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Neighborhood Effects on Cardiovascular Health

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LUND UNIVERSITY

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Neighborhood Effects on Cardiovascular Health

Abstract

Background

Cardiovascular disease (CVD) is a class of diseases that includes coronary heart disease (CHD), ischemic stroke, heart failure (HF) and other heart and vascular diseases. CVD is associated with neighborhood-level socioeconomic status (SES), but several knowledge gaps exist.

The overall aims were to explore contextual effects of neighborhoods and workplaces on CVD. In Study I neighborhood SES and incidence of CHD or ischemic stroke was examined in order to investigate causality. In Study II statin medication rates for myocardial infarction (MI) was studied for patients with different neighborhood SES. In Study III the risk of incident HF for diabetic persons living in neighborhoods of different neighborhood-level SES was examined. In Study IV CHD incidence and the three contextual variables the mean educational level of all employees at each individual's workplace ($education_{work}$) and neighborhood SES for each individual's residence and workplace were investigated.

Methods

All studies were based on Swedish nationwide linked registry data. In Study I, neighborhood SES and incidence of CHD or ischemic stroke was studied in the total population and in full- and half-siblings. In Study II, all patients in Sweden diagnosed with incident MI from January 1st, 2000 until December 31st 2010, were followed (n = 116,840) and analyzed by multilevel logistic regression. In Study III 434,542 adults aged 30 years or older with diabetes mellitus (DM) were followed from 2005 to 2015 in Sweden for incident HF. In Study IV individuals born in Sweden 1943-1957 (n=991,072) were followed 2008-2012 for incident CHD using multilevel and cross-classified logistic regression models.

Results

In Study I, the association between neighborhood SES and CHD showed no decrease with increasing genetic resemblance, particularly in women. In Study II in the full model, the odds were not statistically significant. In Study III, there was an association between level of neighborhood SES and HF in DM patients. The hazard ratios (HRs) were 1.27, 95% CI 1.21-1.33, for men and 1.30, 95% CI 1.23-1.37, for women among DM patients living in high vs low deprivation neighborhoods. In Study IV, low compared to high $education_{work}$ was significantly associated with increased CHD incidence for both men (OR 1.29, 95% CI 1.23-1.34) and women (OR 1.38, 95% CI 1.29-1.47).

Conclusion

The findings indicate that the association between neighborhood SES and CHD incidence is partially causal among women. Patients with DM living in deprived neighborhoods may need extra monitoring for HF. Workplace socioeconomic characteristics, in particular the educational attainment of an individual's colleagues, may influence CHD risk. Taken together, these findings raise important clinical and public health concerns and indicate that solutions need to reframe health problems from a sole focus on individual approaches to a broader focus that includes neighborhoods and workplaces.

Key words Coronary heart disease, Heart failure, Neighborhood, Workplace, Education

Classification system and/or index terms (if any)

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MADE IN SWEDEN

To Anna, Samuel, Eleonora and Avielle

Table of Contents

Abstract

Background

Cardiovascular disease (CVD) is a class of diseases that includes coronary heart disease (CHD), ischemic stroke, heart failure (HF) and other heart and vascular diseases. CVD causes approximately 31% of world-wide deaths and is the leading cause of death in all areas of the world except Africa. CVD is associated with neighborhood-level socioeconomic status (SES), but several knowledge gaps exist.

Aims

The overall aims were to explore contextual effects of neighborhoods and workplaces on CVD. In Study I the association between neighborhood SES and incidence of CHD or ischemic stroke was examined in order to understand if there is an underlying causal relationship. In Study II the aim was to determine whether the statin medication rates for myocardial infarction (MI) patients differ across neighborhoods with different levels of neighborhood SES. In Study III the aim was to investigate whether there is a difference in the risk of incident HF between patients with diabetes mellitus (DM) living in neighborhoods of different neighborhood-level SES. In Study IV the aim was to examine the association between CHD incidence and the three contextual variables the mean educational level of all employees at each individual's workplace ($\text{education}_{\text{work}}$), the neighborhood socioeconomic characteristics of each individual's workplace (neighborhood SES_{work}) and the neighborhood socioeconomic characteristics of each individual's neighborhood of residence (neighborhood $\text{SES}_{\text{residence}}$).

Methods

All studies were based on Swedish nationwide linked registry data including the Swedish National Patient Register, the Swedish Multigeneration Register, the Total Population Register and the Swedish Prescribed Drug Register. In Study I, the association between neighborhood SES and incidence of CHD or ischemic stroke was studied in the total population and in full- and half-siblings to determine whether these associations are causal or a result from familial confounding. In Study II, all patients in Sweden diagnosed with incident MI from January 1st, 2000 until December 31st 2010, were followed (n = 116,840) and were analyzed by multilevel logistic regression. In Study III 434,542 adults aged 30 years or older with DM were followed from 2005 to 2015 in Sweden for incident HF. The association between neighborhood deprivation and the outcome was explored using Cox regression analysis. In Study IV individuals born in Sweden 1943-1957 (n=991,072) were followed. The outcome variable was incident CHD during follow-up 2008-2012. The association between $\text{education}_{\text{work}}$,

neighborhood SES_{work}, neighborhood $SES_{residence}$ and the outcome was explored using multilevel and cross-classified logistic regression models.

Results

In Study I, after adjustment for individual SES, the association between neighborhood SES and CHD showed no decrease with increasing genetic resemblance, particularly in women. In Study II, low neighborhood-level SES was significantly associated with low statin medication rate (Odds Ratio (OR) 0.80). In the full model, which included individual-level factors, the odds no longer remained significant. In Study III, there was an association between level of neighborhood SES and HF in DM patients. The hazard ratios (HRs) were 1.27, 95% CI 1.21-1.33, for men and 1.30, 95% CI 1.23-1.37, for women among DM patients living in low SES neighborhoods compared to those from high SES neighborhoods. After adjustments for potential confounders, the higher HRs became slightly lower. In Study IV, low compared to high $education_{work}$ was significantly associated with increased CHD incidence for both men (OR 1.29, 95% CI 1.23-1.34) and women (OR 1.38, 95% CI 1.29-1.47). After adjusting for potential confounders, the ORs became slightly lower.

Conclusion

The findings indicate that the association between neighborhood SES and CHD incidence is partially causal among women. Neighborhood-level SES was modestly associated with statin medication rates in MI patients but this association was no longer significant after adjusting for individual-level sociodemographic factors. These findings indicate that individual-level approaches may be most important in health care policies regarding statin medication in MI patients. The risk of incident HF was higher among patients with DM living in deprived neighbourhoods than among patients with DM living in affluent neighbourhoods. This shows that patients with DM living in deprived neighbourhoods may need extra monitoring for HF. Workplace socioeconomic characteristics, in particular the educational attainment of an individual’s colleagues, may influence CHD risk. These findings are new and need replication in other settings. Taken together, these findings raise important clinical and public health concerns and indicate that solutions need to reframe health problems from a sole focus on individual approaches to a broader focus that includes neighborhoods and workplaces and an investigation of the mechanisms behind these effects on cardiovascular diseases.

List of papers

This thesis is based on the following four papers referred to in the text by Roman numerals.

I. Forsberg PO, Ohlsson H, Sundquist K. Causal nature of neighborhood deprivation on individual risk of coronary heart disease or ischemic stroke: A prospective national Swedish co-relative control study in men and women. Health Place 2018;50:1-5.

II. Forsberg PO, Li X, Sundquist K. Neighborhood socioeconomic characteristics and statin medication in patients with myocardial infarction: a Swedish nationwide follow-up study. BMC Cardiovasc Disord 2016;16:146.

III. Li X, Sundquist J, Forsberg PO, Sundquist K. Association Between Neighborhood Deprivation and Heart Failure Among Patients With Diabetes Mellitus: A 10-Year Follow-Up Study in Sweden. J Card Fail 2019.

IV. Forsberg PO, Ohlsson H, Sundquist K. Workplace, Neighbourhood Characteristics and Association with Coronary Heart Disease: A Nationwide Follow-up Study. *Submitted for publication.*

Abbreviations

CHD: Coronary heart disease

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

CVD: Cardiovascular disease

DM: Diabetes mellitus

HF: Heart failure

HR: Hazard ratio

ICC: Intraclass correlation

ICD: International classification of diseases

LDL: Low-density lipoprotein

MI: Myocardial infarction

n: Sample size

OR: Odds ratio

SAMS: Small area market statistics

SD: Standard deviation

SE: Standard error

SES: Socioeconomic status

TIA: Transient ischemic attack

Introduction

’Hope deferred makes the heart sick, but a dream fulfilled is a tree of life.’

Proverbs 13:12, The Bible

Preamble

The overall purpose of this thesis project is to analyze neighborhood and workplace socioeconomic characteristics and their effect on cardiovascular disease (CVD). It is well known that low individual socioeconomic status (SES) is strongly associated with CVD (Salomaa et al., 2000, Kunst et al., 1999). In addition to individual-level SES, the socioeconomic characteristics of an individual’s neighborhood of residence is associated with coronary heart disease (CHD), after taking individual-level SES into account (Chaix, 2009, Winkleby et al., 2007b). These previous findings indicate that contextual factors may have their own independent effect in the development of CVD mortality and morbidity.

However, several knowledge gaps exist, of which some are addressed in this thesis. Firstly, causality in the associations between neighborhood socioeconomic factors and CVD has been difficult to prove. Establishing causality is often a challenge in observational studies, including those examining neighborhood effects (Oakes, 2004). This is because it is nearly impossible to perform randomized controlled trials where large numbers of individuals are randomly assigned and adhere to move to different types of neighborhoods (Diez Roux, 2004).

Secondly, medication patterns might be affected by neighborhood socioeconomic characteristics. For example, neighborhood-level deprivation affects prescription patterns of statins in patients with atrial fibrillation, after adjusting for individual-level factors (Carlsson et al., 2015). However, this has not been studied for e.g., myocardial infarction (MI) patients.

Thirdly, previous studies have shown that the prevalence of type 2 diabetes mellitus (DM) is higher in highly deprived than in less deprived or affluent neighborhoods (Andersen et al., 2008, Ismail et al., 1999, Beeching and Gill, 2000, Krishnan et al., 2010). Furthermore, it is known that SES is associated with

HF. However, the association between neighborhood deprivation and HF in patients with DM remains to be established.

Lastly, although several studies already have been conducted on the association between neighborhood socioeconomic characteristics and CHD, important gaps in previous research exist. These gaps include a lack of studies of the association between socioeconomic characteristics of the workplace and CHD. Because people spend a large part of their awake time at work, such studies are needed in order to obtain a fuller representation of the entire contextual influences on people's CHD risk (Chaix, 2009, Fishta and Backé, 2015).

Cardiovascular Disease

Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels. CVD includes Coronary Heart Disease (CHD), ischemic stroke, heart failure and other heart and vascular diseases (Mendis et al., 2011). CVD causes approximately 31% of world-wide deaths and is the leading cause of death in all areas of the world except Africa (Mendis et al., 2011).

The underlying mechanisms vary depending on the disease (Mendis et al., 2011). CHD and stroke involve atherosclerosis, which is caused by several factors e.g., hypertension, smoking, diabetes mellitus, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol consumption (Mendis et al., 2011). Hypertension is estimated to account for approximately 13% of CVD deaths, while smoking accounts for 9%, diabetes mellitus 6%, lack of exercise 6% and obesity 5% (Mendis et al., 2011).

Up to 90% of CVD incidence may be preventable (McGill et al., 2008, O'Donnell et al., 2016). Prevention of CVD involves improving risk factors by e.g., healthy eating, exercise, avoidance of tobacco smoke and limiting alcohol intake (Mendis et al., 2011). Prevention also involves treating risk factors such as hypertension, elevated blood lipids and diabetes mellitus (Mendis et al., 2011).

Age-specific CVD mortality has been increasing in poorer countries, while it has been decreasing in most of the developed world since the 1970s (Moran et al., 2014). CHD and stroke account for 80% of CVD deaths in males and 75% of CVD deaths in females (Mendis et al., 2011). The average age of death from CHD in the developed world is around 80 while it is around 68 in the developing world. Diagnosis of disease typically occurs seven to ten years earlier in men as compared to women (Mendis et al., 2011).

Coronary Heart Disease

Coronary heart disease (CHD), also known as coronary artery disease or ischemic heart disease, involves the reduction of blood flow to the heart muscle due to build-up of plaque in the arteries of the heart (Mendis et al., 2011). CHD includes stable angina, unstable angina, myocardial infarction (MI), and sudden cardiac death (Wong, 2014). CHD is the main global cause of death with approximately 9 million deaths annually (Collaborators, 2018). CHD is also a major cause of morbidity world-wide that confers substantial costs to the society (Benjamin et al., 2017, F Piepoli, 2017).

A large proportion of CHD incidence can be explained by individual-level factors, such as sociodemographic characteristics (age, sex, socioeconomic status (SES)) (Carlsson et al., 2014); health behaviors (smoking, physical inactivity, poor diet) (Huxley and Woodward, 2011, Varghese et al., 2016); and metabolic risk factors (hypertension, diabetes, hypercholesterolemia) (Lynch et al., 1996).

Today, CHD prevention includes both primary and secondary prevention with lifestyle changes as well as medical treatment of risk factors, primarily hypertension, diabetes mellitus, and hypercholesterolemia. HMG CoA-reductase inhibitors, or statins, are a class of cholesterol lowering drugs that are widely used in this context, in particular for secondary prevention of MI (Taylor et al., 2013). Statins reduce both mortality and morbidity for CHD patients (Pedersen et al., 2004).

Ischemic Stroke

Stroke is a condition in which poor blood flow to the brain or bleeding results in cell death (Donnan et al., 2008). There are two main types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding (Donnan et al., 2008). Stroke is the second most common cause of death globally with 6 million deaths annually, approximately split equally between ischemic and hemorrhagic stroke (Collaborators, 2018, Donnan et al., 2008).

The main risk factor for stroke is hypertension (Donnan et al., 2008). Other risk factors include tobacco smoking, obesity, high blood cholesterol, diabetes mellitus, a previous transient ischemic attack (TIA), end-stage kidney disease, and atrial fibrillation (Donnan et al., 2008).

Heart Failure

Heart failure (HF), also known as congestive heart failure, is a condition where the heart may be unable to pump sufficiently to maintain blood flow to meet the body's needs (McMurray and Pfeffer, 2005). Between 1% and 2% of the adult population in western countries have symptomatic heart failure. Heart failure arises as a consequence of an abnormality in cardiac structure, function, rhythm, or conduction. Ventricular dysfunction results mainly from myocardial infarction (systolic dysfunction), hypertension (diastolic and systolic dysfunction), or in many cases both (McMurray and Pfeffer, 2005).

In recent years, the awareness in the scientific community has steadily increased concerning the two-way association between diabetes mellitus (DM) and heart failure (HF) and has also gained more research interest (Kannel et al., 1974, Rawshani et al., 2018). DM is an independent risk factor for HF, with a 5-fold increased risk of HF in women with DM and a 2.4-fold increased risk in men (Kannel et al., 1974). In a recent Swedish population-based study, the hazard ratio for HF was 1.45 in patients with DM compared to controls (Rawshani et al., 2018).

In general, the incidence of HF varies by individual socioeconomic status (SES); higher income has previously been associated with a lower risk of developing HF (Akwo et al., 2018, Cuthbertson et al., 2018). Additionally, risk factors for HF, e.g., hypertension and CHD, also vary with SES (Carlsson et al., 2016). In addition to individual-level socioeconomic factors, there are also neighborhood-level socioeconomic factors that could increase the risk of DM. Previous studies have shown that type 2 DM prevalence is higher in highly deprived than in less deprived or affluent neighborhoods (Andersen et al., 2008, Ismail et al., 1999, Beeching and Gill, 2000, Krishnan et al., 2010). Also, it is known that SES is associated with HF. However, the association between neighborhood deprivation and HF in patients with DM remains to be established. If established, such an association would help identify DM patients at an increased risk of HF and who may need additional monitoring.

Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a high blood sugar level over longer periods of time. There are many different types of DM. Type 1 DM results from the pancreas' inability to produce sufficient insulin due to loss of beta cells. Type 2 DM starts with insulin resistance and as the disease progresses, insulin deficiency often also develops. The most common cause of type 2 DM is a combination of excessive body weight and insufficient exercise (Tripathy, 2012). Also, genetic factors may play a role (Prasad and Groop, 2015). Hyperglycemia and DM are important causes of mortality and morbidity worldwide, through both direct clinical sequelae and increased mortality from cardiovascular and kidney diseases (Danaei et al., 2011).

Individual-level Socioeconomic Status

Socioeconomic status (SES) has a measurable and significant effect on cardiovascular health (Hawkins et al., 2012, Schultz et al., 2018). Three individual-level SES measures have been consistently associated with CVD in high-income countries: income level, educational attainment, and employment status (Schultz et al., 2018). The increased burden of CVD in people with low SES may be attributable to a constellation of biological, behavioral, and psychosocial risk factors that are more prevalent in disadvantaged individuals (Lynch et al., 1996). Interventions targeting patients with low SES have mainly focused on modification of traditional CVD risk factors. However, new promising approaches are emerging that can be implemented on an individual, community, or population level to reduce disparities in outcomes (Schultz et al., 2018). Integration of SES into the traditional CVD risk prediction models may allow for improved management of individuals with high risk, but cultural and regional differences in SES make generalized implementation challenging (Schultz et al., 2018).

Neighborhood-level Socioeconomic Status

In addition to individual-level SES, findings from several studies have established that the socioeconomic characteristics of an individual's neighborhood of residence is also associated with CHD, after taking individual-level SES into account (Chaix, 2009, Winkleby et al., 2007b). These previous findings indicate that contextual factors may have their own independent effect in the development of CHD mortality and morbidity.

The environmental impact of health status and outcomes is driven by both physical and social attributes (Diez Roux, 2003). Examples of physical features of neighborhoods include the presence of sidewalks or recreational spaces, access to transportation, and availability and cost of healthy foods, whereas social attributes include safety, deprivation, social support, and lack of community cohesion (Diez Roux, 2003). More favorable neighborhoods may be associated with reduced cardiovascular risk factors, because long-term exposure to environments with greater access to physical activity and healthy food was associated with a lower incidence of diabetes mellitus and a lower prevalence of overweight or obesity (Christine et al., 2015). Other social characteristics, including neighborhood crime, also contribute to cardiovascular risk. In multiethnic populations, high individual- and neighborhood-level safety was associated with decreasing body mass index over time (Powell-Wiley et al., 2017).

Workplace

Although several studies already have been conducted on the association between neighborhood-level SES and CHD, important gaps in previous research exist. Examples of these gaps include a lack of studies of the association between socioeconomic characteristics of the workplace and CHD. Because individuals spend a large part of their awake time at work, such studies are needed in order to get a fuller representation of the entire contextual influences on people's CHD risk (Chaix, 2009, Fishta and Backé, 2015).

Previous studies of the role of the workplace for CVD have focused on psychosocial stress at work (Backé et al., 2012, Winkleby et al., 2007b), job strain, effort-reward imbalance and long working hours (Kivimäki and Steptoe, 2018, Kivimäki et al., 2012). This thesis will examine contextual effects of people's workplace on CHD.

Statin Medication

High cholesterol levels have been associated with cardiovascular disease (Lewington et al., 2007). HMG-CoA reductase plays a central role in the production of cholesterol. Low-density lipoprotein (LDL) carriers of cholesterol play an important role in the development of both atherosclerosis and CHD. HMG CoA-reductase inhibitors, or statins, are a class of cholesterol lowering drugs. Statins are effective in lowering LDL cholesterol and are therefore widely used for primary prevention in people at high risk of cardiovascular disease, as well as in secondary prevention for those who already have developed CVD, e.g., myocardial infarction (Taylor et al., 2013). Statins reduce both mortality and morbidity for CHD patients (Pedersen et al., 2004). It is possible that statin treatment is not equally distributed to CHD patients, which is examined in Study II.

Aims

Study I

The aim of Study I was to examine the association between neighborhood SES and incidence of CHD or ischemic stroke in the total population and in full- and half-siblings in order to determine whether these potential associations are causal or result from familial confounding factors. These associations were examined in men and women and in different age groups separately.

Study II

The aim of Study II was to determine whether the statin medication rates for MI patients differ across neighborhoods with different levels of neighborhood SES, after taking individual factors into account.

Study III

The first aim of Study III was to investigate whether there is a difference in the risk of incident HF between patients with DM living in deprived neighborhoods and patients with DM living in less deprived/affluent neighborhoods. The second aim was to investigate whether this possible difference remains after accounting for individual-level sociodemographic characteristics (age, marital status, family income, education, employment status, immigration status, region of residence, mobility and co-morbidities).

Study IV

The aim of Study IV was to examine the association between CHD incidence and the three contextual variables the mean educational level of all employees at each individual's workplace ($\text{education}_{\text{work}}$), the neighborhood socioeconomic characteristics of each individual's workplace (neighborhood SES_{work}) and the neighborhood socioeconomic characteristics of each individual's neighborhood of residence (neighborhood $\text{SES}_{\text{residence}}$) in men and women, adjusted for individual-level sociodemographic characteristics.

Ethical considerations

All studies were approved by the Regional Ethical Review Board in Lund, Sweden, and were conducted in accordance with the 1975 Declaration of Helsinki (Ludvigsson et al., 2015).

Material and Methods

The four studies included in this thesis were all register-based studies. An overview of the four studies and their study design is presented in Table 1.

Table 1: Overview of the four studies included in this thesis

	Study I	Study II	Study III	Study IV
Outcome	CHD or stroke	Statin medication	Heart failure	CHD
Participants	3644309	116840	434542	991072
Study design	Follow-up	Follow-up	Follow-up	Follow-up
Data source	Nationwide registers	Nationwide registers	Nationwide registers	Nationwide registers
Measure of risk	Hazard ratio	Odds ratio	Hazard ratio	Odds ratio
Statistical method	Cox regression	Multilevel logistic regression	Cox regression	Multilevel logistic regression
Study period	1990-2013	2000-2010	2005-2015	2008-2012
Age	40-81	30-79	30+	50-64

CHD: Coronary heart disease

Nation-wide registers

The four studies in this thesis used data derived from Swedish nationwide registers provided by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden (Statistiska Centralbyrån). Data were linked using Swedish personal identification number system, a ten-digit unique number assigned to all individuals at birth in Sweden or permanent immigration to Sweden since its introduction in 1947 (Ludvigsson et al., 2011). The identification numbers were pseudonymized in the merged datasets used in the studies.

The Swedish National Patient Register

The Swedish National Patient Register includes data on in- and outpatients in public hospitals. However, primary care is not included. The Inpatient Register, or Hospital Discharge Register, contains inpatient diagnoses from 1964 and has full coverage from 1987. The Outpatient Register contains diagnoses on all hospital-based outpatients in Sweden from 2001. The ninth revision of International Classification of Diseases (ICD-9) was used from 1987-1996. After 1996 the 10th revision is used (ICD-10) (Ludvigsson et al., 2011). The diagnoses in this register have a positive predictive value between 85-95%, and the diagnostic validity of many diseases are even higher; e.g., myocardial infarction (MI) and stroke have a positive predictive value of >95% (Ingelsson et al., 2005, Ludvigsson et al., 2011, Nilsson et al., 1994)

The Swedish Multigeneration Register

The Swedish Multi-generation Register includes data on family relationships, specifically data on biological parents, siblings and adoptions (Statistiska Centralbyrån Flergenerationsregistret). All Swedish residents born after 1932 and registered in Sweden at any time after 1961 are recorded as index persons.

The Total Population Register

The Total Population Register contains data on name, place of residence, sex, age, civil status, place of birth, death, citizenship, immigration (date, country, grounds for settlement), emigration, migration within Sweden, family relations and marital status (Ludvigsson et al., 2016, Statistiska Centralbyrån Registret över totalbefolkningen).

The LISA register

The longitudinal integration database for health insurance and labor market studies (the LISA register) contains, since 1990, information on educational status, family income and the Swedish Standard Classification of Occupations since 1996 (Statistiska Centralbyrån, 2020-05-27).

The Swedish Prescribed Drug Register

This register includes all medical prescriptions that were retrieved at any pharmacy in Sweden from July 1, 2005 (Socialstyrelsen).

Contextual factors

Neighborhood-level socioeconomic status

Neighborhood-level socioeconomic status (neighborhood SES or neighborhood deprivation), was used as a contextual variable in all four studies. The home addresses of all Swedish individuals have been geocoded to small geographical units that have boundaries defined by homogeneous types of buildings. These neighborhood areas, developed by Statistics Sweden, are called small areas for market statistics (SAMS) and have an average of 1000 people each. SAMS can be used as proxies for residential neighborhoods, as in previous research (Cubbin et al., 2006, Sundquist et al., 2006a). A summary index was calculated to characterize neighborhood-level SES (Winkleby et al., 2007b). The neighborhood index was based on information on men and women aged 20–64, who lived in the neighborhood, because people in this age group are the most socioeconomically active. In other words, as a population group they have a stronger impact on the socioeconomic structure of the neighborhood than children, younger men/women and retirees. Deprivation indicators used by past studies were identified to characterize neighborhood environments and then a principal components analysis was applied to select deprivation indicators in the Swedish national database (Winkleby et al., 2007a). The neighborhood index was based on four items: low education level (<10 years of formal education), low income (income from all sources, including that from interest and dividends, defined as less than 50% of the median individual income), unemployment (excluding full-time students, those completing compulsory military service, and early retirees) and receipt of social welfare. A z score was calculated for each SAMS neighborhood. The z scores, weighted by the coefficients for the eigenvectors, were then summed to create the index (Gilthorpe, 1995). Neighborhood SES was approximately normally distributed with a mean value of 0 and a standard deviation (SD) of 1.

Study I

Outcome variable

The outcome variables were incidence of CHD and ischemic stroke during follow-up (until 2013). Incidence was defined as the first registered diagnosis of CHD or ischemic stroke during the study period.

Contextual variable

Neighborhood-level socioeconomic status

Neighborhood SES was used as a continuous variable in the models with the score ranging between -3.2 and 12 with higher values indicating higher levels of neighborhood deprivation. SES was measured at inclusion in the study.

Individual-level variables

Marital status

Individuals were classified as married/cohabitating or widowed/divorced/never married.

Family income

Individualized disposable family income was defined as combined family income minus current taxes divided by the number of people in the family. In order to be able to use the income variable to categorize SES over time, the variable (mean 0 and SD 1) was standardized by sex and year.

Educational attainment

The education variable was primarily based on the number of years of education: less than 9 years; 9 years; 10-11 years; 12 years; 13-15 years; 16 years or more; and having a PhD/ licentiate degree. The education variable was also standardized (mean 0 and SD 1) by sex and year.

Study population

The dataset included all men and women born in Sweden between 1932 and 1966. Time for inclusion in the study of the men and women was between 1990 and

2006. For the variables neighborhood SES, educational attainment, family income and marital status yearly information during the entire inclusion period was available, i.e., 1990 to 2006 for all individuals residing in Sweden. These variables were assessed at time for inclusion in the study in the three different groups, i.e., those who became 40 years (N_{40y}=1,702,541), 50 years (N_{50y}=1,741,835) or 60 years (N_{60y}=1,276,705) somewhere during the inclusion period. The relatively lower number of individuals aged 60 years was because one of the inclusion criteria in this study was to have a registered sibling in the Multi-Generation Register (i.e., brother for the men in the study population or sister for the women in the study population). "Wash-out" was performed in order to secure that all cases were incident cases. For this purpose, all patients with a CHD diagnosis between 1987 and study start were excluded for the CHD analyses and all patients with an ischemic stroke diagnosis between 1987 and study start for the ischemic stroke analyses. The total number of individuals with a CHD registration prior to study start were 97,827 in the three age groups (N_{40y}=3,618, N_{50y}=25,514 and N_{60y}=68,695). Individuals with less than five years of residence in their neighborhood at inclusion were also excluded (N_{40y}=434,337, N_{50y}=320,012 and N_{60y}=175,733). Exclusion of individuals with less than five years of residence was done because these individuals would have had a limited exposure to their current neighborhoods, and, because CHD or stroke most likely develops after longer time exposures. Additionally, all individuals who had lived abroad at some time point (N_{40y}=23,089, N_{50y}=19,366 and N_{60y}=6,408) during the study period were excluded. The follow-up started at time of inclusion and ended at the time of a possible event, death, emigration or at the end of 2013, whichever came first.

Statistical Methods

Cox proportional hazards models were used to assess the risk of CHD as a function of neighborhood SES. In the first model, hazard ratios (HRs) were estimated to assess the risk of CHD from age at inclusion (40, 50 or 60 years) until end of follow-up, death, possible event, or emigration, as a function of neighborhood SES at age at inclusion while controlling for family income, educational attainment, and marital status at inclusion. Then, the models for ischemic stroke were replicated. All models were stratified by sex. In all models, the proportionality assumption was checked. If not fulfilled, two additional analyses were conducted; in the first, a time-dependent variable was added and, in the second, the follow-up period was divided in three time intervals and modeled separately for each time interval.

Next, the degree to which the association between neighborhood SES and the cardiovascular outcomes is a result from confounding by familial risk factors (genetic and/or shared environmental) was assessed using a co-relative design for the full- and half-sibling pairs. A stratified Cox regression model was used, in which all analyses were refitted within strata of the defined relative sets (full-sibling pairs and half-sibling pairs). Only pairs in which the members differed in their exposure to neighborhood SES would contribute to the regression estimates.

Within each stratum, the hazard ratio (HR) is adjusted for the familial cluster, and, therefore, accounts for an array of unmeasured genetic and environmental factors shared within the relative set. All statistical analyses were performed using SAS 9.4.

Study II

Outcome variable

The outcome variable was medication of statins as defined according to the ATC code C10AA for the Medication Register.

The statins (HMG CoA reductase inhibitors, code C10AA) included were:

C10AA01 Simvastatin

C10AA02 Lovastatin

C10AA03 Pravastatin

C10AA04 Fluvastatin

C10AA05 Atorvastatin

C10AA06 Cerivastatin

C10AA07 Rosuvastatin

C10AA08 Pitavastatin

Contextual variable

Neighborhood-level socioeconomic status

The neighborhood SES index was categorized into the three groups: low neighborhood SES (more than 1 SD below the mean), middle neighborhood SES (within 1 SD of the mean), and high neighborhood SES (more than 1 SD above the mean)(Winkleby et al., 2007b). The neighborhood SES index in the year 2000 was used in the models.

Individual-level variables

The individual-level variables were sex, age at the start of the study, marital status, family income, education level, country of origin, urban/rural status, and chronic conditions related to MI (comorbidities) (Zöller et al., 2012, Zöller et al., 2013, Li et al., 2014).

Sex

Male or female.

Age

Age was assessed at start of follow-up. Age was used as a continuous variable in the models.

Marital status

Individuals were classified as married/cohabitating or widowed/divorced/never married.

Family income

Family income by quartile: Information on family income in 2001 came from the Total Population Register, provided by Statistics Sweden. Income was categorized into quartiles: low income, middle-low income, middle-high income, and high income. The income was divided by the number of people in the family. A weighted system was also used; small children were given lower weights than adolescents since the costs of living for a small child are lower than those for an adolescent.

Education level

Education level was classified as completion of compulsory school or less (≤ 9 years), vocational high school or some theoretical high school (10–12 years), and completed theoretical high school and/or college (>12 years).

Country of origin

Born in: 1) Sweden (reference), 2) Finland, 3) Western countries, 4) Eastern European countries, 5) Middle Eastern countries, or 6) other countries.

Urban/rural status

Residence in major cities (Stockholm, Gothenburg or Malmö), southern or northern Sweden.

Chronic conditions related to MI

Chronic conditions related to MI--comorbidities were defined as the first diagnosis (main or additional diagnosis) ten years before the study and during the follow-up period of: 1) chronic lower respiratory diseases (ICD-9: 490-496; ICD-10: J40-J49), 2) alcoholism and alcohol-related liver disease (ICD-9: 291, 303, and 571; ICD-10: F10 and K70), 3) hypertension (ICD-9: 401-405; ICD-10: I10-I19), and 4) diabetes mellitus (ICD-9: 250; ICD-10: E10-E14).

Study population

Inclusion criteria was MI registered as the main diagnosis in the Hospital Discharge Register or Outpatient Register within the study interval (2000 to 2010) using ICD-10 codes I21, I22, and I23. Only patients who previously had no CHD were included. This was achieved by excluding patients with a recorded main or secondary diagnosis of CHD (ICD-10 I20-I25) during a 3-year period, i.e., from 1997 to 1999, before study start. Patients, who died between 1 January 2000 and 30 June 2005, were excluded as medication data was not available for this time period. Also, all patients who died within one month of MI diagnosis were excluded, as it was assumed that some of them might not have had a chance to pick up the medication. Patients above 80 years of age were excluded as the proportion of patients aged 80+ with statin medication was low.

Statistical Methods

Multilevel (hierarchical) logistic regression models were used to estimate odds ratios (OR) for statin medication rates for different levels of neighborhood SES. The analyses were performed using MLwiN version 2.27. The first model only included neighborhood-level SES to determine the crude odds of statin medication by level of neighborhood SES (Model 1). The second model also included the individual-level characteristics age and sex (Model 2). The third model added family income, marital status, country of origin, educational attainment and urban/rural status (Model 3). Last, a full model was created which also included hospitalization due to chronic lower respiratory disease, alcoholism and related liver disease, type 2 diabetes mellitus or hypertension (Model 4, not shown in tables).

Random effects: The between-neighborhood variance was estimated with a random intercept. It was regarded to be significant if it was more than 1.96 times the size of the standard error, in accordance with the precedent set in previous studies (Sundquist et al., 2006c, Johnell et al., 2006a, Johnell et al., 2006b).

The intraclass correlation (ICC)—that is, the intra-neighborhood correlation—was computed in order to estimate to what extent the individual chance of statin medication for individuals, within the same SAMS, was similar compared with individuals in other SAMS areas. The ICC expresses the proportion of the total variance that is at the neighborhood level. The ICC in multilevel logistic regression can be estimated by different procedures. The latent variable method was applied (Snijders et al., 1999) as exemplified by:

$$ICC = \frac{V_n}{V_n + \pi^2/3}$$

where V_n is the variance between neighborhoods and $\pi^2/3$ is the variance between individuals.

The proportion of the second level variance explained by the different variables was calculated as:

$$V_{EXPLAINED} = \frac{V_0 - V_1}{V_0} \times 100,$$

where V_o is the age adjusted variance in the initial model and V1 is the second level variance in the different models.

First order interactions between neighborhood deprivation and individual-level characteristics for statin medication in MI patients were also analyzed.

For comparison, we also calculated logistic regression models using the SAS statistical package (version 9.3; SAS Institute, Cary, NC, USA).

Study III

Outcome variable

The Swedish Hospital Discharge/In-Patient register was used to identify the outcome variable of HF, ICD-10 I50, incident HF. Incident HF was defined as the first hospitalization for HF during the study period, after excluding individuals with preexisting disease.

Contextual variable

Neighborhood deprivation

The neighborhood deprivation index was categorized into three groups: below one standard deviation (SD) from the mean (low deprivation), above one SD from the mean (high deprivation), and within one SD of the mean (moderate deprivation). Higher scores reflect more deprived neighborhoods. Using this categorization, 1383 neighborhoods were categorized as low deprivation (13.3% of the study population), 4791 as moderate (67.4% of the study population), and 1093 as high deprivation neighborhoods (19.3% of the study population) (Study III Supplementary Table 1).

Individual-level variables

All individual-level variables were assessed on 12/31/2005. Separate analyses were conducted for women and men.

Age

Age was used as a continuous variable from age ≥ 30 years.

Marital status

Marital status was divided into two groups: (1) married/cohabitating, and (2) never married, widowed, or divorced.

Educational attainment

Educational attainment was divided into three groups based on: completion of compulsory school or less (< 9 years), practical high school or some theoretical high school (10-12 years), or theoretical high school and/or college (>12 years).

Immigration status

Immigration status was divided into two groups: (1) born in Sweden and (2) born outside Sweden. Mobility (moved) was based on the length of time lived in the neighborhood, categorized as < 5 years or ≥ 5 years.

Region of residence

Region of residence was divided into three groups: large cities (Stockholm, Gothenburg, and Malmö), middle-sized towns, and small towns/rural areas.

Employment status

Employment status was divided into two groups: employed or unemployed.

Comorbidities

Comorbidities were identified from the Swedish inpatient and outpatient registers as follows: hypertension (I10–I15); CHD (I20–I25); obesity (E65–E68); chronic obstructive pulmonary disease (COPD) (J40–J47); alcoholism and related liver disorders (F10 and K70); depression (F32); and stroke (I60-I69).

Family income

Family income was based on the annual family income divided by the number of people in the family, i.e. individual family income per capita. This variable was provided by Statistics Sweden (the Swedish Government-owned statistics bureau). The income parameter also took into consideration the ages of people in the family and used a weighted system whereby small children were given lower weights than adolescents and adults. The calculation procedure was performed as follows: The sum of all family members' incomes was multiplied by the individual's consumption weight divided by the family members' total consumption weight.

Study population

The nationwide prescription register was used to identify all individuals aged 30 years and older with medically treated DM. All individuals that were prescribed insulin or oral antidiabetic agents or picked up a prescription for insulin or oral antidiabetic agents during the entire time period between July 1, 2005 and December 31, 2015 were included in the study population. The ATC-codes A10 were used to identify the patients from the prescription register. In addition, we used the main diagnoses for DM recorded in the In-Patient Register. In the present study, the first-time hospital admission for DM was defined as an incident event according to ICD-10 E10-E14 during the study period. In total, 466,322 unique DM patients were identified during the study period and 11875 (2.6%) individuals who had previously been diagnosed with HF (1997-2004) and 9125 individuals (2.0%) who were diagnosed with HF before the first diagnosis of DM during the study period were excluded. To remove possible coding errors, 10790 (2.3%) individuals who had a reported emigration date before the HF diagnosis were also excluded. A total of 434,542 DM patients (93.2% of the original cohort) remained suitable for inclusion in the study.

Statistical Methods

Person-years were calculated from the start of follow-up until first hospitalization for HF, death, emigration or the end of the study on December 31, 2015. The associations between the individual variables and HF were analyzed with Cox regression models. Cox proportional hazard models are used to study the association between certain variables and the time it takes for a specified event to happen, in this case the first/incident event of HF. The stratified Cox proportional hazards model provides a Hazard ratio (HR) for HF that is adjusted for the individual variables. First, a univariate Cox regression was performed for each variable. Next, a multivariate Cox regression model including all variables was calculated. Interaction tests were performed in order to examine whether the association between neighborhood deprivation and HF among DM patients was affected by any of the individual variables. All statistical analyses were performed using SAS 9.3.

Study IV

Outcome variable

The outcome variable was CHD during follow-up 2008-2012. The CHD diagnoses were defined using International Classification of Diseases (ICD) codes ICD-9: 410-414 or ICD-10: I20-25.

Contextual variable

Educational attainment of colleagues

For each workplace, the mean of the educational attainment of all employees was determined ($education_{work}$). $Education_{work}$ was categorized into three groups: <12 years (low education), 12-14 years (middle education) and >14 years (high education) of education.

Neighborhood SES

The index was categorized into three groups: below one standard deviation (SD) from the mean (high SES), above one SD from the mean (low SES), and within one SD of the mean (middle SES). Each individual in the study had two neighborhood SES values: neighborhood SES of their residence (neighborhood $SES_{residence}$) and neighborhood SES of their workplace (neighborhood SES_{work}).

There was a total of 9,092 SAMS and 95,991 workplaces in this study. The average number of employees per workplace was 192 (25th, 50th and 75th percentiles = 18, 58 and 184, respectively).

Individual-level variables

Individual-level information included age (continuous); annual household income (size-weighted, standardized); marital status (married/cohabiting vs. widowed/divorced/single) and educational attainment ($education_{individual}$, seven levels, used as a continuous variable).

Study population

The main registers included the Hospital Discharge Register containing in-patient data from 1987-2015 and the Outpatient Register containing outpatient data from 2001-2015.

All individuals in Sweden born between 1943-1957 (n=1,547,818) were included. Then, individuals with a CHD diagnosis prior to 2008 (n=67,619), individuals without workplace information (n=481,642) as well as individuals lacking residential address (n=409) or who had unknown parents (n=7,076) were excluded. Finally, 991,072 individuals were included in the study (492,107 men and 498,695 women).

Information from all individuals were assessed at baseline (December 31 2007). Each individual was classified into one neighborhood of residence and one workplace. Neighborhoods were defined from Statistics Sweden's Small Areas for Market Statistics (SAMS). Workplace was defined based on coordinates of the workplace address within a 250 x 250 m grid. It was not possible to separate different workplaces in the same grid from each other.

Statistical Methods

Multilevel and cross-classified logistic regression models with individuals nested within two classifications were used: neighborhoods and workplaces. This model enabled for the investigation of the similarity of CHD within different classifications. If the classifications are relevant for the individual variation in CHD, one would expect a considerable part of the variance to be at the neighborhood and/or workplace level; that is, there would be a clustering of CHD within neighborhoods and/or workplaces.

First, for each of the three contextual variables ($education_{work}$, neighborhood SES_{work} and neighborhood $SES_{residence}$), a model (Model 1) with only one of these contextual variables was created. In the next model (Model 2), individual-level factors were controlled for. In the final model (Model 3), the other two contextual factors were also controlled for in men and women separately.

The variance components attributed to the two different classifications (neighborhood of residence and workplace) are presented as well as the sum of the two variance components. The intraclass correlation for the higher-level ($ICC_{higher-level}$) is also presented. The ICC is interpreted as the proportion of the total variation in CHD incidence that is explained by differences between neighborhoods or workplaces. In order to calculate the ICC the latent variable method was used (Snijders et al., 1999):

$$ICC_{higher\ level} = \frac{V_{residence} + V_{workplace}}{V_{residence} + V_{workplace} + \frac{\pi^2}{3}}$$

where $V_{residence}$ is the variance attributed to the neighborhood of residence and $V_{workplace}$ is the variance attributed to the workplace. The share of higher-level variance that is attributed to each of the two different classifications was also computed. The analyses were performed using MLwiN version 3.02 (Charlton et al., 2017) and SAS version 9.4 (Inc, 2013).

Results

Study I

Table 2 shows the total study population for CHD, the number of CHD cases, the proportion of CHD cases in the total population as well as the median age at CHD diagnosis for the three age groups 40, 50 and 60 years and for men and women separately. In the men, 23,479, 66,978 and 72,257 individuals were diagnosed with CHD during follow-up, yielding a proportion of CHD cases of 3.76%, 9.58% and 14.45% for the three age groups 40, 50 and 60 years, respectively. In the women, 10,383, 30,332 and 42,607 individuals were diagnosed with CHD yielding a corresponding proportion of CHD cases of 1.68%, 4.48% and 8.10% for the three age groups 40, 50 and 60 years, respectively. The sizes of the study populations in tables 1 and 2 differ due to different exclusion criteria.

Table 3 shows the total study population for ischemic stroke, the number of ischemic stroke cases, the proportion of ischemic stroke cases in the total population as well as the median age at ischemic stroke diagnosis for the three age groups 40, 50 and 60 years and for men and women separately. In men, 10,954, 35,510, and 48,489 individuals were diagnosed with ischemic stroke during the follow-up, yielding a proportion of stroke cases of 1.75%, 5.01% and 9.18% for the three age groups 40, 50 and 60 years, respectively. In women, 7,470, 22,404 and 34,752 individuals were diagnosed with ischemic stroke during the follow-up, yielding a proportion of stroke cases of 1.21%, 3.30% and 6.52% for the three age groups 40, 50 and 60 years, respectively.

Table 2. Distribution of study population for coronary heart disease (CHD) for the different age groups

Sex	**Men**			**Women**		
Age group	40	50	60	40	50	60
Marital status						
married/cohabitating	0.537	0.653	0.7	0.615	0.689	0.678
widowed/divorced/never married	0.463	0.347	0.3	0.385	0.311	0.322
n Total	624010	699161	499975	617487	677782	525894
n CHD	23479	66978	72257	10383	30332	42607
% of total	3.76	9.58	14.45	1.68	4.48	8.1
Age at CHD (median)	52	60	66	52	60	66

Table 3. Distribution of study population for ischemic stroke for the different age groups

Sex	**Men**			**Women**		
Age group	40	50	60	40	50	60
Marital status						
married/cohabitating	0.537	0.652	0.7	0.615	0.689	0.678
widowed/divorced/never married	0.463	0.348	0.3	0.385	0.311	0.322
n Total	624642	709138	528284	617172	679632	533364
n Stroke	10954	35510	48489	7470	22404	34752
% of total	1.75	5.01	9.18	1.21	3.3	6.52
Age at CHD (median)	52	61	68	52	61	68

Figures 1 and 2 show the results of the co-relative design that examines the causal nature of neighborhood effects on individual outcomes. If the association between neighborhood SES and incidence of CHD or ischemic stroke is truly causal, one would expect that the association between SES and incidence of CHD or ischemic stroke would be of similar strength in the general population as in relative pairs discordant for their level of neighborhood SES. However, if the association between SES and incidence of CHD or ischemic stroke results partly or entirely from familial confounding, then the association would decrease or disappear entirely in genetically related family members.

Figure 1 shows the results of the Cox proportional hazard modeling for the co-relative design, i.e., the hazard ratios and 95% confidence intervals (CI) for incidence of CHD, based on neighborhood SES, used as a continuous variable, for the three age groups 40, 50 and 60 years, in men and women, respectively, after controlling for marital status, family income and educational attainment. For example, for 40 year old women, the hazard ratio was 1.11 (95% CI 1.09-1.13), 1.09 (95% CI 1.01-1.17) and 1.11 (95% CI 1.07-1.16) for the total population, half siblings and full siblings, respectively, showing no decrease of the HRs with increasing genetic resemblance. For all age groups, neighborhood SES was associated with incidence of CHD for both sexes, but the association seemed to be somewhat stronger in women. The hazard ratios with 95% confidence intervals are also presented in Study I Supplementary Table 1.

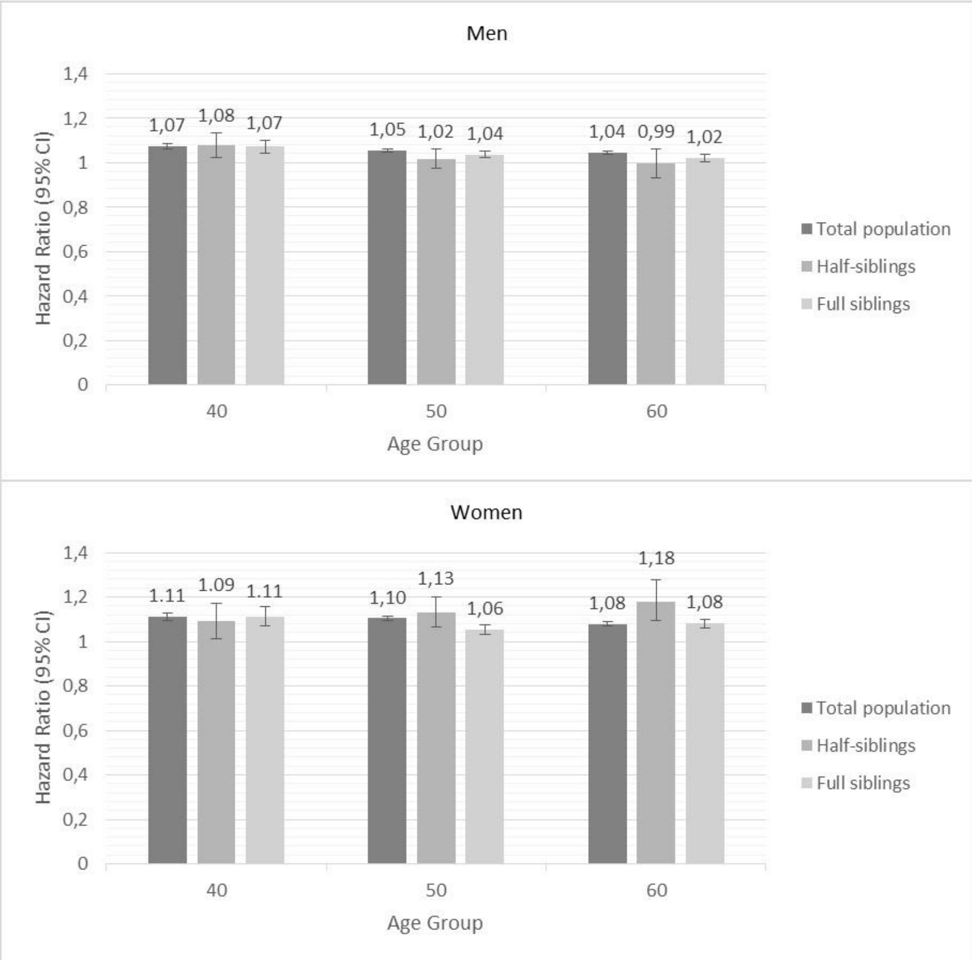

Figure 1. Hazard ratios and 95% confidence intervals for incidence of coronary heart disease (CHD) in men (top) and women (bottom) based on neighborhood socioeconomic status (SES); Results of Cox proportional hazard models.

Figure 2 shows the results of Cox proportional hazard modeling: the hazard ratios and 95% confidence intervals for incidence of ischemic stroke, based on neighborhood SES for the three age groups 40, 50 and 60 years, in men and women, respectively, after controlling for marital status, family income and educational attainment. The association between neighborhood SES and incidence of ischemic stroke seemed to be somewhat weaker than the association between neighborhood SES and CHD. The hazard ratios with 95% confidence intervals are also presented in Study I Supplementary Table 2.

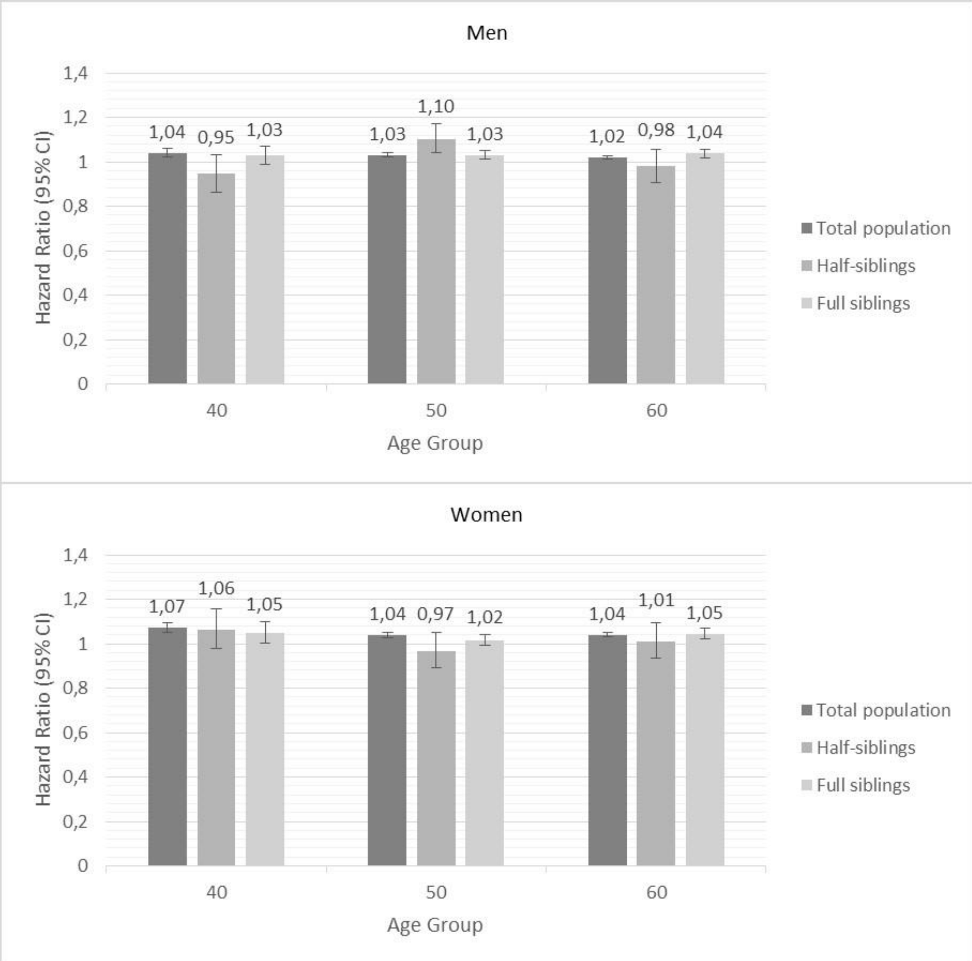

Figure 2. Hazard ratios and 95% confidence intervals for incidence of ischemic stroke in men (top) and women (bottom) based on neighborhood socioeconomic status (SES); Results of Cox proportional hazard models.

Neighborhood SES was used as a continuous variable in the models with higher values indicating higher levels of neighborhood deprivation. As an example, a HR of 1.1 for CHD means that the risk of CHD would increase by 10% for one unit's increase in the neighborhood SES score. An increase in neighborhood SES score by 2.5, roughly corresponding to moving from a neighborhood in the most affluent quintile to a neighborhood in the least affluent quintile, would then give an increased risk of CHD by 21-30% for women and 11-20% for men, depending on age group, after controlling for individual level variables.

Study II

Table 4 shows the distribution of the study population and number of patients receiving statins by neighborhood-level SES. For statin medication, the number (No) of patients receiving statins as well as the share of patients on statin medication within each patient group (%) is presented. Of the 116,840 patients with MI included in this study, 104,766 (89.7%) received statins during the study period. Of the total population, 19%, 62%, and 19% lived in high, middle, and low SES neighborhoods, respectively. Age-standardized statin medication rates was 90.6% in neighborhoods with high SES; 89.7% in neighborhoods with middle SES; and 88.6% in neighborhoods with low SES. This slight difference in statin medication rate by neighborhood-level SES was observed across all individual-level variables, as shown in Table 1.

Table 5 shows the age-adjusted ORs for each covariate. Patients with low family income had significantly lower odds of statin medication (OR 0.49) compared to patients with high family income. Low educational attainment was also associated with lower odds of statin medication (OR 0.71) compared to patients with high educational attainment.

Table 4. Distribution of study population (patients with myocardial infarction, MI), number of statin medication events, and age-standardized rates by neighborhood socioeconomic status (SES)

	Population	**Distribution**	**Statin medication**		**Neighborhood SES**		
		(%)	No.	%	High	Middle	Low
Total population (%)	116840				22172 (19%)	72655 (62%)	22013 (19%)
Statin medication			104766	89.7	90.6	89.7	88.6
Sex							
Men	80351	68.8	73223	91.1	91.8	90.6	89.0
Women	36489	31.2	31543	86.4	87.5	87.6	87.4
Age (years)							
<50	18623	15.9	17185	92.3	92.1	92.5	91.7
50-59	34009	29.1	32147	94.5	95.1	94.6	93.6
60-69	40034	34.3	36786	91.9	92.3	92.1	90.8
70-79	24174	20.7	18648	77.1	78.6	77.4	74.8

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) for statin medication in patients with myocardial infarction; Results of multi-level logistic regression models for each variable, adjusted for age

	OR	95% CI		Variance (S.E.)	*Explained variance (%)*	*Intra class correlation*
Neighborhood-level Socioeconomic status (SES, ref. High)				0.068 (0.011)	22	0.020
Middle	0.93	0.88	0.98			
Low	0.79	0.74	0.84			
Sex (ref. Female)	1.39	1.34	1.45	0.072 (0.011)	17	0.021
Family income (ref. High income)				0.077 (0.011)	11	0.023
Low income	0.49	0.47	0.52			
Middle-low income	0.59	0.56	0.63			
Middle-high income	0.84	0.79	0.89			
Marital status (ref. Married/co-habiting)				0.060 (0.011)	31	0.018
Never married, widowed, or divorced	0.59	0.57	0.62			
Country of origin (ref. Born in Sweden)				0.075 (0.011)	14	0.022
Finland	0.90	0.82	0.99			
Western countries	1.06	0.89	1.26			
Eastern European countries	1.10	0.94	1.28			
Middle eastern countries	0.99	0.84	1.16			
Others	0.80	0.74	0.88			
Educational attainment (ref. > 12 years)				0.075 (0.011)	14	0.022
≤ 9 years	0.71	0.67	0.74			
10-12 years	0.92	0.87	0.98			
Urban/rural status (ref. large cities)				0.059 (0.011)	32	0.018
Southern Sweden	1.28	1.22	1.34			
Northern Sweden	0.98	0.93	1.03			

Table 6 shows the results of the different multilevel logistic regression models. In the crude model (Model 1), the odds of statin medication were lower for patients living in neighborhoods with low SES. The OR for statin medication in patients with MI living in neighborhoods with low compared to high neighborhood-level SES was 0.80 (95% confidence interval (CI) 0.75-0.86). In Model 2, neighborhood-level SES remained significantly associated with statin medication after adjustment for age and sex (OR 0.80, 95% CI 0.75-0.86).

However, in the third model, after adding individual-level sociodemographic variables, the ORs no longer remained significant. The fourth model also included the variables for comorbidities, which did not change the ORs further, and the results are therefore not shown.

The between-neighborhood variance was significant in all models. The explained variance was 6% in Model 1, indicating that the neighborhood variable explained only a small proportion of the total variance, and increased to 23% in Model 2 and 39% in Model 3.

The ICC was low, varying between 1.6% and 2.4% in the different models, indicating that the clustering within neighborhoods was low.

Analyzing first order interactions between neighborhood SES and individual-level characteristics for statin medication in MI patients showed significant interactions between neighborhood level SES and education level only.

Table 6. Odds ratios (OR) and 95% confidence intervals (CI) for statin medication in patients with myocardial infarction; Results of multi-level logistic regression models

	Model 1			Model 2			Model 3			
	OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighborhood-level socioeconomic status (SES, ref. High)										
Middle	0.90	0.86	0.95	0.94	0.89	0.99	1.07	1.01	1.13	0.016
Low	0.80	0.75	0.86	0.80	0.75	0.86	1.03	0.96	1.10	0.368
Age (years)				0.95	0.95	0.95	0.96	0.96	0.96	<0.001
Sex (ref. Female)				1.39	1.33	1.44	1.23	1.19	1.29	<0.001
Family income (ref. High income)										
Low income							0.49	0.46	0.52	<0.001
Middle-low income							0.62	0.58	0.65	<0.001
Middle-high income							0.83	0.78	0.89	<0.001
Marital status (ref. Married/co-habiting)										
Never married, widowed, or divorced							0.61	0.58	0.63	<0.001
Country of origin (ref. Born in Sweden)										
Finland							1.02	0.93	1.12	0.689
Western countries							1.07	0.89	1.27	0.484
Eastern European countries							1.33	1.14	1.55	<0.001
Middle eastern countries							1.33	1.13	1.56	<0.001
Others							0.92	0.84	1.00	0.046
Educational attainment (ref. > 12 years)										
≤ 9 years							0.89	0.84	0.94	<0.001
10-12 years							1.13	1.06	1.21	<0.001
Urban/rural status (ref. large cities)										
Southern Sweden							1.30	1.24	1.37	<0.001
Northern Sweden							1.02	0.97	1.08	0.424
Variance (S.E.)		*0.082 (0.011)*			*0.067 (0.011)*			*0.053 (0.011)*		
Explained variance (%)			*6*			*23*			*39*	
Intra class correlation			0.024			0.020			0.016	

Study III

Table 7 shows the study population comprising a total of 434,542 DM patients, number of HF incident events and incidence of HF in the DM patients by neighborhood-level deprivation. During the follow-up (mean follow-up = 6 years), there were 26,511 and 20,772 HF incident events among the men and women with DM, respectively. There was an apparent gradient for the incidence rate; the HF incidence became higher by increasing neighborhood-level deprivation. The same pattern appeared in most subgroups (data not shown).

The proportion of patients affected with HF increased among individuals living in high-deprivation neighborhoods. Figure 1 shows the Kaplan–Meier curves for the duration of survival until the first incident HF by different levels of neighborhood deprivation. A graded effect appeared with a poorer prognosis for those with a high level of neighborhood deprivation.

Table 8 shows the Hazard ratios (HRs) for HF in men. The results indicate the presence of a gradient where HF incidence became greater with increasing neighborhood deprivation. For men, the HRs were 1.14 (95% CI = 1.10-1.19) and 1.27 (95% CI = 1.21-1.33) in moderate and high deprivation neighborhoods, respectively. The results of the full model show that the HRs decreased, after adjustment for the individual-level variables; the HRs in the full model remained, however, significant in both moderate-deprivation neighborhoods (HR = 1.08, 95% CI = 1.04-1.12) and high-deprivation neighborhoods (HR = 1.11, 95% CI = 1.06-1.16).

Table 7. Distribution of population, number of incident HF, cumulative rates (%) of incident heart failure (HF) in diabetes patients, 2005-2015, Sweden.

	Population		**Incident HF**		**Rate (%) of HF by neighborhood deprivation**			
	No.	%	No.	%	Low	Moderate	High	P-value
Total population	434542				57890 (13.3%)	292812 (67.4%)	83840 (19.3%)	
Total incident HF			47283		5357 (11.3%)	32423 (68.6%)	9503 (20.1%)	
Gender								0.9810
Males	239567	55.1	26511	56.1	9.7	11.3	11.3	
Females	194975	44.9	20772	43.9	8.6	10.8	11.3	
Age (years)								<0.001
30-39	24192	5.6	235	0.5	0.7	0.9	1.2	
40-49	49390	11.4	1192	2.5	2.0	2.4	2.8	
50-59	95456	22.0	4476	9.5	3.6	4.7	5.5	
60-69	119581	27.5	11397	24.1	7.9	9.4	11.3	
70-79	93204	21.4	17435	36.9	16.9	18.7	19.9	
≥ 80	52719	12.1	12548	26.5	22.9	23.9	24.0	

Table 8. Hazard ratios (HR) and 95% confidence intervals (CI) for incident HF in men; Results of Cox regression models

	Model 1			Model 2			Model 3		
	HR	95% CI		HR	95% CI		HR	95% CI	
Neighborhood deprivation (ref. Low)									
Moderate	1.14	1.10	1.19	1.08	1.04	1.12	1.08	1.04	1.12
High	1.27	1.21	1.33	1.12	1.07	1.17	1.11	1.06	1.16
Age	1.07	1.07	1.08	1.06	1.06	1.06	1.06	1.06	1.06
Family income (ref. Highest quartiles)									
Middle-high income	1.31	1.26	1.36	1.11	1.07	1.16	1.16	1.11	1.21
Middle-low income	1.34	1.29	1.38	1.09	1.05	1.13	1.11	1.07	1.15
Low income	1.26	1.22	1.30	1.10	1.06	1.14	1.09	1.05	1.13
Education attainment (ref. ≥ 12 years)									
≤ 9 years	1.25	1.21	1.29	1.19	1.15	1.23	1.14	1.11	1.18
10–11 years	1.20	1.16	1.25	1.15	1.11	1.19	1.10	1.07	1.14
Country of origin (ref. Sweden)	1.10	1.06	1.14	1.02	0.98	1.06	0.98	0.94	1.02
Marital status (ref. Married/cohabiting)	1.20	1.17	1.23	1.12	1.09	1.14	1.17	1.14	1.20
Region of residence (ref. Large cities)									
Southern Sweden	0.95	0.92	0.98	0.96	0.93	0.99	0.99	0.96	1.02
Northern Sweden	0.94	0.90	0.97	0.94	0.90	0.97	0.95	0.91	0.98
Mobility (ref. Not moved)	1.64	1.60	1.68	1.60	1.56	1.65	1.63	1.59	1.67
Employment status (ref. Yes)	1.59	1.53	1.65	1.48	1.43	1.54	1.26	1.21	1.31
Hospitalization of COPD (ref. Non)	2.45	2.37	2.53				2.02	1.96	2.09
Hospitalization of alcoholism and related liver disorders (ref. Non)	1.41	1.33	1.50				1.20	1.13	1.28
Hospitalization of obesity (ref. Non)	2.50	2.37	2.64				1.95	1.85	2.06
Hospitalization of depression (ref. Non)	1.27	1.19	1.37				1.01	0.94	1.08
Hospitalization of hypertension (ref. Non)	1.68	1.64	1.72				1.39	1.35	1.42
Hospitalization of CHD (ref. Non)	3.36	3.27	3.44				3.06	2.98	3.14
Hospitalization of stroke (ref. Non)	1.25	1.21	1.29				1.09	1.05	1.12

HR: Hazard ratio; CI: Confidence interval; HF: Heart Failure; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease.
Model 1: Univariate model, adjusted for age; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Table 9 shows the HRs for HF in women; the corresponding figures of HF for women were 1.16 (95% CI = 1.10-1.21) and 1.30 (95% CI = 1.23-1.37). The results of the full model show that the HRs decreased, after adjustment for the individual-level variables; the HRs in the full model remained, however, significant in both moderate-deprivation neighborhoods (HR = 1.10, 95% CI = 1.05-1.16) and high-deprivation neighborhoods (HR = 1.15, 95% CI = 1.09-1.21).

There was a clear and consistent positive association between neighborhood deprivation and HF in all socioeconomic groups, i.e., any moderation by individual SES ought to be minor and the potential interactions do not seem to be clinically meaningful.

Some of the individual-level variables were significantly associated with HF in the full models. The HRs for HF were higher for men and women with low education, low family income, country of birth outside Sweden, or those who had moved or had a hospitalization for comorbidities (Study III Supplementary Table 2).

Table 9. Hazard ratios (HR) and 95% confidence intervals (CI) for incident HF in women; Results of Cox regression models

	Model 1			Model 2			Model 3		
	HR	95% CI		HR	95% CI		HR	95% CI	
Neighborhood deprivation (ref. Low)									
Moderate	1.16	1.10	1.21	1.11	1.06	1.16	1.10	1.05	1.16
High	1.30	1.23	1.37	1.17	1.11	1.24	1.15	1.09	1.21
Age	1.08	1.07	1.08	1.06	1.06	1.06	1.06	1.06	1.06
Family income (ref. Highest quartiles)									
Middle-high income	1.23	1.16	1.30	1.08	1.01	1.14	1.10	1.03	1.17
Middle-low income	1.34	1.27	1.42	1.13	1.06	1.20	1.10	1.04	1.17
Low income	1.18	1.11	1.25	1.08	1.01	1.15	1.05	0.98	1.12
Education attainment (ref. ≥ 12 years)									
≤ 9 years	1.25	1.20	1.30	1.19	1.14	1.25	1.12	1.07	1.17
10–11 years	1.11	1.06	1.17	1.10	1.05	1.15	1.01	0.96	1.06
Country of origin (ref. Sweden)	1.16	1.12	1.21	1.10	1.05	1.15	1.04	1.00	1.09
Marital status (ref. Married/cohabiting)	1.19	1.15	1.22	1.13	1.10	1.17	1.14	1.11	1.18
Region of residence (ref. Large cities)									
Southern Sweden	0.98	0.95	1.01	1.00	0.97	1.04	1.03	0.99	1.07
Northern Sweden	0.96	0.92	1.00	0.99	0.95	1.03	0.99	0.95	1.03
Mobility (ref. Not moved)	1.63	1.58	1.68	1.63	1.58	1.68	1.64	1.59	1.69
Employment (ref. Yes)	1.93	1.82	2.05	1.86	1.75	1.98	1.51	1.42	1.60
Hospitalization of COPD (ref. Non)	2.63	2.54	2.72				2.17	2.10	2.25
Hospitalization of alcoholism and related liver disorders (ref. Non)	1.39	1.22	1.59				1.11	0.97	1.27
Hospitalization of obesity (ref. Non)	2.14	2.01	2.27				1.74	1.64	1.85
Hospitalization of depression (ref. Non)	1.28	1.19	1.38				1.05	0.98	1.14
Hospitalization of hypertension (ref. Non)	1.65	1.60	1.69				1.37	1.34	1.41
Hospitalization of CHD (ref. Non)	3.18	3.09	3.27				2.79	2.71	2.87
Hospitalization of stroke (ref. Non)	1.36	1.32	1.41				1.19	1.15	1.23

HR: Hazard ratio; CI: Confidence interval; HF: Heart Failure; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease.
Model 1: Univariate model, adjusted for age; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Study IV

Table 10 shows the study population, the number of CHD cases, the individual-level variables and the contextual variables. Of the 991,072 individuals in the study, there were a total of 16,971 (3.5%) and 6,601 (1.3%) CHD cases during follow-up for men and women, respectively. Individuals with CHD were slightly older, were less educated, had fewer colleagues, the colleagues were less educated and the individuals lived in lower SES neighborhoods. Compared to the men, the women had lower income, were more educated, had more colleagues and the colleagues were more educated.

There was an apparent increase in CHD incidence with increased income; however, more men than women were in the higher income brackets.

Tables 11a and 11b show the results of the multilevel and cross-classified logistic regression models in men and women, respectively, with individuals nested within the two classifications workplace and neighborhood of residence. Here $education_{work}$ is used as the primary contextual variable. The tables show the odds ratios (OR), 95% confidence intervals (CI) and intraclass correlations (ICC) for incidence of CHD based on workplace and neighborhood characteristics.

In the first model, model 1, low compared to high $education_{work}$ was significantly associated with increased CHD incidence for both men (OR 1.29, 95% CI 1.23-1.34) and women (OR 1.38, 95% CI 1.29-1.47). After adjusting for individual- and contextual-level characteristics in the full model, Model 3, low compared to high $education_{work}$ remained significantly associated with increased CHD incidence, but with slightly lower ORs, for both men (OR 1.11, 95% CI 1.05-1.17) and women (OR 1.13, 95% CI 1.05-1.22). There also appeared to be a gradient between $education_{work}$ and individual risk of CHD, after adjusting for individual-level variables in all models.

Table 10. Distribution of study population and number of cases of coronary heart disease (CHD)

	Population		Incident CHD		Rate (%) of CHD by Education at work			Rate (%) of CHD by Neighborhood SES work			Rate (%) of CHD by Neighborhood SES residence		
	No.	%	No.	%	Low	Middle	High	High	Medium	Low	High	Medium	Low
Total study population	991072				450665 (45%)	352308 (36%)	188099 (19%)	86482 (10%)	718599 (80%)	89865 (10%)	249742 (25%)	638344 (66%)	99256 (10%)
Total incident CHD			23572	2.4	13107 (55%)	7118 (30%)	3347 (14%)	1793 (9%)	17236 (82%)	2014 (10%)	4991 (21%)	15745 (67%)	2737 (12%)
Sex													
Men	492107	49.7%	16971	72.0	3.8	3.1	2.9	3.1	3.5	3.4	2.9	3.6	3.8
Women	498965	50.3%	6601	28.0	1.5	1.3	1.1	1.2	1.4	1.4	1.1	1.4	1.7
Age (years)													
50-54	351193	35.4%	5606	23.8	2.0	1.3	1.2	1.4	1.6	1.6	1.3	1.6	2.1
55-59	347820	35.1%	8453	35.9	3.0	2.1	1.8	2.1	2.4	2.3	2.0	2.5	2.8
60-64	292059	29.5%	9513	40.4	3.9	2.8	2.4	2.9	3.3	3.0	2.8	3.4	3.6

Table 11a. Odds ratios (OR), 95% confidence intervals (CI) and intraclass correlations (ICC) for incidence of coronary heart disease in men based on education at work; Results of multilevel and cross-classified logistic regression models

	Model 1			Model 2			Model 3		
	OR	95% CI		OR	95% CI		OR	95% CI	
Education at work (ref high)									
Middle	1,11	1,06	1,17	1,06	1,01	1,12	1,06	1,01	1,12
Low	1,29	1,23	1,34	1,13	1,07	1,19	1,11	1,05	1,17
Age				1,07	1,07	1,08	1,08	1,07	1,08
Marital status (ref married/cohabiting)				1,04	0,73	1,48	1,03	0,99	1,07
Education, individual				1,06	1,08	1,05	1,06	1,07	1,05
Income				1,09	1,17	1,02	1,12	1,21	1,04
Neighborhood SESwork (ref high SES)									
Middle							1,07	1,00	1,15
Low							1,02	0,94	1,12
Neighborhood SESresidence (ref high SES)									
Middle							1,13	1,08	1,18
Low							1,21	1,13	1,29
ICC higher level			2,08%			1,91%			2,03%
ICC workplace			1,14%			0,93%			0,96%
ICC neighborhoodresidence			0,96%			0,99%			1,08%
Variance work (S.E.)			0.038 (0.002)			0.031 (0.002)			0.032 (0.002)
Variance neighbourhood (S.E.)			0.032 (0.006)			0.033 (0.008)			0.036 (0.01)

OR: Odds ratio; CI: Confidence interval; ICC: Intraclass correlation; SE: Standard Error
Model 1: Univariate model; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Table 11b. Odds ratios (OR), 95% confidence intervals (CI) and intraclass correlations (ICC) for incidence of coronary heart disease in women based on education at work; Results of multilevel and cross-classified logistic regression models

	Model 1			Model 2			Model 3		
	OR	95% CI		OR	95% CI		OR	95% CI	
Education at work (ref high)									
Middle	1,11	1,04	1,19	1,05	0,97	1,13	1,04	0,96	1,12
Low	1,38	1,29	1,47	1,15	1,06	1,25	1,13	1,05	1,22
Age				1,08	1,08	1,08	1,08	1,07	1,08
Marital status (ref married/cohabiting)				1,11	1,06	1,17	1,09	1,03	1,15
Education, individual				1,10	1,12	1,07	1,09	1,11	1,07
Income				1,67	2,09	1,34	1,58	1,99	1,26
Neighborhood SESwork (ref high SES)									
Middle							1,03	0,94	1,14
Low							1,03	0,91	1,16
Neighborhood SESresidence (ref high SES)									
Middle							1,12	1,05	1,20
Low							1,35	1,23	1,48
ICC higher level			3,60%			2,32%			3,24%
ICC workplace			1,08%			0,51%			1,73%
ICC neighbourhoodresidence			2,58%			1,82%			1,56%
Variance work (S.E.)			0.036 (0.005)			0.017 (0.003)			0.058 (0.01)
Variance neighbourhood (S.E.)			0.087 (0.014)			0.061 (0.014)			0.052 (0.012)

OR: Odds ratio; CI: Confidence interval; ICC: Intraclass correlation; SE: Standard Error

Model 1: Univariate model; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Tables 12a and 12b show the results of the multilevel and cross-classified logistic regression models in men and women, respectively, with neighborhood SES_{work} used as the primary contextual variable.

In the first model, Model 1, low compared to high neighborhood SES_{work} was not significantly associated with increased CHD incidence for men (OR 1.07, 95% CI 0.99-1.16) but for women (OR 1.15, 95% CI 1.03-1.28). After adjusting for individual- and contextual-level characteristics in the full model, Model 3, low compared to high neighborhood SES_{work} was, however, not significantly associated with increased CHD incidence for men (OR 1.02, 95% CI 0.94-1.12) or women (OR 1.03, 95% CI 0.91-1.16).

Tables 13a and 13b show the results of the multilevel and cross-classified logistic regression models in men and women, respectively, with neighborhood $SES_{residence}$ used as the primary contextual variable.

In the first model, Model 1, low compared to high neighborhood $SES_{residence}$ was significantly associated with increased CHD incidence for both men (OR 1.31, 95% CI 1.23-1.39) and women (OR 1.56, 95% CI 1.44-1.70). After adjusting for individual- and contextual-level characteristics in the full model, Model 3, low compared to high neighborhood $SES_{residence}$ remained significantly associated with increased CHD incidence, but with slightly lower ORs for both men (OR 1.21, 95% CI 1.13-1.29) and women (OR 1.35, 95% CI 1.23-1.48).

In all models, CHD incidence showed clustering in both workplaces and neighborhoods of residence for both men (ICC workplace 0,96%, ICC neighborhood residence 1,08%) and women (ICC workplace 1.73%, ICC neighborhood residence 1.56%); results in brackets are for Model 3.

For the individual-level variables (both men and women), high age, low education and low income was associated with increased CHD incidence in all models. For women, being unmarried/cohabitating was also associated with increased CHD incidence.

Table 12a. Odds ratios (OR), 95% confidence intervals (CI) and intraclass correlations (ICC) for incidence of coronary heart disease in men based on neighborhood characteristics at work; Results of multilevel and cross-classified logistic regression models

	Model 1			**Model 2**			**Model 3**		
	OR	95% CI		OR	95% CI		OR	95% CI	
Neighborhood SESwork (ref high SES)									
Middle	1,12	1,05	1,19	1,11	1,05	1,17	1,07	1,00	1,15
Low	1,07	0,99	1,16	1,07	0,99	1,16	1,02	0,94	1,12
Age				1,07	1,07	1,07	1,08	1,07	1,08
Marital status (ref married/cohabiting)				1,04	1,01	1,08	1,03	0,99	1,07
Education, individual				1,08	1,09	1,07	1,06	1,07	1,05
Income				1,13	1,22	1,04	1,12	1,21	1,04
Education at work (ref high)									
Middle							1,06	1,01	1,12
Low							1,11	1,05	1,17
Neighborhood SESresidence (ref high SES)									
Middle							1,13	1,08	1,18
Low							1,21	1,13	1,29
ICC higher level			2,32%			2,20%			2,03%
ICC workplace			1,05%			1,20%			0,96%
ICC neighbourhoodresidence			1,29%			1,02%			1,08%
Variance work (S.E.)			0.035 (0.006)			0.040 (0.003)			0.032 (0.002)
Variance neighbourhood (S.E.)			0.043 (0.008)			0.034 (0.008			0.036 (0.010)

OR: Odds ratio; CI: Confidence interval; ICC: Intraclass correlation; SE: Standard Error

Model 1: Univariate model; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Table 12b. Odds ratios (OR), 95% confidence intervals (CI) and intraclass correlations (ICC) for incidence of coronary heart disease in women based on neighborhood characteristics at work; Results of multilevel and cross-classified logistic regression models

	Model 1			Model 2			Model 3		
	OR	95% CI		OR	95% CI		OR	95% CI	
Neighbourhood SESwork (ref high SES)									
Middle	1,13	1,04	1,23	1,08	0,98	1,19	1,03	0,94	1,14
Low	1,15	1,03	1,28	1,11	0,98	1,25	1,03	0,91	1,16
Age				1,08	1,07	1,08	1,08	1,07	1,08
Marital status (ref married/cohabiting)				1,11	1,05	1,17	1,09	1,03	1,15
Education, individual				1,11	1,13	1,09	1,09	1,11	1,07
Income				1,64	2,06	1,30	1,58	1,99	1,26
Education at work (ref high)									
Middle							1,04	0,96	1,12
Low							1,13	1,05	1,22
Neighborhood SESresidence (ref high SES)									
Middle							1,12	1,05	1,20
Low							1,35	1,23	1,48
ICC higher level			3,06%			1,73%			3,24%
ICC workplace			1,05%			1,32%			1,73%
ICC neighborhoodresidence			2,05%			0,42%			1,56%
Variance work (S.E.)			0.035 (0.004)			0.044 (0.005)			0.058 (0.010)
Variance neighbourhood (S.E.)			0.069 (0.013)			0.014 (0.007)			0.052 (0.012)

OR: Odds ratio; CI: Confidence interval; ICC: Intraclass correlation; SE: Standard Error
Model 1: Univariate model; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Table 13a. Odds ratios (OR), 95% confidence intervals (CI) and intraclass correlations (ICC) for incidence of coronary heart disease in men based on neighborhood residential characteristics; Results of multilevel and cross-classified logistic regression models

	Model 1			**Model 2**			**Model 3**		
	OR	95% CI		OR	95% CI		OR	95% CI	
Neighborhood SESresidence (ref high SES)									
Middle	1,22	1,17	1,27	1,16	1,11	1,21	1,13	1,08	1,18
Low	1,31	1,23	1,39	1,22	1,15	1,30	1,21	1,13	1,29
Age				1,07	1,07	1,08	1,08	1,07	1,08
Marital status (ref married/cohabiting)				1,02	0,99	1,06	1,03	0,99	1,07
Education, individual				1,07	1,08	1,06	1,06	1,07	1,05
Income				1,09	1,17	1,02	1,12	1,21	1,04
Education at work (ref high)									
Middle							1,06	1,01	1,12
Low							1,11	1,05	1,17
Neighborhood SESwork (ref high SES)									
Middle							1,07	1,00	1,15
Low							1,02	0,94	1,12
ICC higher level			2,34%			2,00%			2,03%
ICC workplace			1,29%			1,29%			0,96%
ICC neighbourhoodresidence			1,08%			0,72%			1,08%
Variance work (S.E.)			0.043 (0.007)			0.043 (0.005)			0.032 (0.002)
Variance neighbourhood (S.E.)			0.036 (0.005)			0.024 (0.004)			0.036 (0.010)

OR: Odds ratio; CI: Confidence interval; ICC: Intraclass correlation; SE: Standard Error

Model 1: Univariate model; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Table 13b. Odds ratios (OR), 95% confidence intervals (CI) and intraclass correlations (ICC) for incidence of coronary heart disease in women based on neighborhood residential characteristics; Results of multilevel and cross-classified logistic regression models

	Model 1			Model 2			Model 3		
	OR	95% CI		OR	95% CI		OR	95% CI	
Neighborhood SESresidence (ref high SES)									
Middle	1,24	1,17	1,31	1,15	1,08	1,22	1,12	1,05	1,20
Low	1,56	1,44	1,70	1,38	1,26	1,50	1,35	1,23	1,48
Age				1,08	1,07	1,09	1,08	1,07	1,08
Marital status (ref married/cohabiting)				1,08	1,03	1,14	1,09	1,03	1,15
Education, individual				1,11	1,12	1,09	1,09	1,11	1,07
Income				1,64	2,03	1,33	1,58	1,99	1,26
Education at work (ref high)									
Middle							1,04	0,96	1,12
Low							1,13	1,05	1,22
Neighborhood SESwork (ref high SES)									
Middle							1,03	0,94	1,14
Low							1,03	0,91	1,16
ICC higher level			3,15%			2,05%			3,24%
ICC workplace			1,11%			0,90%			1,73%
ICC neighbourhoodresidence			2,08%			1,17%			1,56%
Variance work (S.E.)			0.037 (0.004)			0.030 (0.004)			0.058 (0.010)
Variance neighbourhood (S.E.)			0.070 (.012)			0.039 (0.008)			0.052 (0.012)

OR: Odds ratio; CI: Confidence interval; ICC: Intraclass correlation; SE: Standard Error
Model 1: Univariate model; Model 2. Adjusted for individual characteristics; Model 3. Full model.

Discussion

Main findings

The main finding of Study I suggests that the association between neighborhood SES and incidence of CHD is, at least in part, causal, as the HRs in both men and women were of similar size for the total population, half-siblings and full siblings. Similar results were found for ischemic stroke in the co-relative analyses, but the associations were somewhat weaker than for CHD.

The main finding of Study II was that MI patients living in low SES neighborhoods had 20% lower odds of statin medication compared to those living in middle and high SES neighborhoods. However, the odds no longer remained statistically significant after adjusting for the individual-level sociodemographic characteristics and comorbidities.

The main finding of Study III was that the risk of incident HF is higher among patients with DM living in deprived neighborhoods than among patients with DM living in less deprived/affluent neighborhoods. This difference was attenuated but remained significant, after adjustment for the individual-level sociodemographic variables and traditional cardiovascular risk factors (COPD, alcoholism and related liver disorders, diabetes, obesity).

The main finding of Study IV was that CHD incidence was significantly associated with the mean educational attainment at work ($\text{education}_{\text{work}}$) as well as with neighborhood residential SES (neighborhood $\text{SES}_{\text{residence}}$) but not with neighborhood SES at work (neighborhood SES_{work}). These finding were consistent for both men and women, after adjusting for potential confounders.

Neighborhood deprivation and heart disease

The causal pathways between neighborhood deprivation and cardiovascular health outcomes are not fully understood (Aslanyan et al., 2003, Sundquist et al., 1999, Sundquist et al., 2004a, Zoller et al., 2012). Several possible mechanisms could, however, explain our findings. One possible mechanism is the potential differences between socioeconomic groups in knowledge, attitudes and beliefs that could lead to differences in lifestyle; these differences may partly explain differences in morbidity risk across socioeconomic strata (Sundquist et al., 1999),(Connolly and Kesson, 1996),(Unwin et al., 1996). For instance, a UK study showed that cardiovascular disease risk factors, including obesity and smoking, were more common among patients with DM living in deprived neighborhoods than among those living in less deprived/affluent neighborhoods (Connolly and Kesson, 1996) (Unwin et al., 1996). A Swedish study showed that cardiovascular disease risk factors, including physical inactivity, obesity, and smoking, were more common among individuals living in deprived neighborhoods than among those living in less deprived/affluent neighborhoods (Sundquist et al., 1999). It is possible that sociocultural norms regarding diet, smoking and physical activity could vary between neighborhoods and affect the health of the residents and the consequent risk for disease. Moreover, access to health care resources for treating metabolic risk factors for CHD, such as hypertension and DM, may differ between neighborhoods (Schultz et al., 2018, Amstislavski et al., 2012).

There are also other potential mechanisms behind the findings. The levels of social capital, which in turn are related to social norms, beliefs and attitudes, are lower in deprived neighborhoods (Derose and Varda, 2009). The crime levels are also higher in deprived neighborhoods (Sundquist et al., 2006b), which could increase psychosocial stress and reduce physical activity due to fear of going outside. It has also been suggested that neighborhood goods, services and resources are poorer in deprived neighborhoods. However, a previous Swedish study showed that the availability of potentially health-promoting goods, services and resources is higher, not lower, in deprived neighborhoods (Kawakami et al., 2011).

Causal nature of neighborhood deprivation

Previous studies have used co-relative designs to examine the causal nature of neighborhood effects on individual CHD in full brothers (Chaix, 2009, Merlo et al., 2013). However, this is the first study that has included both women and men and applied a co-relative design to disentangle the causal nature of neighborhood effects on individual CHD as well as ischemic stroke in both full-siblings and half-siblings and in different age cohorts.

Study I suggests that the association between neighborhood SES and cardiovascular health is stronger in women than in men, at least for CHD and ischemic stroke, indicating that the stress hypothesis may be more salient for women than for men. Traditionally, there has been two different possible explanations used to explain the well-established inverse association between neighborhood SES and cardiovascular disease. The first explanation is social causation or the stress hypothesis, which attributes the association between neighborhood SES and cardiovascular disease to the difficulties and stress associated with low social status, i.e., low neighborhood SES would cause cardiovascular disease (Dohrenwend et al., 1992, Adams, 2003). The second possible explanation that has been used is social selection or the drift hypothesis, which proposes that predisposed persons, i.e., already unhealthy individuals, will drift down to or not be able to rise out of areas with low neighborhood SES. Here, the neighborhood would not cause poor health; rather, already unhealthy individuals would move to or remain in more deprived neighborhoods (Dohrenwend et al., 1992). The results of the present study supports the stress hypothesis, i.e., social causation.

If it would be speculated on the apparent sex differences, the potential neighborhood effects on men may be confounded by genetic factors and shared family environmental factors more than on women. Also, women may often spend more time at home, which could result in a greater exposure to their local neighborhoods. Additionally, men have traditionally been the breadwinners in a family to a higher extent than women, whereas women's SES often has depended on their husband's.

For ischemic stroke, the association between neighborhood SES and stroke incidence was somewhat weaker than for CHD. This might indicate that different neighborhood mechanisms could affect the incidence of CHD differently compared to ischemic stroke. Further studies are, however, needed to confirm these findings.

The results of Study I show that neighborhood SES was associated with incidence of CHD and ischemic stroke and also suggest that these associations were, at least in part, causal. These findings raise important clinical and public health concerns, and indicate that solutions need to reframe health problems from a sole focus on individual approaches to a broader focus that includes neighborhoods. If appropriate interventions at the neighborhood level can be performed, the incidence of CHD and ischemic stroke could potentially decrease in deprived neighborhoods.

Potential influences of equal healthcare

It has been hypothesized that health care access is different between different neighborhoods (Amstislavski et al., 2012). The health care systems in the western world are quite different, comparing e.g., the US insurance-based system to the universal health care in Sweden. It is interesting to investigate whether universal health care leads to better health equality.

It has previously been shown that statin medication rates in CHD patients may vary due to individual-level factors such as the patients' age and comorbidities. Additionally, low individual-level SES may affect medication patterns negatively (Brooks et al., 2014, Reid et al., 2002, Headen et al., 2006, Tuppin et al., 2014) and it has previously been shown that when larger proportion of the medication costs are required from the patients, statin usage decreases, in particular for less regularly compliant patients (Thiebaud et al., 2008). Individuals in neighborhoods with low SES are more likely to have small financial margins (Carlsson et al., 2014), which could affect their willingness to pay for prescribed drugs. The findings in Study II indicate that the lower odds of statin utilisation in MI patients living in deprived neighborhoods may be explained by individual-level socioeconomic factors. This could be interpreted so that the neighborhood in itself does not affect statin medication in this patient group.

Even though Study II was unable to detect a neighborhood effect on statin medication for CHD patients, previous studies have shown that neighborhood-level deprivation is a strong predictor for CHD incidence and fatality, after adjusting for individual-level sociodemographic characteristics (Winkleby et al., 2007b). Additionally, a recent study has shown that neighborhood-level deprivation affects prescription patterns of statins in patients with atrial fibrillation, after adjusting for individual-level factors (Carlsson et al., 2015). Individuals with atrial fibrillation living in high SES neighborhoods more frequently picked up prescribed statins (men and women, OR 1.23) compared to their counterparts residing in middle SES neighborhoods (Carlsson et al., 2015). It is not clear why neighborhood-level deprivation affects statin medication for patients with atrial fibrillation, but not for the MI patients in the present study.

Trying to explain this, one explanation could be that statin medication after MI is started almost exclusively at the hospital, i.e., in immediate relation to the MI, whereas statin medication, for other reasons, e.g., primary prevention, might be started at a local health care center where the potential neighborhood effects may be stronger than in hospitals that cover a wider geographic area. Prior research has shown that prescription patterns among physicians working in local health care centers may be affected by neighborhood SES (Pimenta and Stowasser, 2009). In addition, individuals living in more affluent neighborhoods may be better informed as patients, irrespective of individual-level SES.

Lastly, differences in medication patterns may in some cases be explained by "medication deserts", where pharmacies in low SES neighborhoods may have lower availability of drugs (Amstislavski et al., 2012). However, in Sweden, with universal health care and good availability of drugs, this is unlikely a problem. During the 90's there were significantly fewer pharmacies per capita in Sweden compared to other European countries. In Sweden there were approximately one pharmacy per 10,000 inhabitants compared to one pharmacy per 5,000 inhabitants in the rest of Europe (Apoteket). However, after the deregulation of the pharmacy market in 2009-2010 the number of pharmacies increased rapidly and studies indicate an increased accessibility (Sävlind, 2015) and reduction of drug prices (Bergman et al., 2016).

The results of Study II, including all MI patients in Sweden during the study period, show that statin medication rates for these patients are generally high (89.7%). For comparison, several studies of statin medication for CHD patients in the US have shown medication rates of about 60-70% (Johansen et al., 2014, Goff et al., 2003, Johansen et al., 2015). However, those studies only included a sub-set of MI patients. Additionally, the authors of one of the studies which reported high medication rates explained their findings as a result of only including highly motivated medical institutions (Arnold et al., 2011). It has previously been shown that in countries which lack universal health insurance, lack of individual health insurance is associated with lower likelihood of statin treatment (Arnold et al., 2011, Johansen et al., 2015). It is also possible that generic statin availability will result in lower costs for the patients and improved compliance. The observed high statin medication rates in Study II indicate that universal health care may improve statin medication for MI patients, which could be an argument in support of providing universal health care to the entire population.

Risk of heart failure among patients with diabetes mellitus

Individuals who live in highly deprived neighborhoods have been shown to have an increased risk of morbidities, such as CHD (Winkleby et al., 2007a), and DM (White et al., 2016). In Study III, the incidence rates of HF in DM patients increased with the level of neighborhood deprivation.

One of the most frequent comorbidities of DM is HF. Glucose-lowering therapies that could prevent HF or improve outcomes in individuals with established HF are of crucial importance among patients with DM (Vijayakumar et al., 2018). Even though Sweden has a universal health care system, there might still be differences between neighborhoods with regards to the access of glucose-lowering therapies affecting HF risk of DM. These differences could possibly be related both to individual socioeconomic differences that might affect individuals' possibilities to purchase prescribed medicine (Skoog et al., 2014) and less access to primary health care in deprived neighborhoods (Crump et al., 2011). What previous studies have found together with the findings of Study III illustrate the need for improving health in low resource settings, which is ongoing in Europe (Modesti et al., 2014).

For example, a study in the UK showed social differences in both the prevalence of DM as well as impaired glucose regulation (Moody et al., 2016).

The importance of workplace

Study IV is the first to examine whether two different socioeconomic characteristics at work ($education_{work}$ and neighborhood SES_{work}) are associated with CHD incidence.

The association with neighborhood residential SES and was also examined, in line with research done previously, Study IV confirms that the socioeconomic status of the neighborhood of residence is significantly associated with CHD risk (Forsberg et al., 2018, Winkleby et al., 2007b, Sundquist et al., 2004b, Sundquist et al., 2004a). This is shown for both men and women, after adjustment for individual-level sociodemographic characteristics. The CHD risk in the women appeared to be more strongly associated with neighborhood $SES_{residence}$ compared to in the men, which also is in line with previous research (Forsberg et al., 2018). However, it is important to remember that women have a lower absolute CHD risk than men to start with. During the follow-up of in Study IV, 1.3% of women compared with 3.4% of men were diagnosed with CHD. This indicates that contextual factors may influence the CHD risk to a lesser extent in men.

What has not been studied before, however, are the associations between CHD incidence and the contextual variables educational attainment at work as well as neighborhood SES at work. The findings in Study IV are therefore important as individuals spend a large share of their time at work and are thus exposed to contextual factors at work, which could affect their CHD risk in addition to other environmental exposures such as neighborhood residential SES.

The new findings of an association between lower mean educational attainment of an individual's colleagues and CHD risk is very interesting. Some possible explanations behind our findings could be that people spend a lot of time at work, where the behavior and attitudes of their colleagues could affect them. Prior studies have shown that behaviors and attitudes can be contagious and spread in social networks (Murray et al., 2012, Bot et al., 2016, Christakis and Fowler, 2007). In Study IV, well-educated colleagues could have had better health-related behaviors e.g., having a healthy diet, being more physically active, and refrain from smoking. On the other hand, if person's colleagues smoke, they could encourage the person to join them for a smoke break. However, more studies are needed to uncover these mechanisms. The Study IV findings of 11% and 13% increased risks from the variable $education_{work}$ among the men and women, respectively, may be considered to be modest. However, this risk increase was adjusted for individual-level sociodemographic variables (including education) and, although the individual risk was moderately increased, it could lead to a large number of CHD cases at the population level.

In Study IV there was no significant association between CHD incidence and neighborhood SES_{work} in the full model. One possible explanation for this might be that, although people spend much time at work, most of the time at work may be spent indoors at an office or another type of workplace, rather than in the surrounding neighborhood. People may therefore be more affected by their colleagues than by the surrounding neighborhood at work.

Strengths

These studies have a number of strengths. The large cohorts used in Study I-IV included practically all people in Sweden during the study periods, which increases the generalizability of the results. Another strength is the personal identification number that is assigned to each individual in Sweden. This gave the opportunity to follow the patients without any loss to follow-up. The outcome data were based on clinical diagnoses, registered by physicians, rather than self-reported data, which eliminated any recall bias. An additional key strength was the access to SAMS units that defined geographic boundaries of our study neighborhoods. The SAMS units were small (in the order of 1000-2000 persons) and each unit consisted of relatively homogenous types of buildings. In previous research, small neighborhoods have been shown to correspond well with how the residents define their neighborhoods (Bond Huie, 2001).

The Hospital Discharge register has very high validity and have a positive predictive value of >95% for many diagnoses e.g., MI, angina pectoris and stroke (Ingelsson et al., 2005, Ludvigsson et al., 2011, Nilsson et al., 1994). Both the Hospital Discharge Register and the Swedish Multi-generation Register have almost 100% complete data. For example, only 0.6% of the patients with diabetes were excluded because of missing SAMS codes. It was possible to link clinical data from individual patients to national demographic and socioeconomic data. The national demographic and socioeconomic data were highly complete – less than 1% of the data were missing.

In Study I, using the Swedish Multi-generation Register allows for analysis of causality through co-sibling design, which otherwise is a great challenge in observational studies. Including individuals in three different age group cohorts enables a life-course perspective to the causal nature of neighborhood effects on health. The inclusion of women and men allows for disentangling differences in potential neighborhood effects depending on sex. Finally, studying both CHD and ischemic stroke enables the detection of potential differences in neighborhood effects depending on type of diagnosis - different types of CVD might be differently affected by the neighborhood, and by different mechanisms. Also, the use of cross-classified multilevel modelling helped to separate contextual effects from individual-level effects. For this purpose, it is important not only to investigate average measures of associations, but also the potential clustering in certain contexts (Ohlsson and Merlo, 2011, Merlo et al., 2009). The clustering of CHD in the neighborhoods was of similar magnitude as that in previous studies (Sundquist et al., 2004a, Ohlsson and Merlo, 2011, Merlo et al., 2013).

Limitations

There are several limitations to these studies. The studies are limited to Sweden, although they included the entire population. Residual confounding may exist as socioeconomic measures only represent proxies for individual-level status.

The availability of universal health care in Sweden might mitigate potential negative neighborhood effects on health. In other countries without widespread universal health care, e.g., the United States, neighborhood effects are potentially even more pronounced. The availability of universal health care in Sweden can also be considered to be a strength in studies on neighborhood effects as it holds constant a potential confounder. The outpatient register is only available from 2001 onwards, but this likely has a small impact on the results, since most newly diagnosed CHD and stroke cases are registered at a hospital.

Although mobility was not accounted for, i.e., moving to a different neighborhood during the follow-up period, the mobility in this age group has previously been found to be low (Winkleby et al., 2007b).

For Study I, family based designs do not completely eliminate issues of residual confounding because family members may also differ in life-course exposures to non-shared environmental factors that condition both the selection of neighborhood of residence and the risk to develop CHD or ischemic stroke. The results, with their apparent evidence for a causal relationship between neighborhood SES and incidence of CHD or stroke, could arise entirely from risk factors that predispose both living in deprived neighborhoods and high incidence of CHD or stroke as long as all those risk factors were uncorrelated in relatives. However, the co-relative design allows to greatly reduce the confounding effect of unobserved confounding.

For Study III, there was no data on several risk factors for HF, such as smoking, high-caloric diet or physical inactivity. However, some prior works on SES and HF risk have adjusted for smoking and physical inactivity and still found an independent association (Akwo et al., 2018, Bikdeli et al., 2014). There was no data on quality of health care in the neighborhood.

For Study IV, another limitation was that workplaces were defined based on the geographic location, i.e., the address. This means that colleagues at the same address may be working in different buildings and have little or no interaction with each other. Individuals with missing information on workplace were not included in the study (n=481,642). The majority of these individuals were unemployed (n=445,907) and the scope of Study IV was to examine the potential influence of workplace on CHD. The excluded individuals were slightly older and had lower SES. The proportion of CHD cases in this group was also slightly higher (4.1% and 2.4% in the men and women, respectively).

Conclusions

Neighborhood SES was associated with incidence of CHD and ischemic stroke, and this work suggests that these associations were, at least in part, causal (Study I).

Neighborhood-level SES was modestly associated with statin medication rates in MI patients and this association was no longer significant after adjusting for individual-level sociodemographic factors (Study II). These findings indicate that individual-level approaches may be most important in health care policies regarding statin medication in MI patients.

The risk of incident HF is higher among patients with DM living in deprived neighbourhoods than among patients with DM living in less deprived/affluent neighbourhoods (Study III). This shows that patients with DM living in deprived neighbourhoods may need extra monitoring for HF.

Workplace socioeconomic characteristics, in particular the educational attainment of an individual's colleagues, may influence CHD risk (Study IV). These findings are new and need replication in other settings.

These findings raise important clinical and public health concerns and indicate that solutions need to reframe health problems from a sole focus on individual approaches to a broader focus that includes neighborhoods and workplaces and an investigation of the mechanisms behind these effects on cardiovascular diseases.

Svensk sammanfattning

Hjärt-kärlsjukdom är en grupp sjukdomar som innefattar bland annat kranskärlsjukdom, stroke och hjärtsvikt. Hjärt-kärlsjukdom orsakar årligen ca 31% av alla dödsfall i världen, och är den vanligaste dödsorsaken i nästan hela världen (förutom Afrika). Hjärt-kärlsjukdom är associerat med bostadsområdets socioekonomiska status, men flera kunskapsluckor finns.

Det övergripande syftet med denna avhandling var att utforska de kontextuella effekterna av bostadsområde och arbetsplats för en individs risk för hjärt-kärlsjukdom. I studie I analyserades sambandet med bostadsområdets socioekonomiska status (SES) och insjuknande i kranskärlssjukdom eller stroke för att kartlägga om det kunde finnas ett orsakssamband däremellan. I studie II undersöktes om statin-medicinering för hjärtinfarktpatienter skilde sig åt med olika nivåer av bostadsområdes-SES. I studie III var syftet att undersöka om risken för hjärtsvikt skilde sig åt för diabetespatienter som bodde i områden med olika nivåer av bostadsområdes-SES. I studie IV var syftet att undersöka sambandet mellan insjuknande i kranskärlssjukdom och de tre kontextuella variablerna genomsnittlig utbildningsnivå för alla kollegor på en individs arbetsplats, områdets SES för varje individs arbetsplats och bostadsområdets SES för varje individ.

Alla studier baserades på data från svenska nationella register, inklusive Registret över Totalbefolkningen, Patientregistret, Flergenerationsregistret, Läkemedelsregistret och Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier (LISA).

I studie I undersöktes sambandet mellan bostadsområdets SES och incidensen kranskärlssjukdom eller stroke i hela befolkningen och i hel- och halv-syskon för att avgöra om det finns ett orsakssamband eller om sambandet beror på andra bakomliggande faktorer i familjen. Efter att ha justerat för individuella socioekonomiska faktorer sågs sambandet mellan bostadsområdes-SES och kranskärlsjukdom inte minska med ökande genetisk likhet, särskilt för kvinnor.

I studie II följdes alla individer i Sverige som insjuknat i hjärtinfarkt 1 januari 2000 till 31 december 2010. Låg bostadsområdes-SES var associerat med låg statin-medicinering (oddskvot 0,80). I den fulla modellen, som även inkluderade individuella faktorer, var oddskvoten inte längre statistiskt signifikant.

I studie III följdes 434542 vuxna diabetiker över 30 år under 2005-2015 för att studera om de fick hjärtsvikt. Det fanns ett samband mellan bostadsområdes-SES och hjärtsvikt för diabetespatienter. Hasard-kvoterna var 1,27 för män och 1,30 för kvinnor för diabetespatienter som bodde i fattiga bostadsområden jämfört med diabetespatienter i rika områden.

I studie IV följdes individer födda i Sverige 1934-1957 (n=991072), och insjuknande i kranskärlssjukdom under åren 2008-2012 analyserades. Låg jämfört med hög genomsnittlig utbildningsnivå för alla kollegor på en individs arbetsplats var signifikant associerat med incidens av kranskärlssjukdom för både män (oddskvot 1,29) och kvinnor (oddskvot 1,38).

Dessa fynd indikerar att sambandet mellan bostadsområdes-SES och insjuknande i kranskärlssjukdom är delvis kausalt hos kvinnor. När det gäller statin-medicinering sågs inget samband med bostadsområdes-SES, så individuella strategier kan vara viktigast när det gäller att optimera statinmedicinering för hjärtinfarktpatienter. Risken för insjuknande i hjärtsvikt hos diabetespatienter var större i fattiga bostadsområden jämfört med diabetespatienter som bodde i rikare områden. Detta visar att diabetespatienter som bor i fattiga bostadsområden kan behöva extra kontroller vad gäller hjärtsvikt. Socioekonomiska faktorer på arbetsplatsen, särskilt utbildningsnivån för en individs kollegor, kan påverka risk för kranskärlssjukdom.

Sammantaget väcker dessa resultat kliniska och för folkhälsan viktiga frågeställningar och indikerar att lösningar behöver omformulera hälsoproblem från enbart ett fokus på individuella strategier till ett bredare fokus som även inkluderar bostadsområden och arbetsplatser.

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Appendix

Study I Supplementary Table 1. Hazard ratios and 95% confidence intervals for incidence of coronary heart disease (CHD) in men and women based on neighborhood socioeconomic status (SES); Results of Cox proportional hazard models.

Sex	**Men**			**Women**		
Age Group	40	50	60	40	50	60
Total population	1.07 (1.06-1.09)	1.05 (1.05-1.06)	1.04 (1.04-1.05)	1.11 (1.09-1.13)	1.10 (1.09-1.11)	1.08 (1.07-1.09)
Half-siblings	1.08 (1.02-1.13)	1.02 (0.97-1.02)	0.99 (0.93-1.06)	1.09 (1.01-1.17)	1.13 (1.07-1.20)	1.18 (1.09-1.28)
Full siblings	1.07 (1.04-1.10)	1.04 (1.02-1.05)	1.02 (1.01-1.04)	1.11 (1.07-1.16)	1.06 (1.03-1.08)	1.08 (1.06-1.10)

Study I Supplementary Table 2. Hazard ratios and 95% confidence intervals for incidence of ischemic stroke in men and women based on neighborhood socioeconomic status (SES); Results of Cox proportional hazard models.

Sex	**Men**			**Women**		
Age Group	40	50	60	40	50	60
Total population	1.04 (1.02-1.06)	1.03 (1.02-1.04)	1.02 (1.01-1.03)	1.07 (1.05-1.09)	1.04 (1.03-1.05)	1.04 (1.03-1.05)
Half-siblings	0.95 (0.87-1.03)	1.10 (1.04-1.17)	0.98 (0.91-1.06)	1.06 (0.98-1.16)	0.97 (0.89-1.05)	1.01 (0.93-1.09)
Full siblings	1.03 (0.99-1.07)	1.03 (1.01-1.05)	1.04 (1.02-1.06)	1.05 (1.00-1.10)	1.02 (0.99-1.04)	1.05 (1.02-1.07)

Study III Supplementary Table 1. Population sizes and neighbourhood characteristics by neighbourhood-level deprivation

	Neighbourhood deprivation		
	Low deprivation	Moderate deprivation	High derivation
Number of neighbourhoods	1,383	4,791	1,093
Numbers and percentage distribution of the study population by level of neighbourhood deprivation			
Men	33,635 (14.0%)	162,140 (67.7%)	43,792 (18.3%)
Women	24,255 (12.4%)	130,672 (67.0%)	40,048 (20.6%)
Neighbourhood Deprivation Index Range	-2.8 to <-1	-1 to 1	>1 to 10.1
Components of Neighbourhood Deprivation Index			
<10 years education	10.3%	18.1%	27.7%
Low income	6.9%	9.2%	16.4%
Unemployed	1.7%	3.0%	5.5%
Social welfare recipient	1.1%	3.2%	13.6%

Study III Supplementary Table 2. Hazards ratios (HR) and 95% confidence intervals (CI) for HF; Results of Cox regression models*

	HR	95% CI		P-value
Neighbourhood deprivation (ref. Low)				
Moderate	1.09	1.06	1.12	<.0001
High	1.13	1.09	1.16	<.0001
Age	1.06	1.06	1.06	<.0001
Gender to males (ref. Females)	1.30	1.28	1.33	<.0001
Family income (ref. Highest quartiles)				
Middle-high income	1.13	1.09	1.17	<.0001
Middle-low income	1.10	1.07	1.13	<.0001
Low income	1.07	1.03	1.10	<.0001
Education attainment (ref. ≥ 12 years)				
≤ 9 years	1.14	1.11	1.17	<.0001
10–11 years	1.07	1.04	1.10	<.0001
Country of origin (ref. Sweden)	1.01	0.98	1.04	0.473
Marital status (ref. Married/cohabiting)	1.17	1.15	1.19	<.0001
Region of residence (ref. Large cities)				
Southern Sweden	1.00	0.98	1.03	0.770
Northern Sweden	0.96	0.94	0.99	0.007
Mobility (ref. Not moved)	1.63	1.60	1.66	<.0001
Employment status (ref. Yes)	1.31	1.27	1.36	<.0001
Hospitalization of COPD (ref. Non)	2.09	2.04	2.14	<.0001
Hospitalization of alcoholism and related liver disorders (ref. Non)	1.19	1.12	1.26	<.0001
Hospitalization of obesity (ref. Non)	1.85	1.78	1.93	<.0001
Hospitalization of depression (ref. Non)	1.03	0.97	1.08	0.322
Hospitalization of hypertension (ref. Non)	1.38	1.36	1.41	<.0001
Hospitalization of CHD (ref. Non)	2.94	2.88	2.99	<.0001
Hospitalization of stroke (ref. Non)	1.13	1.10	1.15	<.0001

HR: Hazard ratio; CI: Confidence interval; HF: Heart Failure; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease.

*: Full adjusted model.

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