins prescription in Denmark.[188]

The horizontal inequity we found in prescription of CVD preventive treatments may suggest the impact of awareness, health literacy, health seeking behaviors and demands for treatment by socioeconomic advantaged group, but also by physicians' decision to prescribe a treatment, that has previously been found to be associated with patients' SEP.[218] By analyzing the first prescription in two different antihypertensive drugs, we could observe differences in first and second line treatments. ACE-inhibitors should be prescribed as first line treatment and ARBs should be given as an alternative treatment in patients intolerant to ACE-inhibitors, according to guidelines. The larger SEP inequalities in second line treatment ARBs, which have less side effects, may illustrate the influence of demands, health literacy and health awareness among socioeconomic advantaged groups.

The study has contributed to the knowledge that SEP inequalities in prevention treatment of CVD exist. In Sweden, treatment guidelines for hypertension are largely followed, but socioeconomically advantaged groups seem to benefit from larger use of second-line treatments for hypertension and statins.

7.2 GENERAL DISCUSSION

Regardless, of the large improvements in life expectancy and in modifiable risk factors over the last century, social gradient in CVD has persist over time.

There is a vast literature on health inequalities. Different theories and explanations for why inequalities arise and how to solve it have been suggested. The *Black Report* in 1980,[219] suggested a process of social selection, which implies that inequalities in health are explained by a process of health related social mobility, where healthier individuals are more likely to move upwards in the social hierarchy and individuals with poor health are more likely to move downwards. Others have explained health inequalities in a life course perspective. Indicating that inequalities in adults is partly determinate by factors related to an individual's childhood

situation,[220] such as biological factor or social factors, such as access to material and immaterial resources.[221,222] Also psychosocial stress, culture factors, or SEP differences in earlier adoption of new behaviors and new intervention, have been linked to persistent health inequalities.

Neither the generous welfare states nor the technological developments in health care have been able to eliminate SEP inequalities in health. This is known in the literature as the *Welfare States Paradox*.[223] Rather, it seems that the more developed welfare states and healthcare systems have enlarged the relative differences between SEP groups.[132] However, at the same time, the quality of life and the decrease in incidence of CVD both in MI and IS have been substantial. We could show that disadvantaged SEP groups have lower case-fatality in the 2010 than the highest SEP group had in the 1990. It has also been reported that Sweden has one of the lowest prevalence in Europe.[7]

The debate is still ongoing and several reviews have measured different magnitudes of socioeconomic inequalities in health. Are the health inequalities increasing or decreasing? This important question remains, which has a high impact for public health policies: Is it more important to put the effort in healthcare and provide better health for all individuals or is it more important to decrease the inequalities in health. The Swedish national commission for equity in health has pointed out that inequalities in seven key resources have to be reduced to achieve the goal of decreasing health inequalities [6] Those key resources are "*early life development; skills and education; working conditions and work environment; incomes and economic resources; housing and neighborhood conditions health behaviors; control, influences and participation"*.[6]

7.3 CONCLUSION

Socioeconomically unprivileged groups have indeed benefited from recent changes in modifiable lifestyle factors and improved healthcare, which has resulted in decreasing incidence and case-fatality in CVD over time in Sweden. However, socioeconomic inequalities still exist both in absolute and relative terms. It is important to highlight that in women, the reduction in MI and IS incidence has been smaller than in men.

Further, we can conclude that there are SEP inequalities in prevention of CVD by unequal prescription of preventive drugs according to need; in levels of atherosclerosis biomarkers; in incidence and survival in CVD.

It is important to highlight that treatment for hypertension is almost equally distributed by SEP, which may indicate that implementation of clinical guidelines has been successful. This may

have been the reason of decreasing SEP differences in IS short-term case-fatality. This is an example of how the inequalities can be reduced by targeted prevention to equal health conditions for vulnerable groups.

7.4 IMPLICATIONS AND FUTURE PERSPECTIVES

Taken together, the amount of resources and prevention strategies are not the only factors driving health inequalities. Individual's receptiveness for action, health literacy and social conditions might influence the outcome. From this thesis, we can show that in Sweden, a country based on equal access to healthcare according to need, it is not only a matter of unhealthy behaviors among lower SEP but also a matter of unequal healthcare use.

Recent reports have emphasized that income inequality in Sweden is growing, with a widening gap between the rich and poor in Sweden. There are additional threats to the equal society in Sweden, which may increase the gap in equalities. For example, residential segregation is increasing,[224] which plays an important role for early childhood conditions, education and later occupation and health conditions. In addition, several reports have stressed that obesity and illegal drugs are also an increasing issues in Sweden for future generations.[225,226]

Some important questions are still unanswered. First, we have seen that women did not improve MI/IS incidence to similar extent as men. Previously, it has been reported that women may have different symptoms of MI and IS, and more research on sex and gender differences may shed light in this area.

Furthermore, in this thesis we only investigated first prescription of either ACE-inhibitors or ARBs. More research should focus on the mechanism for prescription inequalities.

Socioeconomically disadvantaged groups, may suffer from different comorbidities, it is also of interest to seek answer how those comorbidities affect the SEP inequalities in diagnosis of CVD and in drug use.

Finally, based on our conclusions, as well as the evidence that MI/IS are affected by modifiable lifestyles factors, the society would benefit from more research with focus on targeted preventions strategies.

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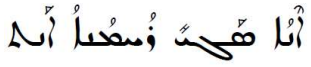
Min bästa vän, min själsfrände, min kärlek, min man **Aziz**. Min resa till Stockholm blev bra, kräftriket och KTH. Hur kul har vi inte haft? kanske min studietid på universitetet var så underbar att jag undermedvetet vill plugga resten av mitt liv (så med andra ord det är ditt fel att jag fortsatte med PhD.) Till allvar, t.o.m. jag tappade orden när jag ska tacka dig (och det händer aldrig, det vet du). Så tack för att du är den du är, tack för all stöd och för att du är en så underbar, förstående och hjälpsam person. Du är mitt stöd och allt är lätt i livet när jag har dig vid min sida. 

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