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IMMIGRATION, MYOCARDIAL INFARCTION, AND TYPE 1 DIABETES IN SWEDEN – USE OF THE MIGRATION & HEALTH COHORT

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ABSTRACT

The aim of this study was to examine the risks for and time trends of first-time myocardial infarction and type 1 diabetes mellitus, and the equity of admission to specialized care and evidence-based treatments after first-time myocardial infarction in association with country of birth, socioeconomic position, sex, and age.

The Migration & Health Cohort was used in all four papers. This cohort was built by linkage between Swedish national registers to study the incidences of cancer, diabetes, injuries, and cardiovascular and psychiatric diseases among immigrants and their descendants compared with Sweden-born residents. Poisson regression was used to estimate incidence rate ratio of first-time myocardial infarction and type 1 diabetes mellitus, logistic regression for odds ratio of admission to coronary care units, and Cox proportional hazard regression to model first-time myocardial infarction case fatality and likelihood of undergoing cardiac procedures.

First, during more than two decades of follow-up of all men and women aged 35–89 years living in Sweden, we identified 571,476 patients with first-time myocardial infarction (*Paper I*). We observed a decreasing trend in incidence and case fatality after day 28 for both sexes regardless of country of birth. The trend was, however, less pronounced among women and those born outside Sweden. Men born in Southern and Western Asia had a 50% higher risk than men born in Sweden. Incidence was 50–80% higher in the least well educated irrespective of sex and country of birth.

Secondly, between 2001 and 2009 we identified 120,609 first-time myocardial infarction patients treated in a coronary care unit (*Paper II*). A low rate of coronary care unit admission after first-time myocardial infarction among women and patients of low socioeconomic position was observed. Foreign-born patients, both men and women, were equally likely to be admitted to coronary care units as Sweden-born patients.

Thirdly, we followed first-time myocardial infarction patients admitted to coronary care units between January 2001 and September 2009 for 90 days after admission (*Paper III*). In total, 61.71% of patients underwent angiography, 45.74% underwent percutaneous coronary intervention, and 9.15% underwent coronary artery bypass grafting. Foreign-born patients were no less likely to undergo these procedures than Sweden-born patient. Furthermore, patients born in Asia had a high rate of access to coronary artery bypass grafting.

Fourthly, we followed 4,469,671 men and 4,231,680 women, aged 0 to 30 years, living in Sweden at any time between 1969 and 2008 (*Paper IV*). Over the study period, the risk of type 1 diabetes mellitus increased among children younger than 15 years, but not among young adults (15–30 years). Compared with Sweden-born individuals, immigrants aged 0 to 14 had about a 40% lower risk of type 1 diabetes mellitus, and the risk was about 25% lower in the offspring of immigrants. Further, immigrants aged 15 to 30 years had about a 30% lower risk, and the offspring of immigrants about a15% lower risk of type 1 diabetes mellitus compared with their Sweden-born counterparts.

Country of birth is associated with risk of first-time myocardial infarction and type 1 diabetes mellitus. First-time myocardial infarction risk is decreasing in all age groups

but type 1 diabetes mellitus is increasing among children less than 15 years of age. Immigrants in Sweden are not disadvantaged in terms of accessing cardiac care after first myocardial infarction, in contrast to women and patients with low socioeconomic position.

LIST OF PUBLICATIONS

This thesis is based on the following four projects, which will be referred to throughout as *Paper I* to *Paper IV*.

Paper I **Yang D**, Dzayee DA, Beiki O, de Faire U, Alfredsson L, Moradi T. Incidence and case fatality after day 28 of first time myocardial infarction in Sweden 1987-2008. *Eur J Prev Cardiol 2012 Dec;19(6):1304-15.*

Paper II **Yang D**, James S, de Faire U, Alfredsson L, Jernberg T, Moradi T. Likelihood of treatment in a coronary care unit for a first-time myocardial infarction in relation to sex, country of birth and socioeconomic position in Sweden.
PLoS ONE 8(4): e62316.

Paper III **Yang D**, James S, de Faire U, Alfredsson L, Jernberg T, Moradi T. Differences in undergoing cardiac procedures after myocardial infarction regarding country of birth. *Manuscript*

Paper IV Hussen HI, **Yang D**, Cnattingius S, Moradi T. Type I diabetes among children and young adults: the role of country of birth, socioeconomic position and sex. *Pediatr Diabetes 2013 Mar;14(2):138-48.*

CONTENTS

LIST OF ABBREVIATIONS

ACC	The American College of Cardiology
AHA	The American Heart Association
APC	Annual percent change
CABG	Coronary artery bypass graft
CCU	Coronary care unit
DIAMOND	The World Health Organization Multinational Project
ECG	Electrocardiography
ESC	The European Society of Cardiology
fMI	First-time myocardial infarction
HR	Hazard ratio
ICD	International classification of diseases
IRR	Incidence rate ratio
MI	Myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
SEP	Socioeconomic position
T1DM	Type 1 diabetes mellitus
WHF	The World Heart Federation
WHO	The World Health Organization

1 INTRODUCTION

Cardiovascular diseases are considered to be the leading cause of mortality around the world[1]. Cardiovascular diseases are among the most important burdens of disease in the Swedish healthcare system with high costs for both the individual and society[2]. Of all cardiovascular diseases, myocardial infarction (MI) costs most years of life lost. The treatment of acute MI is costly. Sweden is among the countries with the highest incidence of type 1 diabetes mellitus (T1DM)[3]. It has been estimated that among children younger than 15 years the risk of T1DM is increasing in many countries and varies significantly by ethnicity[4, 5].

Sweden is a country that provides extremely good opportunities to conduct migration health research for several reasons. First, around 15% of the population in Sweden was born overseas, and immigrants are from almost all over the world[6]. Moreover, for more than 11% of the population born in Sweden, at least one parent was born overseas. Secondly, Sweden has relatively complete registers that include the majority of the Swedish population including immigrants. These registers cover many research areas such as demographic, socioeconomic, and medical information. Many of these registers date back several decades with reasonably high accuracy.

The studies in this thesis are based on information from the newly established M&H Co (Figure 1). This cohort is built by linkage between the 14 Swedish national registers. Linkage has been completed using the Swedish 10-digit unique personal identity number (PIN), which is maintained by the National Tax Board for all individuals who have resided in Sweden since 1947, by Statistics Sweden and the National Board of Health and Welfare.

This thesis includes four register-based cohort studies including the entire Swedish population. We investigated the risk of first-time MI (fMI) and its trends over the last few decades by country of birth, education, and sex, as well as case fatality 28 days after fMI. We also compared the likelihood of admission to a coronary care unit (CCU) and of undergoing cardiac procedures among foreign-born and Sweden-born fMI patients. By using data from the M&H Co., the risk of T1DM and its trends in Sweden regarding country of birth, education, and sex were also evaluated.

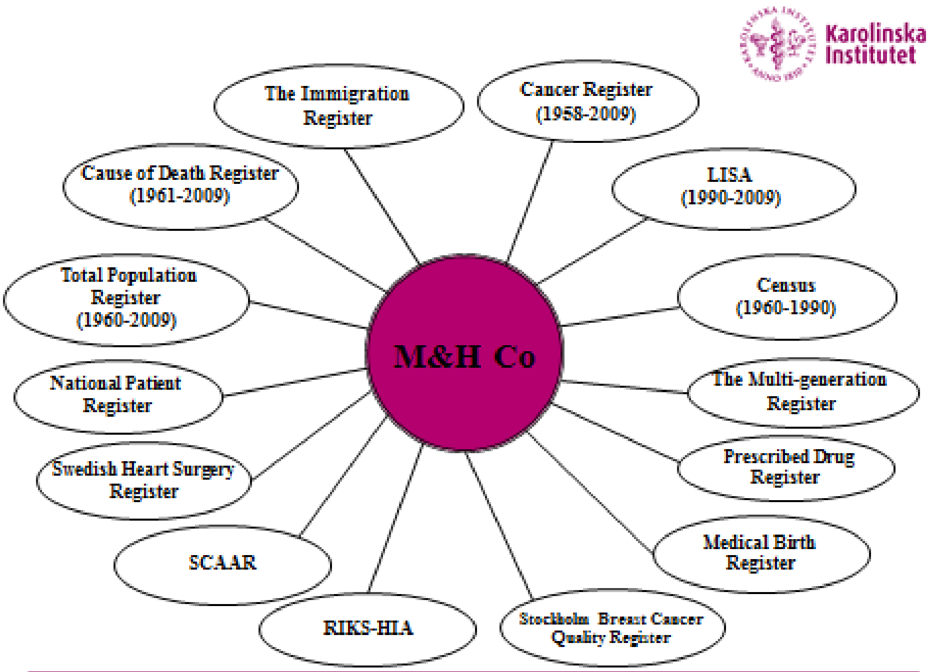


Figure 1: Migration and Health cohort (M&H Co.)

2 BACKGROUND

2.1 IMMIGRANTS IN SWEDEN

There has been an ongoing trend of global movement of people, ideas, and services. Immigrants in Sweden are from almost all over world. In 2011, there were 1,437,296 inhabitants of Sweden who were born abroad[7]. In addition, 1,096,976 persons were born in Sweden with at least one foreign-born parent[7]. With a total population of 9,482,855, about 15% of the population was foreign born, 5% was born in Sweden with two parents born abroad, and 7% was born in Sweden with one parent born outside Sweden. In total, around 26% of the Swedish population had a immigrant background in 2011[7].

The number of immigrants in Sweden has been increasing in recent years and is expected to continue increasing in the future (Figure 2.1). In 2010, there were 1,384,929 foreign-born Swedish residents, which corresponded to 14.3% of the total population[7]. Of these, 859,000 (9.2%) were born outside the European Union (EU) and 477,000 (5.1%) were born in other EU member states[8]. The top 10 source countries of foreign-born individuals living in Sweden in 2010 were: Finland, the Former Yugoslavia, Iraq, Poland, Iran, Germany, Denmark, Norway, Turkey, and Somalia[9].

Sweden has become a country of net immigration from one of net emigration since World War II. A large number of refugees came to Sweden after the war. In 1946, there were more than 70,000 foreign-born residents of Sweden, which was four-fold higher than the number in 1940. From 1949 up to the 1970s, immigrants from Southern Europe and other Nordic countries due to establishment of the first common Nordic labor market. After the 1970s, the immigrant population again mainly consisted of refugees. At first, many refugees were from Chile after the military coup of 1973. At the beginning of the 1980s, refugees from the Middle East arrived after the Iran–Iraq war. In the 1990s, many asylum seekers fled to Sweden because of the Yugoslav Wars. In the 2000s, there were also large inflows of immigrants from the Middle East due to the Iraq war and from Africa[10].

In 2011 the overall numbers of male (694,815) and female immigrants (732,481) were similar[9]. There were 620,084 foreign-born men and 661,497 foreign-born women in 2008. However, the gender distribution was uneven across the 10 main immigration source countries. For example, there were more men than women from Iraq, but more women from Finland and Poland[10].

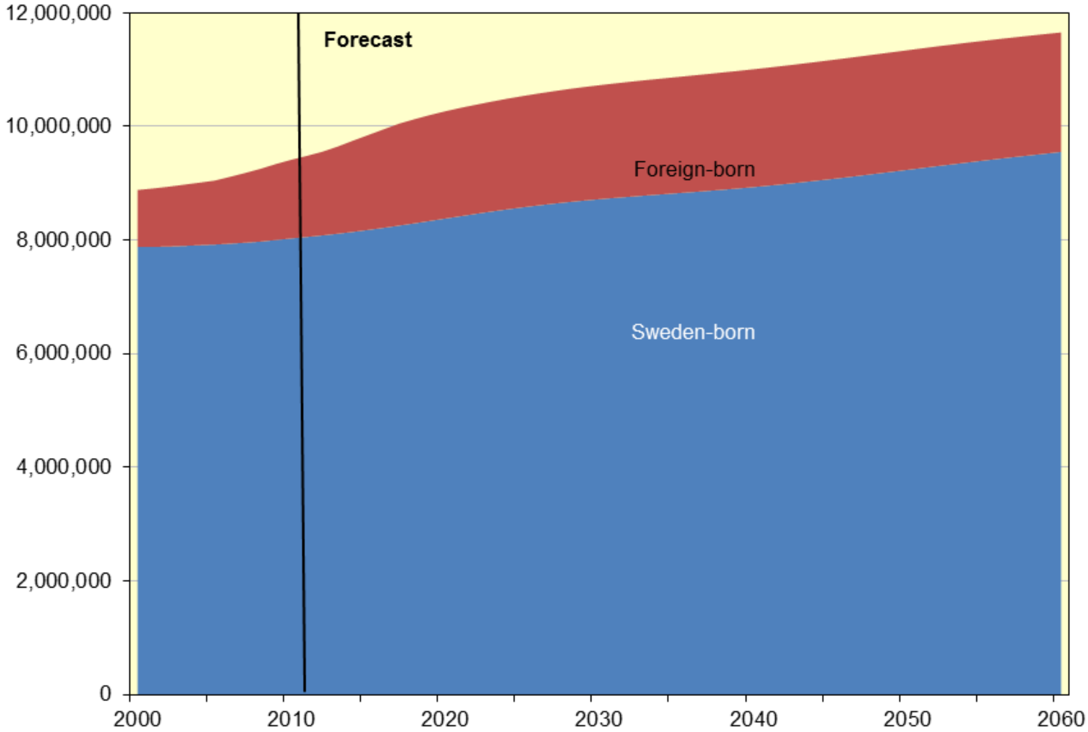


Figure 2.1: Population in 2000–2012 and forecast for 2013–2060 among Sweden- and foreign-born individuals (Source: Statistics Sweden)

2.2 MYOCARDIAL INFACTION

MI, also known as acute MI or heart attack, is the death or damage of heart muscle caused by interruption of blood flow to a part of the heart. It is commonly caused by occlusion of a coronary artery after the rupture of a vulnerable atherosclerotic plaque. A vulnerable atherosclerotic plaque is an unstable collection of white cells and lipids in the wall of an artery. The coronary arteries convey blood and oxygen to the heart. If the arteries are blocked and left untreated for a sufficient length of time, the resulting restriction in blood supply and shortage of oxygen can cause damage to or death of heart cells.

2.2.1 Diagnostic criteria

In 1979, the World Health Organization (WHO) formulated diagnostic criteria for MI: (1) history of ischemic type chest pain lasting for more than 20 minutes; (2) unequivocal changes in electrocardiography (ECG), the development of abnormal persistent Q or QS waves, and evolving injury lasting longer than 1 day; and (3) rise and fall of serum cardiac biomarkers such as creatine kinase-MB fraction and troponin. A diagnosis of MI was made if two of these three criteria were met[11].

In 2000, the European Society of Cardiology (ESC)/American College of Cardiology (ACC) criteria for redefinition of MI were established. A consensus document between the ESC and ACC was produced; either one of the two following criteria were required for a diagnosis of acute MI: “(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischaemic symptoms; (b) development of pathologic Q waves on the ECG; (c) ECG changes indicative of ischaemia (ST segment elevation or depression); (d) coronary artery intervention (e.g., coronary angioplasty). (2) Pathologic findings of an acute MI.”[12] The new guildelines placed more emphasis on cardiac biomarkers than in previous diagnostic criteria[12].

In 2007, the ESC and ACC collaborated with the American Heart Association (AHA) and the World Heart Federation (WHF) to produce a second document re-defining MI. Any of following criteria were required for a diagnosis for MI: “ (1) Detection of increase and/or decrease of biomarkers, preferably troponin, with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with one at least following features: symptoms of ischaemia; ECG changes indicative of new ischaemia; development of pathological Q waves in the ECG; and imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. (2) Sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischeamia, accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death before occurring before blood samples could be obtained, or at a time before the appearance before cardiac biomarkers in the blood. (3) For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3×99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized. (4) For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases biomarkers greater than 5×99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction. 5) Pathological findings of an acute myocardial infarction.”[13]

In 2011, the WHO accepted the universal definition of MI. The 2007 universal definition was not accepted due to concern that it was only suitable for use in Europe and North America, but not in other developing countries. Therefore at that time the WHO definition was developed[14].

In August 2012, the third universal definition of MI was presented and discussed[15]. It was developed by the new Global Task Force, which consisted of 52 member states including new members such as China and Russia, in collaboration with ESC, ACC, AHA, and WHF. The third universal definition is also referred to by the US Food and Drug Administration as the basis for clinical trial protocols. Based on the second universal definition, a new consensus was reached regarding levels of troponin required for a diagnosis of PCI- and CABG-related MI, as well as the levels required for diagnosing MI not due to cardiac procedures or due to cardiac procedures other than PCI and CABG.

2.2.2 Classification

In the clinical setting, patients with acute coronary syndrome based on the 12-lead ECG can be classified into two subgroups: those with new ST-elevation on the ECG that is diagnostic of acute ST-elevation MI and non-ST-elevation MI[16].

The Joint ESC/ACC/AHA/WHF Task Force for the Redefinition of Myocardial Infarction published the universal definition of MI[13]. Type 1: spontaneous MI that is related to ischemia and due to a primary coronary event such as plaque erosion, rupture, fissuring, or dissection; type 2: MI secondary to ischemia caused by either increased oxygen demand or decreased oxygen supply, such as coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension; type 3: MI resulting in death including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by new ST elevation or new LBBB, or evidence of fresh thrombus in a coronary artery, but death occurring when biomarker values are unavailable (i.e. before blood samples could be obtained, at a time before cardiac biomarker levels could rise, or in rare cases because cardiac biomarkers were not collected); type 4: MI associated with PCI or stent thrombosis; type 5: MI associated with CABG.

2.2.3 Epidemiology of MI

There have been many studies to measure the incidence of MI across different populations and settings.

The Framingham Heart Study is a prospective cohort study of cardiovascular disease and risk factors from a sample of the population of the town of Framingham, MA, USA. Trends in disease incidence and outcomes such as MI have been assessed in the Framingham Heart Study under the auspices of the Framingham Cardiovascular Disease Survey[17, 18]. Findings from the study have shown that the incidence of MI along with other manifestations of coronary disease decreased over a 20-year period.

The WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project was created in the early 1980s to evaluate trends in cardiovascular diseases and associations with risk factor changes[19]. The results showed a wide variation across participating countries regarding MI incidence and case fatality[19, 20].

The Global Burden of Disease study was commissioned by the World Bank in 1991[21, 22]. Its goal was to provide summary measures of mortality and morbidity across all world regions by using standardized measures of diseases, including MI. The incidence rates of MI were standardized according to age. The highest rates were observed in Eastern Europe and Central Asia. There was no significant variation between countries within each region. The overall incidence of MI was approximately two-fold higher in men than in women[23].

The Reduction of Atherothrombosis for Continued Health (REACH) Registry is a prospective study[24]. Participants were enrolled from 5,587 physician practices in 44 countries. A total of 61,332 patients were followed up between December 2003 and December 2004. It was found that a higher level of education was associated with a lower risk of cardiovascular events; however, there was no such association in low income countries, particularly for women[24].

The surveillance component of the Atherosclerosis Risk in Communities (ARIC) study was conducted to assess coronary heart disease incidence by ethnicity and by geographic location in the USA[25, 26]. There was no change in the incidence rate of hospitalization due to MI between 1987 and 1994. However, when stratified by ethnicity and sex, black women showed an increase risk of MI.

Many other studies have evaluated trends in and risks of MI. For example, the Minnesota Heart Survey has been following up hospitalized MI patients among residents of the Minneapolis–St. Paul metropolitan area (MN–WI, USA) since the 1970s [27, 28]. The Corpus Christi Heart Project was designed to compare disease burden and outcome between Mexican Americans and Whites the USA[29, 30]. FINAMI is a population-based MI registry to evaluate MI and coronary heart disease death within several geographic areas in Finland[31]. The National Registry of Myocardial Infarction is a large observational study of acute MI in the USA. Since 1990, information has been collected on more than two million patients with a central focus on care management and short-term prognosis[32-34].

2.2.4 Risk factors

Current smoking and hyperlipidemia[35] are two of the strongest risk factors for MI[1, 36]. A strong and positive association was found between the number of cigarettes smoked and risk of MI. Those who smoked more than 40 cigarettes per day had an almost 10 times higher risk than non-smokers[1]. Four other important risk factors were abdominal obesity (waist/hip ratio), history of diabetes, hypertension, and psychosocial factors[37]. Patients with diabetes have been found to have twice the risk of MI compared with the general population[38]. The presence of smoking, hypertension, and diabetes increased the risk of MI more than 13-fold compared with the absence of these risk factors[1]. Consumption of fruits/vegetables and moderate alcohol as well as regular physical activity have been found to be protective[38–41]. The combined effect of these three protective factors showed an almost 80% decreased risk of MI[1], while incorporating all nine independent factors could increase the risk more than 100-fold compared with none of these risk factors[1]. These nine risk factors explain more than 90% of the population-attributable risk, suggesting that these risk factors could account for the majority of the MI risk in the study population[1].

An overall risk ratio of 1.6 was observed among rheumatoid arthritis patients compared with a matched general population[39]. Other inflammatory diseases such as atherosclerosis are also important risk factors for MI[40, 41]. Furthermore, family history of MI is associated with an increased risk of MI[42]. However, in one study it was found that the risk of a family history of MI could be explained by association with other major risk factors[1].

Human immunodeficiency virus was found to increase MI risk by 50%[43]. Rates of MI were shown to increase particularly following influenza outbreaks[44]. Low vitamin D levels were also associated with higher prevalence of cardiovascular disease risk factors and a higher risk of MI[45]. The chronic systemic inflammation present in psoriasis was suggested to explain why moderate to severe psoriasis is an independent risk factor for MI[46].

Epidemiological and family studies have shown that genetic predisposition explains 40% to 60% of the risk for coronary artery disease (CAD)[47]. For example, the locus at 9q34.2 was associated with MI[47]. Two other gene variants in the leukotriene pathway (ALOX5AP and LTA4) have been found to be susceptibility factors for MI[48]. It has been suggested that genetic association studies of MI should also focus on multifactorial pathophysiology and interaction with environmental factors. For example, the findings of a large-scale genetic study including 352 MI cases and 418 control subjects suggested a potential association between MI and three variants of the thrombospondin gene family[49]. In another study of 2819 MI cases and 2242 control subjects, a potential association was identified between MI and single-nucleotide polymorphisms in the connexin 37 and the plasminogen-activator inhibitor type 1 genes[50]. The findings from some genetic studies of MI have been inconclusive [47].

Risk factors might have a different impact on MI according to sex and country of birth. Similar risk among men and women was found for the associations between MI and smoking, hyperlipidemia, abdominal obesity, psychosocial factors, and fruit and vegetable consumption[1]. By contrast, hypertension, diabetes, regular exercise, and consumption of alcohol at least three times per week were more strongly associated with the risk of MI in women than men[1]. Most of the important risk factors for MI are consistently observed in most countries worldwide, including smoking, hyperlipidemia, hypertension, diabetes, abdominal obesity, and psychosocial factors[1].

2.2.5 Coronary angiography, PCI and CABG

Coronary angiography is a procedure that is performed to visualize blood flow through the coronary arteries. A catheter (i.e. a long, thin, flexible tube) is passed through an artery and the tip is moved upward through the arterial system into the major coronary artery. An X-ray contrast agent is administered through the catheter at the site to be visualized. X-ray images are taken to visualize the size of the artery openings and highlight any blockages in blood flow. The procedure may last 30 to 60 minutes.

PCI, also termed angioplasty, is a non-surgical procedure to open the narrowed or blocked coronary arteries of the heart. The coronary arteries narrow as a result of accumulation of cholesterol plaques caused by atherosclerosis. During the procedure, cardiologists use live X-ray imaging to guide the catheter from the inguinal femoral artery or radial artery to the site of the blockage in the heart. A deflated balloon or other device is pushed over the catheter. At the site of the blockage, the balloon is inflated in order to re-open the artery. Inflation of the balloon within the coronary artery crushes the plaque on the wall of the artery. Sometimes, a stent (i.e. a small mesh tube) is placed permanently at the blockage site to keep the artery open. PCI with stenting is an alternative to heart surgery for some types of non-severe CAD.

CABG is a surgical procedure performed to reduce the risk of mortality due to coronary heart disease. It bypasses narrowed or blocked arteries by grafting arteries or vessels from another part of the body to the coronary arteries. It improves blood supply to the coronary circulation supporting the myocardium. CABG is usually conducted while the heart is stopped, using cardiopulmonary bypass. The procedure is often used when a patient has a blockage in one or more coronary arteries.

2.3 TYPE 1 DIABETES MELLITUS

T1DM is a heterogeneous disorder with main features including destruction of pancreatic beta cells, eventually causing absolute insulin deficiency. Most incidences are associated with an autoimmune-mediated destruction of beta cells (type 1a). However a small proportion of cases are attributable to an idiopathic destruction or failure of beta cells (type 1b). T1DM is the most common type of diabetes in children and adolescents even though type II diabetes is increasing among young populations[51]. T1DM accounts for about 5–10% of the total incidence of diabetes worldwide[52].

2.3.1 Epidemiology

The WHO Multinational Project DIAMOND followed children up to 14 years of age in 50 countries worldwide from 1990 to 1994[53, 54]. The age-adjusted incidence of T1DM ranged from 0.1 to 36.8/100,000 person-years. Countries with the lowest incidence included China and Venezuela, while those with highest incidence included Sardinia, Finland, Sweden, Norway, the UK, New Zealand, Canada, and Portugal. The incidence of T1DM in the US population in the study was approximately 10 to 20/100,000 person-years. Further, the average incidence was estimated to be between 5 and 10/100,000 person-years in about half of the populations from European countries included in the present study. The risk was increased with age, with the highest incidence found in the group aged 10 to 14 years. A higher risk among boys than girls was also reported in some countries. Moreover, there was a positive association between rapid social change and variation in T1DM risk profile. In the DIAMOND project, the temporal trend in incidence was also assessed during the period from 1990 to 1999. The overall increase in annual incidence was about 2.8% within the study period. The rate of increase accelerated to about 3.4% in the second half of the study period compared to 2.4% in the first half. Similar increasing temporal trends were observed in most of the 50 participating countries including in Asia, Europe and North America. However, a decreasing trend was found in Central America with annual rate of decrease of 3.6%.

The SEARCH for Diabetes in Youth study conducted in the USA assessed T1DM risk in terms of ethnicity, sex, and age[51, 55]. A total of 1905 individuals below the age of 20 years old with T1DM were identified. The prevalence of T1DM was about 2.28/1000 in this age group. T1DM accounted for almost all cases of diabetes in the group younger than 10 years of age. T1DM incidence rates for non-Hispanic white children were higher than for those of any other ethnic background. The incidence rate increased with age from 0 to 14 years, from about 14.3 to 25.9/100,000 person-years, but decreased thereafter. An increasing temporal trend was also observed in the SEARCH study.

In Europe, 44 centers participated the EURODIAB ACE study from 1989 to 1994[56, 57]. A total of 16,362 incidences of T1DM were identified. The T1DM risk varied significantly among regions. Macedonia had an incidence rate as low as 3.2 compared with 40.2/100,000 person-years in some parts of Finland. The average increase in rate was about 3.4% although it varied between countries.

2.3.2 Risk factors

T1DM has been associated with genetic factors, even though most cases do not have a family history of the disease. In one study after a long period of follow-up, monozygotic twins showed a concordance rate of 60% and dizygotic twins had a rate of 6–10%[58, 59]. The genetic effect is strongest in early childhood-onset disease and modest in T1DM with onset in adulthood[60, 61]. Onset before 5 years of age is a strong indicator of a high family risk and genetic disposition[62]. It was shown that, by the age of 20, the risk for siblings of children with T1DM onset before 5 years of age was increased 5-fold compared to siblings of those with disease onset between 5 and 15 years[62].

Human leukocyte antigen (HLA) complex on chromosome 6, particularly HLA class II, plays the most important role among many other genes involved in susceptibility to T1DM. Two haplotypes in the HLA class II region are considered to be the principle susceptibility markers for T1DM[63]. Around 90% of children with T1DM carry at least one of these markers[64]. Many other diverse genes are also important for genetic susceptibility. For example, the association between T1DM and autoimmune diseases, including autoimmune thyroid disease, Addison’s disease, celiac disease, and autoimmune gastritis, has been well established[65]. These disorders are all related to genes within the major histocompatibility complex[66].

Ethnicity is associated with risk of T1DM. In a migration study conducted in the USA among subjects less than 20 years old, the T1DM incidence rate varied by age and for different ethnic groups: non-Hispanic white, 11.9 to 32.9/100,000; African-American, 9.5 to 21.3/100,000; Hispanic, 8.7 to 18.4/100,000; Asian and Pacific Islanders, 5.2 to 9.1/100,000; and Navajo, 1.15 to 4.03/100,000 person-years. It was concluded from the study that the incidence rate of T1DM for non-Hispanic white youth is among the highest in the world[67-71]. Prevalence of risk factors for diabetic complications, such as increased low-density lipoprotein, overweight, and smoking, was also found to differ across ethnicity groups.

Age, sex, and seasonality are also associated with T1DM. More than 85% of diabetes cases among individuals below 20 years of age are T1DM[51, 72, 73]. Most studies showed that the risk of T1DM increased from birth and reached a peak at around the age of 10 to 14, and thereafter the risk seemed to stabilize in age 15 to 29 years[54-56]. The incidence rate of T1DM for adults was lower than for children[74]. Among populations with high risk of T1DM, there were more male than female cases and, by contrast, , there were more female than male cases among low-risk populations[75, 76]. Season of diagnosis and season of birth have been shown to be associated with risk of T1DM.

Among children and adolescents, the incidence diagnosed is highest during late autumn, winter, and early spring[77]. The seasonal variation in infections has been suggested to play a major role in this seasonal pattern of T1DM incidence, although evidence regarding specific infections is inconclusive[78, 79]. Children born in spring had a higher risk of T1DM compared with those born in autumn[80]. This pattern has been confirmed in the USA, parts of Europe, New Zealand, and Israel[81-86]. In the US SEARCH study, the effect of season of birth was observed in the most northern latitudes[80]. A possible explanation for this is that seasonal variation in vitamin D level might affect both beta cells and immune cells. Lack of sunshine reduces the level of vitamin D, and vitamin D deficiency is associated with an increased risk of T1DM[87, 88].

2.4 THE HEALTHCARE SYSTEM IN SWEDEN

Sweden is a county with high-quality healthcare and the principle of offering a standardized quality of care to all legal residents at low cost. Healthcare is mainly delivered by hospitals, and primary care is provided in health centers. In addition to county hospitals, there are tertiary university hospitals in all six healthcare regions which provide highly specialized medical services. Based on the 1982 Health Care Act, a strong commitment to equality of access to healthcare has been established. According to a report from the Social and Cultural Planning Office in the Netherlands in 2004, the healthcare system in Sweden was one of the best, in terms of waiting time for non-acute care, public confidence in health services, and health status of the general population, among countries including Australia, Canada, New Zealand, the USA, and 25 European Union member states[89].

2.5 RATIONALE FOR STUDIES INCLUDED IN THIS THESIS

Some Swedish studies examined the association between MI incidence and sex, age, country of birth, and socioeconomic position (SEP). During the period 1987 to 1995, a total of 368,905 incidences of MI among 345,254 individuals were identified in Sweden.[90] The incidence rate was lower in women in all age groups, and increased steeply with age for both women and men. A case–control study conducted in Stockholm County from 1977 to 1996 found that overall both for men and women foreign-born individuals had a higher incidence of MI compared with those born in Sweden after adjusting for SEP, even though the incidence rate of MI for foreign-born individuals followed a decreasing trend in the general Swedish population[91]. Another study based on data from Stockholm County showed that the incidence rate ratio (IRR) in low-income compared to high-income neighborhoods was increased 1.88-fold and 1.52-fold in women and men, respectively[92].

MI mortality has also been investigated in terms of sex, age, country of birth, and SEP in Sweden. During the period 1987–1995, the overall crude 28-day case fatality among patients 30–89 years old with acute MI in Sweden was 42% in men and 45% in women[93]. Hospitalized women had a slightly higher 28-day MI fatality rate than men. Over 50% of deaths within 28 days occurred outside hospital. One study showed, that men had higher pre-hospital mortality than women, except among individuals younger than 50 years[94]. These findings were basically consistent with those of other international studies[95-97]. During the period 1987 to 1995, both the 28-day and 1-year MI case fatality rates improved in all age groups in Sweden[93]. A study conducted in

Stockholm showed that male immigrants had a lower adjusted 28-day mortality after the fMI compared to Sweden-born individuals[90]. There was no significant difference in 1-year survival after adjusting for SEP among foreign-born and Sweden-born patients[90]. A study conducted in Malmo showed that men aged below 75 years from low SEP residential areas tended to have a higher 28-day MI case fatality rate compared with men from median and high SEP areas[98]. The decreasing trend in MI case fatality rate was only found in MI patients from median and high but not low SEP residential areas[98].

Previous Swedish studies of access to cardiac care and treatments largely investigated the impact of sex, age, and SEP, but not country of birth. A Swedish study in the city of Gothenburg showed that only 60% of hospitalized MI patients were treated in a CCU[99]. Those MI patients without access to a CCU were mostly women, and were on average 10 years older and had more comorbidities than patients treated within CCUs. Another Swedish study of patients treated for coronary heart disease from 1991 to 2000 showed that men were 1.5 times more likely to undergo revascularization procedures than women after adjusting for confounding factors[100]. High-grade non-manual male workers were more likely to receive CABG compared to unskilled male manual workers; however, the IRR decreased from 1.4 to 1.0 during the study period[100]. Another Swedish study showed that, between 1993 and 1996, MI patients with the highest cumulative income were two or three times more likely to receive revascularization procedures within 1 month than those with low cumulative income[101]. The effect of country of birth has not been investigated in Sweden, even though racial differences in care after acute MI have been widely reported internationally[102-105].

T1DM is a major public health issue and burden for young patients as well as for society[106]. Related studies showed a wide variation in the incidence of T1DM both between and within countries[53, 56], and between socioeconomic[107] and ethnic groups[108]. In Sweden, one study showed an increasing T1DM trend among children[109]. The increase in the number of T1DM patients and an increased need for high-quality disease management create a huge burden for patients and society[110].

It has been suggested that migration studies can provide a way to assess the influence of the interaction of genes and environment on this disorder[111]. If the children of immigrant families have a risk of disease between that of their parents and the general population of the country from which they immigrated to Sweden, it is likely that environmental factors play a role. Although there is evidence for an increasing incidence of T1DM at younger ages, it is still unclear whether this increase is relevant to all population groups with diverse ethnic backgrounds. Moreover, the findings from studies investigating SEP and risk of T1DM have been inclusive[112-115].

3 AIMS OF THIS THESIS

3.1 GENERAL AIM

The aim of this thesis was to examine the effect of country of birth, SEP, sex, and age on the risks and time trends of fMI and T1DM, and on the equity of admission to specialized care and access to evidence-based treatments after fMI.

3.2 SPECIFIC AIMS

The specific aims of the studies described in this thesis were:

- To assess whether the incidence and time trends of fMI vary by country of birth, sex, and SEP (*Paper I*);
- To assess whether case fatality after 28 days of diagnosis of fMI varies by country of birth, sex, and SEP (*Paper I*);
- To assess the differences in admission to a CCU after fMI between immigrants and Sweden-born patients (*Paper II*);
- To assess the differences in admission to a CCU after fMI between men and women (*Paper II*);
- To assess the differences in admission to a CCU after fMI among patients of different SEP (*Paper II*);
- To determine the equity of access to coronary angiography in CCUs after fMI between immigrants and Sweden-born patients (*Paper III*);
- To determine the equity of access to PCI in CCUs after fMI between immigrants and Sweden-born patients (*Paper III*);
- To determine the equity of access to CABG in CCUs after fMI between immigrants and Sweden-born patients (*Paper III*);
- To assess whether the incidence and time trends of T1DM vary by country of birth, sex, and SEP (*Paper IV*).

4 MATERIALS AND METHODS

4.1 MATERIALS

The data used for the four studies in this thesis were from the M&H Co. This cohort was built by linkage between a large number of Swedish national health and demographic registers to study cancer and cardiovascular and psychiatric diseases among immigrants and their descendants compared with Sweden-born residents. The linkage has been completed through the 10-digit PIN by Statistics Sweden and The Swedish National Board of Health and Welfare. The PIN has been removed and replaced by an identification number and the key is kept by these authorities.

The data in the M&H Co were obtained from the following registers.

4.1.1 The Total Population Register

The Total Population Register is the basic register of the Swedish population. Most individuals who were born in Sweden and those who migrate to Sweden are registered. Individuals remain in the register until the date they move abroad or die. It contains information on:

- Name
- Address
- PIN
- Place of birth, in Sweden or abroad
- Citizenship
- Civil status
- Spouse, children, parents, guardian(s), and adoption
- Property, parish, and municipality of registration
- Immigration to and emigration from Sweden
- Address abroad
- Death and place of burial

Registration of population data in Sweden has a long history. It can be dated back to the 17^{th} century and was started by the Church[116]. The Total Population Register was established in 1968 through merging of registers at the country administrative boards. The PIN was also introduced in Sweden when the population registration was computerized. All those registered have a permanent life-long PIN[116]. The PIN shows a person's date of birth (first six digits) and sex (the second last number is odd for men and even for women).

The Swedish Tax Agency is responsible for the Total Population Register, and updates information from other public agencies. Registered residents are required to submit information about themselves including change of address, immigration and emigration, names of newborn children, and certain name changes.

Although the Total Population Register is supposed to cover registration of the entire population in Sweden, both undercoverage and overcoverage are possible. At present, an exact estimation of these errors is not available[10, 117]. Undercoverage, where individuals who should be registered in fact are not, can occur due to late reporting of birth or immigration. It was estimated that the median waiting time for an immigrant to be registered in the Total Population Register was about 21 weeks in 1996[10]. Over coverage, where individuals who should be removed from the register in fact are not, can occur due to late reporting of death or emigration. It is likely that those who no longer live in Sweden are still registered because emigration is self-reported. It was estimated that overcoverage among non-Nordic foreign-born persons can be high as 4–8%[10, 117].

4.1.2 The Patient Register

From 1965, the National Board of Health and Welfare in Sweden began collecting data on individual hospital discharges in the Patient Register[118]. At discharge from hospital, a specific form is completed for each patient without exception. First these forms are computerized locally, and then the data are stored in administrative registers held at the hospitals and the county administrative offices. The data are delivered once a year to the National Board of Health and Welfare. Each record represents one in-hospital episode. In addition to the PIN, administrative information such as admission and discharge dates, hospital and department codes, and up to eight discharge diagnoses are recorded. Diagnoses in the Patient Register are coded according to the Swedish International Classification of Diseases (ICD) system, first introduced in 1964 (adapted from the WHO ICD system)[119]. The ICD 10th revision (ICD-10) was introduced in 1997. The register has had nationwide coverage since 1987[118]. Since 2001, this register has also contained information on outpatient visits to specialist care and day visits to hospital[120].

Each year, the Patient Register includes approximately 1.7 million records of hospital care[118]. The number of patients included in the register in 2008 was about 800,000[121]. Currently, more than 99% of all somatic (including surgery) and psychiatric hospital discharges are recorded in the Patient Register[119]. It has been estimated that the PIN is missing in about 1% of cases and the principle diagnosis is also missing for a further 1%[121]. The positive predict value of diagnosis in the register was found to be about 85% to 95% and it was concluded that this is a very valuable data source for large-scale register-based research[119]. It was also shown that the quality of MI diagnosis in the register was good, and suitable for epidemiological studies[122].

4.1.3 The Cause of Death Register

The Cause of Death Register provides a basis for official statistics on cause of death in Sweden[123]. It is administered by the Swedish Board of Health and Welfare. It covers all deceased persons who at the time of death were registered in Sweden, whether the death occurred within or outside the country. It does not include stillbirths, or deaths of those who died during a temporary stay in Sweden, of asylum seekers who have not yet received a residence permit, or of those who have emigrated and are no longer registered in Sweden.

The register contains data from 1961 and is updated annually. Diagnoses in the Cause of Death Register are coded according to the WHO version of the ICD. It contains an individual's PIN and information on place of residence, underlying cause of death, contributing causes of death, nature of any injury, date of death, sex, marital status, age, whether or not an autopsy was carried out and if so type of autopsy, death abroad, surgery within 4 weeks before death, and intent in cases of injury or poisoning.

The cause of death was estimated to be missing in a maximum of 0.5% of all deaths and there has been no loss since 1997[10]. The change in ICD system might also influence the time trend. New legislation that allows families greater opportunity to decline an autopsy and the changing regulations for forensic death investigation have led to a decrease in the number of autopsies. The proportion of autopsies has decreased from around 50% in the early 1970s to about 12% in 2007[124]. It has been shown that the register is reasonably valid for use in epidemiological studies and mortality statistics with regard to diseases, including ischemic heart disease[125].

4.1.4 The Swedish Population and Housing Census (FoB)

Since 1960, an FoB was conducted every 5 years until 1990. The information in the FoB was obtained partly from the questionnaire sent to the public and partly from available records.

The FoB collected data on individuals and households. The content of different FoBs varied to some extent but all included demographic data on individuals, education level, employment status and occupation. Income data are available in several FoBs. Household data included number of residents, household status, and overcrowding. Data on ownership, the year dwelling built, tenure, and number of rooms were also collected.

4.1.5 Longitudinal integration database for health insurance and labor market studies (LISA)

The database presently holds annual registers since 1990 and includes all individuals 16 years of age and above who were registered in Sweden as of December 31 for each year. The database incorporates existing data from the labor market and from educational and social sectors and is updated each year with a new annual register. The individual person is the main concern of LISA, but links to family and place(s) of employment are also available.

The database provides a basis for longitudinal statistics and research into entire populations/groups or geographic areas, as well as education, employment, and alternatives (studies, parental leave, unemployment, etc.).

The individual section of the database includes information on the following: employment; income or compensations from employment, entrepreneurial activities, studies, national military service, illness, parental leave, unemployment, labor market activity, rehabilitation, partial retirement, early retirement, retirement, occupational pension, annuities, social assistance, private pensions, etc.; disposable income; country of birth and parental country of birth; latest year of immigration; place of residence (county, municipality, parish, and property); place of employment (county and municipality); and highest level of education.

4.1.6 Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA)

The objectives of RIKS-HIA are to support evidence-based development of treatments for acute CAD. It provides continuous information on care needs, treatments, treatment outcomes, and prognosis during hospitalization.

RIKS-HIA was established at the beginning of the 1990s as a regional registry. Since 1995, it has become a national quality register. Registration in RIKS-HIA now includes all admissions for cardiac intensive care in almost every hospital in Sweden. In 2004, 72 hospitals participated in RIKS-HIA and 62,020 hospital admissions were registered, of which 19,516 were due to acute MI. RIKS-HIA is well distributed throughout Sweden covering both urban and sparsely populated areas (Figure 4.1.6). RIKS-HIA is an internationally unique system with relatively complete coverage of all admissions for cardiac intensive care with suspicion of acute MI in the whole of Sweden[126].

Internal and external validation of the recorded data in the registry is continuously conducted. The internet-based data entry system has access to interactive instructions, manuals, definitions, and help functions. The local responsible person performs regular controls of completeness of data entry regarding variables and patients. The register is also monitored through visits to the participating centers for source data verification. The monitoring process is conducted every year in hospitals and around 30 randomly sampled patients are compared with local patient records in each hospital. It was shown that on average 94% of variables are correctly entered into the register[126].

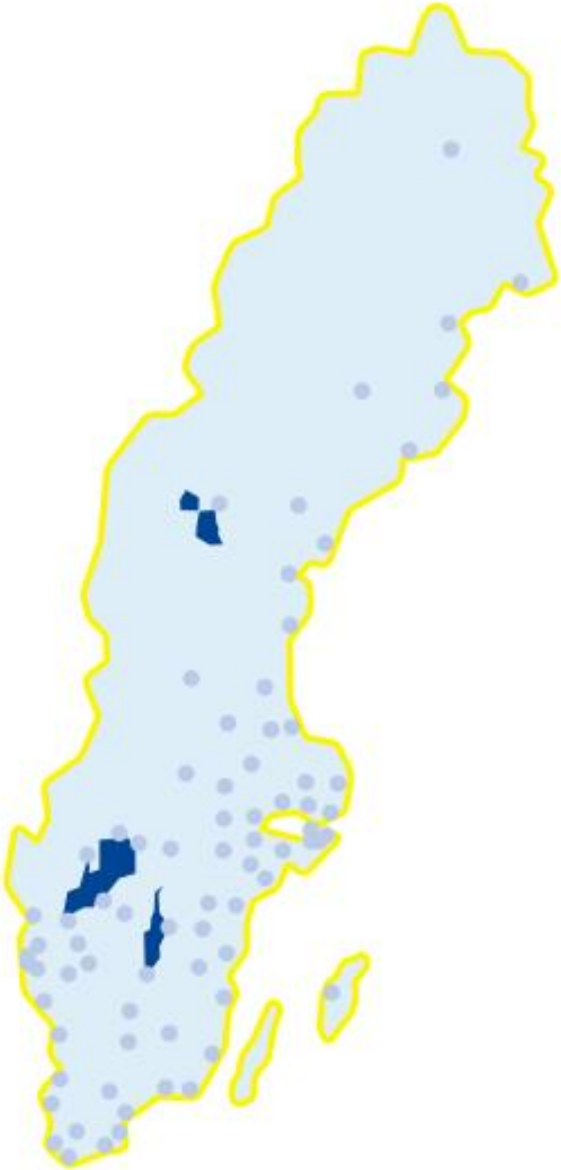


Figure 4.1.6: Hospitals participating in Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) in Sweden in 2004 (Source: RISK-HIA report, 2005)

4.1.7 Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

The total number of patients who undergo coronary angiography or PCI has continuously increased in Sweden as well as internationally. SCAAR is a procedure-related register that contains all relevant information about interventions and procedures performed. It was created in 1991 to register PCI procedures performed in Sweden. In 1992, a coronary angiography register, Acta Coronaria, was set up to record coronary angiographies performed in Sweden. During 1992 to 1998, 60,000 procedures were registered[127]. At the end of 1998, these two registers were merged as a single register, SCAAR.

Coronary angiography is performed at 30 hospitals of which 28 also perform PCI[128, 129]. In 2005, all coronary angiography and PCI procedures were included in SCAAR except for those performed at Skövde Hospital[130]. At the end of 2005, SCAAR recorded information from 201,000 coronary angiography and 116,000 PCI procedures[130]. Information collected included demographic data, risk factors, intervention, puncture site, angiography findings, primary treatment decision after angiography, complications, and clinician who performed the procedure. Stenosis characteristics and type of stent were registered for PCI. Procedure-related data included transillumination time and number and type of X-ray contrast agents, and antithrombotic treatment during the procedure was also recorded[128].

From 2001 onwards, all data have been reported to SCAAR online. The database is located at Uppsala Clinical Research Center (UCR) in Sweden. It is updated daily and all reporting teams have access to analyses and reports. Quality control and monitoring of registry data take place in 28 hospitals performing PCI. About 20 randomly selected interventions per hospital are reviewed. Quality control is performed to assess the reliability and improve the quality of input data. Connecting SCAAR with other registers enables long-term follow-up of procedure outcomes, such as mortality, relapse, and other complications[128].

4.1.8 Swedish Heart Surgery Registry

The Swedish Heart Surgery Register was established in 1992. It has recorded all heart operations performed on children and adults in Sweden since its establishment. Approximately 8000 heart interventions are performed annually. Around 130,000 surgeries had been registered up to 2007.

The register contains patients' demographic information such as age, sex, PIN, and county of residence. Other key variables include waiting time for the procedure, length of hospital stay, type of procedure, presence of diabetes, and certain complications after surgery such as infection, renal failure, stroke, and the need for mechanical circulatory assistance[131].

The participating clinics report four times a year to UCR. UCR reviews the data and provides feedback to the clinics if further clarification or information is needed. All clinics have direct access to their own data for analysis. Apart from annual reports produced by UCR, the information is also used by healthcare professionals at meetings, symposia, and conferences. The register reports provide transparent information on surgical outcomes at the clinical level for comparison of data between clinics[131].

4.2 STUDY POPULATIONS AND DESIGNS

4.2.1 Paper I

In this nationwide population-based cohort study, we used the M&H Co to study trends in fMI incidence and case fatality after day 28 and to examine the role of sex, education as an indicator for SEP, and birth country on these events in Sweden. Between January 1, 1987 and December 31, 2008, 3,426,243 men and 3,326,412 women, aged 35 to 89 years living in Sweden at any time during the study period were included in the study of fMI incidence. Case fatality after day 28 was then studied among the 224,498 male and 141,587 female initially non-fatal cases.

4.2.1.1 Exposure variables

1) The main exposure variable was country of birth. We first used the term 'foreign-born' individuals as an indicator of immigrants and 'Sweden-born' individuals as an indicator of Swedish persons. By definition, a foreign-born person was born in another country outside of Sweden no matter where his/her parents were born; a Sweden-born person was born in Sweden irrespective of his/her parents' countries of origin. Information regarding country of birth was obtained from the Swedish Total Population Register.

   We classified foreign-born individuals into six main geographical regions, Africa, Asia, Europe, Latin-America, Northern America, and Oceania, and into nineteen geographical subregions according to the United Nations classification[132]. At the country level, we reported only countries with five or more MI cases.

   Other migration health studies have used the variable ethnicity instead of country of birth. We considered that ethnicity is a complex subjective and objective classification. Many countries consist of numerous ethnic groups and one ethnic group can be presented in many countries. The ever increasing rate of interracial marriage also complicates the classification of ethnicity[133]. Thus, the definition of country of birth in this thesis is clearly different from that of ethnicity although both are used in migration health studies. We were aware of the potential limitation of use of country of birth in our study to distinguish Swedish and non-Swedish person. It is possible that an individual was born overseas with parents who were both born in Sweden. It is also likely that a Sweden-born person may have at least one parent who was born overseas.

2) Other exposure variables evaluated in the study include SEP and sex. We used highest education level as an indicator of SEP, which is a subjective variable. We believe that health awareness is more strongly associated with health behavior in a person's daily life than other factors such as income. In particular, Sweden offers equal access to health services at minimum cost. Secondly,

education is a table factor during the study follow-up. By contrast, we considered that other indicators such as income and occupation were much less stable. Income might change during the study period because of inflation, marriage, divorce, loss of job, or other significant life events. It is also difficult to classify occupation because participants are very likely to change their jobs during the study follow-up. Moreover, some studies showed that education level was a reasonable surrogate for SEP[134]. We divided levels of education into four categories: 0–9 years, 10–12 years, more than 12 years, and unknown. We retrieved information regarding the highest education level from FoB and LISA. Individuals were classified as men and women, using information obtained from the Total Population Register.

4.2.1.2 Follow-up and outcome variables

1) Follow-up was from January 1, 1987, first immigration date for foreign-born individuals, or 35th birthday, whichever occurred last, until the date of diagnosis of an acute MI (ICD 9th revision (ICD-9) code 410 and ICD-10 code I21), first emigration, death, 90th birthday, or end of follow-up (December 31, 2008), whichever occurred first. Only diagnoses of fMI were counted as an event. Patients with recurrent MI during the 21 years of follow-up were only counted once. Specific diagnosis information was obtained from both the National Patient Register and the Cause of Death Register.

2) Non-fatal incident cases of fMI were followed from the date of diagnosis until the date of death due to MI either as underlying or contributory cause, death due to other causes, first emigration date, 90th birthday, or end of follow-up (December 31, 2008), whichever occurred first. We investigated first death due to MI as an underlying or contributory diagnosis (ICD-9: 410; ICD-10: I21), repeated analysis for coronary heart disease (ICD-9: 410–414; ICD-10: I20–I25), and death due to any causes as an event. The cause of death and date of death were obtained from the Cause of Death Register.

4.2.1.3 Other explanatory variables

Age was arbitrarily divided into eleven groups in 5-year intervals (35–39, 40–44… 80–84, and 85–89). In 2000, WHO criteria for MI were refined to further emphasize the importance of cardiac biomarkers for diagnosis[12]. The adaptation of these new criteria might have affected the incidence of MI[135]. Therefore, we divided the total study period into four time periods: 1987–1990, 1991–1995, 1996–2000, and 2001–2008. Additionally, comorbidity status, including history of diabetes, hypertension, and hyperlipidemia recorded in the Patient Register any time during the study period of 1987–2008, was considered in the analysis (yes/no).

4.2.2 Paper II

In this nationwide cohort study, we examined admission to CCUs in association with country of birth, SEP, and sex after patient diagnosed with fMI (ICD-10: I21). We identified fMI patient who were admitted to hospital and registered in the National Patient Register between 2001 and 2009. Then whether they were admitted to CCU during the same hospitalization was checked in RIKS-HIA. The study period was limited from 2001 was because RIKS-HIA had better nationwide coverage after that. The study population thus comprised 114,387 men (13,903 foreign born) and 85,519 women (9,601 foreign born).

4.2.2.1 Exposure variables

We studied the same exposure variables as in the first study (*Paper 1*): country of birth, SEP, and sex. Furthermore, classification of the exposure variables was exactly the same as in study 1.

We defined the country of birth into two major groups: foreign-born and Sweden-born individuals. We classified foreign-born individuals into six main geographical regions: Africa, Asia, Europe, Latin-America, Northern America, and Oceania, and into nineteen geographical sub-regions according to United Nations classification[71]. At the country level, we reported only data from countries with five or more cases. We used highest education level as an indicator of SEP. The levels of education were classified into four categories: 0–9 years, 10–12 years, more than 12 years, and unknown. The study individuals were classified as men and women, using information obtained from the Total Population Register.

4.2.2.2 Outcome variable

Admission to CCU (yes/no) was the study outcome variable. We retrieved this information from RIKS-HIA. If a patient was admitted to the CCU more than once during the same period of hospitalization, this was treated as one CCU event.

4.2.2.3 Other explanatory variables

Age at diagnosis of fMI was arbitrarily categorized into 13 strata each of 5 years (less than 35, 35–39, 40–44… 85–89, and 90 and above) due to a non-linear relationship with the outcome. We divided the total study period into three arbitrary time periods: 2001–2003, 2004–2006, and 2007–2009. Additional co-variables considered in the analysis were medical conditions including diabetes (ICD-9: 250; ICD-10: E10–E14), hypertension (ICD-9: 401; ICD-10: I10), and hyperlipidemia (ICD-9: 272; ICD-10: E78), as well as a history of stroke (ICD-9: 430–438; ICD-10: I60–I90), heart failure (ICD-9: 428; ICD-10: I50), angina (ICD-9: 413; ICD-10: I20), atrial fibrillation (ICD-9: 427D; ICD-10: I48), pulmonary embolism (ICD-9: 415B; ICD-10: I26), chronic obstructive lung disease (ICD-9: 490–496; ICD-10: J44), and cancer (ICD-9: 140–239; ICD-10: C00–D48). All medical conditions were verified for a fixed period of 14 years. Moreover, to exclude variation between hospitals in the availability of CCUs that might have an impact on the possibility of admission, we classified hospitals into two categories: with and without CCU facilities (yes/no).

4.2.3 Paper III

In this nationwide cohort study, we examined the relationship between country of birth and the utilization of coronary angiography, PCI, and CABG after an fMI. A total of 117,494 fMI patients of all ages who were admitted to CCUs between 2001 and 2009 in Sweden were followed for 3 months after CCU admission.

4.2.3.1 Exposure variable

The exposure variable in the third study was country of birth. Country of birth was classified as in studies 1 and 2. We defined the country of birth into two major groups foreign-born and Sweden-born. We classified foreign-born individuals into six main geographical regions: Africa, Asia, Europe, Latin-America, Northern America, and Oceania, and into nineteen geographical sub-regions according to United Nations world classification[71]. At the country level, we only reported data from countries with five or more cases.

4.2.3.2 Follow-up and outcome variables

Patients were followed from the date of admission to CCU until either the date of undergoing the treatments or censoring within 3 months. Censoring occurred if a patient was lost to follow-up due to death, emigration, or the end of the 3 months of follow-up. Within the follow-up period, a record of angiography, PCI, or CABG was considered as an event separately. Only the first event was considered in this study.

Information regarding angiography, PCI, and CABG was obtained from RIKS-HIA, SCAAR, and the Swedish Heart Surgery Registry.

4.2.3.3 Other explanatory variables

Potential confounders adjusted for in the model included the demographic factors sex, age at diagnosis, and year of diagnosis. The continuous variable age at diagnosis of fMI was classified into 13 strata (less than 35, 35–39, 40–44… 85–89, and 90 and above) due to a non-linear relationship with the outcome variables. We divided the total study period into three arbitrary time periods: 2001–2003, 2004–2006, and 2007–2009.

Medical information was classified into admission information, clinical information during hospitalization, and complications during treatment. Admission information included use of angiotensin-converting enzyme inhibitors at admission, whether or not admitted by ambulance, beta-blockers prior to admission, cardiac shock at admission, ECG QRS complex, ECG rhythm, ECG ST and T (STT) wave changes, type of MI, previous PCI, presenting symptoms, prior cardiac surgery, pulmonary rates, smoking status, and use of statins before hospitalization. Clinical information during hospitalization included beta-blocker use during treatment, diuretic treatment, and anticoagulant therapy. Complications included atrioventricular block (AV block), myocardial re-infarction during hospitalization, and new fibrillation/flutter during hospitalization. Risk factors included diabetes and hypertension. The medical information was obtained from RIKS-HIA.

The highest level of education achieved was used as a proxy for SEP. Education level was divided into four categories: low (0–9 years), medium (10–12) years, high (more than 12 years), and unknown.

4.2.4 Paper IV

In this nationwide population-based cohort study, we investigated associations between country of birth, parental country of birth, and education with respect to risk and time trends of T1DM among children and young adults. We followed a nationwide cohort of 4,469,671 male and 4,231,680 female subjects aged 0–30 years between 1969 and 2008.

4.2.4.1 Exposure variables

1) We studied the effect of country of birth. However, in contrast to the above-mentioned three studies, we defined country of birth in three major groups: individuals born outside Sweden, referred to as immigrants; those born in Sweden with at least one parent born outside Sweden, referred to as offspring of immigrants; and those born in Sweden with both parents born within the country, referred to as Sweden-born individuals.

   We classified foreign-born individuals into six main geographical regions and further into 19 world regions defined by the United Nations Population Division, as in studies 1 and 2: Africa (North, South, East, West, and Central Africa), Asia (East, West, South-Central, and South-East Asia), Europe (North, South, East, and West Europe), Latin America (Caribbean, Central America and South America) Northern America, and Oceania (Australia/New Zealand, Melanesia, and Micronesia/Polynesia). At the country level, we only reported results from countries having at least five cases of T1DM; data from those with fewer than five cases were combined and are presented as 'other' for each geographical region.

2) We classified individuals by their parental level of education as an indicator of SEP. Education was categorized into four levels: 0–9 years, 10–12 years, 13 years or more, and unknown. We used the highest parental education level in the family, i.e. the mother´s education category was used if she had a higher level than the father.

4.2.4.2 Follow-up and outcome variable

Individuals were followed from 1969, their date of birth, or date of immigration for the immigrants, whichever occurred later, until the date of diagnosis of T1DM (code 250 according to ICD 8th revision and ICD-9 between 1969 and 1996, and ICD-10 code E10 from 1997), emigration, death, or end of follow-up in 2008, whichever occurred earlier. The diagnosis of T1DM was obtained from the National Patient Register. Information regarding emigration, immigration, and date of birth was obtained from the Total Population Register, and information regarding death from the Cause of Death Register.

4.2.4.3 *Other explanatory variables*

Age at follow-up was divided into six groups in 5-year intervals (0–4, 5–9, 10–14, 15–19, 20–24, and 25–30 years). The study was divided into four time periods (1969–1979, 1980–1989, 1990–1999, and 2000–2008).

4.3 STATISTICAL ANALYSIS

4.3.1 Poisson regression

We used Poisson regression to calculate IRRs with 95% confidence interval (CI) of fMI and T1DM (*Papers I and IV*).

Poisson regression is often used to model counted data or contingency tables. Poisson models are a form of generalized linear models which use natural logarithm as the link function. Poisson regression assumes that the outcome variable Y has a Poisson distribution. Poisson distribution describes the probability of a given number of events occurring in a fixed interval of time or space if the events are independent of time since previous events and occurred at an average rate. It can be used in other contexts, such as distance and volume. We assumed that the fMI and T1DM events that occurred in a fixed time interval had Poisson distributions[136, 137].

A feature of Poisson distribution is that it assumes the mean of the event number is equal to its variance. In many circumstances, the observed variance is greater than its mean. This is known as over-dispersion. In this case, the standard error of the coefficients might have to be re-estimated, as in the studies included in this thesis. Alternatively other models have been suggested, such as negative binomial regression[138].

4.3.2 Cox proportional hazard regression

We used Cox proportional hazard regression to model fMI case fatality and likelihood of undergoing cardiac procedures. Hazard ratio (HR) with 95% CI was used to compare different groups (*Papers I and III*).

Cox proportional hazard regression has been widely used in the analyses of time to event data with censoring and covariates. It is similar to Poisson regression in that both methods estimate rate ratios. However, it does not assume the nature or shape of the hazard function; instead it assumes that hazard rate is proportional throughout the follow-up period.

4.3.3 Logistic regression

Logistic regression is a form of regression that is applied when the dependent variable is dichotomous. We modeled admission to the CCU (yes/no) using logistic regression. The odds ratio (OR) was calculated to compare the likelihood of admission to the CCU among different comparison groups *(Paper II).*

The logistic regression model is an extension of classical linear models to address non-normal outcomes. In classical linear models, it is assumed that the outcome is independent and normally distributed with equal variance. However, it is not valid for a dichotomous outcome, such as admission or not admission to the CCU. In logistic regression, the outcome is the Logit transformation of the binary variable. It assumes that the transformation of the binary outcome variable is independent and normally distributed with equal variance. Logistic regression is one of the most successful applications of likelihood-based modeling[139].

4.3.4 Joinpoint regression

The Joinpoint regression model was used *(Papers I and IV*) to analyze the time trends in fMI and T1DM.

Joinpoint regression fits a series of joined straight lines on a log scale to the incidence rate data. Line segments are joined at positions termed joinpoints. Each jointpoint is tested if it shows a significant change in overall trend. The method also estimates the annual percent change (APC) to describe the trend and to test whether it is statistically significant. The null hypothesis in the test is that there is no trend in change in incidence rates[140, 141].

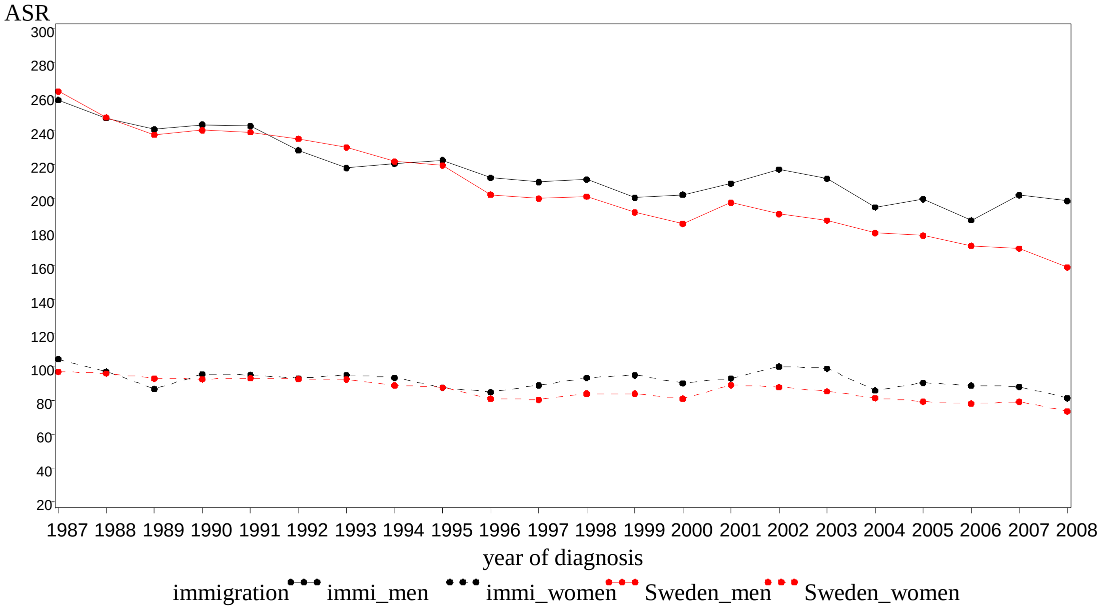
5 RESULTS

5.1 RISK OF FMI AND CASE FATALITY AFTER DAY 28 *(PAPER I)*

fMI incidence

A total of 571,476 cases of fMI (344,349 men, 227,127 women) were observed during the study period between 1987 and 2008. Of these fMI patients, 29,655 were foreign-born men and 20,080 were foreign-born women. Foreign-born individuals were younger (mean age ± standard deviation (SD)) at diagnosis than their Sweden-born counterparts (men: foreign born 64.51 ± 12.01, Sweden born 70.77 ± 11.23 years; women: foreign born 72.12 ± 10.58, Sweden born 76.09 ± 9.83 years).

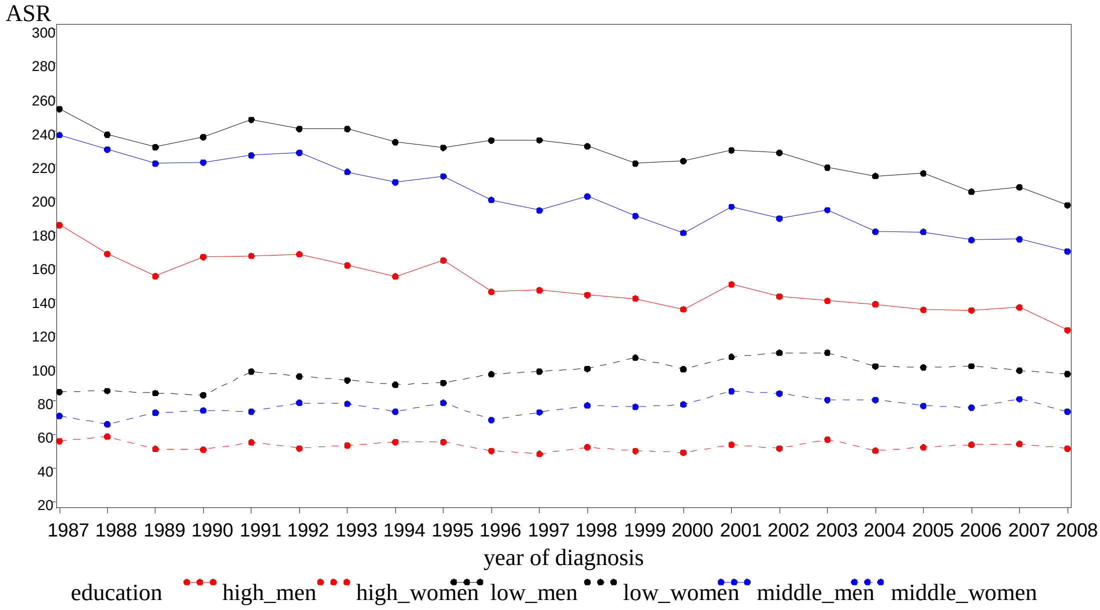
Figure 6.1.1: Age-standardized first MI incidence rate by sex and immigration status, Sweden 1987-2008



ASR=Age-standardized first MI incidence rate per 100,000 person-years

Men had a higher age-standardized incidence rate (ASR) of fMI than women over the entire study period. We observed a clear decrease in ASR of fMI over this period for men, but a less obvious decrease for women (Figure 6.1.1). When stratified by immigration status, there was a significant decreasing trend based on Jointpoint regression analyses during the whole study period which was more pronounced among Sweden-born (men APC, -2.1, p<0.0001; women: APC, -1.0, p<0.0001) than foreign-born individuals (men: APC, -1.2, p<0.0001; women: APC, -0.4, p=0.05).

Figure 6.1.2: Age-standardized first MI incidence rate by education, Sweden 1987-2008



ASR=Age-standardized first MI incidence rate per 100,000 person-years

The analysis of trend was also stratified by level of education. The results showed decreasing trends for men at all educational levels. For women, however, there was no obvious decrease especially for those with fewer than 12 years of education. The absolute risk difference between the highest and lowest educational level was higher among men than women. Most importantly, both men and women with low levels of education always had a higher ASR of MI than those with higher levels of education (Figure 6.1.2).

Poisson regression was used to measure the IRR in relation to countries of birth, regions and continents. Compared with Sweden-born men, those from Southern and Western Asia showed high fMI risk patterns. By contrast, men from Eastern Asia, South-Eastern Asia, and Latin America showed low fMI risk patterns. Within Europe, there seemed to be a slight increasing risk trend from Southern and Western Europe to Northern and Eastern Europe (Table 6.1.1). Women showed similar risk patterns to men, but with fewer countries having a significant effect. Moreover, women from several African countries had a lower fMI risk than Sweden-born women. There were a few examples, notably Bosnia and Serbia in Europe, where countries within the same geographical region showed opposite fMI risk patterns. For specific IRRs relating to country of birth, please refer to *Paper 1*.

Table 6.1.1: Incidence rate ratio of first-time myocardial infarction in Sweden by birth region/country and sex, 1987–2008

	Male			Female		
Region of birth	**Cases**	**PYRS[$]**	**IRR(95% CI)**	**Cases**	**PYRS[$]**	**IRR(95% CI)**
Sweden	314 694	42 853 105	1	207 047	46 751 289	1
Africa	451	261 601	0.92 (0.84-1.01)	116	160 171	**0.67 (0.56-0.80)**
Northern Africa	205	92 646	0.97 (0.85-1.12)	32	39 072	**0.62 (0.44-0.88)**
Southern Africa	26	6 395	1.12 (0.76-1.64)	9		
Western Africa	64	44 860	0.87 (0.68-1.11)	20	23 186	1.14 (0.73-1.76)
Eastern Africa	143	109 610	**0.83 (0.71-0.98)**	48	87 326	**0.54 (0.40-0.71)**
Middle Africa	13	80 90	1.07 (0.62-1.84)	7	5 245	1.26 (0.60-2.64)
Other[γ]	34	29 219	0.76 (0.55-1.07)	16	33 872	0.59 (0.36-0.96)
Asia	3 747	1 048 737	**1.35 (1.31-1.40)**	1 591	960 260	0.96 (0.91-1.01)
Eastern Asia	120	57 314	**0.58 (0.48-0.69)**	82	80 235	**0.57 (0.46-0.71)**
Southern Asia	1 258	364 795	**1.47 (1.39-1.55)**	481	290 986	0.98 (0.90-1.07)
South-Eastern Asia	127	67 814	**0.74 (0.62-0.88)**	81	164 440	**0.55 (0.44-0.68)**
Western Asia	2 242	558 814	**1.47 (1.41-1.53)**	947	424 600	**1.09 (1.02-1.16)**
Other[γ]	36	15 013	1.15 (0.83-1.59)	40	53 891	0.74 (0.54-1.01)
Europe	24 355	3 832 127	**1.06 (1.05-1.07)**	17 665	4 922 030	**1.05 (1.04-1.07)**
Nothern Europe	14 623	2 081 557	**1.07 (1.05-1.08)**	11 690	2 896 335	**1.08 (1.06-1.11)**
Southern Europe	3 861	839 397	**1.11 (1.08-1.15)**	1 756	753 749	1.04 (0.99-1.09)
Western Europe	2 600	416 736	**0.93 (0.89-0.96)**	1 860	489 334	**0.89 (0.85-0.93)**
Eastern Europe	3 271	494 437	**1.10 (1.06-1.14)**	2 359	782 612	**1.06 (1.02-1.11)**
Other[γ]	8	3 029	0.91 (0.46-1.83)	9	11 345	0.59 (0.31-1.13)
Latin America	446	229 134	**0.74 (0.68-0.82)**	242	256 521	**0.58 (0.51-0.66)**
South America	396	202 411	**0.73 (0.66-0.81)**	222	229 364	**0.57 (0.50-0.65)**
Central America	23	15 744	0.70 (0.47-1.06)	9	18 867	**0.42 (0.220.82)**
Caribbean	27	10 980	1.15 (0.79-1.67)	-	-	-
Other[γ]	28	14 423	0.83 (0.57-1.20)	14	34 476	**0.42 (0.25-0.70)**
Northern America	619	947 54	0.97 (0.90-1.05)	435	94 772	0.94 (0.85-1.03)
Oceania	14	10 681	0.92 (0.54-1.55)	9	7 500	1.19 (0.62-2.29)

Study population: 35 to 89 years old with a valid Swedish ID. IRR was adjusted for age at follow-up, calendar period of follow-up, co-morbidity and education. IRR significantly different from 1 is highlighted. Statistically significant IRRs were highlighted.

The incidence of fMI decreased with increasing level of education in both sexes (p for trend <0.0001). Overall, the risk was higher among men and women with less than 9 years of education compared with those with more than 12 years of education. This association was, however, stronger among women (men: IRR 1.66, 95% CI 1.64–1.68; women: IRR 1.99, 95% CI 1.95–2.03) (results not shown in the tables). Stratified analysis by immigration status yielded the same results in both sexes and among both Sweden-born and foreign-born patients. The increased risk remained stronger among women but was more pronounced in individuals born in Sweden than in immigrants (Table 6.1.2).

Table 6.1.2: Incidence rate ratio for first-time myocardial infarction in Sweden by immigration status, sex, and level of education, 1987–2008

	Sweden-born			Foreign-born		
	Cases	PYRS§	IRR* (95% CI)	Cases	PYRS§	IRR* (95% CI)
Men						
Years of education						
less than 9	164 877	15 270 026	**1.60 (1.58-1.62)**	11 820	1 579 919	**1.49 (1.44-1.54)**
9 to 12	85 221	16 970 986	**1.36 (1.34-1.37)**	10 557	2 198 635	**1.29 (1.24-1.34)**
more than 12	29 824	9 388 229	1	4 163	1 380 218	1
P for trend			<0.001			<0.001
unknown	34 772	1 223 863	**1.41 (1.39-1.44)**	3 115	327 946	**1.18 (1.12-1.24)**
Wemen						
Years of education						
less than 9	116 295	16 546 983	**1.85 (1.81-1.89)**	9 712	2 181 397	**1.77 (1.67-1.87)**
9 to 12	39 267	17 549 208	**1.47 (1.44-1.50)**	4 898	2 292 431	**1.46 (1.37-1.55)**
more than 12	10 391	10 532 509	1	1 334	1 465 487	1
P for trend			<0.001			<0.001
unknown	41 094	2 122 589	**1.82 (1.77-1.86)**	4 136	474 956	**1.62 (1.52-1.73)**

§ person-years
* Mutually adjusted for education, age, co-morbidities and calendar years of follow-up when applicable.
Statistically significant IRRs were highlighted.

fMI case fatality after day 28

Cox proportional hazard regression was used to estimate HRs of death due to MI after diagnosis of fMI in terms of education and sex. There were 37,416 and 25,122 cases of MI-specific deaths among men and women, respectively. Overall, multivariable-adjusted survival was lower in men than in women (HR 1.15, 95% CI 1.13–1.17). Patients with a low level of education had approximately a 50% statistically significantly worse prognosis compared with those with more than 12 years of education regardless of sex and country of birth (Tables 6.1.3). When case fatality after day 28 due to coronary heart disease/any causes was estimated, the same protective effect of high education was found but to a lesser degree (results not shown in tables).

Table 6.1.3: Hazard ratio (HR) for death after non-fatal first-time myocardial infarction in Sweden, 1987–2008

	Sweden-born			Foreign-born		
	Cases	**PYRS§**	**HR* (95% CI)**	**Cases**	**PYRS§**	**HR* (95% CI)**
Men						
Years of education						
less than 9	19 651	691 668	**1.41 (1.34-1.47)**	1 105	58 193	**1.44 (1.25-1.66)**
9 to 12	7 783	423 574	**1.21 (1.15-1.27)**	812	54 750	**1.31 (1.13-1.52)**
more than 12	2 222	153 824	1	222	21 342	1
P for trend			<0.001			<0.001
unknown	5 278	45 884	**1.44 (1.36-1.52)**	343	7 710	**1.53 (1.28-1.82)**
Women						
Years of education						
less than 9	13 402	407 090	**1.54 (1.42-1.66)**	965	38 807	**1.47 (1.16-1.87)**
9 to 12	3 181	163 278	**1.32 (1.21-1.43)**	373	20 889	**1.28 (1.00-1.64)**
more than 12	623	43 552	1	73	5 339	1
P for trend			<0.001			<0.001
unknown	6 041	55 980	**1.65 (1.51-1.80)**	464	9 719	**1.43 (1.11-1.84)**

§ person-years
* Mutually adjusted for education, age, co-morbidities and calendar years of follow-up when applicable.
Statistically significant IRRs were highlighted.

5.2 ADMISSION TO CCU (*PAPER II*)

Of a total of 199,906 patients who were admitted to hospital after their fMI during the years 2001 to 2009, 120,609 patients received treatment in a CCU. The total number of fMI patients who were admitted to hospital decreased from 23,356 in 2001 to 19,385 in 2009.

Logistic regression was used to estimate the likelihood of being admitted to a CCU after fMI diagnosis. There was no evidence of an overall association between immigration status and the likelihood of treatment in a CCU. Foreign-born fMI patients showed equal likelihood of admission to a CCU compared with Sweden-born patients, for both men and women. Admission to a CCU was not confounded by the level of education and year of diagnosis.

Table 6.2.1: Odds ratio (OR) and 95% confidence interval (CI) of access to a coronary care unit (CCU) after first-time myocardial infarction by sex and immigration status in patients living in Sweden between 2001 and 2009

Men	**Access to CCU yes/no**	OR* (95% CI)	OR** (95% CI)	OR*** (95% CI)
Foreign born	10,010/3,893	1.00 (0.96–1.05)	1.01 (0.97–1.06)	0.97 (0.93–1.02)
Sweden born	65,215/35,269	1	1	1
Women				
Foreign born	5,639/3,962	1.03 (0.98–1.08)	1.02 (0.97–1.07)	1.01 (0.96–1.06)
Sweden born	39,745/36,173	1	1	1

* Adjusted for age at diagnosis
** Mutually adjusted for other variables in the Table
***Additionally adjusted for medical conditions, and availability of CCU facilities

A lower level of education was associated with a decreased likelihood of being admitted to a CCU. While education had a borderline significant effect on the likelihood of being treated in a CCU among women, regardless of country of birth, the OR for treatment in a CCU was 6% lower (OR 0.94, 95% CI 0.90–0.97) among men with a low level of education born within Sweden and 14% lower (OR 0.86, 95% CI 0.78–0.95) among those born outside Sweden, compared with highly educated Sweden-born and foreign-born men, respectively (Table 6.2.2).

Table 6.2.2: Odds ratio (OR) and 95% confidence interval (CI) of access to a coronary care unit (CCU) after first-time myocardial infarction by sex and level of education in patients living in Sweden between 2001 and 2009

Men	**Access to CCU yes/no**	OR* (95% CI)	OR** (95% CI)	OR*** (95% CI)
Less than 9 years	34,217/20,468	**0.86 (0.83–0.89)**	**0.89 (0.86–0.92)**	**0.93 (0.89–0.96)**
9 to 12 years	19,045/9,226	**0.85 (0.82–0.88)**	**0.86 (0.83–0.90)**	**0.90 (0.86–0.93)**
More than 12 years	20,682/7,681	1	1	1
Unknown	1,281/1,787	**0.67 (0.62–0.73)**	**0.73 (0.67–0.80)**	**0.75 (0.69–0.82)**
Women				
Less than 9 years	25,368/24,474	**0.88 (0.84–0.93)**	**0.92 (0.87–0.96)**	0.95 (0.90–1.00)
9 to 12 years	12,351/8,505	**0.93 (0.88–0.98)**	0.95 (0.90–1.00)	0.97 (0.92–1.03)
More than 12 years	5,990/3,377	1	1	1
Unknown	1,675/3,779	**0.69 (0.64–0.75)**	**0.76 (0.70–0.83)**	**0.80 (0.73–0.87)**

* Adjusted for age at diagnosis
** Mutually adjusted for other variables in the Table
***Additionally adjusted for medical conditions, and availability of CCU facilities.
Bold numbers indicate statistically significant ORs.

In terms of sex difference, the proportion of women treated in a CCU was 13% lower than that of men. This lower proportion was consistently observed among both foreign-born and Sweden-born MI patients; in both groups, female patients had around 10–20% lower odds of being treated in a CCU compared with their male counterparts. This decreased admission rate was not explained by level of education, medical conditions, or hospital characteristics.

The adjusted OR values for patients from individual countries were consistent with the results obtained when foreign-born patients as a whole were compared with those born in Sweden. There were no statistically significant differences in access to CCU treatment among the majority of foreign-born compared to Sweden-born patients.

5.3 EVIDENCE-BASED TREATMENTS AFTER FMI AMONG PATIENTS IN THE CCU *(PAPER III)*

Between January 2001 to December 2009, 120,609 fMI patients were admitted to a CCU in Sweden. To allow at least 3 months of follow-up, 3,115 patients with a diagnosis after September 30, 2009 were excluded from the analyses. Our final cohort thus included 117,494 patients. Of these, 15,174 (12.91%) were born outside Sweden. Compared with Sweden-born patients, among foreign-born patients there was an earlier onset of fMI, higher proportions of high education level, chest pain at admission, and ever or current smokers, and a higher prevalence of diabetes.

During the study period there were 72,503 fMI patients (61.71%) who underwent angiography within 90 days. The mean delay from admission to angiography was 5.69 days (SD 13.82 days) among those who underwent the procedure. The proportion undergoing coronary angiography increased during the study period and the mean delay decreased regardless of sex and country of birth. After adjusting for potential confounders, there was no statistically significant difference in the proportions of foreign-born and Sweden-born MI patients undergoing angiography during the study period. Analyses were further stratified by sex and year of study, and the results were basically unchanged.

Further, 53,747 fMI patients (45.74%) underwent PCI within 90 days after admission to a CCU. The mean delay for PCI was 5.36 days (SD 13.52 days) among those who underwent the treatment. As for angiography, the proportion increased in each subgroup during the study period and the mean waiting time decreased. After adjusting for potential confounders, foreign-born patients had a borderline statistically significantly higher rate of undergoing PCI compared to Sweden-born patients (HR 1.03, 95% CI 1.00–1.05).

Overall, 10,748 fMI patients (9.15%) underwent CABG within 90 days of admission to the CCU. Among these patients, the mean delay for CABG was 19.37 days (SD 19.66 days). After adjusting for potential confounders, foreign-born patients had statistically significant higher rates of CABG than those born in Sweden (HR 1.08, 95% CI 1.02–1.14).

The analyses were further stratified by geographical regions and continents. There was no significant regional variation in terms of rates of undergoing angiography and PCI (Figures 6.4.1 and 6.4.2). Moreover, we found that the increased rate of undergoing CABG was mainly explained by patients from Asia (Figure 6.4.3).

Figure 6.4.1: Adjusted Hazard Ratios of undergoing angiography compared with Sweden-born

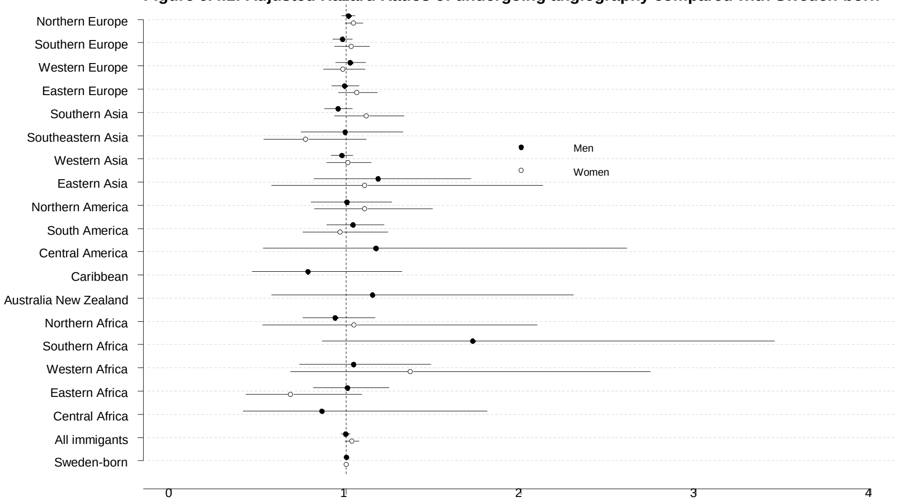


Figure 6.4.2: Adjusted Hazard Ratios of undergoing PCI compared with Sweden-born

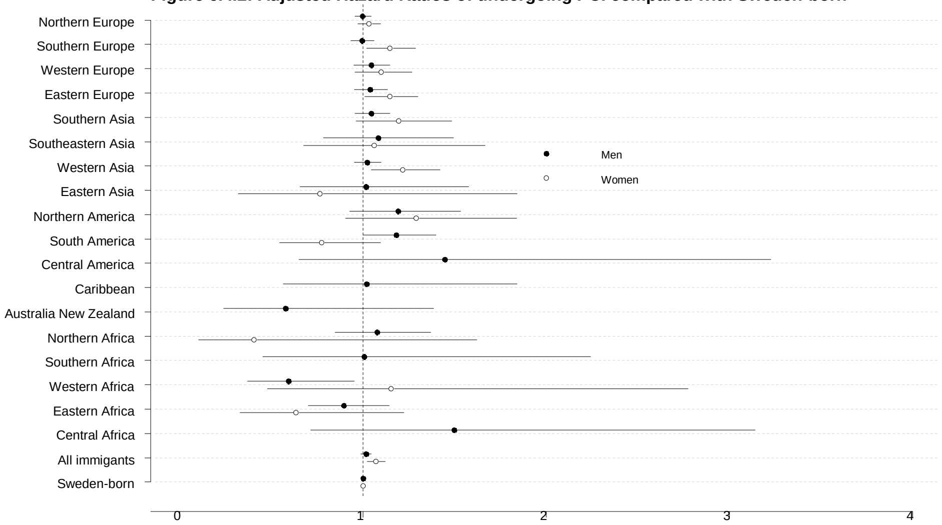
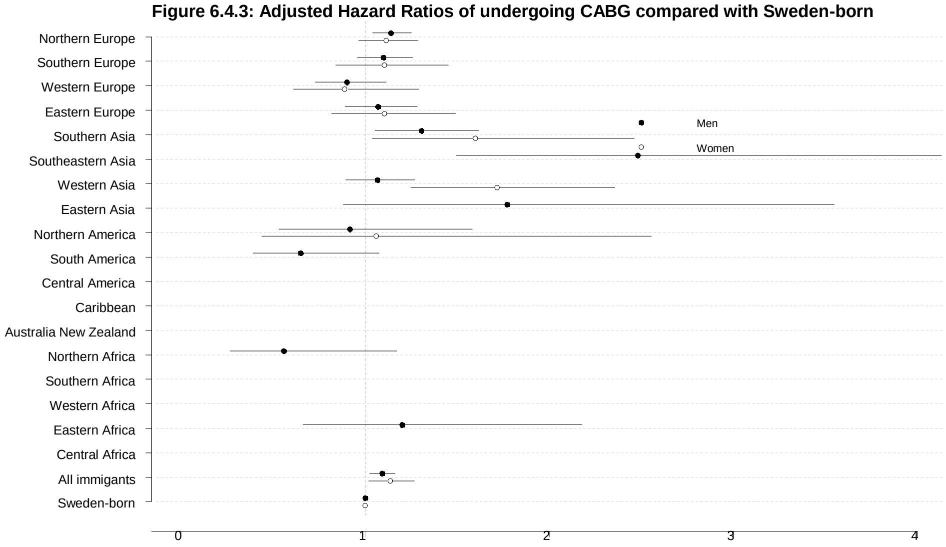


Figure 6.4.3: Adjusted Hazard Ratios of undergoing CABG compared with Sweden-born



5.4 T1DM AMONG IMMIGRANT CHILDREN AND YOUNG ADULTS IN SWEDEN (*PAPER IV*)

We followed 4,469,671 male and 4,231,680 female children and young adults (aged 0 to 30 years) living in Sweden at any time between January 1, 1969 and December 31, 2008. Of these individuals 1,533,082 were immigrants and 1,036,724, were offspring of immigrants. In the age group 0 to 14 years, we observed a total of 15,022 cases of T1DM among those born in Sweden, 464 cases among immigrants, and 2,308 among offspring of immigrants. In the age group 15 to 30 years, the corresponding numbers of cases of T1DM were 14,956, 1,491, and 1,600.

Compared with Sweden-born children and young adults, immigrants aged 0 to 14 years had about a 40% lower risk of T1DM and offspring of immigrants had about a 25% lower risk. Immigrants aged 15 to 30 years had about a 30% lower risk of T1DM and offspring of immigrants had about a 15% lower risk compared with their Sweden-born counterparts. Analyses stratified by sex showed similar results (Table 5.4).

The effect of parental education was also assessed in the analyses. In the age group 0 to 14 years, boys with parents with a low level of education (0–9 years) had a 9% decreased risk of TIDM (p=0.01) compared with boys with parents with a high level of education (at least 13 years), whereas for the same comparison no effect of parental education was observed among girls (p=0.08). In the age group 15 to 30 years, compared to those with parents with at least 13 years of education, young adults of both sexes with parents with <9 years of education had about a 20% increased risk of TIDM.

With a few exceptions, male and female children and young adults born in countries within Asia, Southern Europe (except females born in Spain), Eastern Europe, and Latin America (except females born in Uruguay), had between 40% and 85% lower risks than Sweden-born children/young adults. Similar decreased risks were observed among men born in Western Africa and Northern America and in women born in Ethiopia, the UK, and Greece.

Based on joint point regression analyses, we found increasing trends for incidence of T1DM by year of diagnosis for all levels of parental education in both boys and girls younger than 15 years (p<0.001). However, among young adults aged 15 to 30 years, the pattern was less clear

Table 6.4: Risk of type 1 diabetes mellitus by age group, sex, and immigration status in Sweden, 1969–2008

	Male			Female		
	Cases	**Person-years**	**RR[a] (95% CI)**	**Cases**	**Person-years**	**RR[a] (95% CI)**
0-14 years old						
Immigrant	235	1 282 599	0.56 (0.49-0.64)	229	1 294 355	0.58 (0.50-0.67)
Offspring	1 194	5 025 007	0.73 (0.69-0.78)	1 114	4 763 707	0.76 (0.71-0.81)
Swedes	7 937	25 742 314	1	7 085	24 256 394	1
P for trend			<.0001			<.0001
15-30 years old						
Immigrant	738	3 333 146	0.68 (0.62-0.75)	753	3 443 234	0.78 (0.71-0.86)
Offspring	912	3 746 826	0.86 (0.80-0.92)	688	3 533 440	0.82 (0.76-0.89)
Swedes	8 138	29 227 539	1	6 818	27 595 034	1
P for trend			<.0001			<.0001

[a] Mutually adjusted for generation, parental education, age and calendar years of follow-up.

6 DISCUSSION

6.1 MAIN FINDINGS

In the epidemiological study of fMI, we demonstrated a continuing decreasing trend in the fMI incidence among men as well as the novel finding of a less pronounced decreasing trend among women and foreign-born individuals of both sexes in Sweden between 1987 and 2008. A clear reduction in case fatality after non-fatal fMI regardless of sex or country of birth was noted. We further observed that men and women with a low level of education regardless of their country of birth had an increased risk of and worse prognosis after fMI. More importantly, the number of study subjects and length of observation were sufficient to explore the incidence of and survival after fMI within geographical regions and individual countries of origins. An increased risk of fMI incidence was evident among patients from Southern and Western Asia, for example Bangladesh, Afghanistan, Pakistan, and Iraq. This pattern was clearer for men than for women. However the risk of fMI was low in immigrants from Eastern and South-Eastern Asia, including China, Japan, and Vietnam. Within Europe, a regional pattern was also apparent; a slightly increasing trend of fMI risk was noted from south to north and from west to east. Another region with low fMI risk was Latin America, including in Bolivia, Peru, and Chile. These differences were not explained, as in Sweden, by differences in SEP, age, and risk factor distribution.

We also found that, among hospitalized fMI patients, the probability of being treated within CCUs was equal among immigrants and Sweden-born patients. Although an increasing proportion of fMI patients were treated in a CCU between 2001 and 2009, inequity still exited for female patients and patients with a lower education level; this pattern was observed among both Sweden-born patients and immigrants. The inequity was not explained by differences in age, hospital type, or medical conditions such as history of diabetes, hyperlipidemia, and atrial fibrillation. The large study cohort also allowed us to study inequity of admission to CCUs by regions and individual countries in which immigrants were born. Consistent with overall equity of admission to CCUs, there was essentially no evidence of inequity based on country of birth.

Among fMI patients admitted to CCUs between 2001 and 2009, the adjusted rates of undergoing coronary angiography and PCI were similar between foreign-born and Sweden-born patients. A higher proportion of foreign-born patients received CABG compared with those born in Sweden and the inequality reduced for women but not for men at the end of study period. Higher proportions of female patients from Iraq, State of Palestine, and Poland received PCI compared with women from other countries including those born in Sweden. Moreover, we found that the increased rate of undergoing CABG for foreign-born patients was mainly explained by those from Asia and some European countries, for example men from India, Sri Lanka, and State of Palestine, women from Syria, Iraq, and Turkey, and both groups from Finland and the former Czechoslovakia.

In the epidemiological study of T1DM, we found an increasing trend among children younger than 15 years of age, but not among those who were 15 to 30 years old during the study period between 1969 and 2008. In comparison with Sweden-born individuals, the overall risk of T1DM was lower among those born outside Sweden, and to a lesser extent among offspring of immigrants. These patterns of decreased risk were more pronounced among children than among young adults and were present for both sexes and most countries of birth. We further found a reduced risk with increasing parental education among young adults but not among children. The variations in risk of T1DM over time and generations suggest that the lower risk in male and female immigrants and their offspring cannot be explained solely by genetic differences. Individuals born in Sweden were among those with the highest risk of T1DM; in general male and female children and young adults born in countries within Asia, Southern Europe, Eastern Europe, and Latin America had statistically significantly lower risks than Sweden-born children and young adults.

6.2 RESULTS IN RELATION TO PREVIOUS RESEARCH

6.2.1 Paper I

Our findings of a negative association between SEP, measured as the highest level of education attained, and incidence of and survival after fMI confirmed SEP as an important MI risk indicator[24, 142, 143]. The increased MI incidence among individuals with lower educational levels were, however, relatively stronger for women than for men and for Sweden-born than for foreign-born populations. The poorer prognosis among fMI patients with a low level of education was similar for both sexes and not afftected by immigration status. Education might have an impact on risk of fMI indirectly via known MI risk factors that were not evaluated in our study, such as smoking[1, 144], obesity[144], prolonged exposure to heavy alcohol consumption[145], and high cholesterol levels[146]. Moreover, healthcare-seeking behavior, treatment, and lifestyle awareness between populations with different levels of education might partially explain the different prognosis among patients. Lack of reliable information on these important lifestyle risk factors especially among immigrants in Sweden is a limitation of our study.

We found that, at present, the multivariable-adjusted risk of fMI is continuing to decrease among men irrespective of immigration status. This is in accordance with results of previous studies showing decreased MI trend during the earlier years up to 2004[147]. For women, however, the incidence rate decreased at a slower pace than for men. One possible explanation for this gender difference could be that the prevalence of certain MI risk factors varies among men and women. For example, smoking has historically been more common in men than women[1] but there seems to be an altering trend of an increasing prevalence in women with a decreasing rate in men[93]. The increasing fMI incidence around the year 2001 might be explained by a change in diagnostic criteria that were introduced in 2000 in Sweden. The main change was inclusion of the new criterion of raised troponin T concentration in addition to other factors. Some patients who were classified as having unstable angina according to previous diagnostic guidelines would have been diagnosed with MI since 2000[135].

The increased fMI incidence rate among men and women born in Southern and Western Asia was found in many previous studies conducted in North America and Sweden[148]. There were minimal difference in incidence rate between immigrants born within Europe and Sweden-born individuals. The approximately 10% increased risk among Finnish immigrants compared with Sweden-born patients in our study was significantly lower than the 70% increased risk observed in another Swedish study[147]. A possible explanation for this difference could be that the two studies were conducted during different time periods; the previous study was conducted from 1974 to 1976.

6.2.2 Paper II

The lower rate of treatment in a CCU among women compared with men observed in this study has previously been reported in the USA, UK, and Italy[149-152] and in some small regional studies in Sweden[153-155]. We confirmed this finding even after taking into account age, educational level as an indication of SEP, country of birth, and a number of other potential confounders. A possible explanation for this finding is that the predominant symptoms of MI in women might be different from those in men. It has been shown that women on average have a lower prevalence of chest pain, which is a hallmark symptom among men with MI[156]. Instead, female MI patients might be more likely to experience fatigue, neck pain, syncope, nausea, right arm pain, dizziness, jaw pain, shortness of breath, and weakness[156, 157]. Women also likely have a different attitude toward seeking medical care, such as delaying consultation with healthcare professionals[158]. This is important and should be taken into consideration as it may result in patient- and healthcare-related delays in the diagnosis of MI to a stage when referral to the CCU is not feasible.

In contrast to the findings of studies conducted in countries other than Sweden[159-162], we observed equity of admission to CCUs among Sweden-born and foreign-born fMI patients. This was also true when foreign-born patients were further categorized by individual country of birth. Moreover, the equity was evident across all study periods. The almost cost-free healthcare system for all residents in Sweden might partly explain the equal likelihood of being admitted to a CCU for foreign-born and Sweden-born MI patients.

6.2.3 Paper III

In the study of access to cardiac procedures after fMI, there were some similarities between our results and those of other international studies even though the composition and history of immigrant populations vary across countries. Immigrants from Southern Asia tended to have higher rates of cardiac procedures than white patients in a study based on 10,308 civil servants in London, UK[163]. Non-English speaking populations had higher rates of CABG than native English speakers in public hospitals in Victoria, Australia[164]. Another study in Canada showed higher rates of use of revascularization among new immigrants[165]. By contrast, some studies conducted outside Sweden showed that certain ethnic minority groups had lower rates of undergoing cardiac procedures than white patients[160]. The explanation for this inconsistency might be that we used country of birth rather than ethnicity or race in our study. Being born in a foreign country does not necessarily entail a racial difference or other ethnicity. Foreign-born patients in our study included white, black and other racial groups. In addition, patients born in other Nordic regions were also considered to be foreign born. Our definition of foreign born was similar to the definition of immigrant, or classification by language and world region of origin. Moreover, historical immigration patterns, the healthcare system, and healthcare financing differences might explain the differences in results[166].

6.2.4 Paper IV

The finding in this study of an increasing rate of T1DM incidence among children younger than 15 years of age is further evidence of the well-known global rapid rise in T1DM risk during the past few decades[54, 167] and consistent with studies from many other countries[168, 169]. This indicates that there is considerable opportunity for environmental factors to influence genetic predisposition, for example by changing lifestyle. Various factors in early life, such as rapid fetal growth, viral infection during pregnancy, preeclampsia, caesarean section delivery, older maternal age, high birth weight, and early introduction of cow's milk proteins[170, 171], might be associated with the increasing trend of T1DM among children younger than 15 years. Studies show that genetically non-susceptible individuals are more prone to being affected by environmental factors than those genetically susceptible to T1DM[172, 173].

The observed low T1DM incidence rate among immigrants and the slightly increased rate among their offspring highlight the importance of lifestyle and environmental factors in the etiology of T1DM. In addition, the pronounced lower risk of T1DM observed among children of immigrants compared with young adult immigrants also suggests the influence of environmental factors. In agreement with our findings, some previous studies demonstrated that children of immigrants from countries with a low incidence of T1DM retained the incidence close to that of their parents' countries of origin[174-177], whereas other studies found the opposite[108, 178] or detected no effect of migration[178, 179]. In a study of T1DM in Jewish Ethiopian immigrants in Israel, it was argued that adoption of a Western lifestyle, with increasing exposure to diabetogenic factors over time, could have contributed to the increased incidence of the disease in genetically predisposed individuals[180].

6.3 METHODOLOGICAL CONSIDERATIONS

The major strengths of our studies are first the large study population, which provides high statistical precision and secondly the nationwide design with a long follow-up period including all Sweden-born and foreign-born Swedish residents. Thus it was possible to explore the strength of associations and trends with adjustment for several confounding factors and effect modifiers between study exposures and outcomes with retained statistical power.

Furthermore, the register-based information is of high quality. We had almost complete information on the main exposure of the study: country of birth. From 2001 onwards, the Swedish National Patient Register included information on hospitalized patients as well as outpatient visits to specialist care and day care visits to hospitals throughout Sweden. It has been shown that it is reasonable to identify MI cases[181] and coronary risk factors such as diabetes[182] in this way. The information on diagnosis has been validated and in general found to be of high quality, and particularly suitable for large-scale population-based research with long follow-up[119]. In 2010, based on 132 reviewed papers, the positive predictive value of the Swedish National Patient Register was found to be about 85% to 95%[119]. The drop-out rate of this register for 2007 has been estimated to be less than 1%[118].The coverage of CCU admissions by means of RIKS-HIA is high and is estimated to be at least 95% of all admissions[126, 183].

Migration is not a random process; immigrants are usually self-selected. Thus, immigrants in Sweden might not be representative of the general populations in their countries of origin. For example, immigrants might be from particular geographical areas such as cities or have particular socioeconomic backgrounds (e.g. students, businessmen, or refugees) which might vary by country of origin, time of immigration, and reason of immigration. When interpreting study findings regarding the risk of certain diseases, these potential differences should always be considered.

Some studies showed a 'healthy migrant effect'[184]. That is, migrants are on average healthier than the general population of their country of origin. For instance, Turkish immigrants in Germany were found to have a lower risk of mortality compared with the general population in their home country[185-187]. Some explanations have been proposed for this phenomenon. Migration requires good resources and energy that overall healthier individuals may possess. Also, immigration host countries often impose health criteria that screen out those potential immigrants with certain health issues. However, many other studies showed that the so-called healthy migrant effect varies depending on the health outcome, host country, and immigrant subpopulation, and thus the validity of this effect remains unclear[187, 188]. Therefore, the findings in this thesis cannot be extrapolated to the general population of immigrants' countries of origin.

When measuring the effect of country of birth, several variables that are associated with both exposures and outcomes might be considered as confounders. Two of the most commonly considered confounders in epidemiological research are age and calendar year of diagnosis. Different age distribution between foreign-born and Sweden-born populations might be a strong confounder that biases the estimation of risk comparison. For example, if the foreign-born population in Sweden was on average much younger than the Sweden-born population, it would be expected that the former would have a lower incidence rate of MI due to the positive association between fMI risk and age. This decreased risk is only comparable for populations in the same age group or with the same age group distribution. Similarly, for the year of diagnosis, in order to control for the potential difference, either age standardization or age adjustment can be used. In this thesis, the temporal trends of fMI and T1DM were controlled for foreign-born and Sweden-born populations by age standardization; in the analyses of IRRs, age adjustment was used.

Geographical difference within Sweden is another potential source of confounding. It is possible that, within a country, the population living in different regions might have different risks of diseases[189, 190]. This is particularly relevant when studying admission to healthcare. Immigrants seldom settle in the host country homogeneously; they are likely to live in large cities, for example where there are more job opportunities. In this thesis, overall risk differences have only been estimated at the country level. Further research could be conducted to compare differences at the regional level.

SEP is one of the study exposure variables and also an important confounder in the analysis of country of birth effect. SEP is a subjective measurement. Many researchers use education, income, or occupation as indicators of SEP in epidemiological studies. All indicators have their own limitations. For example, within the same occupation, some individuals work as common clerks whereas others work as managers; this might have a very different impact on many health outcomes. Even working in the same occupation and in a similar position, working during the day might have a different health impact compared with working at night. Income as an indicator of SEP also has its limitations. During a long-term follow-up cohort study, income might change over the study period. However, it is difficult to model such changes over time. In addition, many immigrant families might not have a high income from the new host country, but may have savings from their previous life experiences in their countries of origin. We believe that education is the most suitable indicator with regard to the study outcomes and exposures for several reasons. First, health awareness is more closely associated with health outcomes than income and education level, especially in an almost free healthcare society such as Sweden. Secondly, it is easier to measure and classify the level of education than other indicators since it is more standardized and rarely changes after a certain age. In Sweden, there is relatively complete coverage regarding years of education for both Sweden-born and foreign-born populations in LISA and FoB.

There are many other factors that might confound our results. We were able to adjust for some but not all of them. For example, in addition to age, calendar year of diagnosis, and SEP, we considered history of diabetes, hypolipidemia, and hypotension in the analysis of fMI risk and case fatality (*Paper I*). In the study of admission to the CCU for hospitalized fMI patients (*Paper II*), we also considered medical conditions including diabetes, hypertension, and hyperlipidemia, as well as a history of stroke, heart failure, angina, atrial fibrillation, pulmonary embolism, chronic obstructive lung disease, and cancer. In the study of access to cardiac procedures after fMI (*Paper III*), the high-quality and wide coverage of RIKS-HIA enabled more potential confounders regarding medical information to be considered. Such potential confounders were classified as admission information, clinical information during hospitalization, and complications during treatment. Admission information included use of angiotensin-converting enzyme inhibitors at admission, arrival at hospital by ambulance or not, beta-blocker use prior to admission, cardiac shock at admission, QRS complex, rhythm, and ST and T (ST–T) wave changes on ECG, type of MI, previous PCI, presenting symptoms, prior cardiac surgery, pulmonary rate, smoking status, and statin use before hospitalization. Clinical information during hospitalization included beta-blocker use during treatment, diuretic treatment, and anticoagulant therapy. Complications during treatment included AV block, myocardial re-infarction and new fibrillation or flutter during hospitalization. In the study of T1DM (*Paper IV*), we considered parental SEP as a potential confounder as participants were aged from 0 to 30 years. However, the M&H Co did not include information on certain lifestyle factors such as smoking, physical activity, and alcohol consumption. Many other psychosocial factors such as social networks and stress were also not available. Even after adjustment in the models for these potential confounders, residual confounding existed. For example, we obtained history of hypertension information from the National Patient Register (*Papers I, II*, and *III*). Those patients with hypertension but never hospitalized would be missing from the cohort. Thus, this limitation should be considered in interpreting the results.

Overall, the quality of Swedish registers is high in terms of exposures and outcomes in the present studies as mentioned previously. However, in terms of migrant studies, there were still many limitations. For example, the date of immigration to Sweden was missing for a small proportion of immigrants registered in the Total Population Register. In the calculation of follow-up person-years, for these immigrants we instead used the first date that appeared in any register as an approximation of their first immigration date. Moreover, in calculating the number of person-years of follow-up, it was assumed that immigrants lived in Sweden until their emigration or the end of the study. However, this might not be the case for some immigrants; it is possible that they moved back and forth during the follow-up period. This is similarly also a potential problem for Sweden-born individuals. It is possible that some our study incidence occurred overseas during their travelling and we did not have this information registered in Sweden. It is also possible that both foreign-born and Sweden-born individuals emigrated from Sweden but with a delay in reporting this information to registers. The evaluation of trends may be affected by another limitation related to data quality. The completeness of the coverage of the Patient Register is increasing over time. Therefore it would be reasonable to assume that there were more missed cases in the earlier period of follow-up compared with the later study period. This potential limitation should be considered in interpretation of the study results, particularly with regard to increasing trends.

In the study of risk of T1DM, we lacked specific ICD codes to distinguish between type I and type II diabetes before 1997. To overcome this limitation, we restricted our study population to individuals younger than 30 years in whom diabetes is most likely to be type I disease[191-193]. In addition, the results for sensitivity analyses of data from the period 1997–2008 (during which time specific ICD codes for T1DM were available) were similar to the results for the entire study period.

6.4 CONCLUSIONS

1) The fMI incidence rate in Sweden is decreasing, but this pattern is less evident for women and foreign-born individuals.
2) A clear improvement in prognosis after non-fatal fMI is evident for both Sweden-born and foreign-born men and women.
3) Low education level is associated with increased fMI risk and worse prognosis after fMI.
4) Men and women born in Southern and Western Asia who immigrated to Sweden have a high incidence rate of fMI.
5) The proportion of fMI patients treated in CCUs has been increasing during the past decades. However women and less well educated fMI patients have a lower chance of admission compared with men and those with a high level of education, respectively.
6) Foreign-born and Sweden-born patients are equally likely to be admitted to a CCU after fMI.

7) The overall rates of undergoing coronary angiography and PCI are similar between foreign-born and Sweden-born patients, but are higher among those with a low compared to a high level of education.
8) Foreign-born MI patients undergo CABG at a higher rate compared with Sweden-born patients, with those born in Asia having the highest rate.
9) The incidence of T1DM is increasing among children younger than 15 years of age, but not among young adults.
10) Compared with Sweden-born individuals, the risk of T1DM is decreasing among immigrants and to a lesser degree also among offspring of immigrants. This decreased risk is more pronounced among children than among young adults for both sexes and for most countries of birth. The changes in risk over time and generations indicate that the low risk of T1DM in immigrants and their offspring cannot only be explained by genetic factors.

6.5 FUTURE RESEARCH

Based on the findings of this thesis, nested case–control studies could be designed in order to further understand the relation between migration and health outcomes. Important potential confounders, such as history of smoking and alcohol consumption, family history of various diseases, stress, diet, childhood lifestyle, and many others could be considered in future.

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8 REFERENCES

1. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;**364**(9438):937-52.
2. Moradi T, Allebeck P, Jacobsson A, Mathers C. [The burden of disease in Sweden measured with DALY. Neuropsychiatric diseases and cardiovascular diseases dominate]. Lakartidningen 2006;**103**(3):137-41.
3. Eliasson M, Bostrom G. Chapter 5.2: major public health problems - diabetes. Scand J Public Health Suppl 2006;**67**:59-68.
4. Soltesz G, Patterson CC, Dahlquist G. Worldwide childhood type 1 diabetes incidence--what can we learn from epidemiology? Pediatr Diabetes 2007;**8 Suppl 6**:6-14.
5. Delli AJ, Lindblad B, Carlsson A, Forsander G, Ivarsson SA, Ludvigsson J, Marcus C, Lernmark A. Type 1 diabetes patients born to immigrants to Sweden increase their native diabetes risk and differ from Swedish patients in HLA types and islet autoantibodies. Pediatr Diabetes 2010;**11**(8):513-20.
6. Ststistics_Sweden. The future population of Sweden 2013−2060. In.

BE18 Population projection for Sweden 2013.
7. Sweden S. Number of persons with foreign or Swedish background (detailed division) by region, age in ten year groups and sex. Year 2002 - 2011. 2013.
8. VASILEVA K. 6.5% of the EU population are foreigners and 9.4% are born abroad. Eurostat: Statistics in focus 34/2001 2011.
9. Statistiska_centralbyrån. Tabeller över Sveriges befolkning 2010.
10. Beiki O. Cancer and Migration: Epidemiological studies on relationship between country of birth, socio-economic position and cancer. 2010.
11. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Circulation 1979;**59**(3):607-9.
12. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000;**21**(18):1502-13.
13. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J 2007;**28**(20):2525-38.
14. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mahonen M, Ngu Blackett K, Lisheng L. World Health Organization definition of myocardial infarction: 2008-09 revision. Int J Epidemiol 2011;**40**(1):139-46.
15. Taylor J. Third universal definition of myocardial infarction. Eur Heart J 2012;**33**(20):2506-7.
16. Moe KT, Wong P. Current trends in diagnostic biomarkers of acute coronary syndrome. Ann Acad Med Singapore 2010;**39**(3):210-5.
17. Goldberg RJ, Gorak EJ, Yarzebski J, Hosmer DW, Jr., Dalen P, Gore JM, Alpert JS, Dalen JE. A communitywide perspective of sex differences and temporal trends in the incidence and survival rates after acute myocardial infarction and out-of-hospital deaths caused by coronary heart disease. Circulation 1993;**87**(6):1947-53.
18. Margolis JR, Gillum RF, Feinleib M, Brasch R, Fabsitz R. Community surveillance for coronary heart disease: the Framingham Cardiovascular Disease survey. Comparisons with the Framingham Heart Study and previous short-term studies. Am J Cardiol 1976;**37**(1):61-7.
19. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol 1988;**41**(2):105-14.
20. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality

rates in 38 populations from 21 countries in four continents. Circulation 1994;**90**(1):583-612.
21. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. Science 1996;**274**(5288):740-3.
22. Moran AE, Oliver JT, Mirzaie M, Forouzanfar MH, Chilov M, Anderson L, Morrison JL, Khan A, Zhang N, Haynes N, Tran J, Murphy A, Degennaro V, Roth G, Zhao D, Peer N, Pichon-Riviere A, Rubinstein A, Pogosova N, Prabhakaran D, Naghavi M, Ezzati M, Mensah GA. Assessing the Global Burden of Ischemic Heart Disease: Part 1: Methods for a Systematic Review of the Global Epidemiology of Ischemic Heart Disease in 1990 and 2010. Glob Heart 2012;**7**(4):315-329.
23. Forouzanfar MH, Moran AE, Flaxman AD, Roth G, Mensah GA, Ezzati M, Naghavi M, Murray CJ. Assessing the global burden of ischemic heart disease, part 2: analytic methods and estimates of the global epidemiology of ischemic heart disease in 2010. Glob Heart 2012;**7**(4):331-342.
24. Goyal A, Bhatt DL, Steg PG, Gersh BJ, Alberts MJ, Ohman EM, Corbalan R, Eagle KA, Gaxiola E, Gao R, Goto S, D'Agostino RB, Califf RM, Smith SC, Jr., Wilson PW. Attained educational level and incident atherothrombotic events in low- and middle-income compared with high-income countries. Circulation 2010;**122**(12):1167-75.
25. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. J Clin Epidemiol 1996;**49**(2):223-33.
26. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;**129**(4):687-702.
27. Wang H, Steffen LM, Jacobs DR, Zhou X, Blackburn H, Berger AK, Filion KB, Luepker RV. Trends in cardiovascular risk factor levels in the Minnesota Heart Survey (1980-2002) as compared with the National Health and Nutrition Examination Survey (1976-2002): A partial explanation for Minnesota's low cardiovascular disease mortality? Am J Epidemiol 2011;**173**(5):526-38.
28. Burke GL, Sprafka JM, Folsom AR, Luepker RV, Norsted SW, Blackburn H. Trends in CHD mortality, morbidity and risk factor levels from 1960 to 1986: the Minnesota Heart Survey. Int J Epidemiol 1989;**18**(3 Suppl 1):S73-81.
29. Pandey DK, Labarthe DR, Goff DC, Chan W, Nichaman MZ. Community-wide coronary heart disease mortality in Mexican Americans equals or exceeds that in non-Hispanic whites: the Corpus Christi Heart Project. Am J Med 2001;**110**(2):81-7.
30. Steffen-Batey L, Nichaman MZ, Goff DC, Jr., Frankowski RF, Hanis CL, Ramsey DJ, Labarthe DR. Change in level of physical activity and risk of all-cause mortality or reinfarction: The Corpus Christi Heart Project. Circulation 2000;**102**(18):2204-9.
31. Mahonen M, Salomaa V, Torppa J, Miettinen H, Pyorala K, Immonen-Raiha P, Niemela M, Ketonen M, Arstila M, Kaarsalo E, Lehto S, Mustaniemi H, Palomaki P, Puska P, Vuorenmaa T, Tuomilehto J. The validity of the routine mortality statistics on coronary heart disease in Finland: comparison with the FINMONICA MI register data for the years 1983-1992. Finnish multinational MONItoring of trends and determinants in CArdiovascular disease. J Clin Epidemiol 1999;**52**(2):157-66.
32. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. Circulation 2005;**111**(6):761-7.
33. Wu J, Pride YB, Frederick PD, Gibson CM. Association of initial thrombolysis in myocardial infarction flow grade with mortality among patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a National Registry of Myocardial Infarction-5 (NRMI-5) analysis. Am Heart J 2011;**162**(1):178-83.
34. Pitta SR, Grzybowski M, Welch RD, Frederick PD, Wahl R, Zalenski RJ. ST-segment depression on the initial electrocardiogram in acute myocardial infarction-prognostic significance and its effect on short-term mortality: A report from the

National Registry of Myocardial Infarction (NRMI-2, 3, 4). Am J Cardiol 2005;**95**(7):843-8.
35. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;**366**(9493):1267-78.
36. Godtfredsen NS, Osler M, Vestbo J, Andersen I, Prescott E. Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976-1998: a pooled cohort study. J Epidemiol Community Health 2003;**57**(6):412-6.
37. Smith SC, Jr., Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol 2006;**47**(10):2130-9.
38. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2007;**115**(1):114-26.
39. Holmqvist ME, Wedren S, Jacobsson LT, Klareskog L, Nyberg F, Rantapaa-Dahlqvist S, Alfredsson L, Askling J. Rapid increase in myocardial infarction risk following diagnosis of rheumatoid arthritis amongst patients diagnosed between 1995 and 2006. J Intern Med 2010;**268**(6):578-85.
40. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;**352**(16):1685-95.
41. Smith SC, Jr., Blair SN, Bonow RO, Brass LM, Cerqueira MD, Dracup K, Fuster V, Gotto A, Grundy SM, Miller NH, Jacobs A, Jones D, Krauss RM, Mosca L, Ockene I, Pasternak RC, Pearson T, Pfeffer MA, Starke RD, Taubert KA. AHA/ACC Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 2001;**104**(13):1577-9.
42. Friedlander Y, Kark JD, Stein Y. Family history of myocardial infarction as an independent risk factor for coronary heart disease. Br Heart J 1985;**53**(4):382-7.
43. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D, Rodriguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff M, Watson C, Armah KA, Doebler D, Bryant K, Justice AC. HIV Infection and the Risk of Acute Myocardial Infarction. JAMA Intern Med 2013:1-9.
44. Estabragh ZR, Mamas MA. The cardiovascular manifestations of influenza: A systematic review. Int J Cardiol 2013.
45. Arnson Y, Itzhaky D, Mosseri M, Barak V, Tzur B, Agmon-Levin N, Amital H. Vitamin D Inflammatory Cytokines and Coronary Events: A Comprehensive Review. Clin Rev Allergy Immunol 2013.
46. Puig L. Cardiovascular risk and psoriasis: the role of biologic therapy. Actas Dermosifiliogr 2012;**103**(10):853-62.
47. Roberts R, Stewart AF. Genes and coronary artery disease: where are we? J Am Coll Cardiol 2012;**60**(18):1715-21.
48. Topol EJ, Smith J, Plow EF, Wang QK. Genetic susceptibility to myocardial infarction and coronary artery disease. Hum Mol Genet 2006;**15 Spec No 2**:R117-23.
49. Topol EJ, McCarthy J, Gabriel S, Moliterno DJ, Rogers WJ, Newby LK, Freedman M, Metivier J, Cannata R, O'Donnell CJ, Kottke-Marchant K, Murugesan G, Plow EF, Stenina O, Daley GQ. Single nucleotide polymorphisms in multiple novel thrombospondin genes may be associated with familial premature myocardial infarction. Circulation 2001;**104**(22):2641-4.

50. Yamada Y, Izawa H, Ichihara S, Takatsu F, Ishihara H, Hirayama H, Sone T, Tanaka M, Yokota M. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. N Engl J Med 2002;**347**(24):1916-23.
51. Liese AD, D'Agostino RB, Jr., Hamman RF, Kilgo PD, Lawrence JM, Liu LL, Loots B, Linder B, Marcovina S, Rodriguez B, Standiford D, Williams DE. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics 2006;**118**(4):1510-8.
52. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;**36 Suppl 1**:S67-74.
53. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. Diabetes Care 2000;**23**(10):1516-26.
54. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabet Med 2006;**23**(8):857-66.
55. Dabelea D, Bell RA, D'Agostino RB, Jr., Imperatore G, Johansen JM, Linder B, Liu LL, Loots B, Marcovina S, Mayer-Davis EJ, Pettitt DJ, Waitzfelder B. Incidence of diabetes in youth in the United States. JAMA 2007;**297**(24):2716-24.
56. Variation and trends in incidence of childhood diabetes in Europe. EURODIAB ACE Study Group. Lancet 2000;**355**(9207):873-6.
57. Levy-Marchal C, Patterson CC, Green A. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. European and Dibetes. Diabetologia 2001;**44 Suppl 3**:B75-80.
58. Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for islet autoimmunity among monozygotic twins. N Engl J Med 2008;**359**(26):2849-50.
59. Eringsmark Regnell S, Lernmark A. The environment and the origins of islet autoimmunity and Type 1 diabetes. Diabet Med 2013;**30**(2):155-60.
60. Redondo MJ, Yu L, Hawa M, Mackenzie T, Pyke DA, Eisenbarth GS, Leslie RD. Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. Diabetologia 2001;**44**(3):354-62.
61. Fourlanos S, Dotta F, Greenbaum CJ, Palmer JP, Rolandsson O, Colman PG, Harrison LC. Latent autoimmune diabetes in adults (LADA) should be less latent. Diabetologia 2005;**48**(11):2206-12.
62. Gillespie KM, Gale EA, Bingley PJ. High familial risk and genetic susceptibility in early onset childhood diabetes. Diabetes 2002;**51**(1):210-4.
63. Mehers KL, Gillespie KM. The genetic basis for type 1 diabetes. Br Med Bull 2008;**88**(1):115-29.
64. Virtanen SM, Knip M. Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. Am J Clin Nutr 2003;**78**(6):1053-67.
65. Tsirogianni A, Pipi E, Soufleros K. Specificity of islet cell autoantibodies and coexistence with other organ specific autoantibodies in type 1 diabetes mellitus. Autoimmun Rev 2009;**8**(8):687-91.
66. Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab 2006;**91**(4):1210-7.
67. Mayer-Davis EJ, Bell RA, Dabelea D, D'Agostino R, Jr., Imperatore G, Lawrence JM, Liu L, Marcovina S. The many faces of diabetes in American youth: type 1 and type 2 diabetes in five race and ethnic populations: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;**32 Suppl 2**:S99-101.
68. Dabelea D, DeGroat J, Sorrelman C, Glass M, Percy CA, Avery C, Hu D, D'Agostino RB, Jr., Beyer J, Imperatore G, Testaverde L, Klingensmith G, Hamman RF. Diabetes in Navajo youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;**32 Suppl 2**:S141-7.
69. Lawrence JM, Mayer-Davis EJ, Reynolds K, Beyer J, Pettitt DJ, D'Agostino RB, Jr., Marcovina SM, Imperatore G, Hamman RF. Diabetes in Hispanic American youth: prevalence, incidence, demographics, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;**32 Suppl 2**:S123-32.
70. Mayer-Davis EJ, Beyer J, Bell RA, Dabelea D, D'Agostino R, Jr., Imperatore G, Lawrence JM, Liese AD, Liu L, Marcovina S, Rodriguez B. Diabetes in

African American youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;**32 Suppl 2**:S112-22.
71. Liu LL, Yi JP, Beyer J, Mayer-Davis EJ, Dolan LM, Dabelea DM, Lawrence JM, Rodriguez BL, Marcovina SM, Waitzfelder BE, Fujimoto WY. Type 1 and Type 2 diabetes in Asian and Pacific Islander U.S. youth: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;**32 Suppl 2**:S133-40.
72. Vandewalle CL, Coeckelberghs MI, De Leeuw IH, Du Caju MV, Schuit FC, Pipeleers DG, Gorus FK. Epidemiology, clinical aspects, and biology of IDDM patients under age 40 years. Comparison of data from Antwerp with complete ascertainment with data from Belgium with 40% ascertainment. The Belgian Diabetes Registry. Diabetes Care 1997;**20**(10):1556-61.
73. Thunander M, Petersson C, Jonzon K, Fornander J, Ossiansson B, Torn C, Edvardsson S, Landin-Olsson M. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. Diabetes Res Clin Pract 2008;**82**(2):247-55.
74. Haller MJ, Atkinson MA, Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. Pediatr Clin North Am 2005;**52**(6):1553-78.
75. Green A, Gale EA, Patterson CC. Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. Lancet 1992;**339**(8798):905-9.
76. Karvonen M, Pitkaniemi M, Pitkaniemi J, Kohtamaki K, Tajima N, Tuomilehto J. Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data. World Health Organization DIAMOND Project Group. Diabetes Metab Rev 1997;**13**(4):275-91.
77. Ostman J, Lonnberg G, Arnqvist HJ, Blohme G, Bolinder J, Ekbom Schnell A, Eriksson JW, Gudbjornsdottir S, Sundkvist G, Nystrom L. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002. J Intern Med 2008;**263**(4):386-94.
78. Goldberg E, Krause I. Infection and type 1 diabetes mellitus - a two edged sword? Autoimmun Rev 2009;**8**(8):682-6.
79. Pundziute-Lycka A, Urbonaite B, Dahlquist G. Infections and risk of Type I (insulin-dependent) diabetes mellitus in Lithuanian children. Diabetologia 2000;**43**(10):1229-34.
80. Kahn HS, Morgan TM, Case LD, Dabelea D, Mayer-Davis EJ, Lawrence JM, Marcovina SM, Imperatore G. Association of type 1 diabetes with month of birth among U.S. youth: The SEARCH for Diabetes in Youth Study. Diabetes Care 2009;**32**(11):2010-5.
81. Vaiserman AM, Carstensen B, Voitenko VP, Tronko MD, Kravchenko VI, Khalangot MD, Mechova LV. Seasonality of birth in children and young adults (0-29 years) with type 1 diabetes in Ukraine. Diabetologia 2007;**50**(1):32-5.
82. Jongbloet PH, Groenewoud HM, Hirasing RA, Van Buuren S. Seasonality of birth in patients with childhood diabetes in The Netherlands. Diabetes Care 1998;**21**(1):190-1.
83. Samuelsson U, Johansson C, Ludvigsson J. Month of birth and risk of developing insulin dependent diabetes in south east Sweden. Arch Dis Child 1999;**81**(2):143-6.
84. McKinney PA. Seasonality of birth in patients with childhood Type I diabetes in 19 European regions. Diabetologia 2001;**44 Suppl 3**:B67-74.
85. Willis JA, Scott RS, Darlow BA, Lewy H, Ashkenazi I, Laron Z. Seasonality of birth and onset of clinical disease in children and adolescents (0-19 years) with type 1 diabetes mellitus in Canterbury, New Zealand. J Pediatr Endocrinol Metab 2002;**15**(5):645-7.
86. Laron Z, Shamis I, Nitzan-Kaluski D, Ashkenazi I. Month of birth and subsequent development of type I diabetes (IDDM). J Pediatr Endocrinol Metab 1999;**12**(3):397-402.
87. Snijder M, van Dam R, Visser M, Deeg D, Seidell J, Lips P. To: Mathieu C, Gysemans C, Giulietti A, Bouillon R (2005) Vitamin D and diabetes. Diabetologia 48:1247-1257. Diabetologia 2006;**49**(1):217-8.

88. Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. Diabetologia 2008;**51**(8):1391-8.
89. Planning_Office_of_the_Netherlands_(SCP) SaC. Public sector performance 2004. An international comparison of education, health care, law and order, and public administration. In. The Hague; 2004.
90. Hammar N, Alfredsson L, Rosen M, Spetz CL, Kahan T, Ysberg AS. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. Int J Epidemiol 2001;**30 Suppl 1**:S30-4.
91. Hedlund E, Lange A, Hammar N. Acute myocardial infarction incidence in immigrants to Sweden. Country of birth, time since immigration, and time trends over 20 years. Eur J Epidemiol 2007;**22**(8):493-503.
92. Stjarne MK, Fritzell J, De Leon AP, Hallqvist J. Neighborhood socioeconomic context, individual income and myocardial infarction. Epidemiology 2006;**17**(1):14-23.
93. Rosen M, Alfredsson L, Hammar N, Kahan T, Spetz CL, Ysberg AS. Attack rate, mortality and case fatality for acute myocardial infarction in Sweden during 1987-95. Results from the national AMI register in Sweden. J Intern Med 2000;**248**(2):159-64.
94. Rosengren A, Spetz CL, Koster M, Hammar N, Alfredsson L, Rosen M. Sex differences in survival after myocardial infarction in Sweden; data from the Swedish National Acute Myocardial Infarction Register. Eur Heart J 2001;**22**(4):314-22.
95. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996;**93**(11):1981-92.
96. Sonke GS, Beaglehole R, Stewart AW, Jackson R, Stewart FM. Sex differences in case fatality before and after admission to hospital after acute cardiac events: analysis of community based coronary heart disease register. BMJ 1996;**313**(7061):853-5.
97. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med 1999;**341**(4):217-25.
98. Gerward S, Tyden P, Hansen O, Engstrom G, Janzon L, Hedblad B. Survival rate 28 days after hospital admission with first myocardial infarction. Inverse relationship with socio-economic circumstances. J Intern Med 2006;**259**(2):164-72.
99. Herlitz J, Dellborg M, Karlsson T, Evander MH, Berger A, Luepker R. Epidemiology of acute myocardial infarction with the emphasis on patients who did not reach the coronary care unit and non-AMI admissions. Int J Cardiol 2008;**128**(3):342-9.
100. Haglund B, Koster M, Nilsson T, Rosen M. Inequality in access to coronary revascularization in Sweden. Scand Cardiovasc J 2004;**38**(6):334-9.
101. Rosvall M, Chaix B, Lynch J, Lindstrom M, Merlo J. The association between socioeconomic position, use of revascularization procedures and five-year survival after recovery from acute myocardial infarction. BMC Public Health 2008;**8**:44.
102. Feder G, Crook AM, Magee P, Banerjee S, Timmis AD, Hemingway H. Ethnic differences in invasive management of coronary disease: prospective cohort study of patients undergoing angiography. BMJ 2002;**324**(7336):511-6.
103. Schneider EC, Leape LL, Weissman JS, Piana RN, Gatsonis C, Epstein AM. Racial differences in cardiac revascularization rates: does "overuse" explain higher rates among white patients? Ann Intern Med 2001;**135**(5):328-37.
104. Kressin NR, Petersen LA. Racial differences in the use of invasive cardiovascular procedures: review of the literature and prescription for future research. Ann Intern Med 2001;**135**(5):352-66.
105. Sheifer SE, Escarce JJ, Schulman KA. Race and sex differences in the management of coronary artery disease. Am Heart J 2000;**139**(5):848-57.
106. Dabelea D. The accelerating epidemic of childhood diabetes. Lancet 2009;**373**(9680):1999-2000.

107. Tarn AC, Gorsuch AN, Spencer KM, Bottazzo GF, Lister J. Diabetes and social class. Lancet 1983;**2**(8350):631-2.
108. Neu A, Willasch A, Ehehalt S, Kehrer M, Hub R, Ranke MB. Diabetes incidence in children of different nationalities: an epidemiological approach to the pathogenesis of diabetes. Diabetologia 2001;**44 Suppl 3**:B21-6.
109. Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. Diabetologia 2006;**49**(1):20-4.
110. Milton B, Holland P, Whitehead M. The social and economic consequences of childhood-onset Type 1 diabetes mellitus across the lifecourse: a systematic review. Diabet Med 2006;**23**(8):821-9.
111. Ehehalt S, Popovic P, Muntoni S, Willasch A, Hub R, Ranke MB, Neu A. Incidence of diabetes mellitus among children of Italian migrants substantiates the role of genetic factors in the pathogenesis of type 1 diabetes. European Journal of Pediatrics 2009;**168**(5):613-7.
112. Haynes A, Bulsara MK, Bower C, Codde JP, Jones TW, Davis EA. Independent effects of socioeconomic status and place of residence on the incidence of childhood type 1 diabetes in Western Australia. Pediatr Diabetes 2006;**7**(2):94-100.
113. Tedeschi A, Airaghi L. Is affluence a risk factor for bronchial asthma and type 1 diabetes? Pediatr Allergy Immunol 2006;**17**(7):533-7.
114. Verge CF, Silink M, Howard NJ. The incidence of childhood IDDM in New South Wales, Australia. Diabetes Care 1994;**17**(7):693-6.
115. Baumer JH, Hunt LP, Shield JP. Social disadvantage, family composition, and diabetes mellitus: prevalence and outcome. Arch Dis Child 1998;**79**(5):427-30.
116. Swedish_Tax_Agency. Population registration in Sweden (SKV 717B edition 5). In; 2012.
117. Statistics_Sweden. Background facts, historical population register. In; 2006.
118. Socialstyrelsen. the National Patient Register. 2013.
119. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;**11**:450.
120. Socialstyrelsen. *Kvalitet och innehåll i patientregistret and Cause of Death 2007. 2007 [cited 2010 08-13]*. www.socialstyrelsen.se.
121. Socialstyrelsen. Sjukdomar i sluten vård 1987–2008. In; 2009.
122. Socialstyrelsen. Värdering av diagnoskvaliteten för akut hjärtinfarkt i patientregistret 1987 och 1995. In; 2000.
123. Socialstyrelsen. Dödsorsaker 2007. In; 2009.
124. Socialstyrelsen. *Cause of Death 2007*. www.socialstyrelsen.se.
125. de Faire U, Friberg L, Lorich U, Lundman T. A validation of cause-of-death certification in 1,156 deaths. Acta Med Scand 1976;**200**(3):223-8.
126. RIKS-HIA Sc. RIKS-HIA report In; 2005, 66.
127. Uppsala_Clinical_Research_Center. SCAAR årsrapport 1999. In; 1999.
128. Center UCR. SCAAR Svenska Coronar Angiografi. och Angioplastik Registret: Årsrapport 2005. 2005.
129. Uppsala_Clinical_Research_Center. SCAAR Årsrapport 2007. In; 2008.
130. Uppsala_Clinical_Research_Center. SCAAR årsrapport 2005. In; 2005.
131. Swedish_Association_of_Local_Authorities_and_Regions. National Healthcare Quality Registries in Sweden. In; 2007.
132. United_Nations_publication. Standard country or area codes and geographical regions for statistical use. In; 2013.
133. Heaton TB, Albrecht SL. The changing pattern of interracial marriage. Soc Biol 1996;**43**(3-4):203-17.
134. Devesa SS, Diamond EL. Association of breast cancer and cervical cancer incidence with income and education among whites and blacks. J Natl Cancer Inst 1980;**65**(3):515-28.
135. Pell JP, Simpson E, Rodger JC, Finlayson A, Clark D, Anderson J, Pell AC. Impact of changing diagnostic criteria on incidence, management, and outcome of acute myocardial infarction: retrospective cohort study. BMJ 2003;**326**(7381):134-5.

136. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;**159**(7):702-6.
137. Frome EL, Checkoway H. Epidemiologic programs for computers and calculators. Use of Poisson regression models in estimating incidence rates and ratios. Am J Epidemiol 1985;**121**(2):309-23.
138. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. Psychol Bull 1995;**118**(3):392-404.
139. Pawitan Y. *In All Likelihood: Statistical Modelling and Inference Using Likelihood.* New York: OXFORD University press; 2001.
140. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;**19**(3):335-51.
141. Beiki O, Granath F, Allebeck P, Akre O, Moradi T. Subtype-specific risk of testicular tumors among immigrants and their descendants in Sweden, 1960 to 2007. Cancer Epidemiol Biomarkers Prev 2010;**19**(4):1053-65.
142. Lynch JW, Kaplan GA, Cohen RD, Tuomilehto J, Salonen JT. Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction? Am J Epidemiol 1996;**144**(10):934-42.
143. Mehta RH, O'Shea JC, Stebbins AL, Granger CB, Armstrong PW, White HD, Topol EJ, Califf RM, Ohman EM. Association of mortality with years of education in patients with ST-segment elevation myocardial infarction treated with fibrinolysis. J Am Coll Cardiol 2011;**57**(2):138-46.
144. Power C, Graham H, Due P, Hallqvist J, Joung I, Kuh D, Lynch J. The contribution of childhood and adult socioeconomic position to adult obesity and smoking behaviour: an international comparison. Int J Epidemiol 2005;**34**(2):335-44.
145. Fillmore KM, Golding JM, Graves KL, Kniep S, Leino EV, Romelsjo A, Shoemaker C, Ager CR, Allebeck P, Ferrer HP. Alcohol consumption and mortality. I. Characteristics of drinking groups. Addiction 1998;**93(**2):183-203.
146. Eliasson M, Janlert U, Jansson JH, Stegmayr B. Time trends in population cholesterol levels 1986-2004: influence of lipid-lowering drugs, obesity, smoking and educational level. The northern Sweden MONICA study. J Intern Med 2006;**260**(6):551-9.
147. Alfredsson L, Ahlbom A, Theorell T. Incidence of myocardial infarction among male Finnish immigrants in relation to length of stay in Sweden. Int J Epidemiol 1982;**11**(3):225-8.
148. Gupta M, Singh N, Verma S. South Asians and cardiovascular risk: what clinicians should know. Circulation 2006;**113**(25):e924-9.
149. Jones I, Flather M, Johnson M, Barrow S, Thompson D. A description of the characteristics of patients with non-ST elevation acute coronary syndromes admitted to different settings in the 1990s. Intensive Crit Care Nurs 2008;**24**(5):286-94.
150. Ancona C, Arca M, Saitto C, Agabiti N, Fusco D, Tancioni V, Perucci CA. Differences in access to coronary care unit among patients with acute myocardial infarction in Rome: old, ill, and poor people hold the burden of inefficiency. BMC Health Serv Res 2004;**4**(1):34.
151. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L. Sex differences in medical care and early death after acute myocardial infarction. Circulation 2008;**118**(25):2803-10.
152. Ravn-Fischer A, Caidahl K, Hartford M, Karlsson T, Kihlgren S, Perers E, Rashed H, Johanson P, Herlitz J. Community-based gender perspectives of triage and treatment in suspected myocardial infarction. Int J Cardiol 2010.
153. Herlitz J, Karlson BW, Karlsson T, Svensson L, och Bjorn Kalin EZ. A description of the characteristics and outcome of patients hospitalized for acute chest pain in relation to whether they were admitted to the coronary care unit or not in the thrombolytic era. Int J Cardiol 2002;**82**(3):279-87.
154. Rosvall M, Ohlsson H, Hansen O, Chaix B, Merlo J. Auditing patient registration in the Swedish quality register for acute coronary syndrome. Scand J Public Health 2010;**38**(5):533-40.

155. Alfredsson J, Sederholm-Lawesson S, Stenestrand U, Swahn E. Although women are less likely to be admitted to coronary care units, they are treated equally to men and have better outcome. A prospective cohort study in patients with non ST-elevation acute coronary syndromes. Acute Card Care 2009;**11**(3):173-80.
156. Coventry LL, Finn J, Bremner AP. Sex differences in symptom presentation in acute myocardial infarction: a systematic review and meta-analysis. Heart Lung 2011;**40**(6):477-91.
157. McSweeney JC, Cody M, O'Sullivan P, Elberson K, Moser DK, Garvin BJ. Women's early warning symptoms of acute myocardial infarction. Circulation 2003;**108**(21):2619-23.
158. Henriksson C, Larsson M, Arnetz J, Berglin-Jarlov M, Herlitz J, Karlsson JE, Svensson L, Thuresson M, Zedigh C, Wernroth L, Lindahl B. Knowledge and attitudes toward seeking medical care for AMI-symptoms. Int J Cardiol 2011;**147**(2):224-7.
159. King KM, Khan NA, Quan H. Ethnic variation in acute myocardial infarction presentation and access to care. Am J Cardiol 2009;**103**(10):1368-73.
160. Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. N Engl J Med 2005;**353**(7):671-82.
161. Cohen MG, Fonarow GC, Peterson ED, Moscucci M, Dai D, Hernandez AF, Bonow RO, Smith SC, Jr. Racial and ethnic differences in the treatment of acute myocardial infarction: findings from the Get With the Guidelines-Coronary Artery Disease program. Circulation 2010;**121**(21):2294-301.
162. Chen J, Rathore SS, Radford MJ, Wang Y, Krumholz HM. Racial differences in the use of cardiac catheterization after acute myocardial infarction. N Engl J Med 2001;**344**(19):1443-9.
163. Britton A, Shipley M, Marmot M, Hemingway H. Does access to cardiac investigation and treatment contribute to social and ethnic differences in coronary heart disease? Whitehall II prospective cohort study. BMJ 2004;**329**(7461):318.
164. Renzaho A. Ischaemic heart disease and Australian immigrants: the influence of ethnicity and language skills on treatment and use of health services. HIM J 2007;**36**(2):26-36.
165. Alter DA, Austin PC, Tu JV. Community factors, hospital characteristics and inter-regional outcome variations following acute myocardial infarction in Canada. Can J Cardiol 2005;**21**(3):247-55.
166. Herlitz J, McGovern P, Dellborg M, Karlsson T, Duval S, Karlson BW, Lee S, Luepker RV. Comparison of treatment and outcomes for patients with acute myocardial infarction in Minneapolis/St. Paul, Minnesota, and Goteborg, Sweden. Am Heart J 2003;**146**(6):1023-9.
167. Green A, Patterson CC. Trends in the incidence of childhood-onset diabetes in Europe 1989-1998. Diabetologia 2001;**44 Suppl 3**:B3-8.
168. Harjutsalo V, Sjoberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet 2008;**371**(9626):1777-82.
169. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009;**373**(9680):2027-33.
170. Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA. Perinatal risk factors for childhood Type 1 diabetes in Western Australia--a population-based study (1980-2002). Diabet Med 2007;**24**(5):564-70.
171. Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. Diabetes Care 2002;**25**(10):1755-60.
172. Hermann R, Knip M, Veijola R, Simell O, Laine AP, Akerblom HK, Groop PH, Forsblom C, Pettersson-Fernholm K, Ilonen J. Temporal changes in the frequencies of HLA genotypes in patients with Type 1 diabetes--indication of an increased environmental pressure? Diabetologia 2003;**46**(3):420-5.
173. Gillespie KM, Bain SC, Barnett AH, Bingley PJ, Christie MR, Gill GV, Gale EA. The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. Lancet 2004;**364**(9446):1699-700.

174. Bodansky HJ, Staines A, Stephenson C, Haigh D, Cartwright R. Evidence for an environmental effect in the aetiology of insulin dependent diabetes in a transmigratory population. BMJ 1992;**304**(6833):1020-2.
175. Siemiatycki J, Colle E, Campbell S, Dewar R, Aubert D, Belmonte MM. Incidence of IDDM in Montreal by ethnic group and by social class and comparisons with ethnic groups living elsewhere. Diabetes 1988;**37**(8):1096-102.
176. Hjern A, Soderstrom U. Parental country of birth is a major determinant of childhood type 1 diabetes in Sweden. Pediatr Diabetes 2008;**9**(1):35-9.
177. Soderstrom U, Aman J, Hjern A. Being born in Sweden increases the risk for type 1 diabetes - a study of migration of children to Sweden as a natural experiment. Acta Paediatr 2012;**101**(1):73-7.
178. Muntoni S, Fonte MT, Stoduto S, Marietti G, Bizzarri C, Crino A, Ciampalini P, Multari G, Suppa MA, Matteoli MC, Lucentini L, Sebastiani LM, Visalli N, Pozzilli P, Boscherini B. Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy. Lancet 1997;**349**(9046):160-2.
179. Podar T, Laporte RE, Tuomilehto J, Shubnikov E. Risk of childhood type 1 diabetes for Russians in Estonia and Siberia. Int J Epidemiol 1993;**22**(2):262-7.
180. Zung A, Elizur M, Weintrob N, Bistritzer T, Hanukoglu A, Zadik Z, Phillip M, Miller K, Koren I, Brautbar C, Israel S. Type 1 diabetes in Jewish Ethiopian immigrants in Israel: HLA class II immunogenetics and contribution of new environment. Hum Immunol 2004;**65**(12):1463-8.
181. socialstyrelsen. Värdering av diagnoskvaliteten för akut hjärtinfarkt i patientregistret 1987 och 1995 In. Stockholm; 2000, 35.
182. Elo SL, Karlberg IH. Validity and utilization of epidemiological data: a study of ischaemic heart disease and coronary risk factors in a local population. Public Health 2009;**123**(1):52-7.
183. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart 2010;**96**(20):1617-21.
184. Marmot MG, Adelstein AM, Bulusu L. Lessons from the study of immigrant mortality. Lancet 1984;**1**(8392):1455-7.
185. Razum O, Zeeb H, Rohrmann S. The 'healthy migrant effect'--not merely a fallacy of inaccurate denominator figures. Int J Epidemiol 2000;**29**(1):191-2.
186. Razum O, Zeeb H, Akgun HS, Yilmaz S. Low overall mortality of Turkish residents in Germany persists and extends into a second generation: merely a healthy migrant effect? Tropical Medicine & International Health 1998;**3**(4):297-303.
187. Walsh J, Mahony R, Armstrong F, Ryan G, O'Herlihy C, Foley M. Ethnic variation between white European women in labour outcomes in a setting in which the management of labour is standardised-a healthy migrant effect? BJOG 2011;**118**(6):713-8.
188. Auger N, Luo ZC, Platt RW, Daniel M. Do mother's education and foreign born status interact to influence birth outcomes? Clarifying the epidemiological paradox and the healthy migrant effect. J Epidemiol Community Health 2008;**62**(5):402-9.
189. Rutqvist LE, Carstensen J, Mattsson B, Mardsjo G. Geographic variations of breast carcinoma incidence in Sweden. Are the differences real? Acta Radiol Oncol 1986;**25**(2):99-104.
190. Stattin P, Johansson R, Lodnert R, Andren O, Bill-Axelsson A, Bratt O, Damber JE, Hellstrom M, Hugosson J, Lundgren R, Tornblom M, Varenhorst E, Johansson JE. Geographical variation in incidence of prostate cancer in Sweden. Scand J Urol Nephrol 2005;**39**(5):372-9.
191. Arnqvist HJ, Littorin B, Nystrom L, Schersten B, Ostman J, Blohme G, Lithner F, Wibell L. Difficulties in classifying diabetes at presentation in the young adult. Diabet Med 1993;**10**(7):606-13.
192. Littorin B, Sundkvist G, Schersten B, Nystrom L, Arnqvist HJ, Blohme G, Lithner F, Wibell L, Ostman J. Patient administrative system as a tool to validate the ascertainment in the diabetes incidence study in Sweden (DISS). Diabetes Res Clin Pract 1996;**33**(2):129-33.

193. Lynch KF, Subramanian SV, Ohlsson H, Chaix B, Lernmark A, Merlo J. Context and disease when disease risk is low: the case of type 1 diabetes in Sweden. J Epidemiol Community Health 2010;**64**(9):789-95.