Mind the Gap: Socio-Economic and Gender Inequalities in Service Delivery and Mortality in Patients Hospitalised with Acute Coronary Syndrome

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Abstract

Coronary heart disease persists as the leading cause of death in most countries and is severely affected by health inequalities. This thesis examined socioeconomic and sex disparities in presenting characteristics, treatment and all-cause mortality in patients hospitalized with myocardial infarction (MI) or angina. It is composed of four independent but related studies.

Socioeconomic status and its association with healthcare and mortality after acute coronary syndrome: a systematic review (study 1)

Aims: In the first section of the thesis, a systematic review was conducted to determine the associations of SES with mortality and access to invasive cardiac procedures after ACS hospitalisation.

Methods and results: Electronic databases (Ovid Medline® and Embase) were searched in December 2017. The impact of SES was analysed separately for each outcome: 1) all-cause mortality at 30 days and at 1 year; 2) use of invasive cardiac procedures during hospitalisation split by coronary angiography (CAG) and percutaneous coronary intervention (PCI). Meta-analyses were conducted using random effects models. Subgroup analysis were performed to separate any differences across different measures of SES, countries of study, final diagnosis and year of publication.

Sixty studies were included. The overall results of the meta-analyses provided evidence for significantly higher risk of death among ACS patients in lower socioeconomic categories for both 30-day and 1-year mortality. Compared to ACS patients of the highest socioeconomic position, the risk of death at 30-days in the lowest group increased by 24% (RR 1.24, 95% confidence interval (CI) 1.17-1.31). The lowest socioeconomic category was also associated with increased risk of death at 1-year (RR 1.20, 95% CI 1.14-1.26). Socioeconomic disparities were also found in invasive cardiac procedure rates in patients hospitalised with ACS. Overall, groups with the poorest level of SES had reduced access to coronary angiography (RR 0.70, 95% CI 0.59-0.82) and PCI (RR 0.82, 95% CI 0.74-0.90). Results were consistent across subgroup and sensitivity analyses.

Conclusion: In patients with ACS, it is well established that a person's socioeconomic status has modest but profound effects on the utilisation of invasive cardiovascular services and mortality. These relationships have been demonstrated for different dimensions of area-level and individual level SES measures, across different countries and have not improved over time. Differences in mortality across socioeconomic strata is greatly attenuated after considering treatments and related factors, while targeting poor geographical access to healthcare facilities may be the most efficient way to decrease the inequality gap in utilisation of invasive coronary procedures. In addition, inequalities in utilisation of PCI and in receiving medical attention suggest that inequalities in access to good quality care may play a role in explaining the higher case death of ACS among people with lower SES. However, the magnitude of the contribution of differences in interventional procedures to inequalities in mortality needs to be investigated further using mediation analyses.

Socio-economic inequalities on treatment and mortality after acute coronary syndrome hospitalisation (study 2)

Aim: This is a comprehensive study of socio-economic inequalities in ACS in West of Scotland by linking real world electronic datasets.

Methods and results: A cohort study was conducted with all patients admitted with MI or angina (01 October 2013 to 30 June 2016) from a secondary care acute coronary syndrome e-Registry in NHS Scotland linked with national registers of community drug dispensation and mortality data. SES deprivation at baseline is measured using quintiles of the SIMD 2012 measure.

A total of 7878 patients hospitalized for MI or angina were included. SES remained a factor associated with CAG (SIMD Q1 vs Q5 OR 0.63, CI 0.52–0.75) and PCI (SIMD Q1 vs Q5 OR 0.67, CI 0.56–0.81) use after adjusting for clinical and demographic characteristics in NSTEMI patients. In STEMI patients, there was a slight higher rate of CAG in the most deprived group (OR 1.58 CI 1.02-2.45) compared to the least deprived group but the strict criteria used for PCI eliminates any inequalities subsequent a CAG. Overall, the risk of death at 1 year after admission to hospital differs by SIMD group within STEMI patients but not in non-STEMI patients. The increased risk of death compared to the least deprived group may be mostly attributed to differences in prescription uptake.

Conclusion: Continuation of high performance within hospitals and correcting the differences in secondary prevention treatment should be the first steps towards the reduction of excess case fatality due to socioeconomic disparities.

Healthcare disparities for women hospitalised with acute coronary syndrome (study 3)

Aims: Sex disparities in presenting characteristics, treatment and all-cause mortality in patients hospitalized with myocardial infarction (MI) or angina were examined in this study.

Methods and results: A cohort study of all patients admitted with MI or angina was conducted using the same dataset as study 2; 3161 (40%) were women. Women were older, more deprived, had a greater burden of comorbidity, were more often treated with guideline-recommended therapy preadmission and less frequently received immediate invasive management. Men were more likely to receive coronary angiography (adjusted odds ratio (OR) 1.52, CI 1.37-1.68) and percutaneous coronary intervention (adjusted OR 1.68, CI 1.52-1.86). Women were less comprehensively treated with evidence-based therapies post-MI. Women had worse crude survival, primarily those with ST-elevation myocardial infarction (14.3% vs. 8.0% at 1 year, $P < 0.001$), but this finding was explained by differences in baseline factors. Men with non-ST-elevation myocardial infarction had a higher risk of all-cause death at 30 days (adjusted hazard ratio (HR) 1.72, CI 1.16-2.56) and 1 year (adjusted HR 1.38, CI 1.12-1.69).

Conclusion: After taking account of baseline risk factors, sex differences in treatment pathway, use of invasive management, and secondary prevention therapies indicate disparities in guideline-directed management of women hospitalized with MI or angina.

An exploration of mediation models in acute coronary syndrome health disparities (study 4)

Aims: It is not known whether inequalities in access to guideline recommended procedures and medications translates into inequalities in mortality. This study is aimed to dissect the relationship between gender (and socio-economic status), the provision of PCI, medications and mortality where the direct effect of gender (and SES) on mortality is separated from the indirect effect through treatments.

Methods and results: Parallel and serial multiple mediator models were used to quantify the mediating effect of healthcare inequalities (provision of PCI and secondary medication use) on the relationship between gender (and SES) on 1-year all-cause mortality. All models adjusted for the effects of baseline characteristics.

Inequalities in the provision of PCI mediated the relationship between sex and mortality at 1 year for ACS patients. The effect of less invasive treatment in women is translated into higher mortality by around 10%. The sum of all the specific indirect effects through treatment disparities is statistically significant at OR=1.34 (CI 1.15-1.65). Women have 34% higher odds of death at 1 year through the combined effect of lower invasive and medical treatment compared to men.

Similar associations were found for socio-economic disparities. The odds of death at 1 year were additionally lowered in the least deprived group by 6% through the mediation of unequal invasive treatment rates (OR 0.94, CI 0.90-0.97). Together, through both better invasive and medical treatment access in the least deprived group, the odds of death at 1 year was 13% lower in least deprived SES group (total indirect effect OR 0.87, CI 0.71-1.09) compared to the most deprived group. This further exacerbates the already unequal survival rates in the two groups under equal treatment conditions.

Conclusion: Mediation analysis suggests that even though women have lower risk compared to men when treated the same, treatment disparities reversed this mortality risk. For the most deprived group, who are already at increased risk when treated the same, lower treatment rates exaggerated the unequal risk of death compared to the least deprived group. As most of mediating effect on mortality was through unequal PCI rates, reducing treatment inequalities by increasing PCI rates in women and deprived groups would most effectively diminish the survival gap seen between the sexes, and SES groups.

Table of Contents

List of Tables

List of Figures

Publications and Presentations

Conference Presentations

Abstracts of the research work included in thesis were accepted for presentation at the following conferences:

Informatics for Health 2017 Conference, Doctoral Symposium. Manchester, England. April 2017.

Medicine 24@ Excellence in Health Care. Glasgow, Scotland, June 2017

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European Congress on eCardiology & eHealth. Berlin, Germany. November 2017.

Publications Related to Thesis

JACKSON, A. M., **ZHANG, R.**, FINDLAY, I., ROBERTSON, K., LINDSAY, M., MORRIS, T., FORBES, B., PAPWORTH, R., MCCONNACHIE, A., MANGION, K., JHUND, P. S., MCCOWAN, C. & BERRY, C. 2020. Healthcare disparities for women hospitalized with myocardial infarction and angina. Eur Heart J Qual Care Clin Outcomes, 6, 156-165.

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Author's Declaration

One chapter included in this thesis, which I led and conducted the analysis for, have been published in its entirety with co-authors. Copyright clearance can be found in supplement appendix document A.

Chapter 4: JACKSON, A. M., **ZHANG, R.**, FINDLAY, I., ROBERTSON, K., LINDSAY, M., MORRIS, T., FORBES, B., PAPWORTH, R., MCCONNACHIE, A., MANGION, K., JHUND, P. S., MCCOWAN, C. & BERRY, C. 2020. Healthcare disparities for women hospitalized with myocardial infarction and angina. Eur Heart J Qual Care Clin Outcomes, 6, 156-165.

I declare that I am the sole author of this thesis, except where the contribution of others has been acknowledged. The work in this thesis has not been submitted in any form for another degree or professional qualification.

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Definitions/Abbreviations

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
aINC	Area-based income
APT	Antiplatelet therapy
ARBs	Angiotensin receptor blockers
BP	Blood pressure
CAG	Coronary angiography
CVD	Cardiovascular disease
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
GTN	Glyceryl trinitrate
GJNH	Golden Jubilee National Hospital
GGC	Greater Glasgow and Clyde
HA	Hospitalised (stable or unstable) Angina
HDL	High-density lipoproteins
ICD	International Classification of Disease
IQR	Interquartile range
ISD	Information Services Division
MI	Myocardial infarction
MRA	Mineralocorticoid Receptor Antagonists
NICE	National Institute for Health and Care Excellence
NHS	National health service
NSTEMI	non-ST segment elevation myocardial infarction
PCI	Percutaneous Coronary Intervention
OAC	Oral anticoagulants
SES	Socioeconomic status
SIMD	Scottish Index of Multiple Deprivation
SMR01	Scottish Morbidity Records – General/Acute Inpatient and Day Case
STEMI	ST segment elevation myocardial infarction
TIAs	Transient ischemic attacks
UA	Unstable angina

Chapter 1 General Introduction to CHD and associated inequalities in outcomes and care

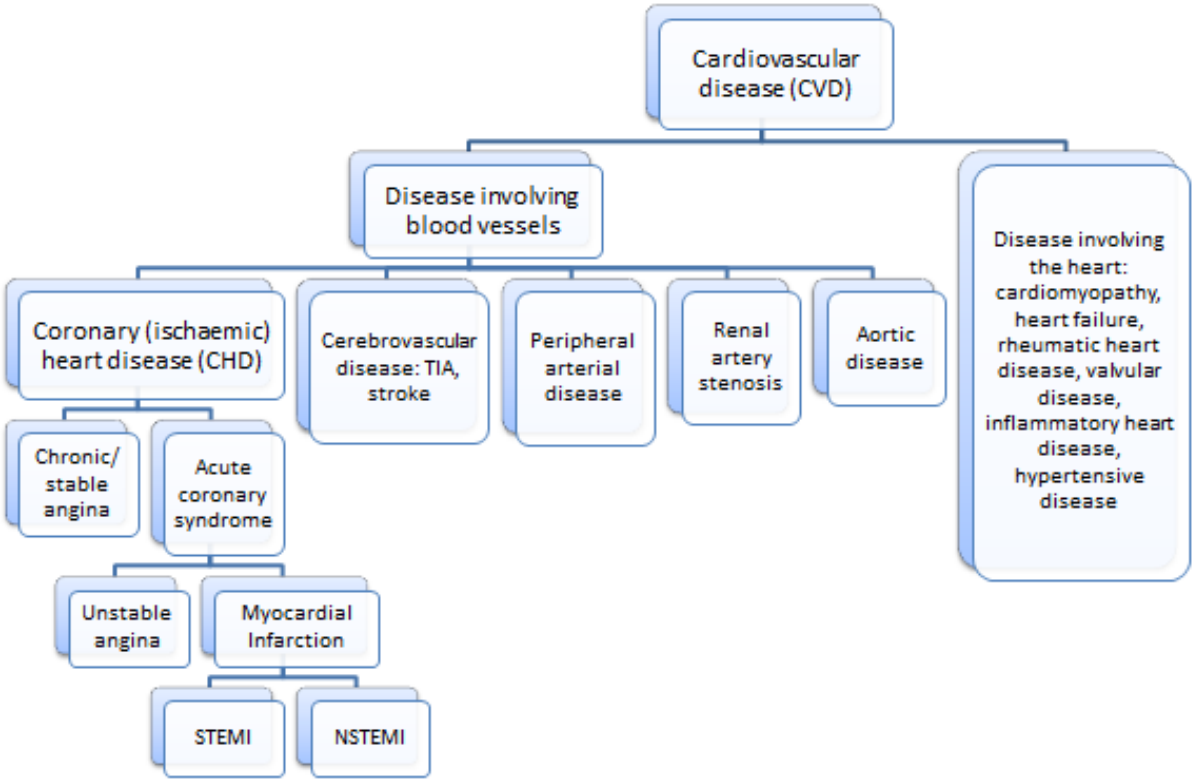
1.1 Coronary heart disease

1.1.1 Classification

Cardiovascular disease (CVD) is a collective term for conditions affecting the heart or blood vessels and can be divided into several different types (Figure 1-1). Coronary heart disease (CHD) is the most common type of CVD.

When the flow of oxygen-rich blood to the heart is blocked or restricted, the increase in strain on the heart muscles causes CHD. The extent of the blockage leads to either i) an angina, where blood flow is restricted and causes chest pain or ii) a myocardial infarction (MI), where the blood flow is suddenly blocked. CHD will be the focus of discussion in this thesis.

Figure 1-1. Classification of CVD



Angina is chest pain caused by reduced blood flow to the heart muscles. Although usually not life threatening, it's a warning for increased risk of a more severe heart attack. There are 2 main types of angina. The more common stable angina is usually due to a “trigger”, such as stress or exercise and stops within a few minutes of resting (NHS UK, 2018a). Unstable angina is more serious and often unpredictable and continuous. Along with myocardial infarction, they are medical emergencies classified as acute coronary syndromes (ACS).

1.1.2 Burden of disease

1.1.2.1 Mortality

CVD is the second most common cause of death in the UK in 2017 at 25%, just behind cancer at 28% (Cancer Research UK, 2018, British Heart Foundation, 2018a). While CHD, the most common type of CVD, by itself is the biggest single cause of death at 14% in men and 9% in women, more than any single type of cancer (British Heart Foundation, 2019, Cancer Research UK, 2016). In Scotland, treating CHD is a “national clinical priority” (NHS Health Scotland Information Services Division, 2018b).

Based on the 2018 CVD statistics mortality data published for the British Heart Foundation, these figures have actually decreased significantly in the past 50 years: the age standardised CHD mortality declined by three quarters in the UK (British Heart Foundation, 2018a). According to the 2017 Scottish Heart Disease Statistics Report published by NHS Scotland ISD, the age and sex adjusted mortality rate for CHD fell by 40% compared to 2007 in Scotland (NHS Health Scotland Information Services Division, 2018b). Healthy lifestyle changes, an increase in the use of drugs to treat risk factors, and improved treatment and access for acute heart attacks and strokes has all contributed to this success. Despite higher survival rates, “the benefits are unevenly distributed within society” (World Health Organization, 2019). There are substantial regional, socioeconomic and gender variations that reflect inequalities in prevention and treatment (Townsend et al., 2015, World Health Organization, 2019). Only by collecting accurate data and analysing the variations in risk factors and in the treatment process can we hope to devise ways to continue to reduce this burden of disease and inequality gap.

1.1.2.2 Regional differences in mortality

Heart and circulatory disease statistics 2018 published by the BHF reported the clear north-south regional divide for CHD mortality in the UK (British Heart Foundation, 2018a). Age standardised death rates were highest in Scotland followed by Wales, Northern Ireland then England. The rate of decrease over the years for CHD mortality is also the lowest in Scotland compared to the other 3 countries (Townsend et al., 2015).

The published statistics show that age-standardised death rates by local authority have regions in North West England and in Scotland with the highest CHD death rate for 2014/2016. Glasgow City which topped all other regions for premature CHD death for 2011/2013 was second for 2014/2016. Five of the ten local authorities with the highest CHD death rates in the UK were in Scotland, while the ten authorities with the lowest death rates were all in England (Table 1-1). As pointed out by an editorial for the BHF CVD statistics, the stark regional differences are more plausibly attributed to a socioeconomic divide of the corresponding areas than anything else (Timmis, 2015).

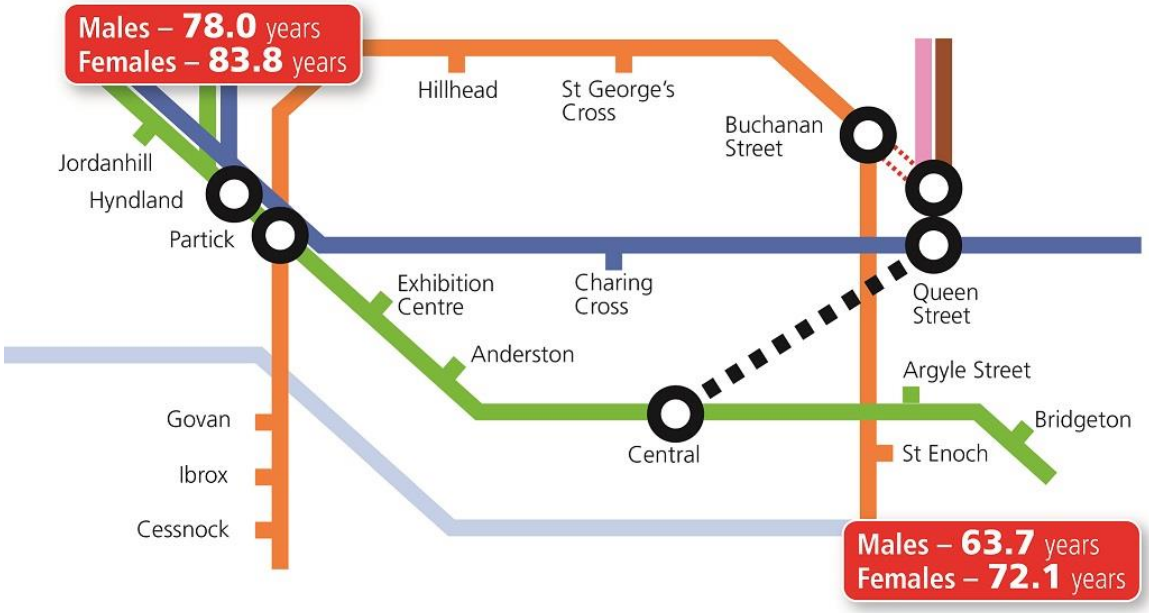
Table 1-1. Ranking for 10 local authorities with highest and lowest CHD mortality rates, UK, 2014/16

Local authority	Region/Nation	Age-standardised death rates per 100,000
Ten highest death rates		
Manchester	North West	186.7
Blaenau Gwent	Wales / Cymru	177.2
Blackburn with Darwen	North West	177.1
Tameside	North West	176.6
Hyndburn	North West	172.7
Shetland Islands	Scotland	171.8
East Ayrshire	Scotland	168.3
West Dunbartonshire	Scotland	166.7
Dundee City	Scotland	164.4
Glasgow City	Scotland	162.6
Ten lowest death rates		
Richmond upon Thames	London	76.9
East Hampshire	South East	76.6
Epsom and Ewell	South East	75.8
Mid Sussex	South East	75.0
Sevenoaks	South East	73.5
Rutland	East Midlands	68.5
Chiltern	South East	68.1
City of London	London	67.5
Hart	South East	60.8
Kensington and Chelsea	London	60.7

Adapted using data from BHF CVD statistics 2018 Chapter One-Mortality (British Heart Foundation, 2018a)

Health inequalities by region not only exist at the national level, but also within local areas. The notorious life expectancy map of Glasgow (McCartney, 2011) is a stark illustration of health inequalities by region. The updated figure using NHS Scottish Public Health Observatory profiles published in June 2015 shows that life expectancy still goes down by 2 years for every station on the train line in Glasgow travelling from the more affluent west end Jordanhill station to the less affluent east end Bridgeton station (NHS Health Scotland, 2019b). Although total life expectancy increased compared to data from 2005, the difference by region not only persisted but have actually increased. As pointed out by NHS Health Scotland, relative inequalities in mortality has increased since 1981, as those in the least deprived groups improved at a faster rate compared to the most deprived group.

Figure 1-2. Life expectancy data of 2015



Obtained with permission from Public Health Scotland website (NHS Health Scotland, 2019b). Adapted from the SPT travel map by Gerry McCartney.

1.1.2.3 Morbidity

The latest statistics provided by BHF indicates that in 2016/17, there were 0.4 million hospital episodes in the UK for CHD, this account for roughly 3.1% and 1.3% of all inpatient episodes in men and women respectively (British Heart Foundation, 2018c). Within Scotland, CHD accounts for about 4.4% and 2.2% of

all hospital episodes in men and women respectively (Townsend et al., 2015, British Heart Foundation, 2018c).

The number of hospital episodes attributed to CHD has stayed quite consistent, at around 0.5 million episodes per year over the past 7 years for all of UK and 50,000 episodes per year in Scotland (British Heart Foundation, 2018c).

There are over 200,000 hospital visits each year due to heart attacks in the UK. If hospital episodes were an exact representation of disease incidence, someone has a heart attack roughly every three minutes in the UK (British Heart Foundation, 2019). In Scotland, the Scottish Morbidity Records – General/Acute Inpatient and Day Case (SMR01) dataset indicate that there has been a steady increase in the number of hospital discharges over the past decade: 15,582 in 2007 to 26,497 in 2017 (NHS Health Scotland Information Services Division, 2018a).

1.1.2.4 Mortality after hospitalisation

As a measure of the outcome of hospitalisation, 30-day mortality is widely used to reflect the quality of care, as well as the severity of disease. Table S1 of the 2017 Scottish Heart Disease Statistics (NHS Health Scotland Information Services Division, 2018b) reports that in those hospitalised with incident ACS (defined as an admission where there has been no admission for the same condition in the previous 10 years), 30-day mortality after admission decreased from 14% from 2007 to 7% in 2017 for MI patients. 30-day mortality for UA patients remained low at around 1% throughout.

The Scottish Heart Disease Statistics report also highlights the difference in CHD mortality and overall mortality after hospitalisation by social deprivation group and by sex. This will be the focus of this thesis.

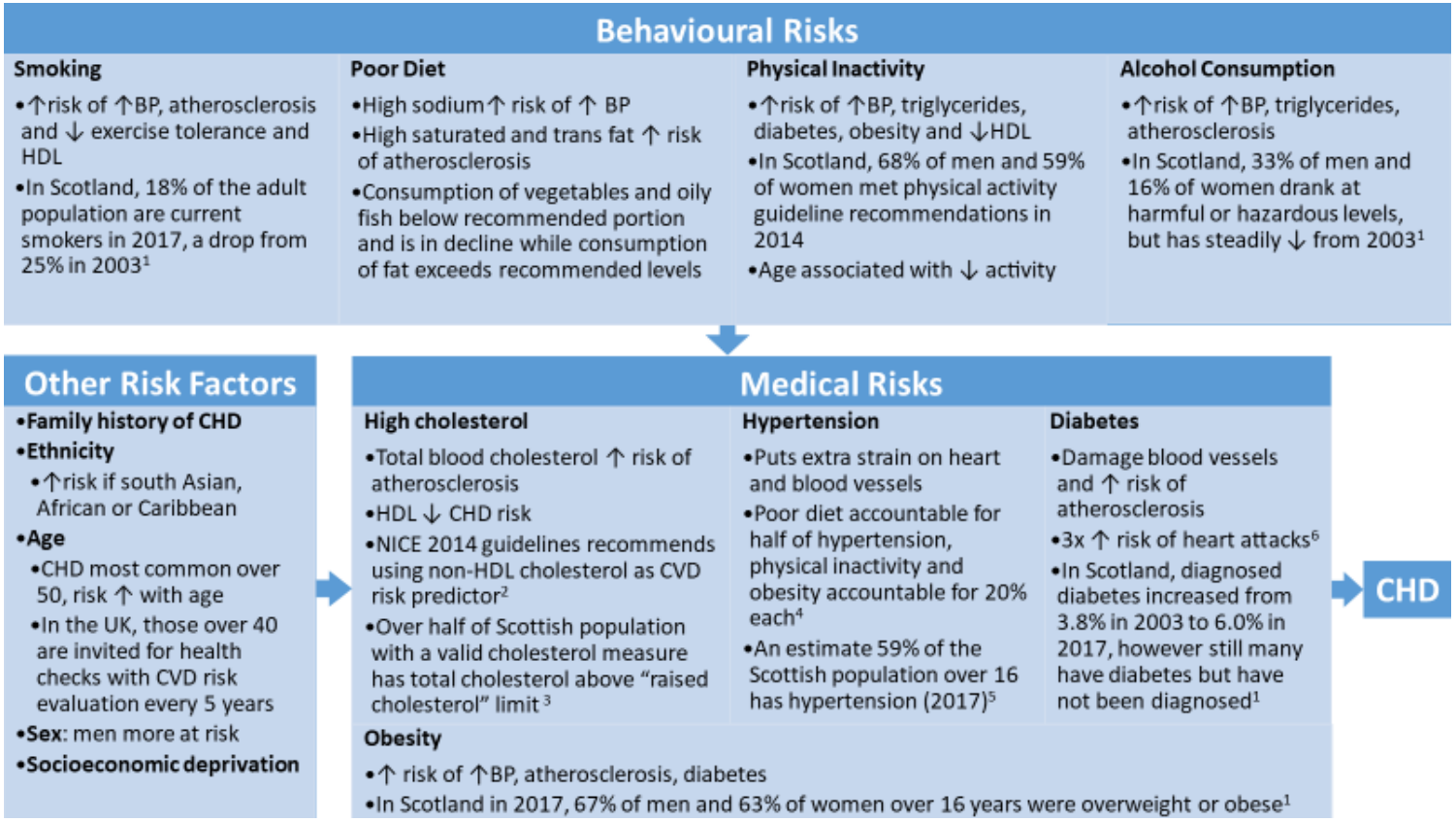
1.1.3 Risk factors

According to the NHS, there are many factors that increase one's risk for CHD (NHS UK, 2018b). Risk factors for CHD can be categorised as behavioural or medical risk factors (Figure 1-3). Preventable behavioural risk factors relate to

unhealthy lifestyles such as excess alcohol consumption, poor (e.g. high-sodium or trans and saturated fats) diet and sedentary behaviours. These behavioural risk factors increases the risk of medical risk factors for CVD. For example, inactivity and smoking may lead to high blood pressure, high cholesterol, diabetes, and obesity, all of which can damage the blood vessels (Townsend et al., 2015, NHS UK, 2018b). In addition, family history of CHD, age (50 or over), gender (men) are also risk factors for CHD.

In Scotland, according to National Statistics Heart Disease Report (NHS Health Scotland Information Services Division, 2018b), there is a strong relationship between social deprivation and these preventable risk factors. Therefore it is intended that these risk factors, where possible, will be included in the analysis section of this thesis when appropriate.

Figure 1-3. Risk factors of CHD



Adapted from NHS UK CVD website and BHF CVD Statistics Report (NHS UK, 2018b, Townsend et al., 2015). 1- The Scottish Health Survey 2017 (The Scottish Government, 2017); 2-NICE Guideline 181 (National Institute for Health and Care Excellence, 2014); 3-ScotPHO Scottish Data High Cholesterol (The Scottish Public Health Observatory (ScotPHO), 2019a); 4-(Campbell et al., 2014); 5-ScotPHO Scottish Data High Blood Pressure (The Scottish Public Health Observatory (ScotPHO), 2018); 6-(Fox et al., 2007)

1.1.4 Assessments and diagnosis

This section is a summary of the assessment and diagnosis for CHD from the NICE Clinical Guideline 95: Chest pain of recent onset: assessment and diagnosis (National Institute for Health and Care Excellence, 2010a).

1.1.4.1 Presentation with acute chest pain (suspected cause by ACS)

A standard initial assessment considers the history and characteristics of the chest pain, presence of cardiovascular risk factors, history of CHD and previous treatment. If an ACS is suspected from the initial assessment, an ECG is usually performed as soon as possible without delaying transfer to hospital and management starts immediately in the order appropriate to the circumstances. An electrocardiogram (ECG) is an important test in suspected ACS. ST-segment changes or other abnormalities from the ECG helps to confirm the final diagnosis, which will help determine the most effective management.

Assessments after arriving in hospital for patients with suspected ACS include a physical examination, a detailed clinical history, an ECG if not performed prior to admission and a blood sample for troponin. Troponins are proteins contained within heart cells. When the heart muscle is damaged, troponins leak into the blood. Therefore it is a test to help assess if there is heart muscle damage. The release is slow, so the level of troponin in the blood usually rises gradually over a few hours which means it might not be detectable if tested too early. This is why troponin levels are not used as a way to decide on immediate treatment. A positive troponin test would confirm that there has been as heart attack. While a negative test several hours after symptoms first started would confirm a diagnosis of unstable angina as there was no damage to the heart muscle.

Coronary angiography (CAG) can identify whether a blockage or narrowing has occurred in the coronary arteries and, if so, locate the exact location of the blockage. Invasive CAG involves inserting a catheter into the coronary arteries and pumping through a contrast agent. The contrast agent would show up on the X-rays, indicating any sites of blockage. A follow-up percutaneous coronary intervention (PCI) would be performed if indicated.

1.1.4.2 Presentation with stable chest pain (suspected cause by stable angina)

Similar to acute chest pain, a standard initial assessment considers the history and characteristics of the chest pain, any associated symptoms, prior physical exertion, presence of cardiovascular risk factors, history of CHD and previous treatment. Patients are often offered glyceryl trinitrate (GTN) to reduce discomfort. An initial diagnosis can usually be made based on the initial assessment and reaction to GTN. Further diagnostic tests in hospital such as non-invasive functional imaging or invasive or CT CAG is needed to confirm the diagnosis.

1.1.5 Initial management

1.1.5.1 Myocardial infarction

Myocardial infarction (MI) was first described pathogenically in western medical literature by James Herrick in 1912 (Herrick, 1983). MIs are nearly always caused by coronary heart disease where the inside of one or more of the coronary arteries become narrowed due to atheroma (fatty deposits) build up within the artery walls. This area is called a plaque. When a plaque cracks damaging the artery wall, a blood clot will form which can block the coronary artery and starve the heart muscle from oxygen, causing a MI.

MIs can be classified into two types: ST segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), as measured from the ST segment of the electrocardiogram (ECG). The classification corresponds to the area of damage inflicted on the heart. The following information on treatment for MIs are summarised from the National Institute for Health and Care Excellence (NICE) clinical guidelines CG95 (National Institute for Health and Care Excellence, 2010a), CG167(National Institute for Health and Care Excellence, 2013a), CG94 (National Institute for Health and Care Excellence, 2010b) and CG172 (National Institute for Health and Care Excellence, 2013b).

1.1.5.1.1 STEMI

A STEMI is the most serious type of ACS, where there is a long interruption to the blood supply causing the heart muscle supplied by the blocked artery to die. The NICE guidelines states that the highest priority in managing STEMI is to restore adequate coronary blood flow as quickly as possible as around half of potentially salvageable myocardium is lost within 1 hour of blockage, and 2/3 lost within 3 hours.

Around 30 years ago, the most effective treatment was to administer thrombolytic agents, which have the ability to dissolve the clot. However, these drugs do not result in coronary reperfusion in around 25% of the cases and can cause bleeding complications such as haemorrhagic stroke in 1% of cases. Following the publication of numerous trials, the national guidance from the Department of Health (UK Department of Health, 2008) now recommends primary percutaneous coronary intervention (primary PCI) as the treatment of choice for STEMI, provided it could be delivered in a timely fashion.

1.1.5.1.1.1 In Hospital Management Strategies

Patients with STEMI should be immediately assessed for eligibility for coronary reperfusion therapy. This means either primary PCI or given thrombolytic drugs. Early treatment can limit the amount of damage to the heart muscle and the therapy administered is fully dependent on timely access to PCI.

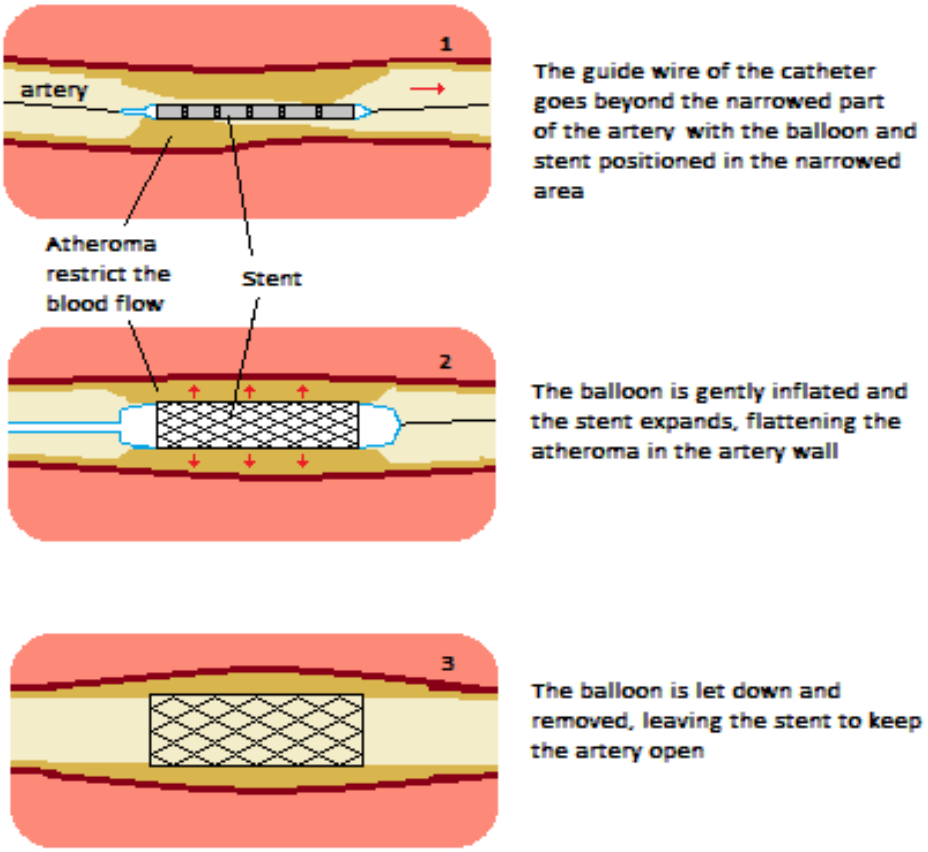
1.1.5.1.1.1.1 Primary PCI

PCI is a group of mechanical techniques to restore coronary flow to improve outcomes. The overarching term primary PCI includes coronary angioplasty, thrombus extraction catheters and stenting. Procedures are performed in a cardiac catheterisation laboratory, or “Cath lab” for short, which deals with heart tests and treatments.

Before a PCI, a coronary angiography (CAG) is performed to assess the blockage of the artery. If indicated, PCI is performed as part of the same procedure. As shown in Figure 1-4, a catheter with a balloon at its tip is first passed through

the plaque. The balloon is then inflated so it squishes the atheroma causing the narrowing. As a result, the narrowed section is widened. In almost all PCIs, a stent is then inserted in the widened artery that takes the place of the balloon to hold the artery open. The deflated balloon and the catheter are then removed. The Cath lab at the Golden Jubilee National Hospital (GJNH) is the only one in NHS Greater Glasgow and Clyde (NHS GGC).

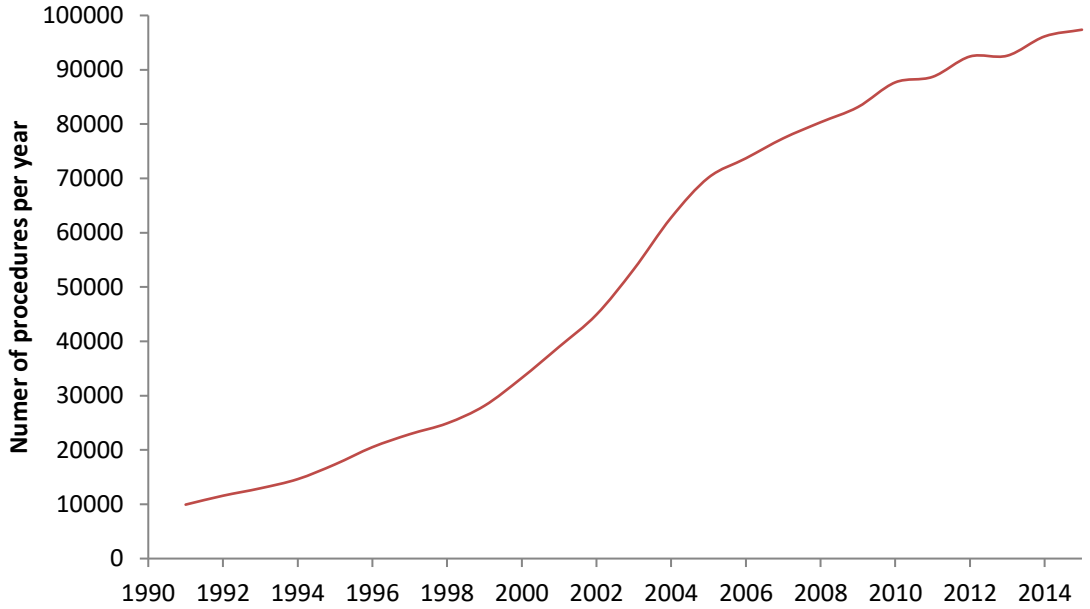
Figure 1-4. Coronary angioplasty with a stent



Adapted from British Heart Foundation, Beating my Heart attacked booklet (McArdle, 2017).

The number of percutaneous coronary interventions (PCI) carried about in the UK in 2015 were more than five times the number compared to two decade ago (Figure 1-5). It was in 2003, that Europe introduced guidelines recommending PCI as the first choice treatment for STEMI (Van de Werf et al., 2003). In the UK, the use of PCI for heart attack started to be offered in a small number of cardiac centres by about 2002, while a formal guidance was put into place in 2008 (UK Department of Health, 2008).

Figure 1-5. Number of percutaneous coronary interventions per year, UK



Using data extracted from British Heart Foundation, Heart and Circulatory Disease Statistics 2018 (British Heart Foundation, 2018b).

Based on the best available evidence, NICE recommends that coronary angiography with follow-on primary PCI is the preferred coronary reperfusion strategy unless primary PCI cannot be delivered with 120 minutes of the time when fibrinolysis could have been given. How quickly primary PCI can be delivered can be influenced by the number of procedures carried out by the catheter lab and the transfer time to the catheter lab. Regardless of the reperfusion method used, delays to treatment are associated with an increased risk of death. Those who have a heart attack and have a PCI usually stay in hospital for 2-3 days (McArdle, 2017).

1.1.5.1.1.2 Thrombolysis

When PCI cannot be given within 120 minutes, thrombolysis, a “clot-busting” medicine such as recteplase or tenecteplase is injected into the bloodstream to dissolve the blood clot, as recommended by NICE. This can be done either in the ambulance or at the nearest hospital. After 60-90 minutes of administration, an ECG is offered to assess residual ST-segment elevation. If the test suggest failed coronary reperfusion, coronary angiography with follow-on PCI if indicated is offered again.

In STEMI patients who are ineligible for reperfusion therapy, medical therapy is offered. These drugs are detailed in Section 1.1.6.1.

1.1.5.1.2 NSTEMI

NSTEMIs are usually less serious than STEMIs. This is because the supply of blood to the heart may be only partially, rather than completely, blocked. As a result, a smaller section of the heart may be damaged. However, in terms of long-term outcomes STEMI and NSTEMI have equal health impacts. Without treatment, it can progress to a STEMI (NHS UK, 2016) (NHS UK, 2016) or lead to worse long term outcomes then STEMI (Terkelsen et al., 2005, Johansson et al., 2017).

Patients diagnosed of NSTEMI should be assessed for future risk of adverse cardiovascular events using an established risk scoring system that predicts 6-month mortality, such as Global Registry of Acute Cardiac Events (GRACE) score. This risk score should determine the initial management of the patient within hospital.

1.1.5.1.2.1 Invasive vs conservative in-hospital management

In those with intermediate or high risk of adverse cardiovascular events, CAG is offered with follow-on PCI if indicated within 96 hours of admission. In NSTEMI patients with low risk (predicted 6-month mortality of 3% or less), conservative management without early coronary angiography to patients is offered. Before discharge, a test for ischemia is offered. If ischemia is demonstrated by testing, then CAG and PCI would be offered. Conservative management includes a range of antiplatelet and antithrombin therapy detailed in Section 1.1.6.1.

However, the 6-year surveillance audit document of the NICE CG94 (National Institute for Health and Care Excellence, 2016) identifies that risk stratification is not used widely and many clinicians prefer to offer an invasive strategy to the majority of patients with a diagnosis of NSTEMI.

1.1.5.2 Unstable angina

Unstable angina (UA) is the least serious type of ACS. However, like NSTEMI, it is still regarded as a medical emergency as it can also progress to serious heart

damage/ STEMI. In UA, the blood supply to the heart is still seriously restricted, but there is no permanent damage, so the heart muscle is preserved. UA shares the same initial (hospital) management guidelines as NSTEMI (National Institute for Health and Care Excellence, 2010b).

1.1.5.3 Stable angina

The risk factors for stable angina are the same as those for CHD. Initial management consists of one or two anti-angina drugs, to prevent episodes of angina, plus secondary prevention of CHD, which are similar to those given for MIs (National Institute for Health and Care Excellence, 2011) as detailed in the next section. For patients with stable angina whose symptoms are not satisfactorily controlled with drug treatment or hospitalised, reperfusion therapy, as offered to MI patients are then considered.

1.1.6 Long term management (Secondary Prevention)

1.1.6.1 Medical Management

Long-term therapy aimed at risk reduction of further CHD, heart failure and death has been shown to be effective in large clinical trials, and recommended by NICE guideline CG172 (National Institute for Health and Care Excellence, 2013b) and CG181(National Institute for Health and Care Excellence, 2014), for the following categories of medicines.

- **Antiplatelets** (APT) reduce the formation of blood clots. The most common APT used is aspirin, which is most likely given for life. Another APT, either clopidogrel, prasugrel, or ticagrelor, is often offered together to be taken for a year. Oral anticoagulants (OAC), which has similar effects as APT, is often taken instead in patients with an indication for OAC (e.g. atrial fibrillation).

- **Beta-blockers** reduce the strain on the heart by decreasing the heart rate and blood pressure and therefore reduce the oxygen demand of the heart. Treatment usually continues for life.

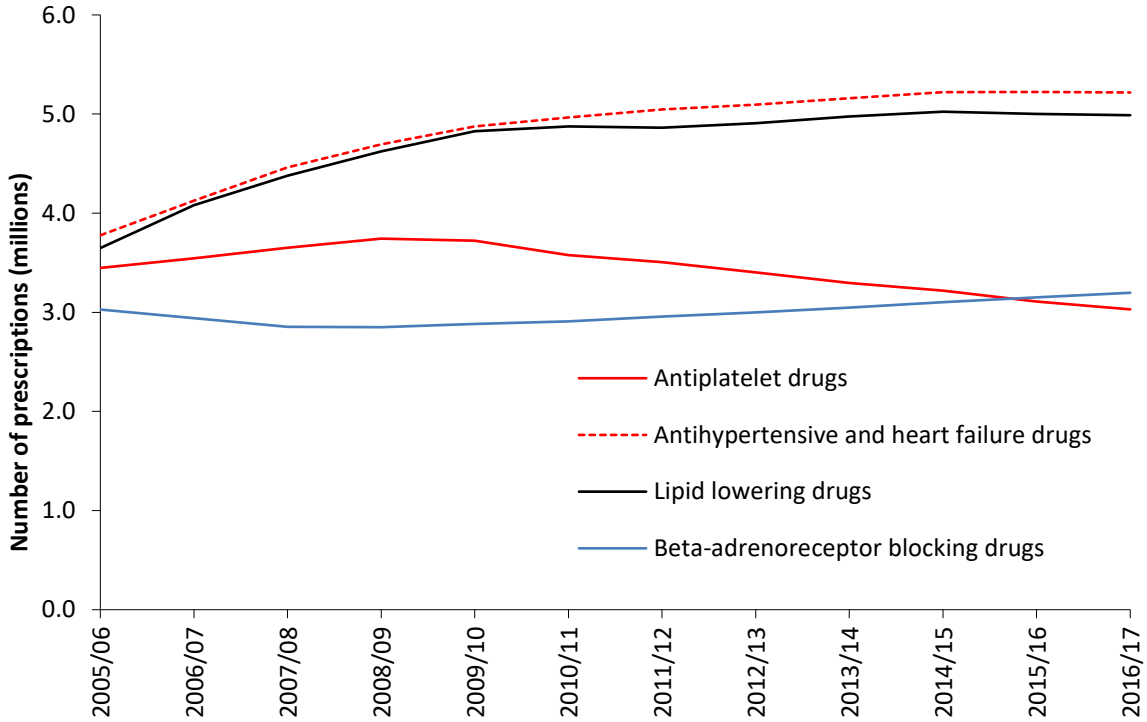
- **ACE (angiotensin-converting enzyme) inhibitors or ARBs (angiotensin receptor blockers)** relax and widen the blood vessels, lowering the blood pressure and improves blood flow to the heart. Most take these drugs long term, often for life to prevent heart failure after ACS.

- **Statins** reduce the cholesterol level, thus lower the risk of atheroma build up in the arteries. They only work if continuously taken, therefore also prescribed for life.

The rapid increase in the number of prescriptions for the treatment and prevention of CVD began in the late 1980s (British Heart Foundation, 2015). More than six times as many prescriptions for CVD in England were dispensed in 2016 compared to 1981. This equates to around 300 million prescriptions in England (British Heart Foundation, 2018b).

In Scotland, data is only available since 2001. More than 24 million prescriptions were dispensed for treating CVD in 2017 and this number has remained fairly consistent since 2008 (Figure 1-6). However, the cost of prescriptions dispensed for CVD drugs has fallen by 38% over the last decade to £124.0 million in 2016/17, reflecting falls in drug prices (NHS Health Scotland Information Services Division, 2018b).

Figure 1-6. Common Prescriptions used in the prevention and treatment of CVD for CHD patients, Scotland 2005/06 to 2016/17



Using data extracted from British Heart Foundation, Heart and Circulatory Disease Statistics 2018 (British Heart Foundation, 2018b).

1.1.6.2 Aftercare

NICE guidelines CG171 (National Institute for Health and Care Excellence, 2013b) recommend integrating cardiac rehabilitation within secondary prevention therapy as research shows that going to cardiac rehabilitation reduces mortality rates in CHD patients. This service offers a broad exercise and health education programme with psychological and social support. Cardiac Rehabilitation in Scotland audit published in 2012 reports that 67% of MI patients and 4% of UA were referred for cardiac rehabilitation across Scotland (NHS Health Scotland Information Services Division, 2013). However, this was the most recent report and it appears that data on cardiac rehabilitation for Scotland is no longer being collected. The National Audit of Cardiac Rehabilitation Project of the BHF (British Heart Foundation, 2018e) excludes Scottish data as well.

1.2 Health inequalities

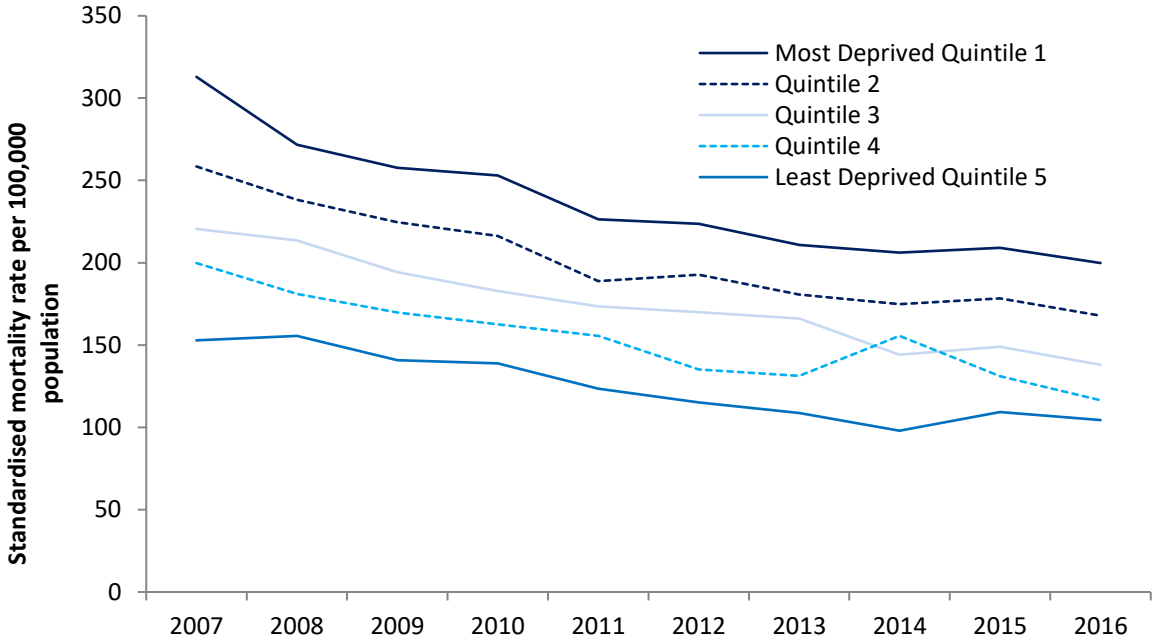
As defined by NHS Health Scotland (NHS Health Scotland, 2019c), health inequalities are unjust and avoidable differences in health between specific

population groups. Certain social circumstances beyond an individual's control disadvantage people and limit their chances to longer and healthier lives. The simplest measure of health inequalities is to compare the health of subjects of different socioeconomic groups (NHS Health Scotland, 2019b). Work on health inequalities often also focus on gender inequalities. Other important inequalities include age, disability, religion, ethnicity and sexual orientation (The Scottish Public Health Observatory (ScotPHO), 2019b). The initial objective of this thesis was to measure the socioeconomic health inequalities in ACS patients in Scotland. Using the same data and methods, I was also able to dissect the current situation on gender inequalities in ACS patients.

1.2.1 Socioeconomic inequalities

A major section of the 2017 Scottish Heart Disease Statistics report focuses on the difference in CHD mortality by social deprivation group. In Scotland, the Scottish Index of Multiple Deprivation (SIMD) is used to measure area deprivation (for more details in SIMD, see section 3.2.5.2). Although a reduction in mortality rates for CHD was seen in both the most and least deprived quintiles over the past decade, it still remains higher in the most deprived group compared to the least deprived group (36.1% to 31.7%). The trend is similar with age and sex adjusted mortality rate. In 2016, the age and sex adjusted mortality rate in the most deprived quintile is twice of that in the least deprived quintile (Figure 1-7).

Figure 1-7. CHD deaths by deprivation (SIMD) quintile



Age and sex adjusted mortality rates per 100,000 population, Scotland. Using data extracted from Table DC7 of Scottish Heart Disease Statistics report (NHS Health Scotland Information Services Division, 2018b).

As seen in Section 1.1.2.2, Scotland, especially GGC is severely affected by health inequalities. As pointed out by the BHF report for healthcare professionals, one major CVD challenge in Scotland is to close these inequality gaps (British Heart Foundation, 2018d). There is a chain of events that likely leads to such disparities in outcomes. Before hospitalisation, those with lower social economic status (SES) tend to have different risk profiles: more baseline cardiac risk factors and more severe disease (Alter et al., 2004a, Bernheim et al., 2007, Tyden et al., 2002). Therefore, patients with low SES likely have a greater need for invasive and pharmacological treatment. At the care-delivery stage, whether patients across the SES spectrum have equal opportunity to access in-hospital and medical therapies remains unclear, despite 3 prior systematic reviews on this topic (Quatromoni and Jones, 2008, Schroder et al., 2016, Moledina and Tang, 2021).

The most recent study by Moledina et al. synthesized studies from Canada only while Quatromoni et al. compared studies from the United Kingdom and the United States only, both noted that low-SES patients had reduced rates of coronary angiography and revascularization. In addition, lower SES is associated with longer waiting for invasive cardiac procedures in the US and UK

(Quatromoni and Jones, 2008) and higher short and longer term mortality after ACS in Canada, highlighting the deep-seated and lasting effects of health inequities (Moledina and Tang, 2021). Schroder et al. however, noted more variability in the literature across the globe (Schroder et al., 2016). Although they too noted that patients with low SES tended to have lower rates of coronary angiography (CAG), for patients who are referred to CAG however, subsequent treatment strategies such as the rate of revascularisation and medical treatment are less influenced by SES. They found only half of the studies exhibited differences in access to drug treatment (Schroder et al., 2016). Contrary to findings from Moledina et al. and Quatromoni et al., they also found that that disparities exist less often in countries with universal health care systems. All 3 reviews did not differentiate cardiac intervention results between different CHD diagnosis when guidelines differ between the groups. Furthermore, neither Quatromoni et al. or Schroder et al. assessed the quality of constituent studies. More importantly, they were not meta-analyses that quantified the association between SES and cardiovascular outcomes and interventions. Only Moledina et al. quantified the associations but was a localised study and did not consider medical therapies. The socioeconomic status of patients can be defined in multiple ways such as according to the patient's occupation, income wealth, education or where they live, and the differences between these measures have not been investigated and warrants a closer look as well.

Clinicians have a responsibility in providing high-quality, equitable care. Therefore, identifying, understanding and improving the relationships between disparities in health, catheter-based interventions and drug therapy has important implications for public health. I have therefore conducted a systematic review and meta-analysis with the objective of determining the associations among SES, mortality and access to cardiac interventions and medical therapies in ACS patients.

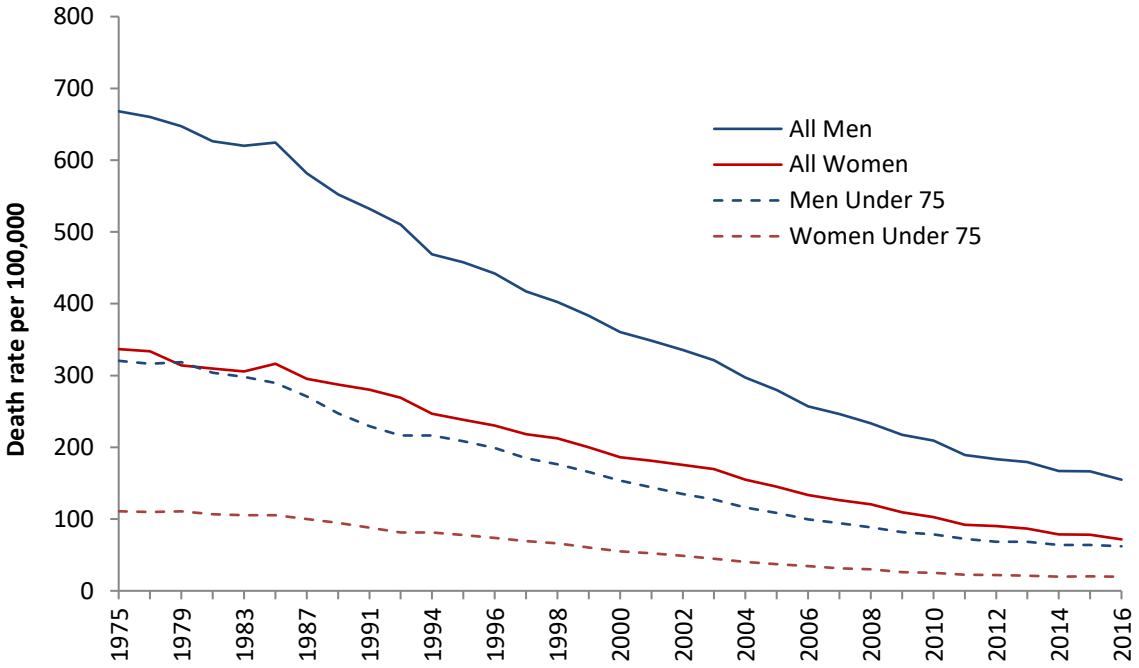
Chapter 2 of this thesis will be the first systematic review to assess not only the associations between SES and mortality outcomes in ACS patients, but also those between SES and access to interventions along a continuum of care for these patients. Subgroup analysis will also be performed to separate any differences across different measures of SES, different country of study, and different CHD

populations, specifically stratified by their final diagnosis. Studies will also be stratified year of publication, to tease out data from the late 1990s and 2000s that may not be fully represent recent practice patterns.

1.2.2 Gender inequalities

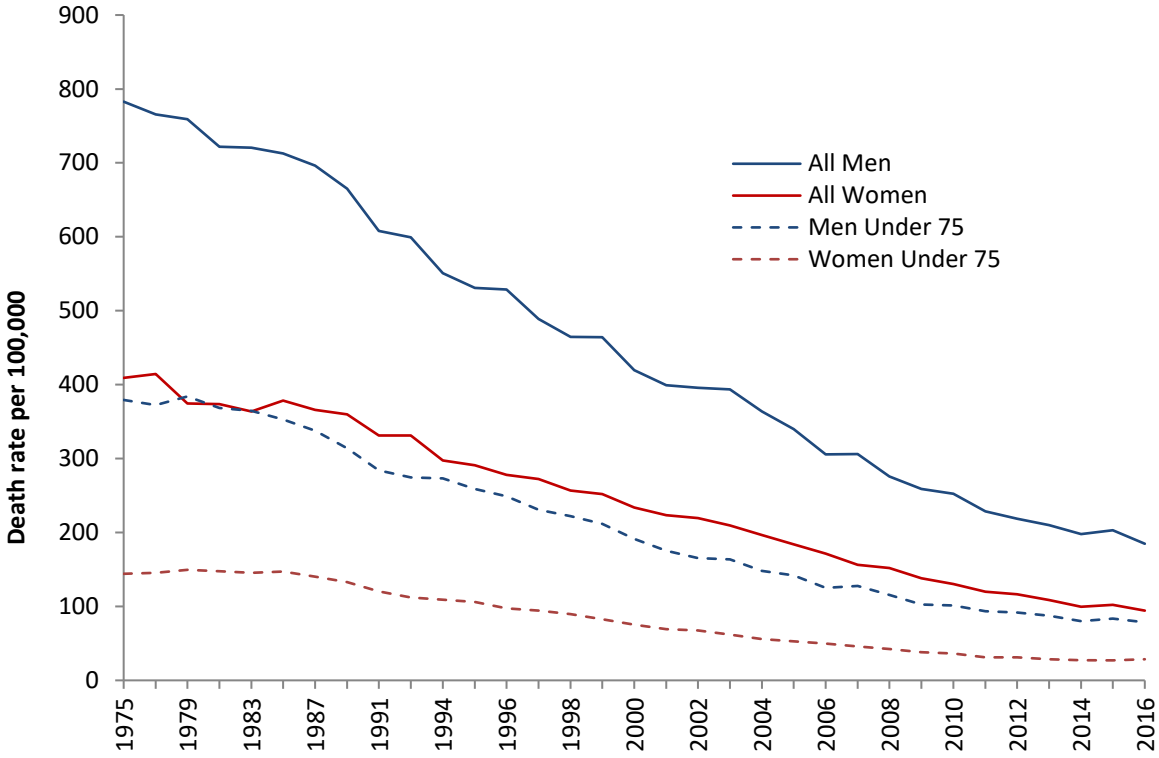
Another popular inequalities topic overtaking the headlines of CHD research is health and healthcare inequalities between men and women. As Figure 1-8 and Figure 1-9 shows, age-standardised CHD death rates in men are more than twice as high as those in women in both Scotland and UK-wide and pre-mature deaths from CHD (before the age of 75) are three times as high for men (British Heart Foundation, 2018a).

Figure 1-8. CHD deaths by gender, UK



Age adjusted mortality rates per 100,000 population, all ages and under 75. Using data extracted BHF CVD statistics 2018, Table 1.5 and 1.6 (British Heart Foundation, 2018a).

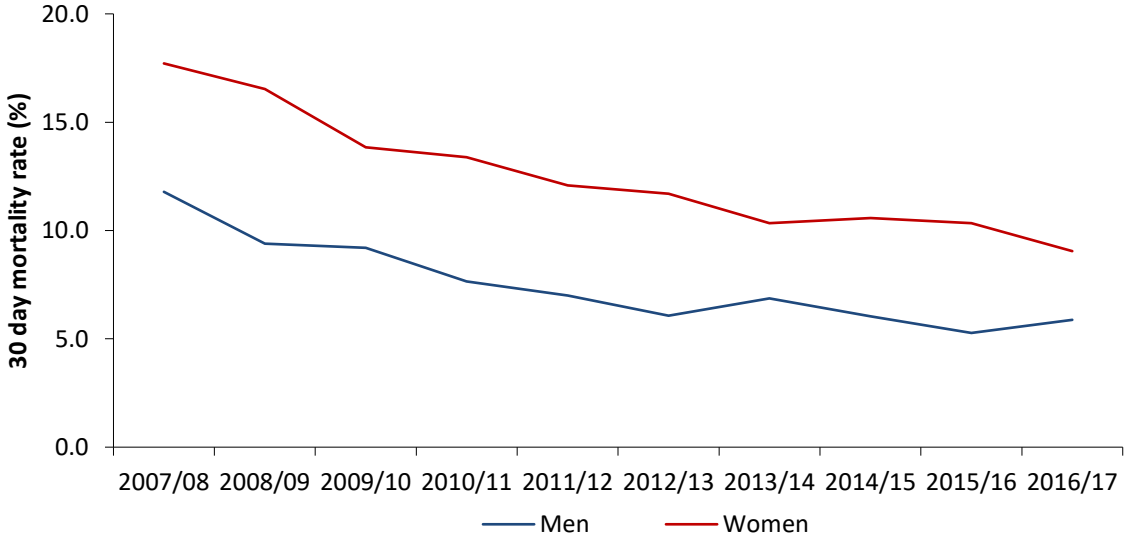
Figure 1-9. CHD deaths by gender, Scotland



Age adjusted mortality rates per 100,000 population, all ages and under 75. Using data extracted BHF CVD statistics 2018, Table 1.5 and 1.6 (British Heart Foundation, 2018a).

However, for 30-day mortality after hospitalisation for incident MI, there also exist a gap in mortality between men and women as reported by NHS Scotland ISD Statistics (Figure 1-10), but in the opposite direction. Females with a MI after hospitalisation have poorer outcomes.

Figure 1-10. 30-day mortality (%) in MI patients after first admission, Scotland



Using data extracted from Table S1 of 2017 Scottish Heart Disease Statistics Report (NHS Health Scotland Information Services Division, 2018b).

These contradicting results warrants further investigation. Persistent sex disparities were found in all five systematic reviews that look into the outcomes after invasive coronary revascularisation, although they did not consider disparities in revascularisation treatment. Similar to other deprived populations, before hospitalisation, females with CHD are generally older, have more baseline cardiac risk factors and more severe disease due to presenting later to hospital (Otten et al., 2013, Zanchi et al., 2009, Khamis et al., 2016, Hanratty et al., 2000). All five meta-analysis found the crude in-hospital and long-term mortality were significantly higher in women compared to men after PCI (Bavishi et al., 2015, Pancholy et al., 2014, van der Meer et al., 2015, Conrotto et al., 2015, Guo et al., 2018). However, these differences were markedly attenuated following adjustment for clinical differences, with mid-term (Conrotto et al., 2015) and long-term mortality no longer significantly different between two genders (Bavishi et al., 2015, Pancholy et al., 2014, van der Meer et al., 2015, Guo et al., 2018). It seems that the longer symptom-to-balloon time in women in addition to more adverse cardiovascular risk profiles compared with males can explain the higher mortality in women with STEMI after PCI.

One major fundamental cause of health inequalities between these groups are due to unequal distribution of resources and access to services. All 5 reviews however, focused only on STEMI patients treated with PCI and therefore did not measure the extend of unequal healthcare utilization between sexes. Only one other meta-analysis included all comers with STEMI and investigated gender disparities in hospital care, and found that females not only experienced significantly longer delays to first medical contact, the door-to balloon time was also longer in females (Shah et al., 2021). Importantly, females also received less PCI compared to males (Shah et al., 2021). Studies in the UK found females less likely to be given thrombolytic therapy, aspirin and have angiography or revascularisation. There is general agreement among studies that despite females being higher risk partly due to age and co-morbidities they were treated less aggressively than males (Clarke et al., 1994, Hanratty et al., 2000, Radovanovic et al., 2007). However, it is difficult to know if this now represents contemporary real world data as these studies precedes 2000. The results of these studies also do not explain and sometimes even contradict the higher crude CHD mortality in males as seen above. It remains unclear if sex differences

in outcomes exists in CHD patients of GGC Scotland, favouring which gender, and how much of any observed difference in mortality between sexes can be explained by differences in health care utilization within hospital or differences in long term medical therapy between sexes.

Therefore, the focus of the NHS Health Scotland (NHS Health Scotland, 2019a) has been to tackle health inequalities by understanding the factors that undermine disadvantaged groups to health and identifying actions to make improvements. Thus, it is important to assess invasive and medical treatment and clinical outcomes in unselected female and male patients admitted for CHD in Scotland and to put these results in the perspective of their baseline characteristics, comorbidities and management. It is hoped that this thesis could contribute a little by not just identifying any inequalities, but also to understanding the gaps in health and service provision for CHD patients in GGC Scotland through employing novel statistical methods.

1.3 Aims and objectives

The primary aim of this thesis is to explore socioeconomic inequalities in the management and outcomes of treatment for ACS in Scotland. Secondary aims include an exploration of gender inequalities and using mediation analyses to identify specific treatment inequalities most likely to be effective in reducing health inequalities when itself is reduced. In order to meet these aims, this thesis address the following specific research questions by analysing patients hospitalised with ACS:

1. Is socioeconomic status associated with differential use of evidence-based therapies, including prescriptions and other aspects of the care process?

2. Is socioeconomic status linked to all-cause mortality?

3. How are the observed disparities in mortality (Q2) mediated by differences in healthcare (variables in Q1)?

4. In addition to SES, how does gender contribute to health and healthcare inequalities (Q1-Q3 by gender)?

1.4 Structure of thesis

To achieve the primary aim of this thesis, it is necessary to lay the foundations of the study through comprehension of existing academic literature. Accordingly, Chapter Two discusses the academic literature relating to socio-economic status and treatment and outcomes after ACS hospitalisation.

Chapter Three addresses the primary aim of this thesis. It is a detailed study of socio-economic inequalities on treatment and mortality for patient after ACS hospitalisation.

Using the same data and methods, Chapter Four presents a study of gender inequalities in the process and outcomes of treatment for CHD in GCC. This chapter have been published in full in the European Heart Journal: Quality of Care and Clinical Outcomes with co-authors (Jackson et al., 2020).

The final chapter on mediation analyses evaluates specific treatment inequalities' effect on mortality. These findings are valuable for understanding which factors might be most useful for authorities to target to reduce CHD mortality.

In summary, this thesis is broadly composed of 4 different studies. A summary of the thesis outline can be found in Table 1-2.

Table 1-2. Thesis outline summary

Study	Chapter	Description
-	1	Introduction
A	2	A literature review of social-economic inequalities on treatment and mortality after ACS hospitalisation
B	3	A comprehensive study of socio-economic inequalities in ACS in West of Scotland by linking real world electronic datasets
C	4	Address gender related disparities in health and healthcare using similar approaches detailed in Chapter 3
D	5	Assessing gender (and SES) disparities in health will require addressing the pathways by which gender (and SES) affects health. This final study assesses how management differences mediate the effects of gender (and SES) on outcomes after controlling for baseline patient and hospital characteristics.

Chapter 2 Socioeconomic status and its association with healthcare and mortality after acute coronary syndrome: a systematic review

2.1 Introduction

2.1.1 Background

Cardiovascular disease (CVD) is estimated to take 17.9 million lives every year (World Health Organization). Although outcomes have improved significantly in the past 50 years, it is still a pandemic complication accounting for 23% of all deaths in developed countries and over 31% worldwide (World Health Organization, Oakes, 2019). In addition, there are substantial regional and socioeconomic variations in mortality that reflect inequalities in prevention and treatment (Townsend et al., 2015, British Heart Foundation, 2018a, Timmis, 2015).

In the UK, eliminating disparities in health is a major CVD challenge (British Heart Foundation, 2018d, Beeston et al., 2014), and eliminating disparities in healthcare resources has been governed largely by the Health and Social Care Act 2012 and the Equality Act 2010 (NHS). Similar initiatives exists around the world (US Department of Health and Human Services, 2000, van der Wel et al., 2016, EuroHealthNet), with the ultimate goal to achieve quality healthcare and equitable outcomes for all, regardless of SE situation.

There is a chain of events that likely leads to such disparities in outcomes by socioeconomic status. Before hospitalisation, it is well known that there is an increased burden of cardiovascular disease and its risk factors among patients with lower social, environmental and economic status (SES) (World Health Organization Europe, 2014, Alter et al., 1999, Barakat et al., 2001, Bergstrom et al., 2015, Blais et al., 2012, Jakobsen et al., 2012b). Therefore, patients with low SES likely have a greater need for invasive and pharmacological treatment. At the care-delivery stage, whether patients across the SES spectrum have equal opportunity to access in-hospital and medical therapies remains unclear, despite 3 prior systematic reviews on this topic (Quatromoni and Jones, 2008, Schroder et al., 2016, Moledina and Tang, 2021).

Both Moledina et al. and Quatromoni et al. noted that low-SES patients had reduced rates of coronary angiography and revascularization in Canada and the United Kingdom and United States, respectively. In addition, lower SES is associated with longer waiting for invasive cardiac procedures in the US and UK (Quatromoni and Jones, 2008). Schroder et al. however, noted more variability in the literature across the globe (Schroder et al., 2016). Although they too noted that patients with low SES tended to have lower rates of coronary angiography (CAG), for patients who are referred to CAG however, subsequent treatment strategies such as the rate of revascularisation and medical treatment are less influenced by SES. They found only half of the studies exhibited differences in access to drug treatment (Schroder et al., 2016). Contrary to findings from Moledina et al. and Quatromoni et al., they also found that that disparities exist less often in countries with universal health care systems. All 3 reviews did not differentiate cardiac intervention results between different CHD diagnosis when guidelines differ between the groups. Furthermore, neither Quatromoni et al. or Schroder et al. assessed the quality of constituent studies. More importantly, they were not meta-analyses that quantified the association between SES and cardiovascular outcomes and interventions. Only Moledina et al. quantified the associations but was a localised study and did not consider medical therapies.

In addition, SES is a complex measure which encompass multiple determinants of health. Traditionally, SES has been defined according to one's education, income or employment status. More recently, measures related to social support/isolation or geographical access to healthcare facilities have also been used to represent SES. Each component reflects different resources, displays different relationships to various health outcomes, and would be addressed by different policies (Adler and Newman, 2002). The differences between these measures have not been investigated and a systematic review of the SE patterning of ACS management and outcomes is warranted. In a world with a range of healthcare systems and evolving practice guidelines, debates as to whether socioeconomic-specific differences in clinical course and management of ACS exist or not are only relevant when considering the whole spectrum of different markers of SES and the healthcare environment for the region under

investigation. This chapter looks into the extensively studied socio-economic differentials in ACS patient management and outcomes.

2.1.2 Aims

The purpose of the literature review is to gain a comprehensive overview of previous research related to the influence of SES on clinical outcomes and care of hospitalised patients with ACS. This would the first known review with a quantitative assessment of the socioeconomic differentials in ACS patient management and mortality. To address the issue of social inequality in ACS further, the individual contribution of different SES indicators, along with trends by time and region is also investigated.

2.2 Methods

2.2.1 Search strategy

A computerized search using the Ovid Medline® and Embase was undertaken to identify articles published in English after 1990 using search strategy based on the Population Intervention Comparison Outcome (PICO) framework (Richardson et al., 1995, Huang et al., 2006): Population: hospitalised patients with ACS; Intervention and Comparison: socio-economic status; Outcome: mortality, access to invasive cardiac procedures or medications.

An initial set of search terms were piloted using Google and Google Scholar search engines prior to selection and comprised of ACS and related clinical presentation terms, socioeconomic and inequality terms, and clinical outcomes of interest. Synonyms for the search terms were identified using MeSH subject descriptors by mapping and inspecting the tree for each term. Relevant terms mentioned in articles identified in a pilot internet search of the literature were also added. Any key articles which had been previously found in the initial pilot search but not returned in the formal search results were further investigated with additional search terms added or adjusted so to incorporate these articles. Table 2-1 shows the final set of search terms.

Table 2-1. Search strategy

PICO	Element	Search # and terms
Population	Hospitalised patients with ACS	1. *Myocardial Infarction/ or Myocardial Infarction.ti. 2. Acute Coronary Syndrome/ or acute myocardial infarction.ti. or acute coronary syndrome.ti. 3. *Angina, Unstable/ 4. Non-ST Elevated Myocardial Infarction/ 5. ST Elevation Myocardial Infarction/ 6. 1 or 2 or 3 or 4 or 5
Intervention and Comparison	Socio-economic measures at individual or aggregate level	7. Socioeconomic.tw. 8. exp Socioeconomic Factors/ 9. exp Social Class/ 10. Healthcare Disparities/ 11. health status disparities/ 12. "inequit*".tw. 13. "inequalit*".tw. 14. "disparit*".tw. 15. deprivation.tw. 16. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
Outcome	Mortality or access to invasive cardiac procedures (cardiac catheterization, percutaneous coronary intervention (PCI), and coronary artery bypass graft surgery (CABG))	17. *mortality/ or exp "cause of death"/ or exp hospital mortality/ or exp mortality, premature/ or exp survival rate/ or treatment outcome/ or "mortality".tw. 18. Angioplasty, Balloon, Coronary/ 19. Coronary Artery Bypass/ 20. Cardiac Catheterization/ 21. Health Services Accessibility/ 22. "Outcome Assessment (Health Care)"/ 23. 17 or 18 or 19 or 20 or 21 or 22
Other Restrictions	All studies published in English after 1990	24. 6 and 16 and 23 25. limit 24 to english language 26. limit 25 to yr="1990 -Current"

The search was not restricted by type of study. Limiting the search to all epidemiological (cross-sectional, case-control, cohort, and observational), registry and review articles would exclude many relevant articles as many authors do not indicate their study type in either the title or abstract, nor are the articles marked with the appropriate MeSH terms. All published articles in English after 1990 were considered eligible for review. As social conditions, ACS care practice guidelines, treatment uptake and main cardiovascular risk factors evolve over time, limiting the literature to this time period will ensure that publications are as relevant as possible to the present day. Full citation results of the extracted studies were downloaded into EndNote X7 reference management software with duplicate publications removed.

2.2.2 Study selection

Titles and abstracts returned from the search were subsequently screened as per inclusion and exclusion criteria (Table 2-2) as not all extracted papers were related to the question of interest. If it was not clear from the title or abstract whether analyses by SES or for outcomes of interest after ACS had been performed, the full text of the article was retrieved and examined. The full texts of the studies of interest were fully assessed as per inclusion and exclusion criteria.

Table 2-2. Inclusion and exclusion criteria for study selection.

Criterion	Inclusion	Exclusion
Sample	The sample is population-based; Participants are diagnosed with ACS and admitted to hospital; original data	A clinical sample or specific case-studies; samples with undiagnosed/complains regarding MI; Population unit not at the individual patient level, but hospital level, region level or country level; Majority of data before 1990
SES	SES is measured via occupation, employment status, income, education, geographic access to healthcare, environment or a combination of these and other factors; SES can be measured at an individual or neighbourhood level	SES is measured by the parental SES, childhood SES or life course SES; using ethnicity/nationality/country of birth as only proxy measure for SES (reflect unequal health coverage/language/access-to-care/lifestyle issues but without directly quantifying associations with other SES factors); SES measured by job stress, measure of income inequality, insurance; the following measures used separately as SES indictors (not as part of nSES measure): rent, living in poverty, crowding within household, and self-reported financial stress were also excluded (<2 studies, as these are not usually considered SES measures unless part of overall index measure); country level income (n=3 studies)
Design	The study is empirical and quantitative or a review article	Absence of relative risk estimates
Outcome 1: Mortality	Mortality after ACS diagnosis	Life expectancy as outcome Only data on long term mortality
Outcome 2: In-hospital Care	Access to invasive cardiac procedures (cardiac catheterisation, percutaneous coronary intervention (PCI), and coronary artery bypass graft surgery (CABG)) among ACS patients	

2.2.3 Data extraction

Articles which passed all the inclusion/exclusion criteria had the following information extracted: citation details including author and year of publication; study details including country, sample size and the ACS population; the type of SES measure; outcome details; and information on adjustment for potential confounding and mediating factors. The impact of SES investigated by multivariable analyses and related measures of precision, i.e. 95% confidence intervals were extracted along with results from any subgroup analyses. Where the SES measure was multi-categorical, the risk measure of the most deprived socioeconomic group in comparison with the least one was used. Where the SES measure was continuous (e.g. per $10000), outcomes were reported as continuous measures per unit decrease.

Insights from conference abstracts or editorials without extractable quantitative data were also integrated into the synthesis of the findings to ensure all relevant information was included through a narrative review with tabulation of the results where possible.

2.2.4 Quality assessment

The quality of each included study was assessed concurrently with data extraction using a modified Newcastle-Ottawa scale (Wells et al.). The following aspects of study quality were captured: representativeness of the sample; measurement and definition of SES and outcomes; adjustment for age, sex or other baseline characteristics (as low SES is often associated with various baseline characteristics such as advanced disease), and adequacy of follow-up (Table 2-3). For all the quantitative studies included in meta-analyses, each aspect of quality was rated for a potential aggregate score from 0 (lowest quality score) to 9 (highest quality score). Studies with a quality score of 5 or lower were excluded from this review.

Table 2-3. Adapted Newcastle-Ottawa Quality Assessment Scale

Criterion	Points
Selection	
1) Representativeness of the exposed cohort	
a) truly representative of the average ACS patient with low SES in the community	1
b) somewhat representative of the average ACS patient with low SES	1
c) selected group of users e.g. veterans, volunteers	0
d) no description of the derivation of the cohort	0
2) Selection of the non-exposed cohort	
a) drawn from the same community as the exposed cohort	1
b) drawn from a different source	0
c) no description of the derivation of the non-exposed cohort	0
3) Ascertainment of SES	
a) secure record (e.g. registry records)	1
b) structured interview	1
c) self-report	0
d) no description	0
4) Demonstration that outcome of interest was not present at start of study (i.e. measures overall cumulative mortality)	1
a) yes	0
b) no	
Comparability	
1) Comparability of cohorts on the basis of the analysis	
a) study controls for age and sex	1
b) study controls for any comorbidities or additional factors for mortality and revascularisation outcomes, or comorbidities + revascularisation for medication outcomes	1
Outcome	
1) Assessment of outcome	
a) record linkage	1
b) independent blind assessment	1
c) self-report	0
d) no description	0
2) Was follow-up long enough for outcomes to occur	
a) yes (30-day mortality, 1 year mortality)	1
b) no	0
3) Adequacy of follow up of cohorts	
a) complete follow up - all subjects accounted for	1
b) subjects lost to follow up unlikely to introduce bias (<5% lost or description provided of those lost)	1
c) follow up rate < 95% and no description of those lost	0
d) no statement	0

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

2.2.5 Independent check of extracted papers

Titles and abstracts of 10% of the extracted studies (n=137) were randomly selected and independently screened by a second reviewer [Alice Jackson (AJ)] for relevancy. If unclear from the title or abstract whether analyses by SES or for mortality/invasive treatment/medication after ACS have been performed, the full text of the article was assessed as per inclusion and exclusion criteria. In addition, 10% of the screened papers (n=18) were randomly selected with the data extracted and quality assessed by AJ according to methods of Section 2.2.3 and 2.2.4. Findings were compared and disagreements discussed to reach consensus.

2.2.6 Statistical analysis

The impact of SES was analysed separately for each outcome: 1) all-cause mortality after admission to hospital, at around 30 days (approximately expresses in-hospital mortality) and at 1 year (including 30-day to 1-year mortality); 2) use of invasive cardiac procedures during hospitalisation split by coronary angiography (CAG) and percutaneous coronary intervention (PCI). Hazard ratios, odds ratios, risk ratios are assumed to represent nearly the same relative risk and are collectively described as risk ratios (RR) in the pooled analyses. Pooled RRs were estimated using random effect models by DerSimonian and Lard (DerSimonian and Laird, 1986) to incorporate heterogeneity inherent in both how SES is defined and differences across regions, weighting for the inverse of the variance due to varying ways of measuring SES. The pooled RRs were calculated using inverse-variance weighted averaging and were depicted in forest plots.

If the study reported risk estimates (RRs) for more than one measure of SES, each estimate was included separately for the subgroup analyses but incorporated only once in the overall pooled result, prioritised by the frequency of appearance as an SES measure in the included studies: 1) income 2) education 3) an overall SES index 4) geographical access to healthcare. If the study reported multiple RRs by subgroups, all were included in the pooled analyses if the subgroups consist of separate populations (e.g., by age group or gender). If

the subgroup populations overlap, the data were included only once prioritising estimates providing maximally adjustments.

Statistical heterogeneity between studies were assessed by the Chi square test for heterogeneity in combination with the I^2 statistic that describes the percentage of variability in effect estimates due to heterogeneity rather than chance (Higgins et al., 2003, Higgins and Thompson, 2002). Publication bias was explored with funnel plot asymmetry for each individual outcome if a minimum of 10 studies was included in the analysis.

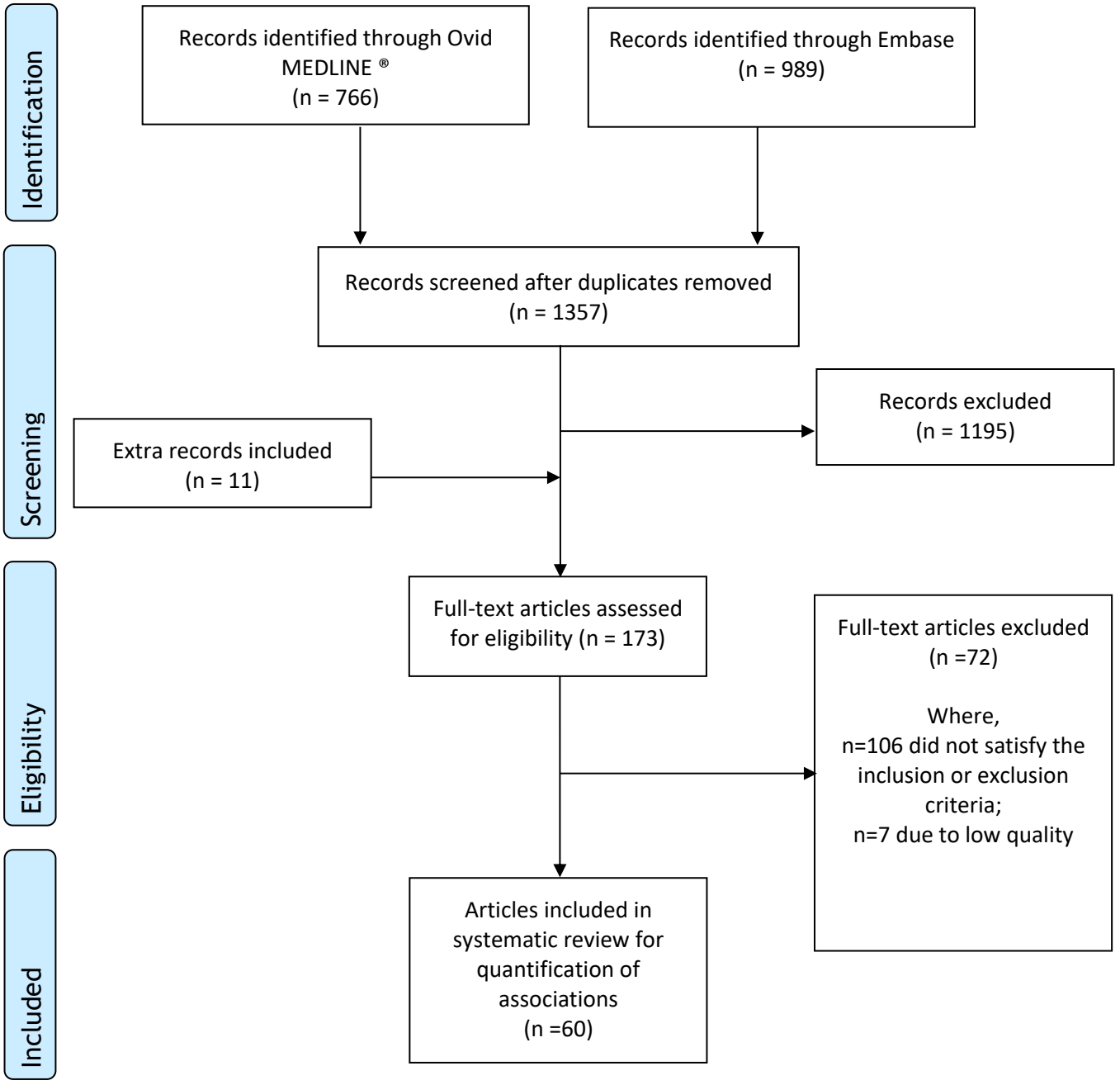
A series of subgroup analyses were conducted to investigate the effect of different surrogate measures of SES on the outcomes of interest, as well as compare inequalities by other study-level factors. The studies were stratified by the type of SES measure, geographical region, the adjustment strategy for mortality (any adjustments for treatment factors or not), age group, gender, ACS type and publication year (before 2000, 2001-2010 and after 2011). Heterogeneity was also explored in the subgroup analyses.

2.3 Results

2.3.1 Search results

The database search was conducted in December 2017 and yielded a total of 1755 references. 398 duplicates were removed from the combined results of the database searches. This left a total of 1357 references, of which 1195 were excluded on the basis of title or abstract. An additional 11 articles were obtained from bibliographies of studies deemed relevant by title and abstract alone. Evaluation of 173 full-text articles for eligibility led to the exclusion of 106 records. This led to a final 60 articles included in the meta-analysis on all-cause mortality after admission to hospital and the use of invasive cardiac procedures. Seventeen articles were excluded for looking at long term mortality only, these are excluded as there are no standardised length to define “long term”. In addition, in the set of articles that were excluded due to absence of relative risk estimates (n=7), a majority (n=5) expressed that there were no SES

Figure 2-1. Flow diagram for literature review study identification



differences. Figure 2-1 details the progress of citations through the screening process. For all studies included, the prognostic impact of SES investigated by multivariable analysis is reported in the appendix (Table A) in full.

Heterogeneity among effect sizes was high for all outcome parameters (Figure 2-5). There is no register for published and unpublished studies with SES exposure, therefore there is a potential for publication bias. Publication bias was assessed separately for each outcome as all had over 10 studies, which showed possible publication bias (Figure 2-7). For interpretation of funnel plots, it should be noted that asymmetry can also originate from other sources than

publication bias (Ioannidis and Trikalinos, 2007). A closer look of the funnel plots suggest most studies included are of larger sizes, this is expected as studies looking at SES disparities are usually large real world data studies. While larger studies cluster around the null, smaller studies tend to show larger SES disparities in treatment and mortality. The study from South Korea (Hong and Kang, 2014) in particular is an outlier showing extreme SES disparities. A sensitivity analysis was then performed by excluding this study.

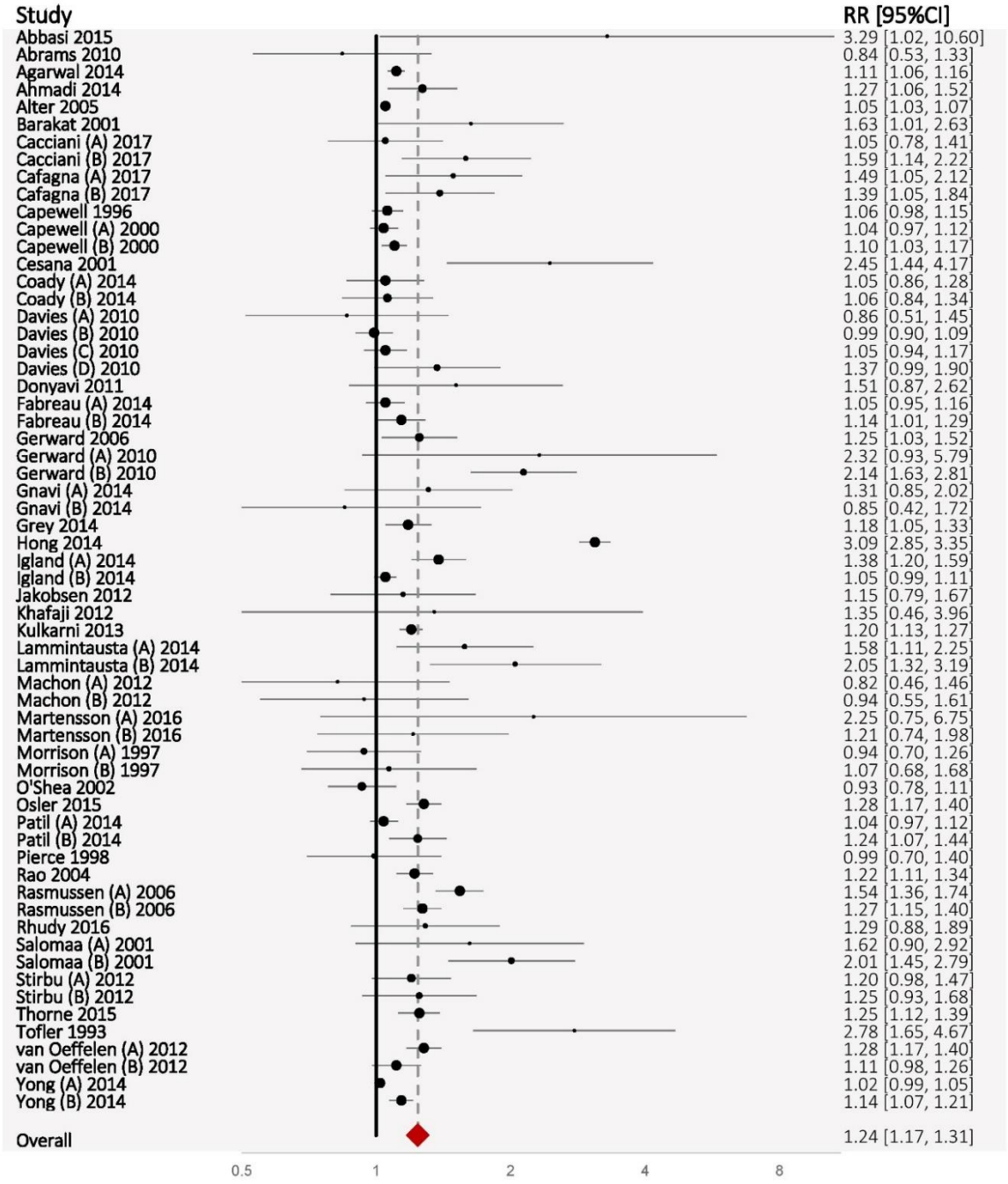
The SES measures studied in the included articles can be broadly categorised into: education (Abbasi et al., 2015, Ahmadi et al., 2014, Alter et al., 2004b, Alter et al., 2005, Ambugo and Hagen, 2015, Cacciani et al., 2017, Cafagna and Seghieri, 2017, Coady et al., 2014, Donyavi et al., 2011, Gnavi et al., 2014a, Hetemaa et al., 2004, Igland et al., 2014, Jakobsen et al., 2012b, Martensson et al., 2016, Mehta et al., 2011, Osler et al., 2015, Patil et al., 2014, Rasmussen et al., 2006, Rasmussen et al., 2007b, Salomaa et al., 2001, Tofler et al., 1993), income (Agarwal et al., 2014, Alter et al., 1999, Alter et al., 2004b, Alter et al., 2005, Ambugo and Hagen, 2015, Bernheim et al., 2007, Casale et al., 2007, Chang et al., 2007, Coady et al., 2014, Fabreau et al., 2014b, Hetemaa et al., 2004, Jakobsen et al., 2012b, Philbin et al., 2000, Rao et al., 2004, Rasmussen et al., 2006, Rasmussen et al., 2007b, Salomaa et al., 2001, Stirbu et al., 2012, van Oeffelen et al., 2012, Yong et al., 2014), geographical access (Abrams et al., 2010, Hassan et al., 2009, Hong and Kang, 2014, Hvelplund et al., 2011, Kulkarni et al., 2013, Pierce et al., 1998, Randall et al., 2013, Rhudy et al., 2016, Spatz et al., 2014), social support (Ambugo and Hagen, 2015, Gerward et al., 2010, Hadi Khafaji et al., 2012, Lammintausta et al., 2014, O'Shea et al., 2002), employment (Cesana et al., 2001, Gerward et al., 2010, Hetemaa et al., 2004, Jakobsen et al., 2012b) and composite SES index (Barakat et al., 2001, Bergstrom et al., 2015, Blais et al., 2012, Capewell et al., 1996, Capewell et al., 2000, Coory et al., 2002, Davies and Leyland, 2010, Gerward et al., 2006, Grey et al., 2014, Korda et al., 2009, Machon et al., 2012, MacLeod et al., 1999, Morrison et al., 1997, Randall et al., 2013, Thorne et al., 2015). Education and income were commonly measured at both the individual level and neighbourhood level, geographic access and composite indices at the neighbourhood level only, and social support and employment at the individual level.

2.3.2 Mortality risks

The overall results of the meta-analyses provided evidence for significantly higher risk of death among ACS patients in lower socioeconomic categories for both 30-day and 1-year mortality (Figure 2-2, Figure 2-3). Compared to ACS patients of the highest socioeconomic position, the risk of death at 30-days in the lowest group increased by 24% (RR 1.24, 95% CI 1.17-1.31). The lowest socioeconomic category was also associated with increased risk of death at 1-year (RR 1.20, 95% CI 1.14-1.26).

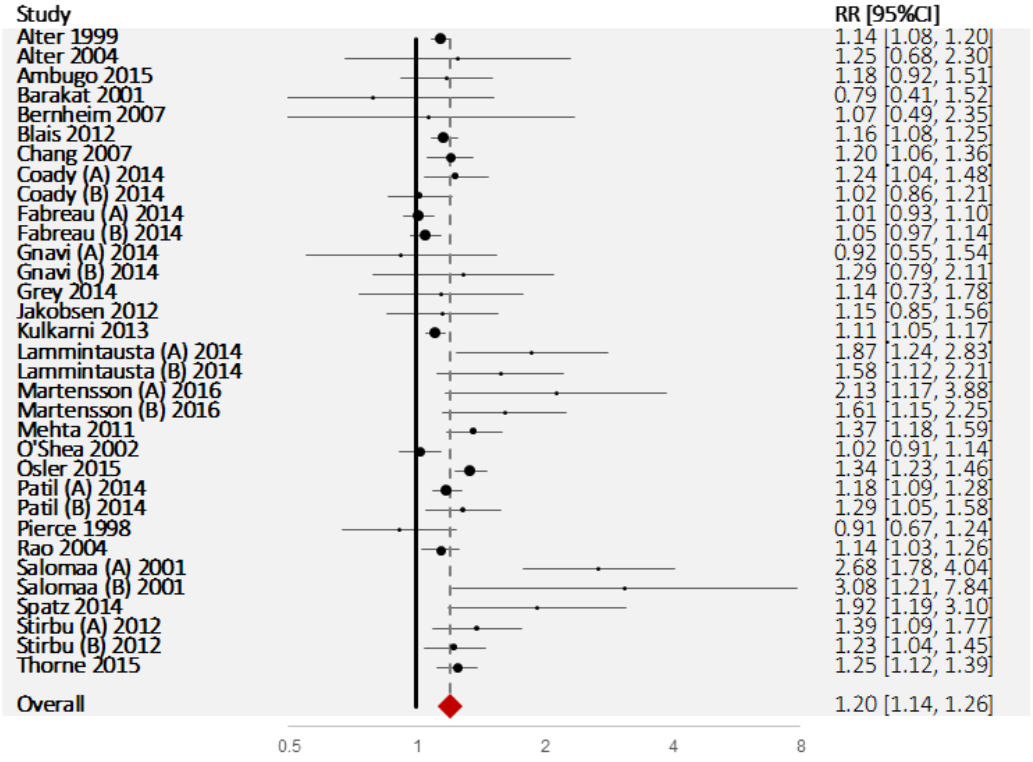
The slightly worse prognosis of patients from the lowest socioeconomic group were still apparent in the subgroup analyses, although the association between SES and mortality varied slightly for different definitions of SES, as well as by publication time and region (Figure 2-5). Worse prognosis was seen in the most deprived patients regardless of which facet of SES is being investigated: let it be education, social support, income or an overall composite index as well as the level of SES measurement: at the individual level or community level. The only exceptions were for geographical access and occupation as the SES measure, which consisted of studies with mixed definitions of "access" or classifications for occupation, respectively. Despite most of the studies included are from egalitarian/developed countries with universal healthcare systems, prognosis after ACS is directly associated with the SES of patients. Furthermore, the situation has not improved over time. When adjusted for baseline risk factors only, prognosis in the most deprived group was worse compared to studies with additional adjustments for treatment-related variables including waiting time and interventional procedures. Indicating that differences in mortality across socioeconomic strata is mediated by differences in treatments and related factors. As expected, the risk of death at 30-days in the lowest group was slightly better at an increased rate of 18% compared to the highest SES group (RR 1.18, 95% CI 1.14-1.22, I^2=77%) in the sensitivity analysis which excluded the study from South Korea that showed extreme disparities. Heterogeneity also decreased moderately from I^2=93% to 77%.

Figure 2-2. Risk Ratios (RRs) of all-cause mortality at 30 days after admission to hospital in ACS patients of lowest socioeconomic position in comparison with the highest one.



Circle size proportional to the weight of contribution to the random-effect summary estimate.

Figure 2-3. Risk Ratios (RRs) of all-cause mortality at 1-year in ACS patients of lowest socioeconomic position in comparison with the highest one..



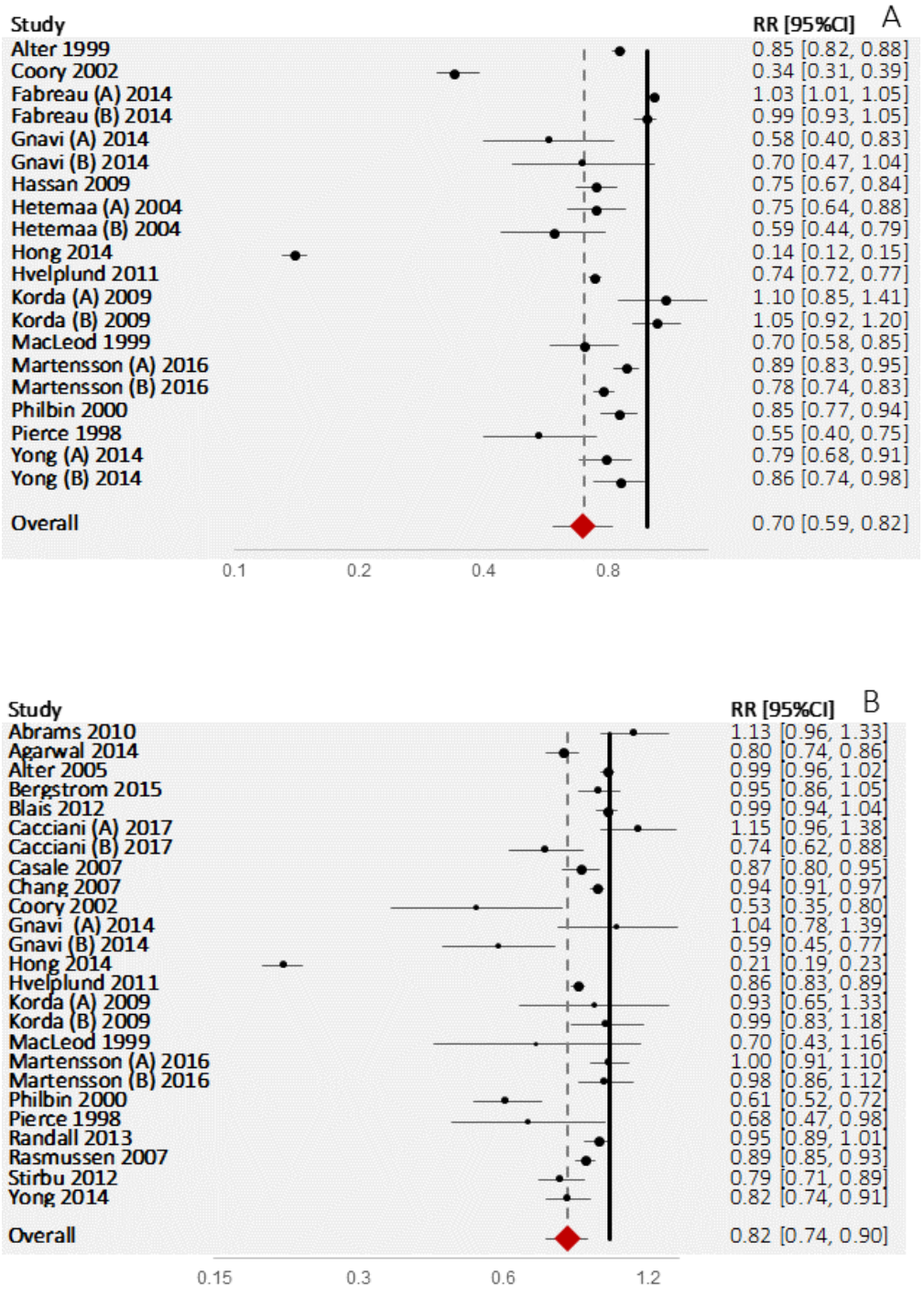
Circle size proportional to the weight of contribution to the random-effect summary estimate

2.3.3 Catheterisation and revascularisation

Socioeconomic disparities were also found in invasive cardiac procedure rates in patients hospitalised with ACS (Figure 2-4). Overall, groups with the poorest level of SES had reduced access to coronary angiography (RR 0.70, 95% CI 0.59 to 0.82) and PCI (RR 0.82, 95% CI 0.74 to 0.90). For all socioeconomic indicators, the pattern was similar: patients with lower socioeconomic status underwent procedures less often than patients with higher socioeconomic status, with the most exaggerated relationship for healthcare access barriers as the definition of SES (Figure 2-6). Invasive examination and treatment patterns associated with SES were consistent in all countries. Even in countries that provide universal coverage, people of lower SES did not appear to use health services at the same rate that their wealthier counterparts did. With PCI becoming the mainstream treatment for ACS around 1990, unequal invasive cardiac care has not improved over time. As expected, by excluding the study from South Korea that showed extreme disparities in the sensitivity analysis, those with lower SES still had

reduced access to coronary angiography (RR 0.77, 95% CI 0.70 to 0.85) and PCI (RR 0.89, 95% CI 0.85 to 0.93), but to a lesser extent.

Figure 2-4. Risk Ratios (RRs) of coronary angiography rate (Panel A) and percutaneous coronary intervention rate (Panel B) in ACS patients of lowest socioeconomic position in comparison with the highest one.



Circle size proportional to the weight of contribution to the random-effect summary estimate.

Figure 2-5. Subgroup analyses. Pooled Risk Ratios (RRs) of all-cause mortality at 30-days and 1-year in ACS patients of lowest socioeconomic position in comparison with the highest one.

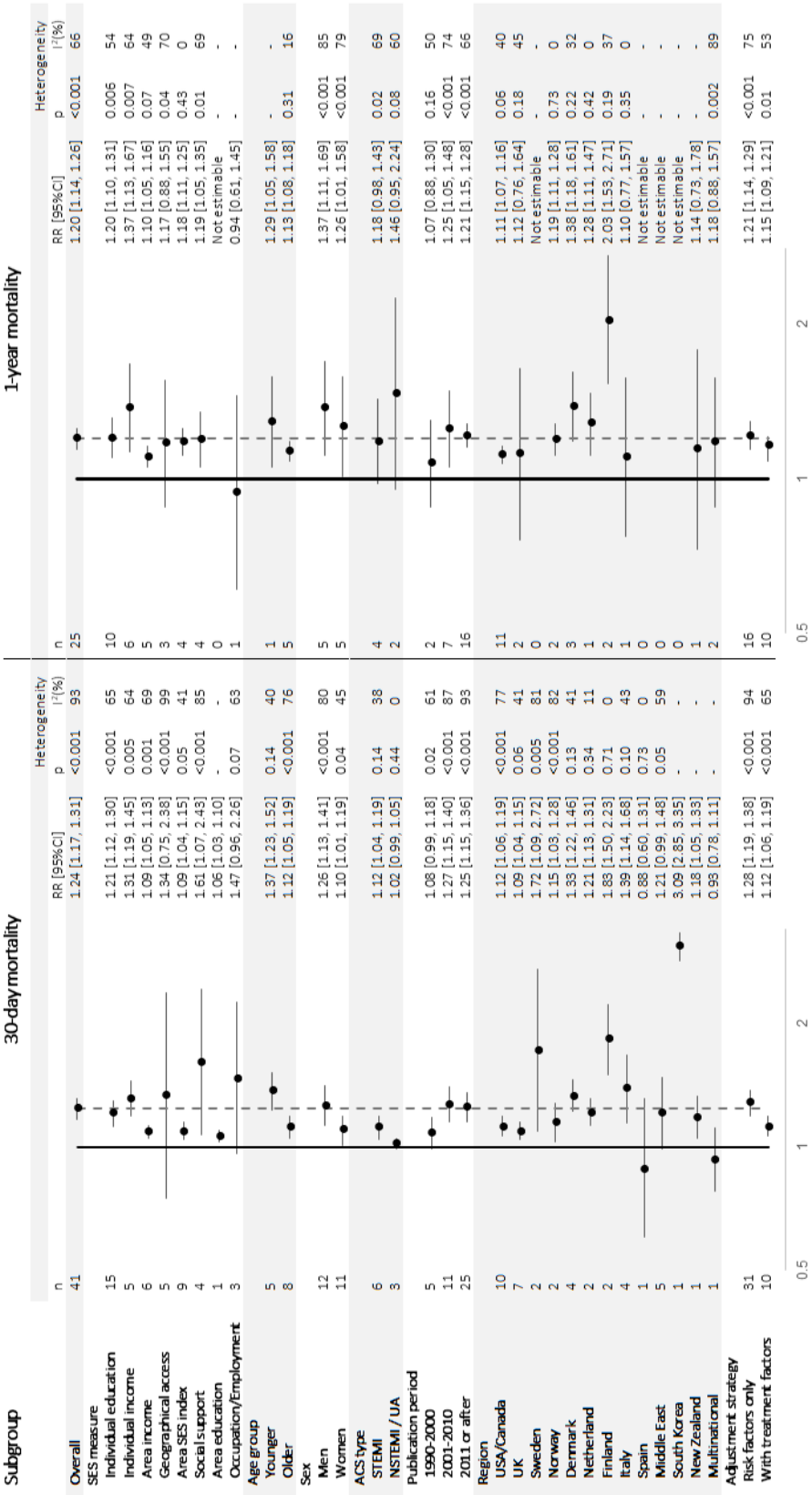


Figure 2-6. Subgroup analyses. Pooled Risk Ratios (RRs) of coronary angiography (CAG) rate and percutaneous coronary intervention (PCI) rate in ACS patients of lowest socioeconomic position in comparison with the highest one.

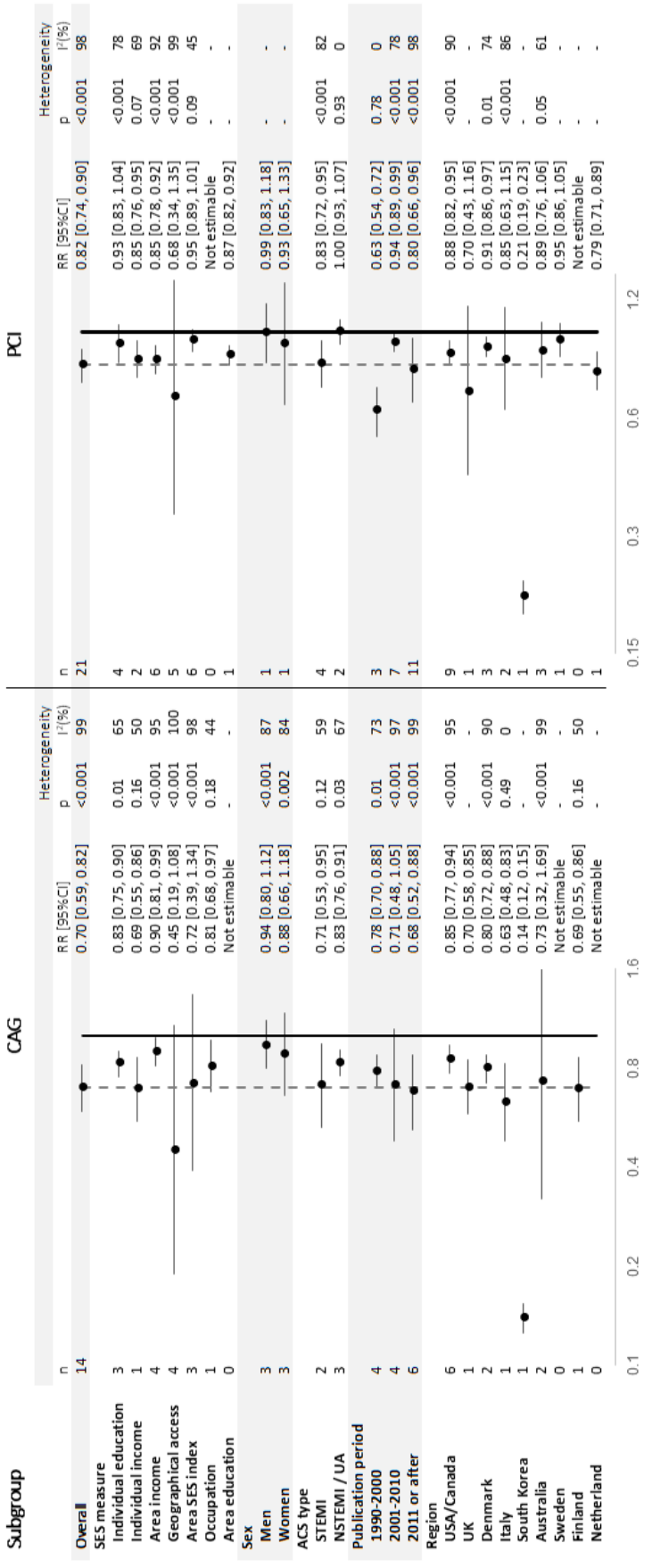
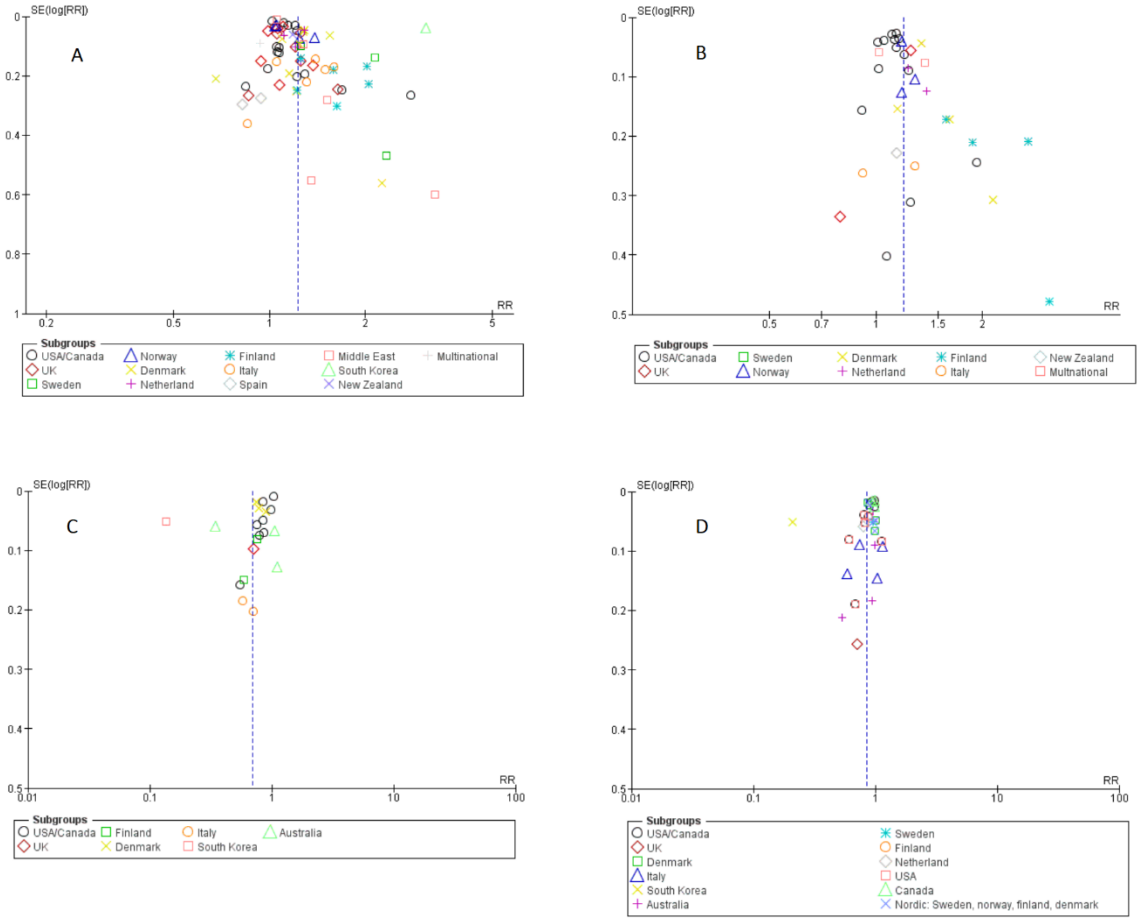


Figure 2-7. Analysis of publication bias. Funnel plot for A. All-cause mortality at 30-days; B. All-cause mortality at 1 year; C. coronary angiography (CAG) rate and D. Percutaneous coronary intervention (PCI) rate



2.4 Discussion

2.4.1 Summary

This literature review found important differences in survival and treatment after hospitalisation with ACS according to SES. Even though the majority of the included studies were from developed countries with similar practice guidelines, low socio-economic groups, in general, still suffer from higher mortality at 30 days (24%) and at 1 year (19%) and receive invasive cardiac care less often (30% and 28% reduction in CAG and PCI use, respectively) compared to patients of the least deprived group. Subgroup analysis stratified by different SES measures show disparities exist regardless of which facet of SES is being investigated: let it be education, social support, income or an overall composite index as well as the level of SES measurement: at the individual level or community level. The only exceptions were for geographical access and occupation as proxy SES

measures, which consisted of studies with mixed definitions of “access” and “occupation class”, as well as for deprivation index’s effect on invasive care.

2.4.2 Contribution of different SES measures

SES is a complex notion related to many different aspects of life. Of the included studies, income was the most frequently used indicator of SES (n=35), followed by education (n=34), SES index (n=22), geographical access to healthcare (n=17), social support (n=7) and occupation (n=4). This review attempted to identify the independent contribution of different SES markers. A discussion of the different SES markers is summarised below after review of the included articles.

2.4.2.1 Income

Income has so far been the most frequently used indicator of SES (Jakobsen et al., 2012b). It most directly reflects the material resources available that could provide means for purchasing health care, better nutrition, housing, schooling, and recreation (Adler and Newman, 2002). However, effects of higher income may also be due to the “healthy worker” effect but is usually overlooked.

The use of area-level income (aINC) as a measure of SES could mean that any associations seen are due to individual-level risk factors or deprivation at the community-level such that there is underinvestment in public goods and welfare in neighbourhoods of low average income (Chang et al., 2007, Philbin et al., 2000, Perelman et al., 2009). This implies that highly stratified societies take an additional toll on health beyond that associated with individual-level deprivation (Adler and Newman, 2002).

For differences at the individual-level, it was suggested that physicians preferentially selected more affluent patients for discretionary procedures when faced with increasing supply or capacity for procedures, especially in those with lower levels of clinical urgency or necessity (Kee et al., 1994, Philbin et al., 2000). Therefore, simply increasing the funding and supply may perpetuate rather eliminate access inequities. Initiatives such as earmarking funds to specific income or clinical subgroups may help (Khaykin et al., 2002).

2.4.2.2 Education

Education has been considered better than other measures of SES as it not only correlates with other SES measures by shaping future occupational opportunities and earning potential, education won't decline after reaching a certain age and is better at predicting long term health through providing knowledge and life skills that promote health (Ross and Wu, 1995). In the multinational study by Mehta et al., the prognostic importance of education was found to be second to age based on the model chi-square after ACS hospitalisation (Mehta et al., 2011).

For studies that investigated all-cause mortality, although all studies accounted for baseline risk factors, only a few adjusted for procedure related (drugs, stent) and medical treatment during follow-up (clopidogrel, ß-blocker, ACE-inhibitor, diuretics, nitro-glycerine). Pooled study results suggest that access to primary care and adherence to secondary prevention treatment may be pathways by which educational inequality affects mortality. Exact measures of differences in medication after discharge is apparent but rarely accounted for. Differences in survival may reflect higher prevalence of other diseases in the less educated group that have not been considered, as risk factors included in most studies are cardiac related; poorer overall health may also be compounded by psychosocial factors such as stress, isolation, depression (Tonne et al., 2005). In the limited number of studies that compared crude mortality to adjusted ones have found that treatment within hospital and prescriptions at discharge tend to attenuate, sometimes eliminate inequalities in mortality suggesting that inequalities in care exist and is a determinant of inequalities in survival. The magnitude of the contribution of differences in medication and interventional procedures to inequalities in mortality needs to be investigated.

In addition, other factors that contribute to unequal mortality after admission to hospital have been suggested. It was suggested that less educated patients may have worse outcomes owing to poor compliance to follow-up management and they were also not as likely to modify behavioural risk factors, such as smoking cessation (Tofler et al., 1993). Moreover, it has been suggested that patients with more education can negotiate their treatments more effectively. Less

educated groups may find identifying symptoms more difficult due to less exposure to the symptoms either through personal experience or educational programs.

To the extent that education is key to health inequality, policies encouraging more years of schooling and supporting early childhood education may have health benefits and decrease healthcare costs, among other merits of investment in education (Adler and Newman, 2002). Simple education programs that provide counselling on appropriate and rapid responses to symptoms may also be appropriate when tackling any inequalities found.

2.4.2.3 Composite SES index

In health disparities research, using single SES indicators such as income or education can simplify things but aggregates of different measures: SES indexes, are also commonly used and provide additional insight into the field. A total of 25 studies used area-level SES indexes to study inequalities in care in patients with ACS. This contained 15 different indices that combined different dimensions of deprivation: income, employment, education, housing, occupational class, others, living instability, social environment, access to services, physical environment, health and crime, in the order of frequency of use.

A study that investigated the incremental prognostic value of different SES measures suggested composite SES indices has the most prognostic value (Molshatzki et al., 2011). It is often measured at the neighbourhood-level and reflects the socioeconomic context of the community, which often makes a simple source target for healthcare regulations and standards.

Worse prognosis for patients living in communities encompassing multiple aspects of deprivation (housing, healthcare access, crime etc.) suggests highly stratified societies take an additional toll on health beyond that associated with absolute deprivation (Adler and Newman, 2002).

Like other area-level measures, misclassification results from using area-SES to proxy person-level SES (Gerber et al., 2010a).

2.4.2.4 Geographical access

Several related but different definitions of “access” exist in the literature, some of which measure the regional density of cardiologists, driving distance to the nearest catheter lab or emergency room, or remoteness of location of residence (rural vs urban). The differences in access to health services between groups is a significant source of heterogeneity for the pooled analyses and may lead to different care-seeking behaviours and treatment pathways that could be targeted to tackle health care delivery issues.

Geographic access to healthcare is often related to income positively (Kulkarni et al., 2013) and education negatively (Rhudy et al., 2016), therefore should be considered as a separate SES measure. A closer look at the studies show that invasive examination and treatment within 30 days to 6 months were less likely the further away from an invasive centre the patients resided as expected. Centralisation of tertiary cardiac services is associated with significant disparities in access to services according to location of residence, but these disparities do not seem to be associated with worse outcomes. The opposite relationship of education and income on geographical access would explain why geographical access is the only SES measure to have no statistical significant relation with mortality other than occupation.

Therefore any associations of geographical access with healthcare intensity and patient outcomes should be separated from associations of access with other SES disparities or their associations with treatment and mortality, i.e. it is important to account for other SES characteristics when studying geographical access to avoid bias by confounding. This is a major limitation of studies in this category as only 2 studies in section considered the effect of other SES measures simultaneously.

2.4.2.5 Social support

In recent years, social aspects as a dimension of SES have received increased attention (Diez Roux, 2003). It has been suggested that the social aspect of SES such as isolation and lack of engagement in social networks are strong predictors

of health. Marital status (Schmaltz et al., 2007) and cohabitation status (Quinones et al., 2014) reflects the social support one may get.

A strong support group could act as a strong buffer for life stresses (Greenwood et al., 1995b), thus influencing health behaviours positively, such as engaging in a healthier lifestyle, encouragement to seek medical attention more urgently and to comply more stringently to prescriptions (Mookadam and Arthur, 2004, Hayes et al., 2016, Dupre et al., 2009, Floud et al., 2014).

The risk apportioned by a lack of a social support network remains so when the usual predictors of premature mortality, including other SES measures (Molshatzki et al., 2011, Gerber et al., 2010b, Austin et al., 2014, Wells et al., Lee et al., 2013, Ambugo and Hagen, 2015) are accounted for by regression analysis. Therefore attention to the role of the social support network as part of public health strategies and risk-stratification may be beneficial.

Other kinds of social support include neighbourhood social interactions and safety/crime levels. Safety and crime are characteristics of social environments used in many neighbourhood level SES indicators, such as the IMDs in the UK, but have never been studied individually.

2.4.2.6 Occupation/ employment

Employment is a more complex variable, and its effect, if any, depends on how employment is measured. One aspect is simply whether or not one is employed, another being the type of work involved in those who are employed. Employment and occupation could have multiple consequences on income, social interactions, housing conditions and are also highly reflected by the amount of education one receives. At the same time, it has many characteristics unique to the occupation that may ultimately affect health status but are unrelated to other SES markers such as the associated amount of psychological stress (Torbica et al., 2015, Gallo et al., 2000) or exposure to certain physical risks such as toxic substances or other occupational injuries or benefits (Schnall et al., 1992). For example, job strain and lack of control over work are greater the lower one's occupational status and largely accounted for differences in coronary heart

disease incidence by occupational grade in the Whitehall study of British civil servants (Marmot et al., 1997, Adler and Newman, 2002).

The classification of occupational groups is quite inconsistent between studies and is not used often as an indicator of social class. Substantial changes in the composition of the occupation groups over time has resulted in wide variations in mortality (Liberatos et al., 1988). Although the literature is consistent in showing evidence that unemployment/unfavourable occupations are associated with worse prognosis, subgroup analyses of the pooled results show that these associations are not significant for 30-day mortality, 1-year mortality, or PCI use. In addition, effects of employment is often due to the "healthy worker" (Adler and Newman, 2002) effect in which most studies cannot fully account for. Therefore it is not possible to infer any causality especially for this SES measure.

2.4.3 Heterogeneity

The nature of observational studies introduces methodological and clinical sources for heterogeneity. Important methodological sources of heterogeneity include inconsistencies in operational definitions of SES and variability in handling confounders. While both methodological heterogeneity and clinical sources from patient (sex, age, ACS type) or contextual (region, year) characteristics of the study population were addressed statistically, the interplay between these sources of heterogeneity could not be addressed in detail. As a result, heterogeneity rarely decrease to a moderate level (I^2<60) in the subgroup analyses and the pooled results should be interpreted with caution.

There is substantial dissimilarity in SES measurement within each SES measure as well. The most apparent example is the multiple definitions for geographical access to healthcare. But even for education, cut-offs for the levels are not always the same. To reduce the inconsistency in SES stratification and to obtain meaningful and comparable measures of SES inequality, it has been suggested that the difference between the extreme categories of SES should be measured (Braveman et al., 2005, Shavers, 2007). The suggested approach was applied to this study (in rare cases continuous risk measures were used) but impaired the possibility of studying the social gradient.

2.4.4 Limitations

These findings should be interpreted within the context of several potential limitations. Differences in access to a life-saving technology is quite unlikely in areas with universal healthcare and an era of PCI with clear guidelines for the treatment of ACS, as well as availability of hemodynamic labs, that a selection of patients based on social characteristics could occur for treatment (Gnavi et al., 2014a). It is more likely that the clinical severity and indications for revascularisation have not been correctly adjusted for. Indeed, only a handful of studies adjust for the severity of ACS or type of ACS, the main factors which modify therapeutic choice. Similarly, poorer overall health may be compounded by unmeasured psychological factors, environment factors and lifestyle. Studies cannot rule out that some of the inequalities left after adjustment could be caused by residual confounding from risk factors (Patil et al., 2014). Consideration of events after hospital discharge, such as the use of cardiac rehabilitation, which likely account for the detected disparities in survival was not possible in most studies.

For ease of interpretation and to reduce the number of sub-group analyses by type of risk measure, hazard ratios, odds ratios, and risk ratios were assumed to represent nearly the same relative risk and were collectively described as risk ratios when pooling study results together. In the literature about these ratios, there is general agreement that if the outcome is rare, the odds ratio and hazard ratio is analogous to the risk ratio (Cummings, 2009). The 1-year mortality rate after ACS is approximately 11% (Findlay et al., 2018b), therefore combining the three different ratios to estimate the relative risks of mortality should be appropriate. However, the intervention rate in ACS patients is not rare, therefore the magnitude of effect in the pooled analysis should be interpreted with care although the results of a sensitivity analysis of using a pooled odds ratio to measure the association of SES and PCI/CAG rate found the same magnitude of effect as the risk ratio. The pooled estimates would only give guidance as to whether statistically significant differences between SES group exist or not.

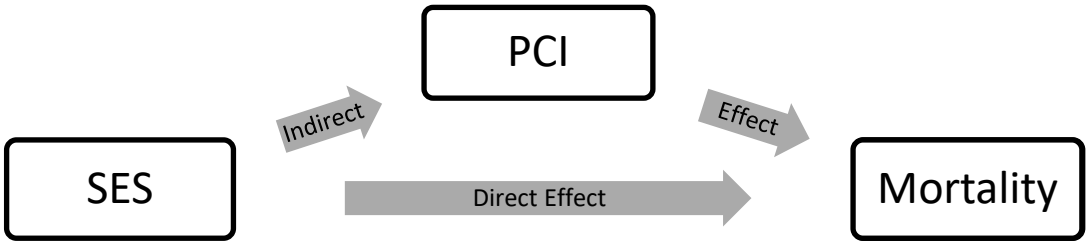
For studies that use area/ neighbourhood-level SES, the absence of person-level information on studies that investigate area-level SES makes it impossible to determine whether differences across neighbourhoods result from the features of the neighbourhoods or to the socioeconomic characteristics of the people who live in them (Tonne and Wilkinson, 2013). Therefore, misclassification of SES results from using area-level SES to proxy person-level SES (Gerber et al., 2010a). Note for future studies for estimating mortality risks, Cox modelling is more appropriate, especially for registry studies because it considers all data points, not simply the total mortality experienced at a single time point.

For studies that use SES indices: since it is a composite measure of SES that includes several variables might provide limited information regarding the independent roles of the different dimensions of SES. In the current body of evidence for SES indices, a key challenge in understanding SES-related inequalities is the investigation of specific features of neighbourhood that may be relevant and find which aspect made the most substantial contribution. This will require moving beyond aggregate socioeconomic characteristics of neighbourhoods to isolating specific features. It would be more beneficial to have both aggregate and single measures of SES analysed. In this literature review, I attempted to address the independent, as well as aggregate contributions of each SES indicator on the outcomes of interest.

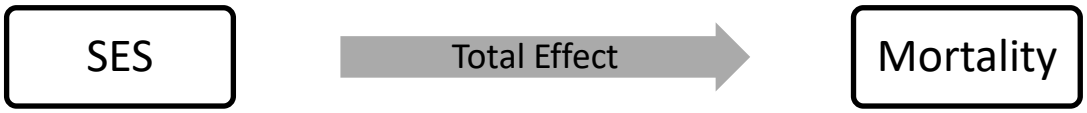
2.4.5 How SES actually influence prognosis: motivation for mediation analysis

Inequalities in utilisation of PCI and in receiving medical attention suggest that inequalities in access to good quality care may play a role in explaining the higher case death of ACS among people with lower SES. A specific paper worth mentioning is the study by Hagen et al. (Hagen et al., 2015). Different from other studies, the relationships between SES, the use of cardiac procedures and mortality are modelled within a path analysis model where the variable describing the provision of the procedure is an intermediate variable that lies on the causal pathway between SES and mortality. As a result, both the direct effect of SES on mortality and the indirect effect of SES on mortality as mediated by the use of PCI have been quantified. The definitions of the direct,

indirect and total effect of SES on mortality in terms of statistical analysis are as follows. According to this definition, all other studies included in this review only look for the total or direct effects.



Model with mediator



Model without mediator

Table 2-4. Description of pathways in mediation analysis.

Effects	Description	Statistical Method
Total effect of SES on mortality	The sum of the direct and indirect effects of SES on mortality	Estimate of SES effect with mortality as the dependent variable, not adjusting for use of PCI
Direct effect of SES on mortality	Effect of SES on mortality, while use of PCI remains unaltered (i.e. take mediation effect into account).	Estimate of SES effect with mortality as the dependent variable, adjust for use of PCI
Direct effect of PCI use on mortality	Effect of PCI on mortality, while SES remains unaltered. (B in figure)	Estimate of PCI use effect with mortality as the dependent variable, adjust for SES
Direct effect of SES on use of PCI	Effect of SES on PCI use (A in figure)	Estimate of SES effect with use of PCI as the dependent variable
Indirect effect of SES on mortality	income influence the probability of receiving PCI to such an extent that it carries on to mortality	Total effect of SES on mortality-Direct effect of SES on mortality or Direct effect of SES on PCI use*Direct effect of PCI on mortality (A*B)

Of particular importance in this analysis was that most of the total effect on mortality was through the direct path. Even though it was found that the highest level of income increased the likelihood of a PCI by about 4.0% compared to the lowest group, the indirect effects on mortality along this path were minor, by

less than 0.4%. Hence, the income gradient in the use of PCI adds to income difference in mortality to little or no extent. Conversely, the direct effects of SES on mortality were larger, with values five to six times greater than the indirect effects.

In spite of the abundant literature on the relation between SES and ACS outcomes, there is no clear explanation of the mechanisms through which it operates. In other words, we have seen that SES is an important predictor of mortality, but SES is not the decisive force that determines mortality, SES must be acting through some other measured or unmeasured factors that directly affect health in ACS patients.

Subgroup analyses stratified by adjustment strategy indicate that treatment within hospital tend to attenuate inequalities in mortality (Ahmadi et al., 2014, Coady et al., 2014, Grey et al., 2014, Patil et al., 2014, Yong et al., 2014, Chang et al., 2007, Blais et al., 2012), while a closer look of studies that further adjusted for prescriptions found use of secondary prevention medications (Machon et al., 2012, Barakat et al., 2001, Jakobsen et al., 2012b) eliminated inequalities in mortality. This suggest that inequalities in care exist and could be the main determinant of inequalities in survival.

Ultimately, these actual determinants of health that vary with SES might be the pathways by which SES affects health outcomes after ACS, but these effects, known as mediation effects, have not been quantified yet. All studies included in this review simply adjust for them in models or look for associations between SES and the risk factors. The magnitude of the contribution of differences in medication and interventional procedures to inequalities in mortality needs to be investigated further using mediation analyses. A study of what factors explain or mediate socioeconomic differences could shed light on disease aetiology by helping to identify and compare mediators, thereby suggest effective interventions to improve survival. This new statistical method goes beyond the usual research on inequalities and should be applied to further investigations in this area. Simple interpretations of the comparison of adjusted and unadjusted estimates, such as “x% of the difference is explained by standard risk factors,” or “the effect of SES have been attenuated by x%” are not enough. We lack a

holistic study that shows the effect of SES on mortality outcomes as a consequence of SES' effects on mediators, i.e. how the effect of SES on the provision of treatments translates into mortality. The mediators could then be compared, giving policy makers guidance as to the most efficient target to address health disparities. This is the motivation for the last chapter of this thesis.

2.5 Conclusion

In patients with ACS, it is well established that a person's socioeconomic status has modest but profound effects on the utilisation of invasive cardiovascular services and mortality. These relationships have been demonstrated for different dimensions of area-level and individual level SES measures, across different countries and have not improved over time. Differences in mortality across socioeconomic strata is greatly attenuated after considering treatments and related factors, while targeting poor geographical access to healthcare facilities may be the most efficient way to decrease the inequality gap in utilisation of invasive coronary procedures. Public health policies aimed at reducing mortality in ACS patients should address SES both in the promotion and the evaluation of prevention and treatment strategies.

Chapter 3 Mind the gap 1: Socio-economic inequalities on treatment and mortality after acute coronary syndrome hospitalisation

3.1 Introduction

3.1.1 Background

Socioeconomic related disparities in healthcare and health outcomes are prevailing public health problems worldwide. In patients with ACS, results from the literature review in Chapter 2 established that a person's socioeconomic status are modestly but profoundly associated with mortality (Mehta et al., 2011, Patil et al., 2014, Martensson et al., 2016, Grey et al., 2014). As reviewed in detail in Chapter 2, a range of reasons for the link between SES and mortality has been investigated. Relating to cardiovascular care, a lack of conformity to evidence-based treatments and practice guidelines known to improve clinical outcomes between SES groups have consistently been found. Specifically, a person's socioeconomic status varies with the use of a number of cardiovascular life-saving procedures including cardiac catheterization and percutaneous coronary intervention. Differences also exist in prescription rates of evidence-based medications and rehabilitation services that may translate into disparities in outcomes. Patients with lower socioeconomic status are often presented later to hospital but did not usually differ in time to invasive-cardiac treatment after arrival at hospital compared to their counterparts. While CHD related risk factors such as certain health behaviours and the number of comorbidities are another source of disparity in outcomes. These relationships have been demonstrated for different dimensions of area-level and individual-level SES measures. It remains unclear, however, if the same management and health disparities exist in Scotland using contemporary data. There is also little evidence on the role of healthcare utilisation in the association between outcomes and SES in ACS patients in Scotland where free healthcare is provided to the entire population but still has a high rate of ACS (Townsend et al., 2015, British Heart Foundation, 2018c) and significant SES disparities in cardiovascular outcomes (NHS Health Scotland Information Services Division, 2018b).

3.1.2 Objectives

This chapter is a comprehensive retrospective, observational cohort study of socio-economic inequalities in ACS in West of Scotland by linking routinely collected data from multiple sources. The Scottish national registries for prescribing, inpatient and mortality are linked with the ACS electronic registry (e-Registry), composed of hospital administrative data for ACS patients, for analyses.

Specifically, this study aims to address the following questions by analysing patients hospitalised with acute coronary syndrome (ACS):

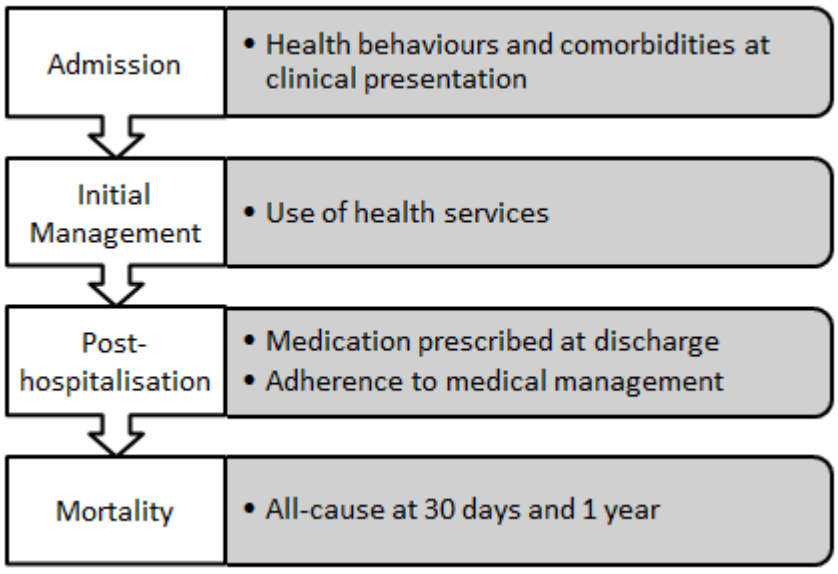
1. Are there socioeconomic inequalities in morbidity?

2. Is socioeconomic status associated with differential use of evidence-based therapies, including prescriptions and other aspects of the care process?

3. Is socioeconomic status linked to mortality?

The primary outcome is all-cause mortality at 1 year. Other measures encompass the whole care pathway including risk factors at clinical presentation, the quality of care during hospitalisation and post-hospitalisation medical care. Specific variables are detailed in the methods section.

Figure 3-1. Study measures



3.2 Methods

3.2.1 Data sources

Scotland has a world-leading health informatics system with a long tradition of using linked health service and outcomes data for research (NHS Research Scotland, 2019). Its excellent infrastructure of routinely collected, high quality and well-maintained hospital-level and national-level administrative datasets and existence of unique patient identifiers enables data linkage across multiple sources in evaluating health inequalities and interventions for the benefit of the population's health (The Scottish Government, 2016a).

Given the complexity of the healthcare process of patients hospitalised with ACS, health datasets held across several databases have been linked together for analysis in the study. These datasets are described below.

Information Services Division (ISD) is part of NHS National Services Scotland (NSS) and holds a wide range of health related administrative data on its behalf (NHS National Services Scotland, 2010). Many of the national-level datasets used for this project came from ISD. Table 3-1 details the datasets provided by ISD for the analysis of this study.

Table 3-1. Datasets provided by ISD.

Database	Description
Prescribing Information System (PIS)	Prescribing database with information relating to all medicines dispensed in the community in Scotland
Scottish Morbidity Record 1 (SMR01)	The General/ Acute Inpatient and Day Case dataset contains patient level information on care received in hospital and general acute specialities in Scotland.
National Records of Scotland (NRS)	Deaths Data contains records of all deaths occurring in Scotland along with its causes
	Scottish Index of Multiple Deprivation index is a relative measure of area-level deprivation

Prescribing Information System (PIS) holds prescribing information supplied to ISD by the Practitioner Services, which is responsible for the processing and

payment of all dispensed prescriptions in Scotland (Information Services Division of NHS National Services Scotland, 2012). In Scotland, all cardiovascular medications require a prescription, except aspirin. All drug prescriptions issued in hospitals or in GP practice and dispensed in the community are included; however prescriptions dispensed within hospitals are not (NHS National Services Scotland, 2016c). For patients hospitalised with ACS, drugs given during the hospitalisation usually should last them about 7 days after discharge but are not recorded here. Dispensing information from PIS was used to determine frequency and use of drugs both before the ACS index date and after discharge from hospital.

Scottish Morbidity Record 1 (SMR01), also known as the Acute and Inpatient Day Case dataset holds information relating to acute hospital admissions in Scotland from 1960 onwards (NHS National Services Scotland, 2016b). Continuous patient level data including primary and previous diagnoses on all inpatient and day case discharged from acute specialities in Scottish hospitals are collected. Comorbidities of interest were identified by linkage to hospitalisation data recorded on the SMR01.

National Records of Scotland (NRS) death registrations are submitted to ISD and holds a record for each death registered in Scotland since 1974 (National Records of Scotland, 2019a).

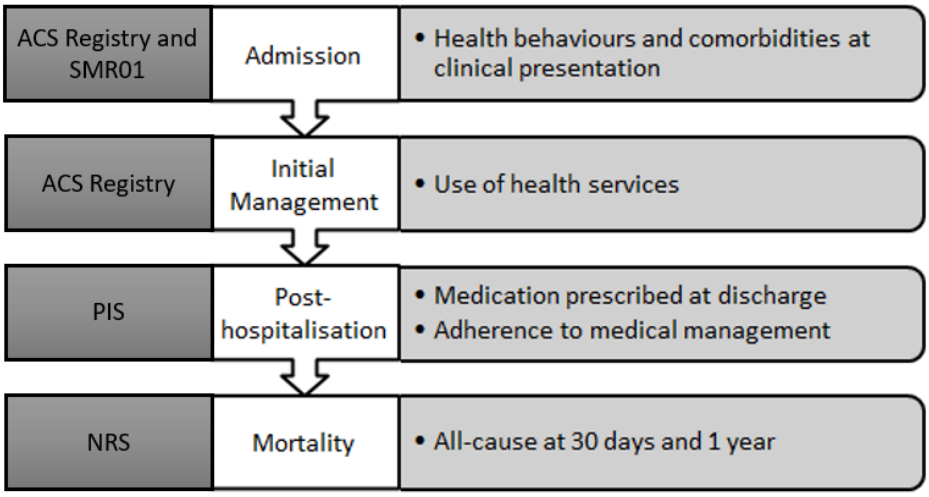
The NRS also store SES data for the Scottish population known as the Scottish Index of Multiple Deprivation (SIMD) index (NHS National Services Scotland, 2017). The SES level for the population of a small geographical area is estimated from 38 indicators across 7 domains derived from the census and other routine sources. The SIMD is a measure of deprivation which assumes that deprivation is not one dimensional but consist of multiple aspects (National Records of Scotland, 2019b). The 7 domains expressed as a % of the overall SIMD weight are: income (28%), employment (28%), health deprivation and disability (14%), education (14%), geographic access to services (9%), crime (5%) and housing (2%) (Scottish Government, 2016a). The result is an overall index and “official tool” used by the Scottish Government to measure relative deprivation across Scotland (The Scottish Government, 2016b). The area’s deprivation level is often used as

the best available estimate of the deprivation level of individuals residing there(NHS National Services Scotland, 2016a).

Scottish Care Information (SCI) Store, is an information repository implemented by NHS national services Scotland that stores patient laboratory reports (SCI NHS National Services Scotland). It contains biochemistry, haematology, pathology, and various other laboratory tests. These data were also extracted and explored for the ACS patient population in this study but were excluded from further analysis due to large number of missing data. However, as SCI Store is under continual development and has lots of potential, especially it current plans to include ECG results (SCI NHS National Services Scotland) follows through.

The ACS e-registry was established in the NHS in the West of Scotland. GGC has a tax-financed universal healthcare system, with free access for all citizens to hospitals and essential operations, including CAG and PCI procedures. Invasive cardiac care is organized such that there is one cardiac centre that provide all PCI procedures. This e-registry contains electronic health records for patients hospitalised with a suspected or known ACS at the Golden Jubilee National Hospital and 7 acute secondary care NHS GGC hospitals, serving a population of approximately 1.2 million. The Golden Jubilee National Hospital is a regional cardiothoracic intervention centre that provides invasive cardiology and cardiothoracic services for this population, amongst others, but is administratively distinct from NHS GGC. The ACS e-registry was used to obtain details of the ACS episode of care from the time of initial contact with NHS until discharge of hospitalisation. A summary of all the data sources used are depicted in Figure 3-2.

Figure 3-2. Data sources for study measures.



3.2.2 Extraction and storage

In Scotland, a centrally maintained unique identifier allocated to all GP-registered patients evolved from a regional database developed in the 1970's to having national coverage by the late 2000's (Scottish Government, 2013c). This numbering system, the Community Health Index (CHI), are unique to each patient, and enable patient records across different health databases mentioned above to be linked together for the patients identified from the ACS e-registry.

The NHSGGC Safe Haven (SH), like the other Safe Havens in Scotland, provides an approved governance route and record linkage service which assists the research community by enabling linkage and data access for analysis on a secure platform (Scottish Government, 2015, NHS Greater Glasgow and Clyde Safe Haven). After the study cohort was identified from the ACS e-registry, the NHSGGC SH extracted all other relevant data for the patient population from sources mentioned in Section 3.2.1 using CHI numbers as the matching variable. Individual datasets were pseudonymised and stored in a secure area on the SH for me to access and analyse. Only approved researchers have access to the securely stored data within the SH, researchers cannot see personal identifiers of patients, and monitoring software blocks and logs any attempts to upload or download software or data on the platform (Information Services Division of NHS National Services Scotland, NHS Greater Glasgow and Clyde Safe Haven). Any statistical outputs must be cleared for disclosure by the SH Research Co-ordinator through the Statistical Disclosure Control process.

3.2.3 Steps to identify cohort and linkage

The study population included all GGC residents admitted to a hospital between 1 October 2013 and 30 June 2016 with a diagnosis of ACS. The ACS diagnoses were based on the discharge summary recorded by the attending clinician(s) in usual care electronic health records. In the local hospitals the diagnoses are coded per the International Classification of Disease (ICD)-10 and in the invasive centre the discharge diagnosis is recorded in a standardised text format (Findlay et al., 2018a). ACS is defined by the ICD-10 diagnosis codes for MI (I210 and I229) and angina (I200-I209). Only the first ACS hospitalisation episode for each patient during the study period was included. An ACS episode was considered to be a continuous period of hospital admission that may encompass between hospital transfers, an initial discharge from a local hospital with a referral for cardiac interventions and re-admission to the Cath lab or simply a direct admission to the Cath lab among other possibilities. The ACS e-registry outputs a single dataset with details regarding the first ACS episode of care during the study period.

Unique study index numbers were given to each patient following the identification of the ACS cohort. Health data from other sources were extracted by the NHSGGC SH, who hold CHI numbers to this population used for extraction. Data from all sources had the CHI numbers deleted and replaced with study index numbers and stored in the SH as separate files. Within the SH, I linked the ACS population in the ACS e-Registry to the separate files: NRS SIMD, PIS, SMR01, SCI Store and NRS deaths datasets using the study index number. By linking patients to SMR01 records provided by NHS GGC, the cohort was limited to residents of GGC.

3.2.4 Governance

The project was supported by the National Advisory Committee for Coronary Heart Disease on behalf of the Scottish Government as an extension of the Joint Working Project between NHS health boards, including Greater Glasgow and Clyde (NHS GGC) and the Golden Jubilee National Hospital (GJNH) and AstraZeneca UK Ltd. The Joint Working Project was approved by hospital

management and the Caldicott Guardian for clinical governance in each Health Board.

The Safe Havens in Scotland that handle NHS patient data for research operate within a robust research governance framework (Scottish Government, 2015). An application to the NHSGGC Safe Haven seeking permission for access to health data was approved in November 2016 (Study number: GSH13CA002).

As the data gathered in this study was collected as part of routine clinical care, access to all data had been granted and approved by NHSGGC SH, and release of all statistical results gone through NHSGGC SH' Statistical Disclosure Control process in which output files needs to be cleared for disclosure, the NHS West of Scotland Research Ethics Service (NHS Health Research Authority, 2018) advised that a formal ethics approval for use of anonymised data was not necessary.

3.2.5 Analytical methods by health outcomes and process of care

3.2.5.1 Basic principles

Analyses was performed separately by ACS diagnosis, as STEMI, NSTEMI and hospitalised angina have different clinical profiles and require different treatment strategies.

For descriptive statistics, continuous variables will be summarised by the number of observations, number of missing values, mean, standard deviation (SD), median, quartiles and range. Categorical variables will be summarised by the number of observations, number of missing values and the number and percentage of individuals in each category. Cells with counts <5 will be blinded for privacy purposes per Scotland's electronic Data Research and Innovation Service (eDRIS) policy. This applies to patient characteristics as well as any other study variables investigated.

This chapter examined differences in patient characteristics and treatment characteristics and clinical outcomes by SES. Sections 3.2.5.3 to 3.2.5.6 detail the patient characteristics, care procedures, use of evidence-based medications and mortality outcomes compared and analysed by SES quintiles detailed in

Sections 3.2.5.2. As an extension to this study, sections 3.2.5.7 and 3.2.5.8 introduce additional studies detailed in Chapters 4 and 5.

Data manipulation, linkage and analyses were undertaken using SAS Enterprise Guide 5.1.

3.2.5.2 SIMD

The Scottish Indices of Deprivation (SIMD) provide a relative measure of deprivation at the neighbourhood level across Scotland based on the postcode of the patient's home address. Areas are ranked from least deprived to most deprived for the overall composite measure of multiple deprivation which combines information from seven different dimensions of deprivation. The dimensions used in the Indices of Deprivation are: income deprivation; employment deprivation; education deprivation; housing deprivation; health deprivation and disability; crime deprivation; and geographical access deprivation (Scottish Government, 2016b). The SIMD version used for this study population as measure of SES deprivation at baseline is 2012.

For this study, SES deprivation at baseline is measured using quintiles of the SIMD 2012 measure (Scottish Government, 2016a). Quintile 1 represents the highest level of deprivation with quintile 5 representing the least deprived. The top 20% most deprived data zones in Scotland are in the first quintile, with the distribution of Glasgow City's data zones being 49%, 19%, 13%, 10.5%, 8.5% (Q1-Q5) (Scottish Government, 2012). Since no linear or constant increase in the outcomes of interest could be assumed. Therefore, outcomes of patients in the second, third, fourth, and fifth quintiles are compared individually with the first quintile, considered as reference.

3.2.5.3 Clinical presentation

The following patient characteristics at clinical presentation was summarised overall by ACS type and compared across SES levels.

Demographics:

- Age

- Gender

Comorbidities measured by (available using ICD-10 codes from SMR01):

- Charlson index
- Elixhauser index
- Ontario acute myocardial infarction mortality prediction variables

Those with any diagnosis record of comorbidities or prescriptions of interest are included, while those without any record are assumed to never had the comorbidities or prescriptions. This method means there are no missing data associated with comorbidities and outcomes.

Laboratory test measures recorded on day of admission were explored. To minimize the amount of missing data, blood measures on second day of admission will also be included if there were no test data on day of admission. However, exploratory analysis showed that lab measurements were not well recorded as these are not mandatory fields for entry in ACS patients, with eGFR measures missing in 21.9% of patients and glucose measures missing in 41.7%. During the study period, high-sensitive cardiac troponin I assays replaced traditional troponin assays so both measures also contained high levels of missing data and are not recommended to be analysed as one. Due to a significant amount of missing data, including lab measures would likely distort the representativeness and accuracy of the results if analysed further. Therefore lab measures will no longer be used in the analyses.

3.2.5.3.1 A simple embedded study of comorbidity measures

3.2.5.3.1.1 Background

Observational studies using administrative data require proper comorbidity adjustment to reduce bias (Kaplan and Feinstein, 1974). Three popular methods are the Charlson co-morbidity index (CCI) (Charlson et al., 1987), the Elixhauser comorbidity system (Elixhauser et al., 1998), and the Ontario AMI prediction comorbidities (Tu et al., 2001).

The Charlson index is developed in 1987 as a prognostic index for 1- and 10-year mortality of comorbid patients. It is a weighted sum of the presence or absence of 19 diseases with each condition assigned with a score of 1,2,3 or 6 depending

on the risk of dying associated with this condition. Regretfully this method has some deficiencies: including the fact that it was developed over 30 years ago using only 559 patients and the absence of many important for prognosis disorders. In a systematic review of comorbidity indices for administrative data (Sharabiani et al., 2012), the Deyo (Deyo et al., 1992) variant of Charlson with 17 diseases was the most commonly used followed by the Elixhauser measure.

The Elixhauser comorbidity measure is a sum of presence or absence of 30 comorbidities, and was developed in 1998 for the prediction of length of hospital stay and mortality. Elixhauser shows a better predictive performance for long- and short-term mortality risk compared to other comorbidity indices including CCI (Sharabiani et al., 2012). In addition, a composite score provides an attractive advantage over multiple indicators by reducing overfitting risk. A popular adapted weighted version was developed in 2009 (van Walraven et al., 2009) and used in this study. This weighted Elixhauser score was also found to be superior to the CCI in predicting in-hospital mortality (Thompson et al., 2015).

The Ontario AMI predication comorbidities was developed and validated in 2001 with hospital discharge administrative databases to predict 30-day and 1-year mortality in 52616 acute myocardial infarction (AMI) patients. While the Ontario AMI mortality comorbidities are more appropriate for this study population, it is a simple summary of the comorbidities count, under the questionable (Thompson et al., 2015) assumption that each comorbidity equally affects outcome.

Incorporating comorbidities when analysing SES effect on treatment and clinical outcomes are important as studies found comorbidities such as diabetes (Hung et al., 2009), and CVD (Lee et al., 2010) to be associated with lower uptake of guideline recommended medications and invasive therapies, and worse outcomes. No studies are available to evaluate and compare the ability of these indices to predict mortality in ACS subjects. The objective of this small study was to compare the three measures for predicting age and sex adjusted 1-year all-cause mortality and determine the best comorbidity measure to be used for risk prediction for further analyses of this ACS population.

3.2.5.3.1.2 Statistical methods

Comorbidities are defined as any SMR01 diagnosis before or at admission date (except MI) using the associated International Statistical Classification of Diseases, 10th Revision (ICD-10) codes (Table 3-2). Dichotomous variables indicating the presence or absence of each Charlson, Elixhauser or Ontario AMI predication comorbidity were created, and their associations with mortality were assessed using chi-square tests. In addition, the weighted scores were computed according to Table 3-3 and further stratified into groups (CCI: 0, 1–3, ≥ 4; Elixhauser: < 0, 0, 1–5, 6-13, ≥ 14; Ontario AMI: continuous count). Comorbidity scores were then calculated for each patient by summing the individual weights of all comorbidities.

Predictive effects of each comorbidity for different indices of age- and sex-adjusted Cox-proportional hazard models of 1-year all-cause mortality were investigated to test the appropriateness of the comorbidity indices in ACS patients. The proportional hazard assumption of each categorical comorbidity was assessed by a graphical analysis as well as including time dependent covariates in the Cox model. The linear effect of age on the logarithm of hazard was assessed by 1) assessing significance of adding age squared to the age and sex adjusted model and also 2) a plot of martingale residuals of the gender adjusted model (logarithm of hazard) versus continuous age.

The possibility of an adapted clinical comorbidity index for this ACS population was examined. Using a backwards selection model of all comorbidities from the 3 indices and compared with the above comorbidity indices using model AIC/BIC and C-statistics, a selection of individual comorbidities as predictive confounders of outcome were explored. The best predictive comorbidity index of age- and sex- adjusted mortality will be included as a covariate in multivariate models in the next sections, in addition to age and sex.

Out of the prognostic comorbidities identified above, comorbidities that are significantly associated with SES were identified using both ordinal logistic models adjusted for age, sex with backwards selection. The proportional odds assumption in ordinal logistic regressions must be satisfied.

Table 3-2. ICD-10 Coding Algorithms for Comorbidities.

Comorbidities	Charlson Index*	Elixhauser Comorbidity**	Ontario AMI predication***
Myocardial infarction	I21, I22, I252	N/A	N/A
Congestive heart failure	I50, I110 I130 I132	I50, I099 I110 I130 I132 I255 I420 I425 I426 I427 I428 I429 I43 P290	I50, I099 I110 I130 I132 I255 I420 I425 I426 I427 I428 I429 I43 P290
Cardiac Arrhythmia	N/A	I47 I48 I49,I441 I442 I443 I456 I459 R000 R001 R008 T821 Z450 Z950	I47 I48 I49,I441 I442 I443 I456 I459 R000 R001 R008 T821 Z450 Z950
Valvular Disease	N/A	I05 I06 I07 I08 I34 I35 I36 I37 I38 I39,A520 I091 I098 Q230 Q231 Q232 Q233 Z952 Z953 Z954	N/A
Pulmonary Circulation Disorders	N/A	I26 I27,I280 I288 I289	N/A
Peripheral vascular disease	I70 I71 I72 I73 I74 I77 R02, I790 I739	I70 I71,I731 I738 I739 I771 I790 I792 K551 K558 K559 Z958 Z959	N/A
Hypertension Uncomplicated	N/A	I10	N/A
Hypertension complicated	N/A	I11 I12 I13 I15	N/A
Cerebrovascular disease	I60 I61 I62 I63 I64 I65 I66 I67 I68 I69 G45 G46	N/A	I60 I61 I62 I63 I64 I65 I66 I67 I68 I69 G45 G46
Dementia	F00 F01 F02 F03 G30, F051	N/A	N/A
Paralysis	N/A	G81 G82,G041 G114 G801 G802 G830 G831 G832 G833 G834 G839	N/A
Other Neurological Disorders	N/A	G10 G11 G12 G13 G20 G21 G22 G32 G35 G36 G37 G40 G41 R56,G254 G255 G312 G318 G319 G931 G934 R470	N/A
Chronic pulmonary disease	J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J66 J67, J684 J701	J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J66 J67,J684 J701 J703 I278 I279	N/A
Connective tissue disease	M05 M06 M08 M09 M30 M31 M32M34, M332 M353		N/A
Rheumatoid Arthritis/collagen	N/A	M05 M06 M08 M30 M32 M33 M34 M35 M45, L940 L941 L943 M120 M123 M310 M311 M312 M313 M461 M468 M469	N/A
Ulcer disease	K25 K26 K27 K28, K221		N/A
Peptic Ulcer Disease excluding bleeding	N/A	K257 K259 K267 K269 K277 K279 K287 K289	N/A
Mild liver disease	B18 K71 K73 K74, K700 K701 K702 K703 K709 K760		N/A
Diabetes without complications	E109 E119 E129 E139 E149	E109 E119 E129 E139 E149	N/A
Diabetes with complications	E100 E101 E102 E103 E104 E105 E106 E107 E108 E110 E111 E112 E113 E114 E115 E116 E117 E118 E120 E121	E100 E101 E102 E103 E104 E105 E106 E107 E108 E110 E111 E112 E113 E114 E115 E116 E117 E118 E120 E121 E122 E123 E124 E125 E126 E127 E128 E132	E100 E101 E102 E103 E104 E105 E106 E107 E108 E110 E111 E112 E113 E114 E115 E116 E117 E118

	E122 E123 E124 E125 E126 E127 E128 E132 E130 E131 E133 E134 E135 E136 E137 E138 E140 E141 E142 E143 E144 E145 E146 E147 E148	E130 E131 E133 E134 E135 E136 E137 E138 E140 E141 E142 E143 E144 E145 E146 E147 E148	E120 E121 E122 E123 E124 E125 E126 E127 E128 E132 E130 E131 E133 E134 E135 E136 E137 E138 E140 E141 E142 E143 E144 E145 E146 E147 E148
Hypothyroidism	N/A	E00 E01 E02 E03,E890	N/A
Hemiplegia	G81 G82	N/A	N/A
Moderate/severe renal disease	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61, N054	N/A	N/A
Chronic Renal Failure	N/A	N18 N19, I120 I131 N250 Z490 Z491 Z492 Z940 Z992	N18 N19, I120 I131 N250 Z490 Z491 Z492 Z940 Z992
Any tumour (without metastasis)	C0 C1 C2 C3 C4 C5 C6, C71 C72 C73 C74 C75 C76	C00 C01 C02 C03 C04 C05 C06 C07 C08 C09 C10 C11 C12 C13 C14 C15 C16 C17 C18 C19 C20 C21 C22 C23 C24 C25 C26 C30 C31 C32 C33 C34 C37 C38 C39 C40 C41 C43 C45 C46 C47 C48 C49 C50 C51 C52 C53 C54 C55 C56 C57 C58 C60 C61 C62 C63 C64 C65 C66 C67 C68 C69 C70 C71 C72 C73 C74 C75 C76 C97	N/A
Leukaemia	C91 C92 C93 C94 C95	N/A	N/A
Lymphoma	C81 C82 C83 C84 C85 C88 C90 C96, C961	C81 C82 C83 C84 C85 C88 C96,C900 C902	N/A
Metastatic solid tumour	C77 C78 C79 C80, C801	C77 C78 C79 C80	N/A
Moderate/severe liver disease	K72 I85, B150 B160 B162 B190 K704 K766	N/A	N/A
Liver Disease	N/A	B18 I85 K70 K72 K73 K74,I864 I982 K711 K713 K714 K715 K717 K760 K762 K763 K764 K765 K766 K767 K768 K769 Z944	N/A
Coagulopathy	N/A	D65 D66 D67 D68,D691 D693 D694 D695 D696	N/A
Obesity	N/A	E66	N/A
Weight Loss	N/A	E40 E41 E42 E43 E44 E45 E46 R64,R634	N/A
Fluid and Electrolyte Disorders	N/A	E86 E87, E222	N/A
Blood Loss Anaemia	N/A	D500	N/A
Deficiency Anaemia	N/A	D51 D52 D53,D508 D509	N/A
Alcohol Abuse	N/A	F10 E52 T51,G621 I426 K292 K700 K703 K709 Z502 Z714 Z721	N/A
Drug Abuse	N/A	F11 F12 F13 F14 F15 F16 F18 F19,Z715 Z722	N/A
Psychoses	N/A	F20 F22 F23 F24 F25 F28 F29,F302 F312 F315	N/A
Depression	N/A	F32 F33,F204 F313 F314 F315 F341 F412 F432	N/A
Shock	N/A	N/A	R57
Cancer	N/A	N/A	C
Pulmonary edema	N/A	N/A	J81,J182
Acute renal failure	N/A	N/A	N17 R34
AIDS	B20 B21 B22 B23 B24	B20 B21 B22 B24	N/A

ICD-10 codes normally in Axx.x format where A is a letter and x are numbers, codes in Axx format are inclusive of all numbers in category (Axx.x), for example I21 includes all I21.x. * with some alterations based on (Quan et al., 2005); ** http://mchp-appserv.cpe.umanitoba.ca/Upload/SAS/_ElixhauserICD10.sas.txt; * (Vermeulen et al., 2007)**

Table 3-3. Comorbidities score weights

Weight	Morbidity
Charlson's Comorbidity Index	
1	Myocardial infarction, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Connective tissue disease, Ulcer disease, Mild liver disease, Diabetes without complications
2	Hemiplegia, Moderate/severe renal disease, Diabetes with complications, Any malignancy (including leukaemia and lymphoma)
3	Moderate or severe liver disease
6	Metastatic solid tumour, AIDS
Elixhauser Comorbidity	
0	Hypertension Uncomplicated, Hypertension complicated, Peptic Ulcer Disease excluding bleeding, Diabetes without complications, Diabetes with complications, Hypothyroidism, Alcohol Abuse, Psychoses, AIDS
2	Peripheral vascular disease
3	Chronic pulmonary disease, Rheumatoid Arthritis/collagen, Coagulopathy
4	Pulmonary Circulation Disorders, Any tumour (without metastasis)
5	Cardiac Arrhythmia, Chronic Renal Failure, Fluid and Electrolyte Disorders
6	Other Neurological Disorders, Weight Loss
7	Congestive heart failure, Paralysis
9	Lymphoma
11	Liver Disease
12	Metastatic solid tumour
-1	Valvular Disease
-2	Blood Loss Anaemia, Deficiency Anaemia
-3	Depression
-4	Obesity
-7	Drug Abuse
Ontario AMI predication	
1	Cerebrovascular disease, Pulmonary edema, Acute renal failure, Chronic renal failure, Cardiac dysrhythmias, Shock, Diabetes with complications, Congestive heart failure, Cancer

3.2.5.4 Initial management

In-hospital quality measures to be explored were identified based on the national guidance for the treatment of heart attacks from the Department of Health (UK Department of Health, 2008) and other process of care measures, including:

- Admission length, including length of hospital stay and length of ACS episode (patients may be admitted to invasive centre following discharge and referral from local hospital so entire ACS episode not necessarily always in hospital)
- Admission method:
    - (1) Emergency admission to the invasive centre, including direct admissions to the invasive centre and direct transfers from the

Local Accident and Emergency/Emergency room to the invasive centre
    - (2) Non-emergency/ elective (no referral from local hospital) admission to the invasive centre
    - (3) Emergency admission to the local hospital
    - (4) Non-emergency admission to local hospital, including self-presentations and inter-hospital transfers
- Rate of use of invasive management (CAG) and revascularisation (PCI), by admission method
- In those that received PCI, waiting times for invasive treatment:
    - Call to door time (min)
    - Door to balloon time (min)
    - Call to balloon time (min)
    - Weekend vs weekday of admission
    - Day (6am to 11pm) vs night of admission

For cardiologists, comorbidities are important in knowing how aggressively to treat a condition. In addition, the identification and targeting of patient-related factors associated with delayed presentation and inappropriate access to medical services (CAG with no follow-on PCI) is essential in improving quality of care. Therefore the association between SES quintiles, as well as other baseline characteristics, with the receipt of CAG, PCI and No PCI in those that received CAG was examined using multivariable logistic regression.

3.2.5.5 Long-term medical management

Baseline pre-admission use: To evaluate the association of SES and evidence-based medication use prior to the ACS event, baseline medication use was defined as claim of prescription for the drug within 90 days of the date of admission among patients discharged alive after first hospitalisation for ACS between 2013 and 2016. The following medication or combinations of medications were considered by the rate of use:

- Statins
- ACE inhibitor/ARB

- Beta blocker (BB)
- Antiplatelets:
    - Aspirin
    - Clopidogrel
    - Ticagrelor
    - Single antiplatelet therapy (SAPT): any of the above 3 antiplatelets
    - Dual antiplatelet therapy (DAPT): aspirin with (clopidogrel or ticagrelor)
- Mineralocorticoid Receptor Antagonists (MRA)
- Oral anticoagulants (OAC)
- 3 or more of the above

Initiation post discharge: Any SES differences in secondary prevention following ACS was evaluated by analysing differences in prescription rates within 90 days of discharge for the above medications for all patients discharged alive. Although some used 60 days to define claim of prescription, we felt that 90 days is more appropriate due to the nature of the data source: date of prescription provided are not exact dates when prescriptions are claimed but dates when prescriptions are dispensed/claimed by pharmacies, which usually happen at the second and last week of each month. A sensitivity analysis was performed to compare prescription rates at 60 days and 90 days.

Continuation: In patients that initiated the drugs and are still alive at each follow up point, continued use of the drugs is defined as claim of prescription at 6 month or 1 year post discharge +/- 45 days.

Hierarchies: After discussion with cardiologists (AJ, PJ), the following hierarchy of drug use post discharge was also analysed:

- OAC or SAPT
- OAC or SAPT + Statins
- OAC or SAPT + Statins + BB
- OAC or SAPT + Statins + BB + ACE inhibitor/ARB
- OAC or SAPT + Statins + BB + ACE inhibitor/ARB +MRA

To analyse the effect of SIMD on drug treatment, three analyses using mixed effects logistic models were performed for each drug/drug combination: (1) claim of prescription at a pharmacy within 90 days of discharge as outcome (in all patients alive at discharge), adjusted for the baseline characteristics: age, sex, SIMD, use of respective drug within 90 days before index admission (a.k.a. baseline use, a dichotomous variable), co-morbidities and if revascularisation procedures were performed, as well as clustering at the discharge hospital level; (2) continuation of prescription at 6 months or (3) 1 year after discharge as outcome (only for patients who initiated treatment within 90 days of discharge and alive at follow up), adjusted for the same baseline characteristics as above. Models that analysed drug hierarchies did not adjust for pre-admission drug use. Linearity is tested between age and log odds by adding the interaction term to the logistic model, if violated then categorical age is used instead.

3.2.5.6 Mortality

To investigate SES inequalities in short- and long-term case-fatality rates in ACS patients, the primary outcomes of the study are all-cause mortality at 30 days and at 1 year. Cumulative incidence curves were generated for all-cause death by SES, any differences were assessed using a log-rank test. The association between low versus high SES and mortality was investigated using age- and sex-adjusted Cox proportional hazards models as well as adjusting for additional comorbidities and in-hospital quality of care characteristics.

The effects of comorbidities, in-hospital quality of care characteristics and secondary prevention prescription rates on age and sex-adjusted mortality were also evaluated. Any variables with $p<0.10$ was included in a final multivariate Cox-proportional hazards model adjusted for age, sex. The proportional hazards assumption was tested for each significant variable graphically and by adding time - dependent variables to the original model.

3.2.5.7 Mediator analyses

Healthcare has contributed to improvement of health outcomes. However, it may aggravate health inequity if there are socioeconomic disparities in access to health care services or quality of health care. Healthcare interventions may

cause health inequalities if there are differences in effectiveness among different socioeconomic groups. The extent of the effect of SES on mortality through healthcare disparities can be calculated through mediation analyses.

The mediator and indirect effects of SES on mortality through variables in section 3.2.5.3 to 3.2.5.5 will be examined to investigate the myriad of clinical characteristics, invasive and conservative treatment strategies as mediators of health inequity in ACS patients.

Figure 3-3. A multiple mediator model of SES and mortality.

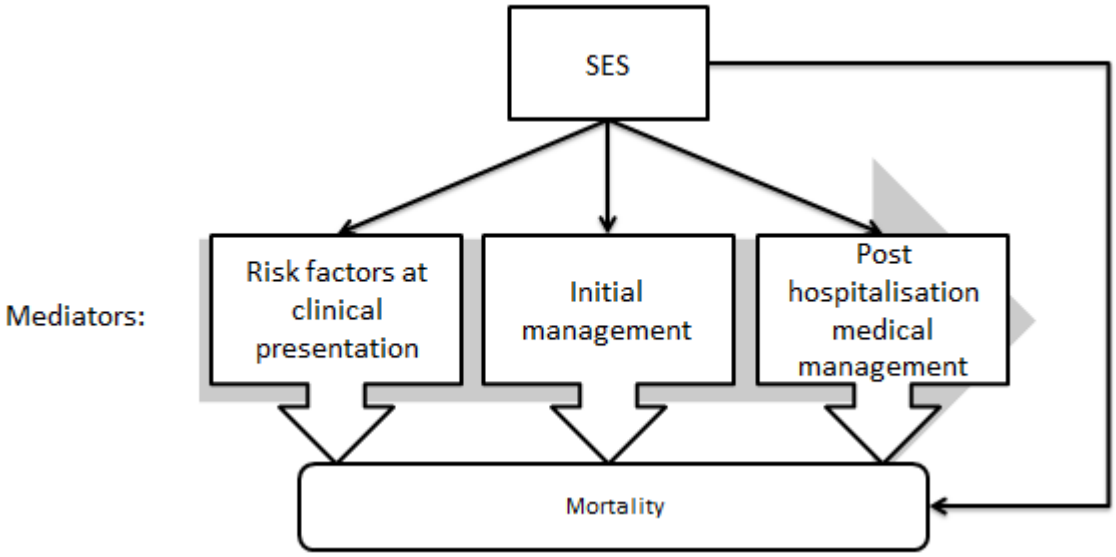


Figure above depicts a mediation model. Key research question includes whether the possible higher rate of baseline risk factors or lower rate of PCI or medications after discharge for patients with low SES has any additional effect on mortality. The ultimate goal is to investigate the effects of SES on mortality while modelling a process in which SES causes mediator 1: risk factors at clinical presentation (e.g. baseline medications), which in turn causes mediator 2: initial management in hospital, which in turn causes mediator 3: post hospitalisation medical management, concluding with mortality as the final consequent. Chapter 5 is dedicated to mediator analyses.

This will be the first study to dissect the relationship between SES, the provision of PCI, medications and mortality where the direct effect of SES on mortality is separated from the indirect effect through treatments.

3.2.5.8 Other analyses of health inequalities

In addition to SES, gender differences in the clinical profiles and quality of care and how they mediate inequalities in outcomes after ACS will be evaluated by repeating the main analyses with gender as the independent variable and reported in detail in Chapters 4.

3.3 Results

3.3.1 Patients Characteristics

3.3.1.1 Population

Of 7878 patients diagnosed with ACS between October 2013 and June 2016, 25.9% had a STEMI, 50.2% had NSTEMI, 18.1% had unstable angina and 5.8% had unspecified MI. Patients diagnosed with STEMI were younger and composed of more males than the other ACS groups. The distribution of social class was similar among different diagnosis, with more patients (41.5%) in the most deprived SIMD category. Table 3-4 details the patient demographics of the study population.

Table 3-4. Patient demographics and lab results by diagnosis.

	All (N = 7878)	STEMI (N = 2042)	NSTEMI (N = 3957)	Unspecified MI (N = 454)	HA (N = 1425)
DEMOGRAPHICS					
Age (years)	66.3 (13.65)	62.7 (13.81)	67.0 (13.42)	73.8 (13.80)	67.2 (12.56)
Age Group					
<55	1702 (21.6%)	617 (30.2%)	789 (19.9%)	47 (10.4%)	249 (17.5%)
55-65	1883 (23.9%)	561 (27.5%)	916 (23.1%)	63 (13.9%)	343 (24.1%)
65-75	1845 (23.4%)	403 (19.7%)	982 (24.8%)	85 (18.7%)	375 (26.3%)
75+	2448 (31.1%)	461 (22.6%)	1270 (32.1%)	259 (57.0%)	458 (32.1%)
Male (%)	4717 (59.9%)	1399 (68.5%)	2322 (58.7%)	247 (54.4%)	749 (52.6%)
SIMD2012 QUINTILE					
1 (most deprived)	3265 (41.5%)	849 (41.6%)	1572 (39.7%)	195 (43.0%)	649 (45.5%)
2	1418 (18.0%)	368 (18.0%)	733 (18.5%)	81 (17.8%)	236 (16.6%)
3	1126 (14.3%)	324 (15.9%)	555 (14.0%)	68 (15.0%)	179 (12.6%)
4	993 (12.6%)	234 (11.5%)	503 (12.7%)	60 (13.2%)	196 (13.8%)
5 (least deprived)	1074 (13.6%)	266 (13.0%)	593 (15.0%)	50 (11.0%)	165 (11.6%)
Missing	2	1	1	0	0

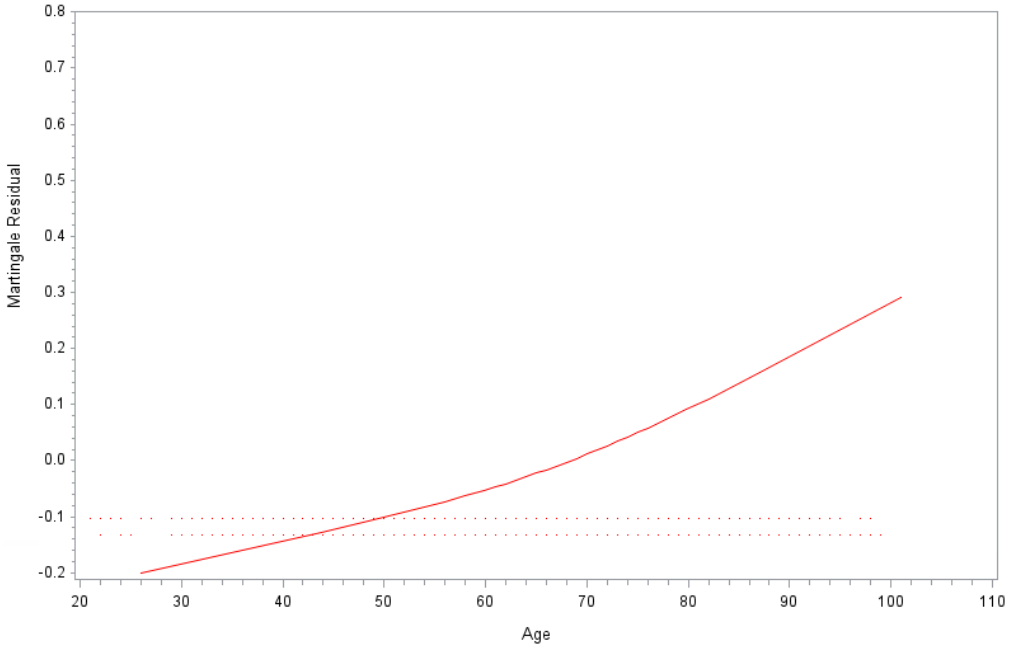
Numbers are presented as mean (SD) or numbers (%) or median [IQR].

3.3.1.2 Assessment of age- and sex- adjusted Cox proportional hazard model adequacy

Since the next few sections look at the association of different variables with 1-year mortality in a multivariate proportional-hazards model adjusted for at least continuous age and sex, the adequacy of continuous age- and sex- adjusted survival model must be assessed. This was assessed by Cox proportional hazard model specific assumptions, namely: linear effect of age on the logarithm of hazard and the proportional hazard assumption.

The linear effect of age was assessed by 1) assessing the significance of adding age squared (P=0.564) to the age and sex adjusted model and also 2) a plot of martingale residuals of the gender adjusted model (logarithm of hazard) versus continuous age. The residuals form a roughly straight line.

Figure 3-4. Graphical analysis of martingale residuals of the gender adjusted model (logarithm of hazard) versus continuous age.



Both methods lead to the similar conclusion - age has linear effect on logarithm of hazard. Thus, the assumption of log - linear relation between hazard and age is satisfied.

The proportional hazard assumption was assessed by adding time - dependent variables to the original model (i.e., product of age and logarithm of time and

product of sex and logarithm of time). If such variable is statistically significant then it can be concluded that the assumption of proportional hazards is not satisfied for the given covariate. However, both time-dependent age and sex were not statistically significant (p=0.616 and P=0.168 respectively), which indicates that proportional hazard assumption for both covariates is satisfied.

3.3.1.3 Comorbidities

The prevalence of comorbidities at baseline ranged from 0.04% for acquired immunodeficiency syndrome to 24.0% for uncomplicated hypertension. The frequency of each comorbidity is detailed in Table 3-5 to Table 3-7, stratified by the three different comorbidity scores: Charlson, Elixhauser and OAMI, with the distributions of the overall comorbidity indices shown in Table 3-8.

Table 3-5. Frequency of Charlson Comorbidities by diagnosis.

'	All	STEMI	NSTEMI	Unspecified MI	UA
Existing Charlson Comorbidities					
Myocardial infarction	19.9	10.9	22.5	21.4	25.2
Congestive heart failure	9.8	3.7	11.2	18.7	11.6
Peripheral vascular disease	7.0	4.5	7.1	10.4	9.3
Cerebrovascular disease	7.3	4.3	7.5	13.0	9.6
Dementia	1.6	1.1	1.4	5.9	1.4
Chronic pulmonary disease	14.0	8.9	14.4	18.9	18.6
Connective tissue disease	2.3	1.6	2.5	3.5	2.2
Ulcer disease	3.2	2.6	2.9	4.8	4.2
Mild liver disease	1.3	1.1	1.2	1.1	1.9
Diabetes without complications	14.4	7.8	16.3	18.3	17.2
Diabetes with complications	2.5	1.1	3.3	4.2	1.6
Hemiplegia	0.6	0.4	0.5	0.9	1.1
Moderate/severe renal disease	11.4	5.7	12.7	23.1	12.2
Any tumour	6.8	4.8	7.1	10.4	7.5
Leukaemia	0.2	0.0	0.2	0.4	0.1
Lymphoma	0.5	0.5	0.5	1.1	0.6
Metastatic solid tumour	1.1	0.8	1.1	1.8	1.2
Moderate/severe liver disease	0.4	0.3	0.3	0.7	0.5
AIDS	0.0	0.1	0.0	0.0	0.0

Numbers are percentages.

Table 3-6. Frequency of Elixhauser Comorbidities by diagnosis.

	All	STEMI	NSTEMI	Unspecified MI	UA
Existing Elixhauser Comorbidities					
Congestive Heart Failure	10.0	3.9	11.5	19.2	11.6
Cardiac Arrhythmia	15.0	8.0	15.8	26.4	19.4
Valvular Disease	7.1	3.0	8.4	10.1	8.3
Pulmonary Circulation Disorders	2.1	0.7	2.4	5.7	2.4
Peripheral Vascular Disorders	7.0	4.2	7.1	10.6	9.8
Hypertension Uncomplicated	24.0	13.6	26.4	28.9	30.6
Hypertension Complicated	1.2	0.6	1.4	1.1	1.5
Paralysis	0.8	0.5	0.6	1.3	1.4
Other Neurological Disorders	3.2	2.6	2.8	6.6	4.1
Chronic Pulmonary Disease	14.3	8.9	14.6	20.0	19.1
Diabetes Uncomplicated	14.4	7.8	16.3	18.3	17.2
Diabetes Complicated	2.5	1.1	3.3	4.2	1.6
Hypothyroidism	2.6	1.2	2.6	3.5	4.1
Renal Failure	8.1	3.7	9.1	15.9	8.9
Liver Disease	1.7	1.5	1.6	1.8	2.5
Peptic Ulcer Disease excluding bleeding	1.4	1.4	1.2	2.2	1.8
AIDS/HIV	0.0	0.1	0.0	0.0	0.0
Lymphoma	0.5	0.5	0.5	1.1	0.6
Metastatic Cancer	1.1	0.8	1.1	1.8	1.2
Solid Tumour without Metastasis	5.7	4.0	6.1	8.4	5.8
Rheumatoid Arthritis/collagen	2.4	1.8	2.6	3.7	2.6
Coagulopathy	0.5	0.1	0.5	0.9	1.0
Obesity	4.2	3.5	3.6	3.1	6.8
Weight Loss	2.7	2.2	2.6	5.5	3.0
Fluid and Electrolyte Disorders	3.9	2.0	4.5	7.3	4.0
Blood Loss Anaemia	0.1	0.0	0.1	0.0	0.2
Deficiency Anaemia	4.2	1.8	4.8	5.9	5.7
Alcohol Abuse	4.6	4.1	4.4	5.5	5.6
Drug Abuse	0.9	1.2	0.7	0.4	1.1
Psychoses	0.5	0.2	0.5	0.7	0.6
Depression	2.1	1.6	2.1	2.9	2.7

Numbers are percentages.

Table 3-7. Frequency of Ontario AMI Comorbidities by diagnosis.

	All	STEMI	NSTEMI	Unspecified MI	UA
Ontario AMI Mortality Comorbidities					
Shock	0.3	0.8	0.2	0.2	0.1
Diabetes with complications	2.5	1.1	3.3	4.2	1.6
Congestive heart failure	10.0	3.9	11.5	19.2	11.6
Cancer	7.4	5.3	7.8	11.0	8.4
Cerebrovascular disease	7.3	4.3	7.5	13.0	9.6
Pulmonary edema	1.8	0.9	2.2	3.3	1.3
Acute renal failure	5.2	3.0	5.6	12.6	5.0
Chronic renal failure	8.1	3.7	9.1	15.9	8.9
Cardiac dysrhythmias	15.0	8.0	15.8	26.4	19.4

Numbers are percentages.

STEMI patients were, in general, healthier than other ACS groups (most likely due to the lower average age). Comorbidity scores were lowest in STEMI patients and highest in unspecified MI patients for continuous measures. Similarly, there were more patients with lower categorical scores in STEMI patients compared to other ACS groups. During the follow-up year, 861(10.9%) deaths occurred, with 386(4.9%) occurring during the first 30 days after admission.

Table 3-8. Distributions of 3 comorbidity scores and outcomes by diagnosis.

	All	STEMI	NSTEMI	Unspecified MI	UA
Charlson index (cont)	1.3 (1.96)	0.8 (1.53)	1.4 (2.00)	2.1 (2.44)	1.6 (2.01)
Charlson index (catg)					
0	54.9%	68.5%	51.5%	46.5%	47.4%
1-3	37.8%	27.7%	40.6%	39.0%	44.2%
>4	7.3%	3.8%	7.9%	14.5%	8.4%
Elixhauser index (cont)	3.3 (5.79)	1.8 (4.53)	3.5 (5.87)	6.1 (7.15)	3.9 (6.13)
Elixhauser index (catg)					
<0	6.6%	5.7%	6.4%	7.0%	8.3%
0	54.2%	69.0%	52.1%	35.9%	44.5%
1-5	17.3%	13.0%	18.2%	17.2%	20.8%
6-13	15.6%	9.2%	16.7%	26.7%	18.6%
>14	6.3%	3.1%	6.6%	13.2%	7.9%
Number of Ontario AMI mortality comorbidities (/9)					
0	65.9%	79.4%	63.1%	45.2%	60.9%
1	19.5%	13.6%	20.8%	23.8%	22.7%

2	8.7%	4.5%	9.7%	17.2%	9.5%
3	3.8%	1.8%	4.0%	8.8%	4.4%
4	1.5%	0.6%	1.6%	4.4%	1.9%
5	0.5%	0.1%	0.6%	0.4%	0.6%
6	0.1%	0.0%	0.2%	0.2%	0.1%
7	0.0%	0.0%	0.0%	0.0%	0.0%
Mortality					
30 days	4.9%	6.9%	2.8%	27.8%	0.6%
1 year	10.9%	10.0%	10.0%	41.4%	5.1%

Numbers are presented as mean (SD) or percentages.

3.3.1.4 Performance of comorbidity indices

Not all comorbidities included in the common comorbidity indices were associated with mortality in this study population and in modern time. Of the 19 Charlson comorbidities, 4 were not associated with 1-year mortality in a multivariate proportional-hazards model adjusted for age and sex. Similarly, 10 out of 31 Elixhauser comorbidities were not associated with age- and sex-adjusted mortality at 1 year. Table 3-9 illustrates the age- and sex-adjusted hazard ratios for mortality within 1 year after ACS admission for each comorbidity index group. An overall score for each index is also included. An overall Elixhauser score lower than 0 should be associated with lower mortality while scores over 0 should be associated with higher mortality. However, this was not the case in this ACS population, patients with scores 0-5 had lower hazard ratios compared to those with scores lower than 0. This indicates that the Elixhauser score might not be appropriate as indicators of comorbidities in this ACS population. The proportional hazard assumption were checked for each covariate in all models and were all satisfied.

Table 3-9. Risk-adjusted hazard ratio for mortality within 1 year for each comorbidity index group.

Charlson Comorbidities		Elixhauser Comorbidities		Ontario AMI Mortality Comorbidities	
	HR (95%CI)		HR (95%CI)		HR (95%CI)
Myocardial infarction	1.25 (1.08-1.46)	Congestive Heart Failure	2.21(1.89-2.58)	Shock	12.11(7.37-19.89)
Congestive heart failure	2.22 (1.90-2.59)	Cardiac Arrhythmia	1.34(1.15-1.56)	Diabetes with complications	2.78(2.05-3.77)
Peripheral vascular disease	1.85 (1.53-2.24)	Valvular Disease	1.21(0.99-1.48)*	Congestive heart failure	2.21(1.89-2.58)
Cerebrovascular disease	1.46 (1.20-1.78)	Pulmonary Circulation Disorders	2.10(1.58-2.80)	Cancer	1.867(1.55-2.22)
Dementia	2.21 (1.67-2.94)	Peripheral Vascular Disorders	1.84(1.52-2.23)	Cerebrovascular disease	1.46(1.20-1.78)
Chronic pulmonary disease	1.48 (1.25-1.74)	Hypertension Uncomplicated	1.05(0.91-1.22)*	Pulmonary edema	2.76(2.07-3.68)
Connective tissue disease	1.77 (1.29-2.44)	Hypertension Complicated	1.75(1.17-2.60)	Acute renal failure	1.99(1.64-2.42)
Ulcer disease	1.32 (0.97-1.80)*	Paralysis	1.34(0.70-2.59)*	Chronic renal failure	1.79(1.51-2.12)
Mild liver disease	1.08 (0.54-2.16)*	Other Neurological Disorders	1.48(1.09-2.00)	Cardiac dysrhythmias	1.34(1.15-1.56)
Diabetes without complications	1.58 (1.34-1.85)	Chronic Pulmonary Disease	1.52(1.30-1.79)	Overall score	1.41 (1.34 - 1.48)
Diabetes with complications	2.78 (2.05-3.77)	Diabetes Uncomplicated	1.58(1.34-1.85)		
Hemiplegia	1.06 (0.48-2.37)*	Diabetes Complicated	2.78(2.05-3.77)		
Moderate/severe renal disease	1.91 (1.64-2.23)	Hypothyroidism	0.98(0.68-1.42)*		
Any tumour	1.79 (1.48-2.15)	Renal Failure	1.79(1.51-2.12)		
Leukaemia	3.73 (1.54-8.99)	Liver Disease	0.97(0.55-1.72)*		
Lymphoma	2.73 (1.61-4.63)	Peptic Ulcer Disease excluding bleeding	1.42(0.91-2.22)*		
Metastatic solid tumour	4.07 (2.96-5.60)	AIDS/HIV	9.15(1.29-65.08)		
Moderate/severe liver disease	1.11 (0.36-3.45)*	Lymphoma	2.73(1.61-4.63)		
AIDS	9.15 (1.29-65.08)	Metastatic Cancer	4.07(2.96-5.60)		
Overall score (1 unit)	1.20 (1.17-1.23)	Solid Tumour without Metastasis	2.02(1.66-2.46)		
Overall score		Rheumatoid Arthritis/collagen	1.70(1.23-2.35)		
1-3 vs 0	1.20 (1.03-1.40)				
>4 vs 0	3.04 (2.53-3.64)				
		Coagulopathy	0.71(0.27-1.90)*		
		Obesity	1.38(0.98-1.93)*		
		Weight Loss	1.58(1.16-2.14)		
		Fluid and Electrolyte Disorders	1.82(1.44-2.29)		
		Blood Loss Anaemia	0.00(0.00-NA)*		
		Deficiency Anaemia	1.33(1.04-1.70)		

	Alcohol Abuse	1.45(1.05-2.01)
	Drug Abuse	3.12(1.47-6.60)
	Psychoses	5.10(2.53-10.28)
	Depression	1.28(0.81-2.03)*
	Overall score (1 unit)	1.06 (1.05 - 1.07)
	Overall score	
	0 vs <0	0.64 (0.48-0.86)
	1-5 vs <0	0.90 (0.66-1.23)
	6-13 vs <0	1.23 (0.91-1.65)
	>14 vs <0	2.35 (1.73-3.19)

*** *P* > 0.05.**

A backwards selection model of all comorbidities resulted in 14 comorbidities that are independently associated with age- and sex-adjusted mortality at 1 year (Table 3-10).

Table 3-10. Risk-adjusted hazard ratio for mortality within 1 year.

Variable	HR (95%CI)
Age	1.07 (1.06-1.08)
Male	1.21 (1.06-1.39)
Shock	9.76 (5.89-16.23)
Diabetes with complications	1.83 (1.32-2.53)
Congestive Heart Failure	1.65 (1.39-1.95)
Pulmonary edema	1.66 (1.23-2.23)
Peripheral vascular disease	1.46 (1.19-1.78)
Dementia	2.19 (1.64-2.91)
Connective tissue disease	1.66 (1.20-2.29)
Moderate/severe renal disease	1.39 (1.18-1.65)
Lymphoma	2.28 (1.34-3.89)
Metastatic solid tumour	2.89 (1.97-4.20)
Hypertension Uncomplicated	0.80 (0.68-0.93)
Chronic Pulmonary Disease	1.22 (1.03-1.44)
Solid Tumour without Metastasis	1.47 (1.17-1.87)
Psychoses	4.02 (1.99-8.16)

The C-statistics favoured individual comorbidities instead of using a single index. As seen in Table 3-11, c-statistics of age- and sex-adjusted models with individual comorbidities were above 0.8 while those of index scores were all below 0.8. Similarly, AIC/BIC favoured individual comorbidities over single scores as well (lower the better). Note BIC are proportionately higher than AIC in models with individual comorbidities as it penalizes for the number of parameters used.

Table 3-11. Performance of different comorbidity indices

	Continuous score		Categorical score		Individual items	
	Model AIC/BIC	C-stat	Model AIC/BIC	C-stat	Model AIC/BIC	C-stat
Charlson Index	12358 12372	0.796	12426 12445	0.785	12332 12432	0.805
Modified Charlson Index	12363 12378	0.796	12452 12471	0.779	12341 12407	0.801
Elixhauser Index	12392 12406	0.790	12400 12429	0.789	12343 12500	0.807
Ontario AMI Mortality Comorbidities	NA	NA	NA	NA	12342 12394	0.800
Updated Group of 14 Prognostic Comorbidities	NA	NA	NA	NA	12258 12334	0.813

All models adjusted for age, sex and individual comorbidities/ comorbidity scores. C-statistics come from logistic regression; model ACI/BIC from cox regression.

The updated group of 14 individual comorbidities performed best in predicting 1-year mortality using both criterion; the c-statistic was 0.813 and AIC/BIC the lowest compared to other common comorbidity scores in models including age and sex. This finding represents an improvement of 0.051 (6.3%) over an age- and sex model alone (c=0.761). The other common comorbidity scores all performed significantly worse (P-difference<0.05) than the updated comorbidities, regardless of whether in individual comorbidities or continuous or categorical scores were used.

This group of 14 comorbidities were best at predicting 1-year mortality and will be used from now on. The limitation of using this group of comorbidities is that it is specific to this group of ACS patients. The process that I've gone through however, can be applied by other researchers to find the set of comorbidities that are significantly associated with mortality for their own datasets.

3.3.2 Socioeconomic status and comorbidities

Table 3-12 illustrates patient demographics and significant prognostic comorbidities across SIMD quintiles. ACS patients in the more deprived groups were younger and comprised of a lower proportion of males compared to less deprived groups (p-difference <0.001). The distribution of STEMI and NSTEMI patients also differed across social class quintiles, although a trend is not immediately apparent. The proportion of patients presenting with diabetes, chronic pulmonary disease and psychosis were significantly associated with SIMD quintiles, being most common in patients from SIMD quintile 1 (most deprived areas), while none of the prognostic comorbidities were the most frequent among the least deprived group. Dementia was also a significant different factor (p=0.030) but there is no gradient across groups. Multivariate analysis showed that only chronic pulmonary disease was independently associated with SES after adjusting for age, sex, and diagnosis (p<0.001).

Table 3-12. Patient demographics and comorbidities by SIMD quintiles.

	All (N = 7878)	SIMD Quintile 1 (N = 3265)	SIMD Quintile 2 (N = 1418)	SIMD Quintile 3 (N = 1126)	SIMD Quintile 4 (N = 993)	SIMD Quintile 5 (N = 1074)	p-value
Age (years)	66.3 (13.65)	64.5 (13.86)	66.3 (13.80)	66.6 (13.41)	68.4 (13.14)	69.4 (12.66)	<0.001
Male (%)	4717 (59.9%)	1865 (57.1%)	833 (58.7%)	720 (63.9%)	623 (62.7%)	675 (62.8%)	<0.001
Final diagnosis							0.001
STEMI	2042 (25.9%)	849 (26.0%)	368 (26.0%)	324 (28.8%)	234 (23.6%)	266 (24.8%)	
NSTEMI	3957 (50.2%)	1572 (48.1%)	733 (51.7%)	555 (49.3%)	503 (50.7%)	593 (55.2%)	
Unspecified MI	454 (5.8%)	195 (6.0%)	81 (5.7%)	68 (6.0%)	60 (6.0%)	50 (4.7%)	
Hospitalised Angina	1425 (18.1%)	649 (19.9%)	236 (16.6%)	179 (15.9%)	196 (19.7%)	165 (15.4%)	
Comorbidities							
Shock	27 (0.3%)	10 (0.3%)	7 (0.5%)	<5	7 (0.7%)	<5	0.116*
Diabetes with complications	194 (2.5%)	96 (2.9%)	35 (2.5%)	31 (2.8%)	18 (1.8%)	14 (1.3%)	0.024
Congestive Heart Failure	789 (10.0%)	349 (10.7%)	147 (10.4%)	115 (10.2%)	86 (8.7%)	92 (8.6%)	0.171
Pulmonary edema	139 (1.8%)	71 (2.2%)	25 (1.8%)	16 (1.4%)	11 (1.1%)	16 (1.5%)	0.143
Peripheral vascular disease	551 (7.0%)	253 (7.7%)	104 (7.3%)	76 (6.7%)	59 (5.9%)	59 (5.5%)	0.071
Dementia	125 (1.6%)	55 (1.7%)	15 (1.1%)	16 (1.4%)	26 (2.6%)	13 (1.2%)	0.030
Connective tissue disease	179 (2.3%)	81 (2.5%)	22 (1.6%)	24 (2.1%)	25 (2.5%)	27 (2.5%)	0.330
Moderate/severe renal disease	897 (11.4%)	396 (12.1%)	155 (10.9%)	121 (10.7%)	108 (10.9%)	117 (10.9%)	0.550
Lymphoma	43 (0.5%)	17 (0.5%)	8 (0.6%)	6 (0.5%)	7 (0.7%)	5 (0.5%)	0.950*
Metastatic solid tumour	84 (1.1%)	34 (1.0%)	19 (1.3%)	10 (0.9%)	9 (0.9%)	12 (1.1%)	0.803
Hypertension Uncomplicated	1888 (24.0%)	792 (24.3%)	341 (24.0%)	249 (22.1%)	248 (25.0%)	258 (24.0%)	0.586
Chronic Pulmonary Disease	1123 (14.3%)	621 (19.0%)	184 (13.0%)	123 (10.9%)	118 (11.9%)	77 (7.2%)	<0.001
Solid Tumour without Metastasis	446 (5.7%)	182 (5.6%)	73 (5.1%)	57 (5.1%)	61 (6.1%)	73 (6.8%)	0.339
Psychoses	36 (0.5%)	22 (0.7%)	5 (0.4%)	6 (0.5%)	<5	<5	0.027*

P-values are ANOVA tests for continuous variables and chi-squared or *fisher's exact tests for categorical variables.

In general, more deprived patients were in similar health compared to less deprived groups except those shown in Table 3-13: the significant comorbidities associated with SES. The proportional odds assumption in ordinal logistic regressions are all satisfied (Score test for the proportion odds assumption are P=0.080, P=0.228 and P=0.068 for STEMI, NSTEMI/HA and all ACS respectively).

In all ACS patients, congestive heart failure (OR=1.21; 1.05-1.39), peripheral vascular disease (OR=1.21; 1.02-1.42) and chronic pulmonary disease (OR=1.95; 1.73-2.21) were more common in more deprived patients after adjustments for age and sex in the backwards selection model. The same also applies in NSTEMI or unstable angina patients. In STEMI patients, only pulmonary edema and chronic pulmonary disease was independently associated with social class in the backwards selection model.

Table 3-13. Statistically significant comorbidities associated with SES, stratified by diagnosis

All ACS		STEMI		NSTEMI or Hospitalised Angina (HA)	
Univariate	**Multivariate***	**Univariate**	**Multivariate***	**Univariate**	**Multivariate***
Diabetes with complications				Diabetes with complications	
	Congestive Heart Failure			Congestive Heart Failure	Congestive Heart Failure
			Pulmonary edema		
	Peripheral vascular disease			Peripheral vascular disease	Peripheral vascular disease
Dementia					
Chronic Pulmonary Disease	Chronic Pulmonary Disease	Chronic Pulmonary Disease	Chronic Pulmonary Disease	Chronic Pulmonary Disease	Chronic Pulmonary Disease
Psychoses					

Multivariate ordinal* logistic models include age, sex, all prognostic comorbidities identified in previous section and diagnosis where applicable with backwards selection**

3.3.3 Socioeconomic status and in-hospital management

The outcomes of interest for this section are associated with service delivery, which consists of treatments during hospitalisation and the characteristics associated with it.

3.3.3.1 Service delivery by diagnosis for all patients

As expected, the admission method and intervention rates varied depending on diagnosis. STEMI patients were much more likely to be admitted directly to the Catheter lab (74.7%) and subsequently receive a coronary angiography (CAG) and percutaneous coronary intervention (PCI) (88.1% and 77.7%) while other ACS patients were more likely to be admitted to a local hospital first. Among patients with NSTEMI, 71.5% underwent CAG while only 37.1% underwent revascularisation by PCI. The median total duration of episode for patients with a diagnosis of NSTEMI was also longer, possibly affected by transfer times from local hospitals to the Cath lab. Other characteristics of service delivery by diagnosis are provided in Table 3-14.

Table 3-14. Service delivery by diagnosis.

	All (N = 7878)	STEMI (N = 2042)	NSTEMI (N = 3957)	Hospitalised Angina (N = 1425)
Admission Method				
Emergency to Cath lab	1473 (18.7%)	1386 (67.9%)	83 (2.1%)	<5
Non-emergency to Cath lab	997 (12.7%)	139 (6.8%)	787 (19.9%)	67 (4.7%)
Emergency to local hospital	4986 (63.3%)	410 (20.1%)	2893 (73.1%)	1271 (89.2%)
Non-emergency to local hospital	422 (5.4%)	107 (5.2%)	194 (4.9%)	84 (5.9%)
Received CAG	4866 (61.8%)	1804 (88.3%)	2837 (71.7%)	183 (12.8%)
Grace score >140	909 (38.0%)	117 (53.2%)	773 (37.5%)	13 (14.8%)
Grace score <140	1488 (62.1%)	103 (46.8%)	1288 (62.5%)	75 (85.2%)
Received PCI	3149 (40.0%)	1586 (77.7%)	1476 (37.3%)	72 (5.1%)
	(64.7%)*	(87.9%)*	(52.0%)*	(39.3%)*
Length of stay in hospital (days)	4 [2 , 7]	4 [3 , 6]	5 [3 , 8]	2 [1 , 3]
Length of episode (days)	5 [3 , 12]	4 [4 , 7]	8 [4 , 18]	2 [1 , 3]
Admission on weekday	6165 (78.3%)	1484 (72.7%)	3156 (79.8%)	1174 (82.4%)

Numbers are presented as median [IQR] or number of patients (%). *Out of those with CAG.

The rate of invasive treatment not only varies by diagnosis, but is also clearly affected by the admission method. When directly admitted to the Cath lab, the

rate of CAG is close to 100% regardless of diagnosis, with a drop in reperfusion (PCI) rate in non-STEMI patients. When admitted to a local hospital first, the rate of invasive treatment is much lower in the hospitalised angina patients.

Table 3-15. CAG and PCI rate by admission method.

	All	STEMI	NSTEMI	HA
Emergency to Cath lab				
Received CAG	100%	100%	100.0%	100.0%
Received PCI	90.3%	92.9%	51.8%	0.0%
Non-emergency to Cath lab				
Received CAG	99.8%	100%	99.7%	100.0%
Received PCI	52.1%	81.3%	47.0%	50.7%
Emergency to local hospital				
Received CAG	45.2%	63.2%	64.3%	8.0%
Received PCI	24.5%	41.7%	34.6%	2.7%
Non-emergency to local hospital				
Received CAG	34.1%	18.7%	56.7%	13.1%
Received PCI	19.0%	14.0%	31.4%	4.8%

3.3.3.2 Service delivery by SES

Table 3-16 compares service delivery across SIMD quintiles for STEMI patients and NSTEMI/ HA patients separately. In STEMI patients, the rate of CAG differed across social class quintiles, with a higher rate in the most deprived quintile compared to the last deprived one (90.0% vs 82.7%), but did not affect the rate of PCI. In NSTEMI patients, the distribution of admission method and rates of invasive management varied across social class. The most deprived group were more likely to me admitted to local hospital first and subsequently had lower rates of CAG and PCI, despite a lack of differences in GRACE score across the SIMD groups. In those that received CAG, subsequent PCI rates do not differ across SIMD groups, indicating that inequalities are restricted at the CAG level. These numbers indicate that the issue of inappropriate access to medical services (self-presentation to a hospital without reperfusion facilities) is more likely in the most deprived group for NSTEMI patient. This in turn decrease the likelihood of CAG rates in the most deprived group. However, the strict criteria used for PCI eliminates any inequalities subsequent a CAG.

Table 3-16. Distributions of service delivery by SIMD for STEMI and NSTEMI/HA patients.

	All	SIMD Q1	SIMD Q2	SIMD Q3	SIMD Q4	SIMD Q5	p-value
STEMI (N)	2041	849	368	324	234	266	
Admission Method							0.126
Emergency to Cath lab	1386 (67.9%)	589 (69.4%)	256 (69.6%)	216 (66.7%)	153 (65.4%)	172 (64.7%)	
Non-emergency to Cath lab	139 (6.8%)	56 (6.6%)	25 (6.8%)	25 (7.7%)	21 (9.0%)	11 (4.1%)	
Emergency to local hospital	410 (20.1%)	164 (19.3%)	72 (19.6%)	69 (21.3%)	47 (20.1%)	58 (21.8%)	
Non-emergency to local hospital	107 (5.2%)	40 (4.7%)	15 (4.1%)	14 (4.3%)	13 (5.6%)	25 (9.4%)	
Received CAG	1804 (88.3%)	764 (90.0%)	331 (89.9%)	282 (87.0%)	206 (88.0%)	220 (82.7%)	0.018
Grace score >140	117 (53.2%)	45 (47.9%)	23 (56.1%)	17 (53.1%)	16 (66.7%)	16 (55.2%)	0.557
Grace score <140	103 (46.8%)	49 (52.1%)	18 (43.9%)	15 (46.9%)	8 (33.3%)	13 (44.8%)	
Received PCI	1586 (77.7%)	672 (79.2%)	293 (79.6%)	249 (76.9%)	178 (76.1%)	194 (72.9%)	0.215
	(87.9%)**	(88.0%)**	(88.5%)**	(88.3%)**	(86.4%)**	(88.2%)**	0.962
Length of stay in hospital (days)	4 [3 , 6]	4 [4 , 6]	4 [4 , 6]	4 [3 , 6]	4 [3 , 6]	4 [4 , 6]	0.780*
Length of episode (days)	4 [4 , 7]	4 [4 , 7]	4 [4 , 7]	4 [4 , 7]	4 [3 , 7]	5 [4 , 7]	0.726*
Admission on weekday	1484 (72.7%)	612 (72.1%)	260 (70.7%)	237 (73.1%)	177 (75.6%)	198 (74.4%)	0.663
NSTEMI/ HA (N)	5381	2221	969	734	699	758	
Admission Method							0.001
Emergency to Cath lab	86 (1.6%)	31 (1.4%)	11 (1.1%)	18 (2.5%)	14 (2.0%)	12 (1.6%)	
Non-emergency to Cath lab	854 (15.9%)	304 (13.7%)	148 (15.3%)	141 (19.2%)	112 (16.0%)	149 (19.7%)	
Emergency to local hospital	4164 (77.4%)	1788 (80.5%)	750 (77.4%)	533 (72.6%)	529 (75.7%)	563 (74.3%)	
Non-emergency to local hospital	278 (5.2%)	98 (4.4%)	60 (6.2%)	42 (5.7%)	44 (6.3%)	34 (4.5%)	
Received CAG	3020 (56.1%)	1171 (52.7%)	543 (56.0%)	441 (60.1%)	399 (57.1%)	465 (61.3%)	<0.001
Grace score >140	786 (36.6%)	298 (34.7%)	143 (36.8%)	115 (38.9%)	112 (40.3%)	117 (36.1%)	0.454
Grace score <140	1363 (63.4%)	561 (65.3%)	248 (63.4%)	181 (61.1%)	166 (59.7%)	207 (63.9%)	
Received PCI	1548 (28.8%)	586 (26.4%)	274 (28.3%)	229 (31.2%)	201 (28.8%)	257 (33.9%)	0.001
	(51.3%)**	(50.0%)**	(50.5%)**	(51.9%)**	(50.4%)**	(55.3%)**	0.402
Length of stay in hospital (days)	4 [2 , 7]	4 [2 , 7]	4 [2 , 7]	4 [2 , 7]	4 [2 , 7]	4 [2 , 7]	0.869*
Length of episode (days)	6 [2 , 15]	6 [2 , 14]	6 [2 , 16]	6 [2 , 16]	5 [2 , 13]	7 [3 , 16]	0.018*
Admission on weekday	4330 (80.5%)	1782 (80.2%)	790 (81.5%)	602 (82.0%)	548 (78.4%)	607 (80.1%)	0.425

Numbers are presented as median [IQR] or number of patients (%). SIMD Q1=most deprived. *p-values from Kruskal Wallis test. **Out of those with CAG.

When looking at rates of invasive treatment by admission method (Table 3-17), there were no differences across SIMD quintiles for STEMI patients. In NSTEMI/ HA patients, patients in the most deprived group admitted directly to a local hospital via emergency services were less likely to receive CAG and PCI compared to the least deprived group (p-difference: 0.018 and 0.007).

Table 3-17. CAG and PCI rate by admission method across SIMD quintiles.

	All	SIMD Q1	SIMD Q2	SIMD Q3	SIMD Q4	SIMD Q5	p-value
STEMI (N)							
Emergency to Cath lab							
Received CAG	1386 (100%)	589 (100.0%)	256 (100%)	216 (100.0%)	153 (100%)	172 (100.0%)	-
Received PCI	1287 (92.9%)	548 (93.0%)	241 (94.1%)	203 (94.0%)	136 (88.9%)	159 (92.4%)	0.314
Non-emergency to Cath lab							
Received CAG	139 (100%)	56 (100%)	25 (100.0%)	25 (100%)	21 (100.0%)	11 (100.0%)	-
Received PCI	113 (81.3%)	44 (78.6%)	21 (84.0%)	20 (80.0%)	17 (81.0%)	11 (100.0%)	0.559
Emergency to local hospital							
Received CAG	259 (63.2%)	108 (65.9%)	48 (66.7%)	38 (55.1%)	31 (66.0%)	34 (58.6%)	0.477
Received PCI	171 (41.7%)	72 (43.9%)	30 (41.7%)	24 (34.8%)	24 (51.1%)	21 (36.2%)	0.393
Non-emergency to local hospital							
Received CAG	20 (18.7%)	11 (27.5%)	<5	<5	<5	<5	0.451*
Received PCI	15 (14.0%)	8 (20.0%)	<5	<5	<5	<5	0.752*
NSTEMI/ HA (N)							
Emergency to Cath lab							
Received CAG	86 (100.0%)	31 (100.0%)	11 (100.0%)	18 (100.0%)	14 (100.0%)	12 (100.0%)	-
Received PCI	43 (50.0%)	13 (41.9%)	5 (45.5%)	11 (61.1%)	7 (50.0%)	7 (58.3%)	0.714
Non-emergency to Cath lab							
Received CAG	852 (99.8%)	304 (100.0%)	147 (99.3%)	141 (100%)	112 (100.0%)	148 (99.3%)	0.440
Received PCI	404 (47.3%)	135 (44.4%)	82 (55.4%)	64 (45.4%)	54 (48.2%)	69 (46.3%)	0.265
Emergency to local hospital							
Received CAG	1961 (47.1%)	792 (44.3%)	364 (48.5%)	262 (49.2%)	251 (47.4%)	291 (51.7%)	0.018
Received PCI	1036 (24.9%)	413 (23.1%)	180 (24.0%)	144 (27.0%)	127 (24.0%)	171 (30.4%)	0.007
Non-emergency to local hospital							

Received CAG	121 (43.5%)	44 (44.9%)	21 (35.0%)	20 (47.6%)	22 (50.0%)	14 (41.2%)	0.564*
Received PCI	65 (23.4%)	25 (25.5%)	7 (11.7%)	10 (23.8%)	13 (29.5%)	10 (29.4%)	0.121*

SIMD Q1=most deprived. *p-value by fishers exact test

Waiting times for PCI were available for most STEMI patients that have received a CAG. Within STEMI patients that have received CAG, 87.9% received a PCI. Social class was not associated with the rate of PCI or other characteristics associated with waiting time within this population (Table 3-18).

Table 3-18. Waiting times for invasive treatment across SIMD quintiles in STEMI patients with CAG.

	STEMI	SIMD Quintile 1	SIMD Quintile 2	SIMD Quintile 3	SIMD Quintile 4	SIMD Quintile 5	p-value
Received PCI	87.9%	88.0%	88.5%	88.3%	86.4%	88.2%	0.962
Call to door (min)	73 [60, 94]	73 [60, 92]	72 [59, 95]	72 [59, 104]	79 [64, 99]	73 [60, 93]	0.272*
Call to balloon (min)	96 [82, 120]	95 [82, 116]	96 [81, 120]	96 [82, 128]	102 [85, 126]	96 [82, 118]	0.356*
Door to balloon (min)	21 [18, 27]	22 [18, 28]	22 [18, 27]	21 [18, 27]	22 [18, 28]	21 [17, 27]	0.669*
Call time from 6am to 11pm	78.6%	77.4%	81.6%	78.2%	76.0%	80.9%	0.644
Door time from 6am to 11pm	77.7%	76.9%	79.9%	77.8%	74.0%	80.4%	0.537
Balloon time from 6am to 11pm	76.5%	75.7%	78.7%	75.1%	72.4%	81.6%	0.284
Call time on weekday	72.6%	71.4%	71.5%	73.7%	75.2%	74.5%	0.872
Door time on weekday	72.1%	72.0%	70.5%	72.7%	73.4%	73.0%	0.963
Balloon time on weekday	71.7%	72.2%	70.8%	71.2%	71.3%	72.4%	0.992

SIMD Q1=Most deprived. Numbers are presented as means (SD) or number of patients (%). *p-values from Kruskal Wallis test.

3.3.3.4 Predictors of CAG and PCI

After adjusting for differences in age, sex and comorbidities, deprivation was an independent predictor of both coronary angiography and PCI in all patients, which was mainly driven by the non-STEMI population (Table 3-19). For patients with STEMI, the most deprived group were more likely to receive coronary angiography [adjusted odds ratio (OR) 1.58, confidence interval (CI) 1.02–2.45] but not in PCI (adjusted OR 1.27, CI 0.90–1.80) compared to the least deprived group. Other SES groups (Q2-4) do not differ in rate of coronary angiography or PCI. On the contrary, for patients with non-STEMI (NSTEMI or hospitalised angina), the most deprived group was less likely to receive coronary angiography [adjusted OR 0.63, CI 0.52–0.75] and PCI [adjusted OR 0.67, CI 0.56–0.81]. The social gradient is not linear but S-shaped (Figure 3-5) in non-STEMI patients, where SES Q1, Q2, Q4, but not Q3 are less likely to receive invasive care compared to Q5. In part this may be attributable to differences in the type of hospital where the patient was initially admitted to. An investigation of service delivery above found a remarkable drop in patients that received PCI compared to CAG in NSTEMI patients and STEMI patients that were admitted to a local hospital first. An analysis of patients that received CAG did not find that SIMD predicts PCI rate (Table 3-19 last column).

Using the multivariable adjusted model 2, several baseline characteristics were found to be independently associated with lower use of coronary angiography and PCI in patients with STEMI including older age, women, atrial fibrillation, prior MI and dementia (Figure 3-5). There were more baseline characteristics associated with lower use of CAG and PCI in NSTEMI or UA patients including cerebrovascular disease, heart failure, renal disease, metastatic solid tumour and psychoses (Figure 3-5).

Table 3-19. Association of SIMD (most deprived vs least deprived) and coronary angiography (CAG) and PCI according to diagnosis.

	CAG			PCI			No PCI|Angio		
	OR (95%CI)	P-value	C-statistic	OR (95%CI)	P-value	C-statistic	OR (95%CI)	P-value	C-statistic
All	n/N=7876/7878			n/N=7876/7878			n/N=4864/4866		
Age and Sex-adjusted	0.63 (0.54-0.74)	<0.001	0.704	0.73 (0.63-0.84)	<0.001	0.662	1.07 (0.89-1.28)	0.501	0.571
Multivariable-adjusted 1	0.71 (0.61-0.83)	<0.001	0.728	0.80 (0.69-0.93)	<0.001	0.691	1.03 (0.85-1.24)	0.783	0.603
Multivariable-adjusted 2	0.72 (0.62-0.85)	<0.001	0.735	0.81 (0.70-0.94)	0.006	0.698	1.03 (0.86-1.25)	0.728	0.609
STEMI	n/N=2041/2042			n/N=2041/2042			n/N=1803/1804		
Age and Sex-adjusted	1.54 (1.03-2.30)	0.037	0.693	1.27 (0.91-1.75)	0.157	0.629	0.99 (0.62-1.58)	0.963	0.575
Multivariable-adjusted 1	1.66 (1.10-2.52)	0.017	0.711	1.34 (0.96-1.87)	0.091	0.646	0.99 (0.61-1.61)	0.977	0.593
Multivariable-adjusted 2	1.58 (1.02-2.45)	0.039	0.773	1.27 (0.90-1.80)	0.169	0.689	0.99 (0.61-1.61)	0.971	0.615
NSTEMI/HA	n/N=5381/5382			n/N=5381/5382			n/N=3019/3020		
Age and Sex-adjusted	0.55 (0.46-0.66)	<0.001	0.688	0.61 (0.51-0.73)	<0.001	0.645	1.24 (0.99-1.54)	0.057	0.556
Multivariable-adjusted 1	0.61 (0.51-0.74)	<0.001	0.707	0.67 (0.55-0.80)	<0.001	0.664	1.19 (0.96-1.49)	0.119	0.576
Multivariable-adjusted 2	0.63 (0.52-0.75)	<0.001	0.711	0.67 (0.56-0.81)	<0.001	0.669	1.20 (0.96-1.50)	0.112	0.577

Multivariable adjustment 1 include age, sex, Charlson comorbidities. Adjustment 2 includes age, sex, hypertension, diabetes, atrial fibrillation, renal failure, respiratory disease, cerebrovascular disease, peripheral vascular disease, heart failure, previous MI, dementia, depression.

Figure 3-5. Association of baseline characteristics with coronary angiography (CAG) and PCI in STEMI patients.

Adjusted odds ratio and 95%CI shown for 10-year increase in age, SIMD quintiles vs least deprived quintile, men vs women, or presence vs absence of comorbidity. Adjusted for all measures depicted.

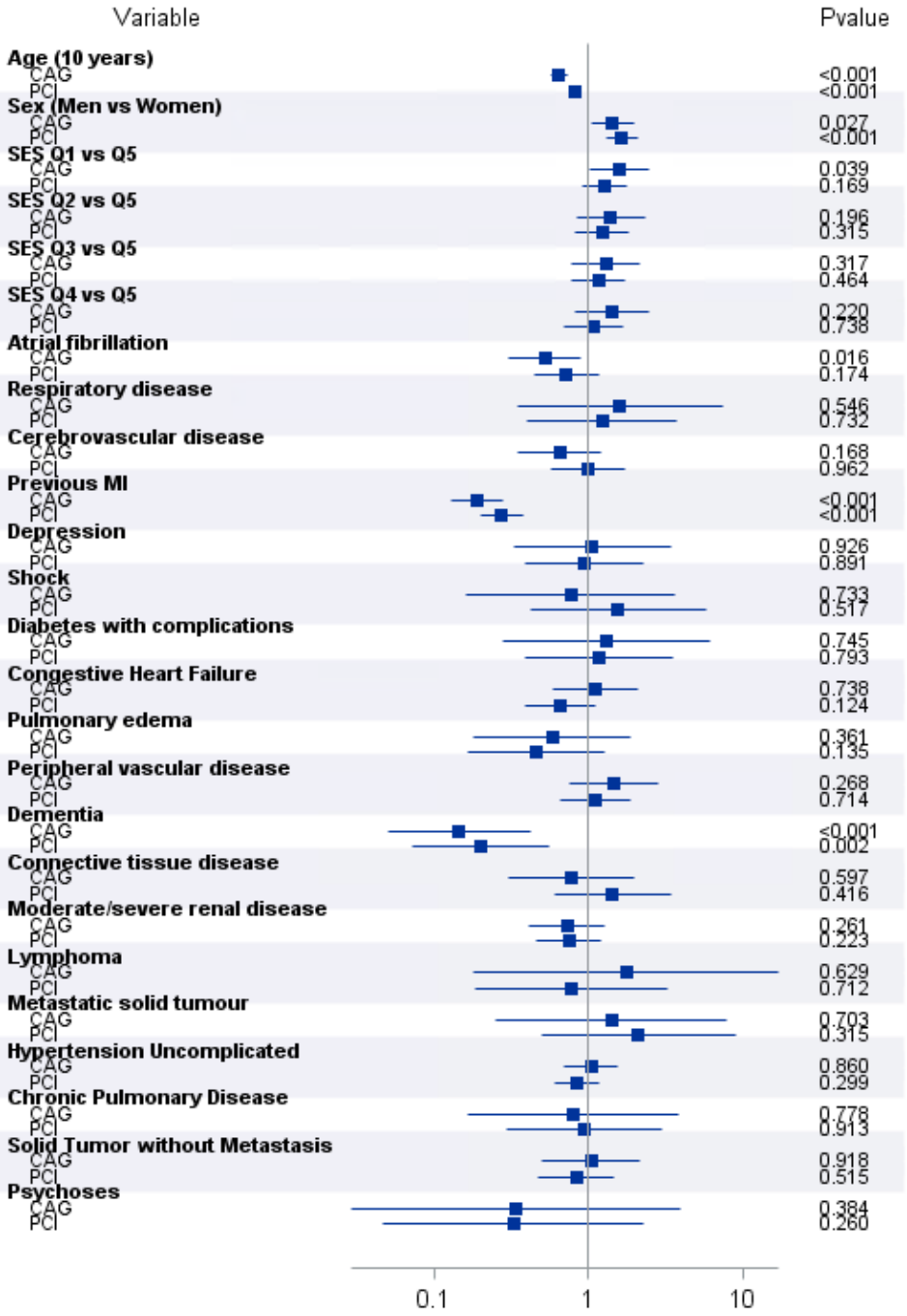
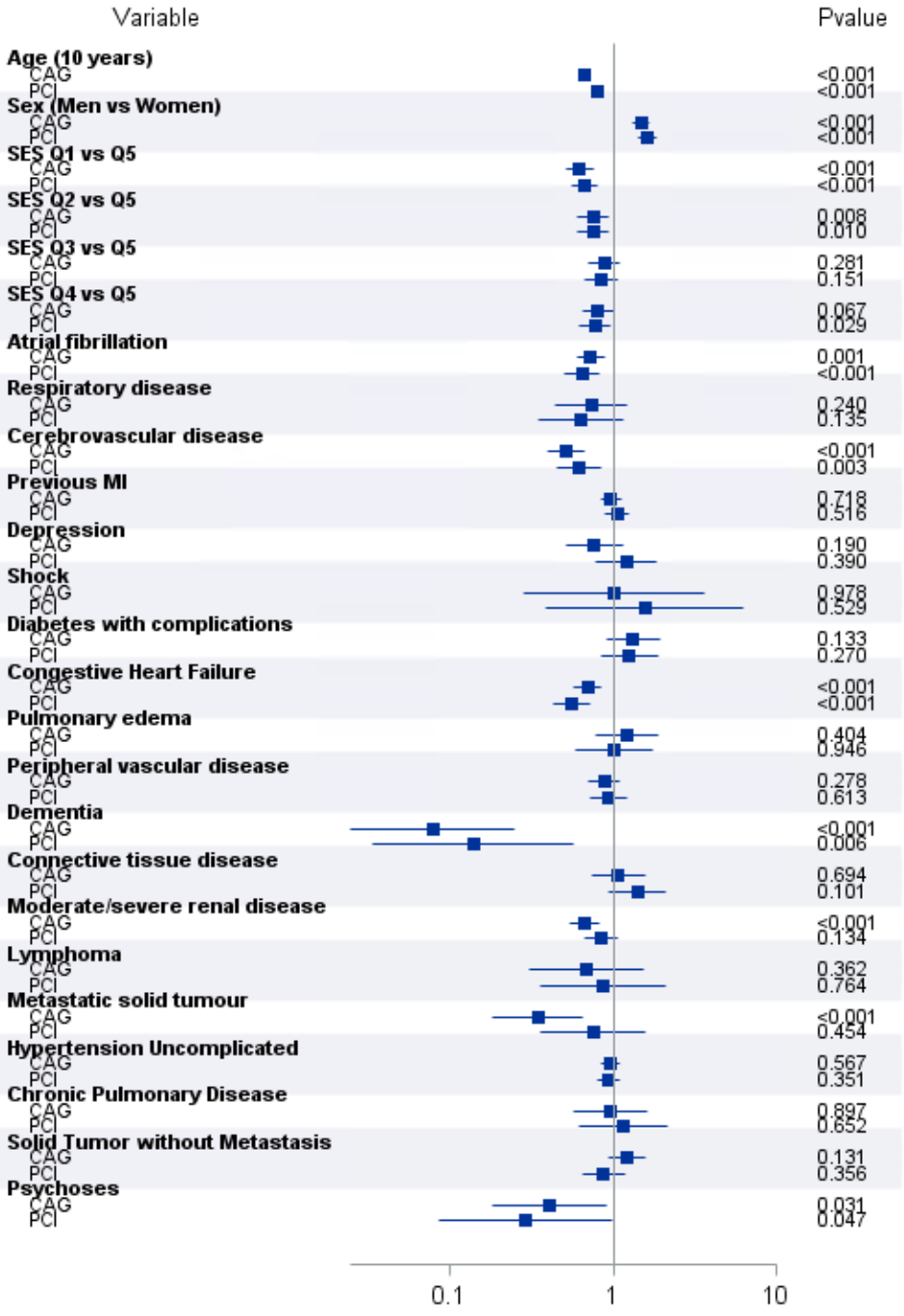


Figure 3-6. Association of baseline characteristics with coronary angiography (CAG) and PCI in non-STEMI patients.

Adjusted odds ratio and 95%CI shown for 10-year increase in age, SIMD quintiles vs least deprived quintile, men vs women, or presence vs absence of comorbidity. Adjusted for all measures depicted.



3.3.3.5 Summary

In STEMI patients, out of all the service delivery outcomes analysed, receipt of CAG was the criteria that differed across SIMD groups in univariate analysis. Clinical and demographic characteristics did not eliminate the difference between the most deprived and least deprived groups in multivariate analysis. There was a slight higher rate of CAG in the most deprived group (OR 1.58 CI 1.02-2.45) compared to the least deprived group but the strict criteria used for PCI eliminates any inequalities subsequent a CAG. While other SIMD quintiles did not differ in service delivery outcomes compared to the least deprived group.

In NSTEMI patients, the admission method, receipt of CAG and PCI differed across SIMD groups in univariate analysis. Further analysis revealed the decreased CAG in more deprived groups occurred only in those who are admitted via emergency services to a local hospital. SES remained a factor associated with CAG (SIMD Q1 vs Q5 OR 0.63, CI 0.52–0.75) and PCI (SIMD Q1 vs Q5 OR 0.67, CI 0.56–0.81) use after adjusting for clinical and demographic characteristics.

3.3.4 Socioeconomic status and prescriptions

A total of 7526 patients were discharged alive after a first hospitalisation for ACS between 2013 and 2016. Out of this group, 416 patients did not have any information regarding prescriptions recorded and were therefore assumed to have not been prescribed any drugs during the study period. Compared to the entire ACS study population (n=7878), the age of those discharged alive are younger (mean=65.7 yrs vs 66.3 yrs). Other baseline characteristics are similar to the entire ACS study population (see Table 3-20 vs Table 3-4).

Table 3-20. Patient demographics by diagnosis.

	All (N = 7526)	STEMI (N = 1924)	NSTEMI (N = 3852)	Unspecified MI (N = 329)	HA (N = 1421)
Age (years)	65.7 (13.49)	61.9 (13.47)	66.6 (13.32)	71.3 (14.55)	67.2 (12.55)
Male (%)	4537 (60.3%)	1339 (69.6%)	2270 (58.9%)	180 (54.7%)	748 (52.6%)
SIMD2012 QUINTILE					
1 (most deprived)	3123 (41.5%)	799 (41.5%)	1539 (40.0%)	136 (41.3%)	649 (45.7%)
2	1365 (18.1%)	356 (18.5%)	712 (18.5%)	64 (19.5%)	233 (16.4%)
3	1058 (14.1%)	295 (15.3%)	537 (13.9%)	47 (14.3%)	179 (12.6%)

4	944 (12.5%)	215 (11.2%)	490 (12.7%)	44 (13.4%)	195 (13.7%)
5 (least deprived)	1034 (13.7%)	258 (13.4%)	573 (14.9%)	38 (11.6%)	165 (11.6%)
Missing	2	1	1	0	0
No ACS medication	640	171	347	26	96
No prescription data	416	115	254	8	39

Numbers are presented as mean (SD) or numbers (%).

3.3.4.1 Baseline

Baseline prescription is defined as claim of prescription within 90 days before index admission. In general, the baseline prescription rate is lower for STEMI patients compared to other ACS patients. (OAC+SAPT and OAC+DAPT contain numbers below 5 so will not be shown here).

Table 3-21. Drug use before admission, defined as claim of prescription within 90 days before index admission.

	All (N = 7526)	STEMI (N = 1924)	NSTEMI (N = 3852)	HA (N = 1421)
Statins	3371 (44.8%)	525 (27.3%)	1773 (46.0%)	927 (65.2%)
ACE inhibitor/ARB	2621 (34.8%)	433 (22.5%)	1436 (37.3%)	630 (44.3%)
Beta blockers (BB)	2410 (32.0%)	318 (16.5%)	1279 (33.2%)	690 (48.6%)
Antiplatelets				
Aspirin	2475 (32.9%)	327 (17.0%)	1314 (34.1%)	721 (50.7%)
Clopidogrel	691 (9.2%)	88 (4.6%)	358 (9.3%)	209 (14.7%)
Ticagrelor	116 (1.5%)	8 (0.4%)	86 (2.2%)	17 (1.2%)
Mineralocorticoid Receptor Antagonists (MRA)	135 (1.8%)	18 (0.9%)	72 (1.9%)	36 (2.5%)
Oral Anticoagulants (OAC)	427 (5.7%)	42 (2.2%)	225 (5.8%)	130 (9.1%)
Combinations				
Single anti-platelet therapy (SAPT)	2978 (39.6%)	396 (20.6%)	1572 (40.8%)	869 (61.2%)
Dual anti-platelet therapy (DAPT)	295 (3.9%)	26 (1.4%)	178 (4.6%)	78 (5.5%)
OAC or SAPT	3328 (44.2%)	432 (22.5%)	1754 (45.5%)	975 (68.6%)
OAC or DAPT	717 (9.5%)	66 (3.4%)	401 (10.4%)	207 (14.6%)
Population initiated with 3 or more recommended medications	5883	1659	3119	876
3 or more pre-admission	2145 (36.5%)	252 (15.2%)	1161 (37.2%)	644 (73.5%)

Numbers are presented as numbers (%).

Table 3-22 and Table 3-23 presents the baseline prescription level stratified by SIMD level in STEMI and NSTEMI/HA patients respectively. For both STEMI and NSTEMI/HA, a higher proportion of patients with lower compared to higher socioeconomic status received statins, aspirin and any single anti-platelet therapy (SAPT). For STEMI patients, rate of receiving 3+ recommended medications also differed between SIMD quintiles. Pre-admission rate of 3+ medications was lower for STEMI compared to NSTEMI/HA. Although results in previous section did not find SIMD to be associated with any CVD prognostic of mortality except congestive heart failure, the differences in ACS-related medications between SIMD groups at baseline for STEMI patients indicate a higher previous ACS rate in the most deprived group.

Table 3-22. Drug use before admission, defined as claim of prescription within 90 days before index admission. In STEMI patients across SIMD quintiles.

	STEMI (N = 1923)	SIMD Quintile 1 (N = 799)	SIMD Quintile 2 (N = 356)	SIMD Quintile 3 (N = 295)	SIMD Quintile 4 (N = 215)	SIMD Quintile 5 (N = 258)	p-value
Statins	525 (27.3%)	256 (32.0%)	96 (27.0%)	77 (26.1%)	46 (21.4%)	50 (19.4%)	0.003
ACE inhibitor/ARB	433 (22.5%)	194 (24.3%)	73 (20.5%)	71 (24.1%)	36 (16.7%)	59 (22.9%)	0.148
Beta blockers	318 (16.5%)	150 (18.8%)	55 (15.4%)	45 (15.3%)	31 (14.4%)	37 (14.3%)	0.272
Antiplatelets							
Aspirin	327 (17.0%)	160 (20.0%)	60 (16.9%)	38 (12.9%)	30 (14.0%)	39 (15.1%)	0.029
Clopidogrel	88 (4.6%)	39 (4.9%)	12 (3.4%)	17 (5.8%)	10 (4.7%)	10 (3.9%)	0.627
Ticagrelor	8 (0.4%)	<5	<5	<5	<5	<5	0.405*
Mineralocorticoid Receptor Antagonists (MRA)	18 (0.9%)	<5	<5	<5	<5	<5	0.165*
Oral Anticoagulants (OAC)	42 (2.2%)	16 (2.0%)	5 (1.4%)	8 (2.7%)	5 (2.3%)	8 (3.1%)	0.635
Combinations							
Single anti-platelet therapy (SAPT)	396 (20.6%)	192 (24.0%)	67 (18.8%)	52 (17.6%)	36 (16.7%)	49 (19.0%)	0.034
Dual anti-platelet therapy (DAPT)	26 (1.4%)	10 (1.3%)	6 (1.7%)	<5	<5	<5	0.880*
OAC or SAPT	432 (22.5%)	207 (25.9%)	71 (19.9%)	59 (20.0%)	39 (18.1%)	56 (21.7%)	0.038
OAC or DAPT	66 (3.4%)	25 (3.1%)	11 (3.1%)	11 (3.7%)	9 (4.2%)	10 (3.9%)	0.918
Population initiated with 3 or more recommended medications	1659	730	301	236	159	233	
3 or more pre-admission	252 (15.2%)	133 (18.2%)	38 (12.6%)	37 (15.7%)	18 (11.3%)	26 (11.2%)	0.021

SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test

Table 3-23. Drug use before admission, defined as claim of prescription within 90 days before index admission. In NSTEMI/ UA patients across SIMD quintiles.

	NSTEMI/HA (N = 5273)	SIMD Quintile 1 (N = 2188)	SIMD Quintile 2 (N = 945)	SIMD Quintile 3 (N = 716)	SIMD Quintile 4 (N = 685)	SIMD Quintile 5 (N = 738)	p-value
Statins	2700 (51.2%)	1218 (55.7%)	485 (51.3%)	328 (45.8%)	313 (45.7%)	356 (48.2%)	<0.001
ACE inhibitor/ARB	2066 (39.2%)	866 (39.6%)	359 (38.0%)	265 (37.0%)	258 (37.7%)	318 (43.1%)	0.111
Beta blockers	1969 (37.3%)	849 (38.8%)	359 (38.0%)	244 (34.1%)	238 (34.7%)	279 (37.8%)	0.113
Antiplatelets							
Aspirin	2035 (38.6%)	907 (41.5%)	366 (38.7%)	252 (35.2%)	235 (34.3%)	275 (37.3%)	0.002
Clopidogrel	567 (10.8%)	284 (13.0%)	98 (10.4%)	60 (8.4%)	64 (9.3%)	61 (8.3%)	0.000
Ticagrelor	103 (2.0%)	48 (2.2%)	17 (1.8%)	7 (1.0%)	15 (2.2%)	16 (2.2%)	0.273*
Mineralocorticoid Receptor Antagonists (MRA)	108 (2.0%)	46 (2.1%)	22 (2.3%)	12 (1.7%)	8 (1.2%)	20 (2.7%)	0.272
Oral Anticoagulants (OAC)	355 (6.7%)	151 (6.9%)	60 (6.3%)	41 (5.7%)	46 (6.7%)	57 (7.7%)	0.622
Combinations							
Single anti-platelet therapy (SAPT)	2441 (46.3%)	1112 (50.8%)	436 (46.1%)	295 (41.2%)	282 (41.2%)	316 (42.8%)	<0.001
Dual anti-platelet therapy (DAPT)	256 (4.9%)	119 (5.4%)	45 (4.8%)	24 (3.4%)	32 (4.7%)	36 (4.9%)	0.260*
OAC or SAPT	2729 (51.8%)	1233 (56.4%)	486 (51.4%)	328 (45.8%)	318 (46.4%)	364 (49.3%)	<0.001
OAC or DAPT	608 (11.5%)	270 (12.3%)	105 (11.1%)	65 (9.1%)	76 (11.1%)	92 (12.5%)	0.162
Population initiated with 3 or more recommended medications	3995	1714	720	503	463	595	
3 or more pre-admission	1805 (45.2%)	798 (46.6%)	323 (44.9%)	223 (44.3%)	213 (46.0%)	248 (41.7%)	0.336

SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test

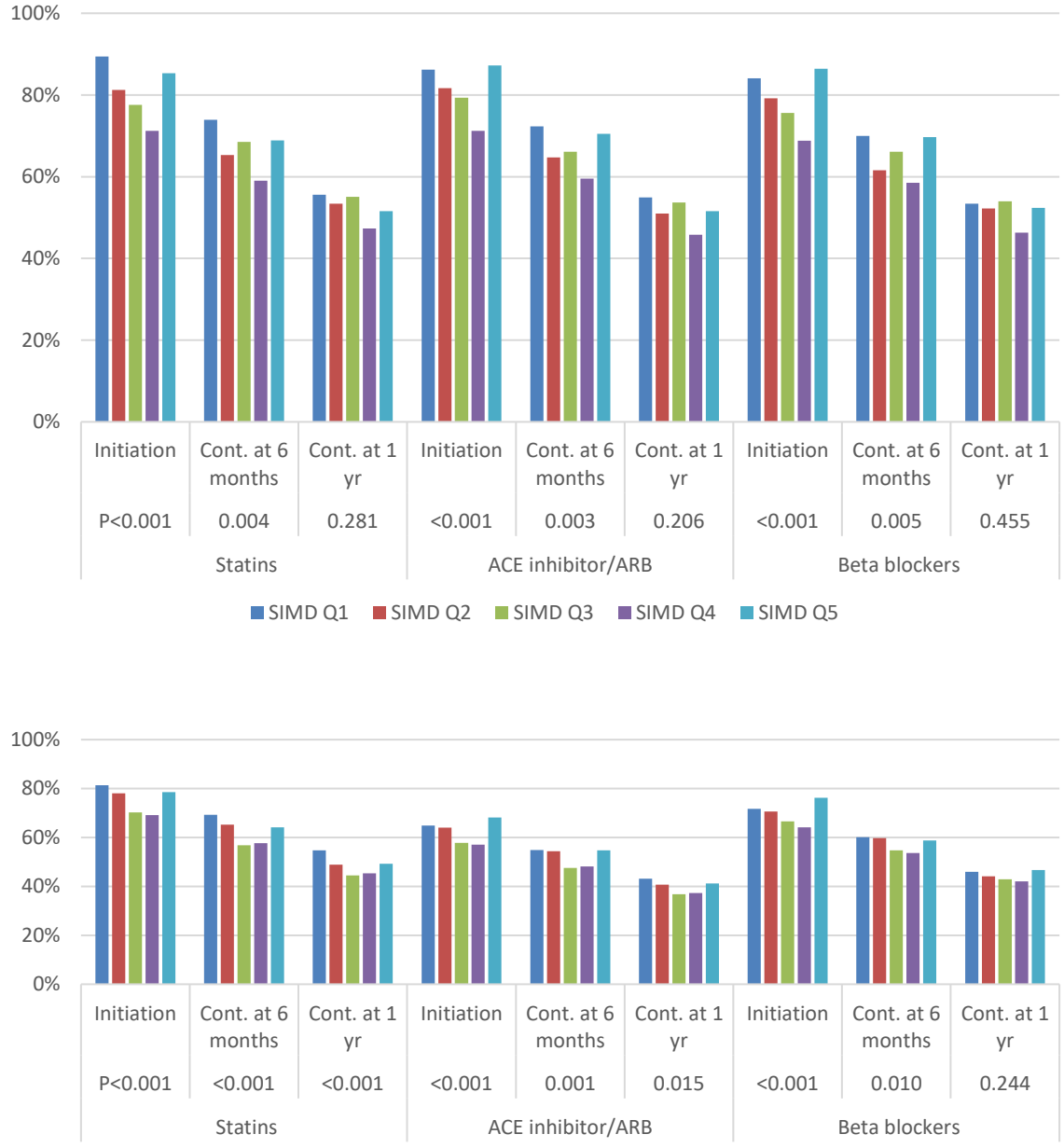
3.3.4.2 Initiation of treatment

Of all STEMI patients who were discharged alive after first hospitalisation for ACS, 83.4%, 82.7%, 80.5% claimed a prescription within 90 days of discharge for statins, ACE inhibitors/ARB and Beta blockers respectively. The proportion of STEMI patients claiming these prescriptions within 90 days of discharge is different across SIMD groups (Figure 3-7 Upper). The least deprived (Q5) and most deprived (Q1) groups had similar rates of prescription, but there is a possible decreasing trend for drug initiation with more affluent groups of Q1-Q4 less likely to initiate treatment. A similar trend is seen for NSTEMI/UA patients (Figure 3-7 Lower).

3.3.4.3 Continuation at 6 month and 1 year

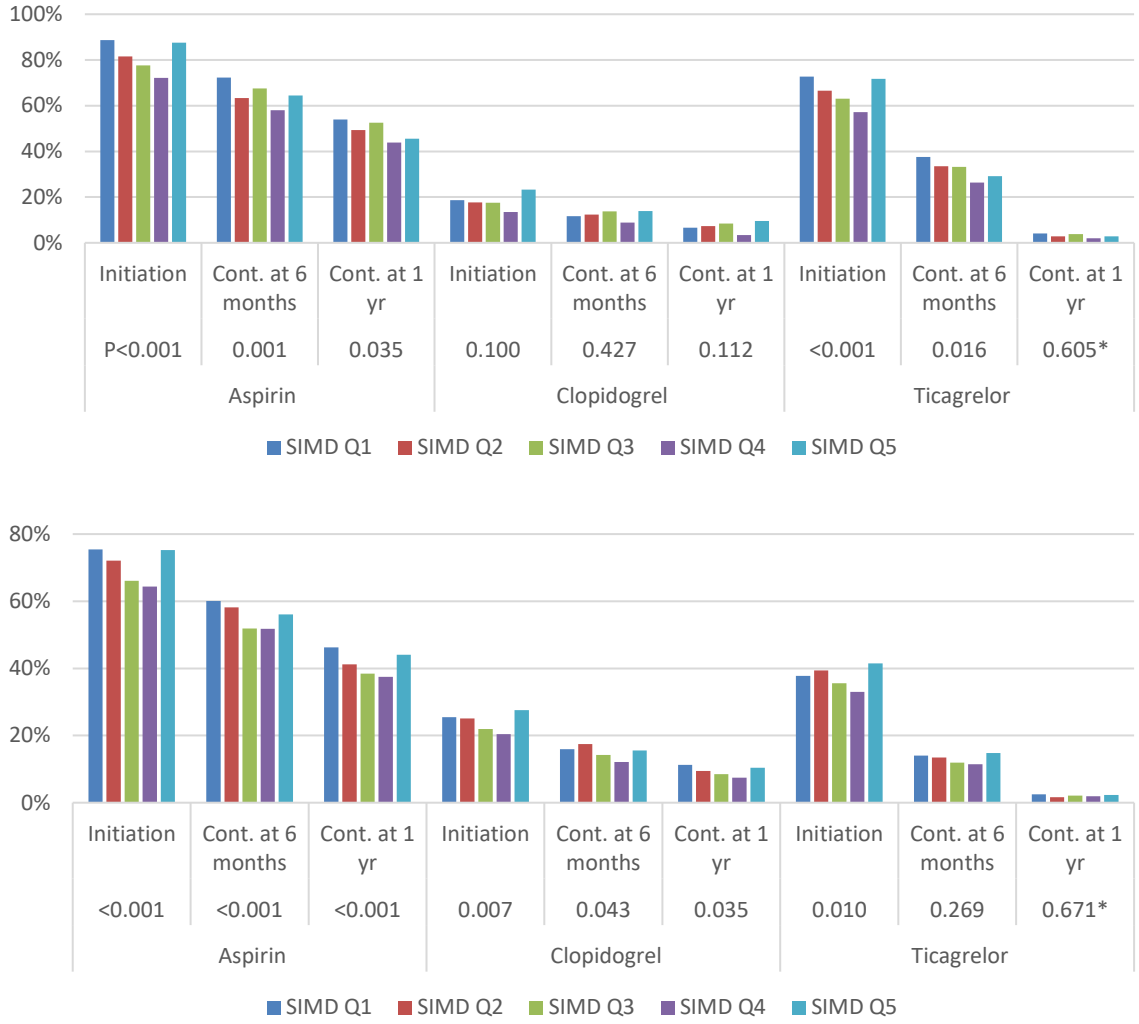
Continuation is defined as claim of prescription at 6 month or 1 year post discharge +/- 45 days. Numbers are out of those that are still alive at each follow up point. As expected, the general use of evidence-based medications is lower at 1 year than at 6 months. Continuation of statins, ACE inhibitors/ARB and beta blockers differs between SIMD groups at 6 months for both STEMI and NSTEMI/UA. There is a possible decreasing trend for drug continuation at 6 month with more affluent groups less likely to continue treatment (Figure 3-7). The use of aspirin and Ticagrelor in STEMIs show similar patterns (Figure 3-8). In general, the prescription rates are higher for STEMI patients compared to NSTEMI/HA patients (although baseline rates before ACS hospitalisation are lowest in STEMIs). The use of and Clopidogrel are much lower compared to the other two antiplatelet.

Figure 3-7. Drug use post discharge in patients still alive at each time point in STEMI (upper panel) and NSTEMI/HA (lower panel) by SES



Initiation defined as claim of prescription within 90 days post discharge, Continuation defined as claim of prescription at 6 month or 1 year post discharge +/- 45 days. In ACS patients across SIMD quintiles. SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test

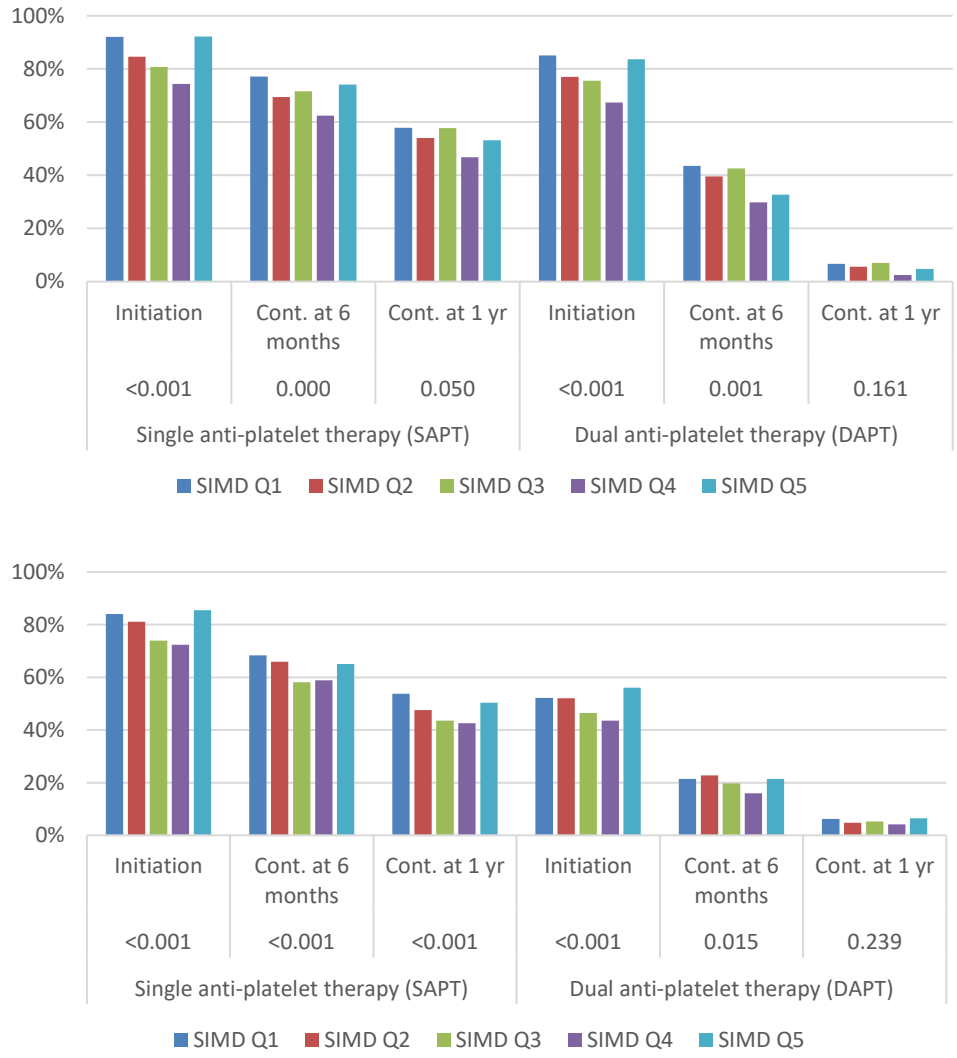
Figure 3-8. Drug use post discharge in patients still alive at each time point in STEMI (upper panel) and NSTEMI/HA (lower panel) by SES



Initiation defined as claim of prescription within 90 days post discharge, Continuation defined as claim of prescription at 6 month or 1 year post discharge +/- 45 days. In ACS patients across SIMD quintiles. SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test

Concerning continuation of any single anti-platelet therapy (SAPT), there was an inverse relation with SIMD, such that a higher proportion of patients in the more deprived quintiles than less deprived quintiles continue to take SAPT at 6 months and 1 year after hospital discharge (Figure 3-9). Similar patterns are seen for DAPT at 6 months but there was no difference between SIMD and use of DAPT at 1 year post-discharge.

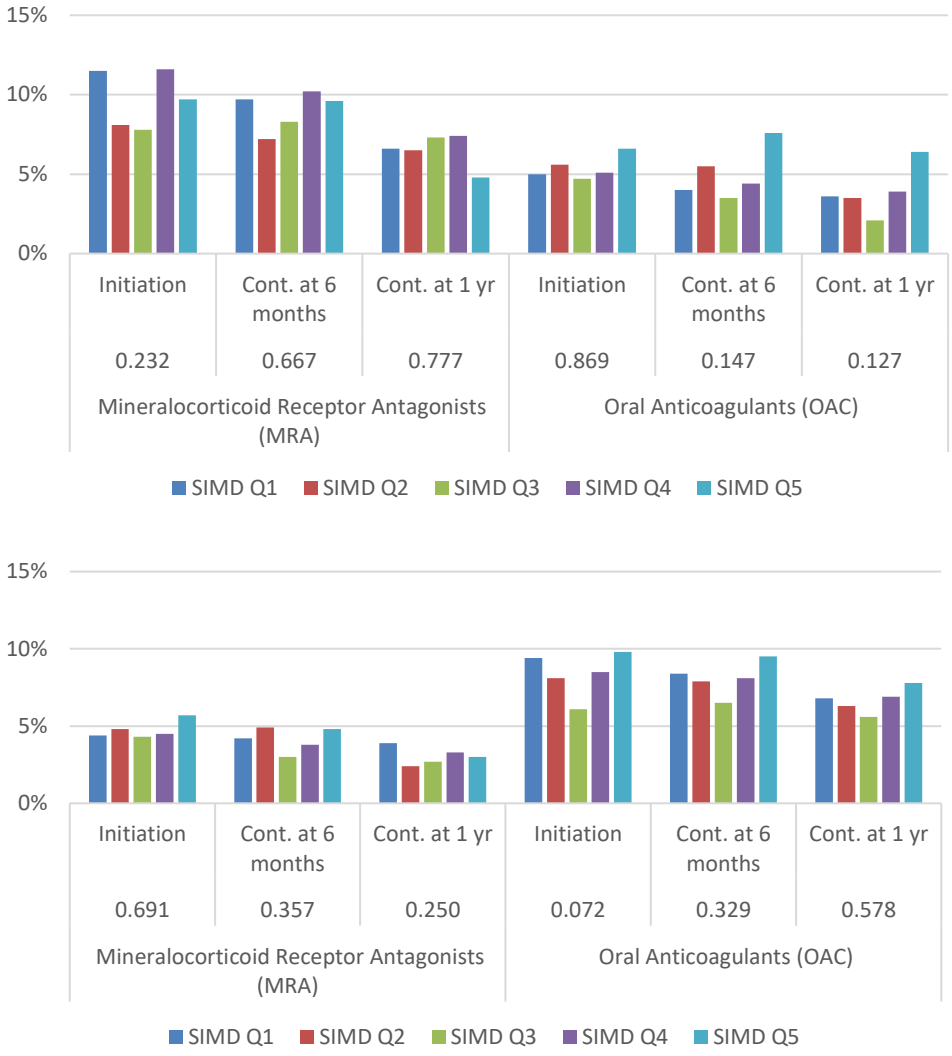
Figure 3-9. Antiplatelet use post discharge in patients still alive at each time point in STEMI (upper panel) and NSTEMI/HA (lower panel) by SES



Initiation defined as claim of prescription within 90 days post discharge, Continuation defined as claim of prescription at 6 month or 1 year post discharge +/- 45 days. In ACS patients across SIMD quintiles. SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test

There was no relationship between SIMD and use of mineralocorticoid receptor antagonists (MRA) or oral anticoagulants (OAC) at all follow-up points (Figure 3-10).

Figure 3-10. MRA and OAC use post discharge in patients still alive at each time point in STEMI (upper panel) and NSTEMI/HA (lower panel) by SES

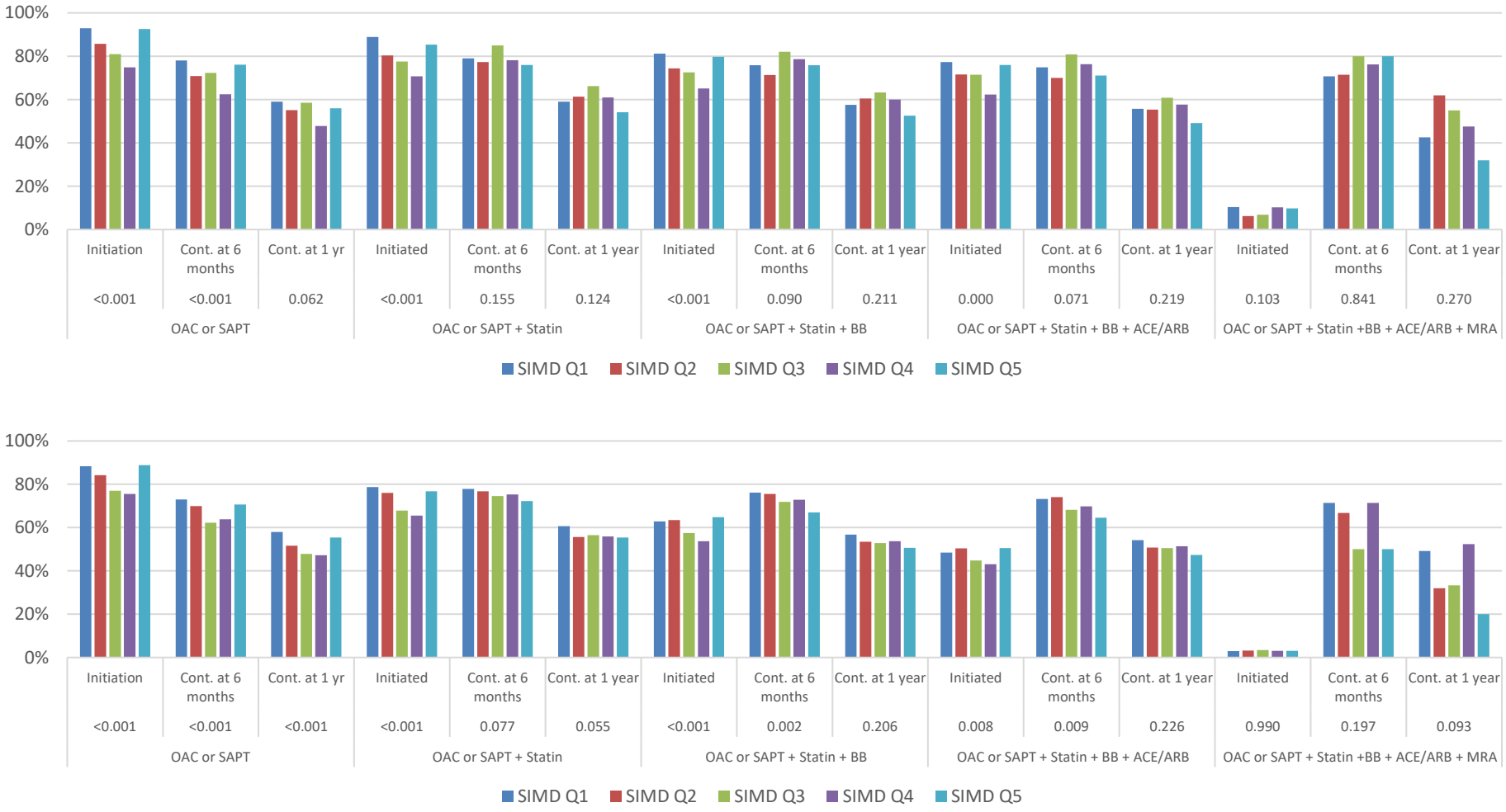


Initiation defined as claim of prescription within 90 days post discharge, Continuation defined as claim of prescription at 6 month or 1 year post discharge +/- 45 days. In ACS patients across SIMD quintiles. SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test

3.3.4.4 Combination therapies

The prescription rate for OAC or SAPT at discharge is 87.6% for STEMI patients and 84.4% for NSTEMI/UA patients (Figure 3-11). The addition of statins, beta blockers and ACE/ARB to this prescription remains around 80% but significantly decreases to less than 10% after adding MRA. Out of those that were initiated on a prescription at discharge, the continuation rate at 6 month is around 80% for all prescriptions and 50% at 1 year. The prescription rates at initiation differ across SIMD groups and less so at 6 months and 1 year, especially after adding other drugs to OAC or SAPT.

Figure 3-11. Prescription hierarchy for OAC or SAPT post discharge in patients still alive at each time point in STEMI (upper) and NSTEMI/HA (lower panel)



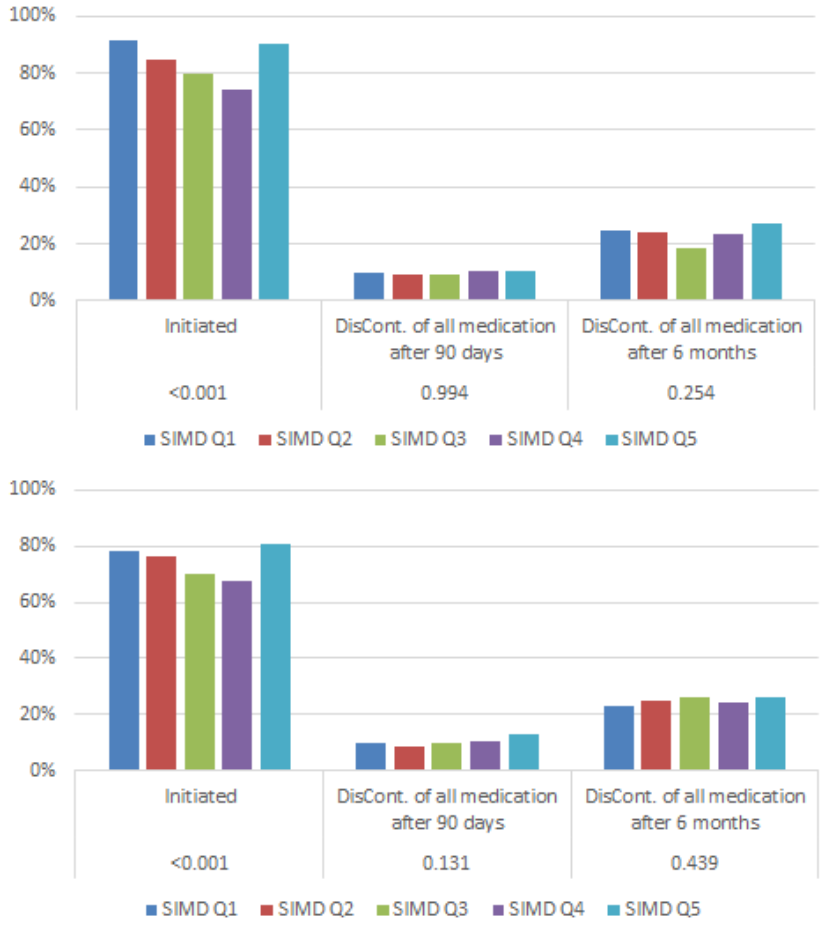
Initiation defined as claim of prescription within 90 days post discharge, Continuation defined as claim of prescription at 6 month or 1 year post discharge +/- 45 days. In ACS patients across SIMD quintiles. SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test

3.3.4.5 Three or more recommended medications

For both STEMI and non-STEMI ACS patients, receiving 3+ recommended medications after discharge differed between SIMD groups, but not between SIMD Q1 vs Q5 (STEMI: 91.4% vs 90.3%; non-STEMI:78.3% vs 80.6%) (Figure 3-12).

Discontinuation of all medications at 90 days and at 6 months did not differ between the SIMD quintiles in both subgroups. As expected, a higher proportion of patients discontinued all medications at 6 months (~25%) than at 90 days (~10%).

Figure 3-12. Percent population initiated with 3 or more recommended medications in STEMI (upper panel) and NSTEMI/HA (lower panel) by SES



Prescription rates in patients' still alive and initiated 3+ medications. Discontinuation defined as no more claims for prescriptions after 90 days and 180 days post-discharge. In ACS patients across SIMD quintiles. SIMD Q1=most deprived. P-values by chi-squared or *fishers exact test.

3.3.4.6 Predictors of initiation, continuation of treatment

To analyse the effect of SIMD on each drug treatment, three analyses using mixed effects logistic models were performed for each drug/drug combination: (1) initiation: claim at a pharmacy within 90 days of discharge as outcome (all patients alive at discharge), adjusted for the baseline characteristics; age, sex, SIMD, use of respective drug within 90 days before index admission (aka baseline use, dichotomous variable), co-morbidities and if revascularisation procedures were performed. Furthermore, we adjusted for clustering at the discharge hospital level; (2) continuation of prescription at 6 months or (3) 1 year after discharge as outcome (only for patients who initiated treatment within 90 days of discharge and alive at follow up), adjusted for the same baseline characteristics as above.

The assumption of linear relationships for continuous age and log odds was tested by adding the interaction term to the logistic model and was significant, therefore the remedial measure for correcting the violation is to use categorical age instead. The effect of SIMD on medication use was not affected by the change of adjustment from continuous age to categorical age.

For both STEMI and non-STEMI (NSTEMI or HA) patients, SIMD (the most deprived vs least quintile) was not an independent predictor of treatment with most recommended medications immediately after discharge (Table 3-24). While non-STEMI patients in the most deprived group were 27-167% more likely than the least deprived group to be treated with statins, ACE inhibitors or ARBs, beta-blockers, aspirin or MRA during follow up. On the contrary, SIMD was not an independent predictor of medical treatment at 6 months or 1 year in STEMI patients, except for aspirin.

Table 3-24. Association of SIMD (most deprived vs least deprived quintile) with medical therapy at discharge, 6 months and 1 year according to drug(s) and diagnosis.

	Initiation		Continuation at 6 months		Continuation at 1 year	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Statins						
STEMI	1.29 (0.83, 2.02)	0.261	1.13 (0.77, 1.67)	0.553	1.16 (0.82, 1.64)	0.400
NSTEMI/HA	1.04 (0.83, 1.31)	0.741	1.43 (1.13, 1.81)	0.003	1.40 (1.14, 1.73)	0.002
ACE inhibitor/ARB						

STEMI	0.85 (0.55, 1.33)	0.487	1.10 (0.74, 1.63)	0.631	1.16 (0.82, 1.63)	0.399
NSTEMI/HA	1.02 (0.83, 1.25)	0.867	1.28 (1.00, 1.65)	0.051	1.30 (1.04, 1.63)	0.021
Beta blockers						
STEMI	0.77 (0.50, 1.18)	0.229	1.04 (0.70, 1.54)	0.856	1.05 (0.74, 1.48)	0.783
NSTEMI/HA	0.83 (0.67, 1.02)	0.079	1.62 (1.28, 2.06)	<0.001	1.27 (1.03, 1.58)	0.028
Antiplatelets						
Aspirin						
STEMI	1.02 (0.65, 1.62)	0.926	1.44 (1.00, 2.08)	0.053	1.41 (1.00, 1.97)	0.048
NSTEMI/HA	0.99 (0.80, 1.22)	0.903	1.41 (1.13, 1.77)	0.002	1.20 (0.97, 1.48)	0.090
Clopidogrel						
STEMI	0.91 (0.62, 1.33)	0.629	1.05 (0.55, 1.98)	0.883	0.83 (0.40, 1.73)	0.626
NSTEMI/HA	0.78 (0.63, 0.96)	0.020	1.07 (0.75, 1.53)	0.719	0.99 (0.66, 1.49)	0.962
Ticagrelor						
STEMI	0.87 (0.61, 1.23)	0.425	1.34 (0.94, 1.92)	0.102	1.23 (0.51, 2.93)	0.645
NSTEMI/HA	1.02 (0.84, 1.23)	0.861	1.05 (0.77, 1.43)	0.777	1.00 (0.52, 1.92)	0.992
Mineralocorticoid Receptor Antagonists (MRA)						
STEMI	1.23 (0.76, 2.00)	0.394	0.56 (0.16, 2.03)	0.379	1.44 (0.51, 4.06)	0.484
NSTEMI/HA	0.84 (0.53, 1.34)	0.469	1.23 (0.50, 3.00)	0.651	2.67 (1.09, 6.55)	0.032
Oral Anticoagulants (OAC)						
STEMI	1.04 (0.54, 2.01)	0.951	0.64 (0.15, 2.86)	0.560	0.76 (0.18, 3.19)	0.709
NSTEMI/HA	1.04 (0.70, 1.55)	0.834	0.88 (0.43, 1.81)	0.735	0.85 (0.45, 1.61)	0.618
Combinations						
Single anti-platelet therapy (SAPT)						
STEMI	0.94 (0.54, 1.63)	0.815	1.20 (0.81, 1.77)	0.357	1.25 (0.90, 1.75)	0.188
NSTEMI/HA	0.78 (0.61, 1.01)	0.055	1.31 (1.05, 1.64)	0.015	1.22 (1.00, 1.50)	0.048
Dual anti-platelet therapy (DAPT)						
STEMI	1.01 (0.67, 1.54)	0.948	1.48 (1.07, 2.06)	0.019	1.54 (0.77, 3.05)	0.220
NSTEMI/HA	1.00 (0.83, 1.20)	0.987	1.11 (0.86, 1.44)	0.424	0.92 (0.61, 1.40)	0.703
Hierarchies *						
OAC or SAPT						
STEMI	1.00 (0.57, 1.77)	0.993	1.13 (0.76, 1.69)	0.500	1.18 (0.84, 1.66)	0.330
NSTEMI/HA	0.85 (0.64, 1.12)	0.249	1.22 (0.97, 1.53)	0.085	1.20 (0.98, 1.46)	0.079
OAC or SAPT + Statin						
STEMI	1.46 (0.94, 2.26)	0.091	1.16 (0.80, 1.70)	0.431	1.28 (0.92, 1.80)	0.146
NSTEMI/HA	1.11 (0.91, 1.36)	0.311	1.43 (1.14, 1.79)	0.002	1.36 (1.10, 1.67)	0.004
OAC or SAPT + Statin + BB						
STEMI	1.06 (0.73, 1.54)	0.760	0.95 (0.65, 1.40)	0.790	1.25 (0.89, 1.77)	0.198
NSTEMI/HA	0.97 (0.81, 1.16)	0.740	1.62 (1.28, 2.05)	<0.001	1.35 (1.08, 1.69)	0.009
OAC or SAPT + Statin + BB +ACE/ARB						
STEMI	1.00 (0.70, 1.42)	0.992	1.14 (0.78, 1.66)	0.498	1.27 (0.89, 1.80)	0.183
NSTEMI/HA	1.03 (0.86, 1.22)	0.779	1.53 (1.18, 1.99)	0.001	1.37 (1.06, 1.76)	0.015
OAC or SAPT + Statin + BB +ACE/ARB + MRA						
STEMI	1.08 (0.67, 1.75)	0.754	0.59 (0.19, 1.84)	0.361	1.38 (0.46, 4.15)	0.560
NSTEMI/HA	0.95 (0.58, 1.55)	0.826	2.70 (0.93, 7.82)	0.067	5.49 (1.37, 22.04)	0.017

Adjusted odds ratio and 95%CI shown for most deprived vs least deprived SIMD quintile.
***Hierarchy drugs are not adjusted for pre-admission drugs.**

3.3.5 Socioeconomic status and mortality

All-cause mortality at 30 days was 4.9% in all ACS patients, 6.9% in STEMI patients and 2.2% in non-STEMI patients. All-cause mortality at 1 year was 10.9% in all patients, 10% in STEMI 8.7% in non-STEMI patients. Survival was worse in SIMD quintiles 1, 3, and 4 for STEMI patients, but was not significantly different between SIMD quintiles for non-STEMI patients (Figure 3-13).

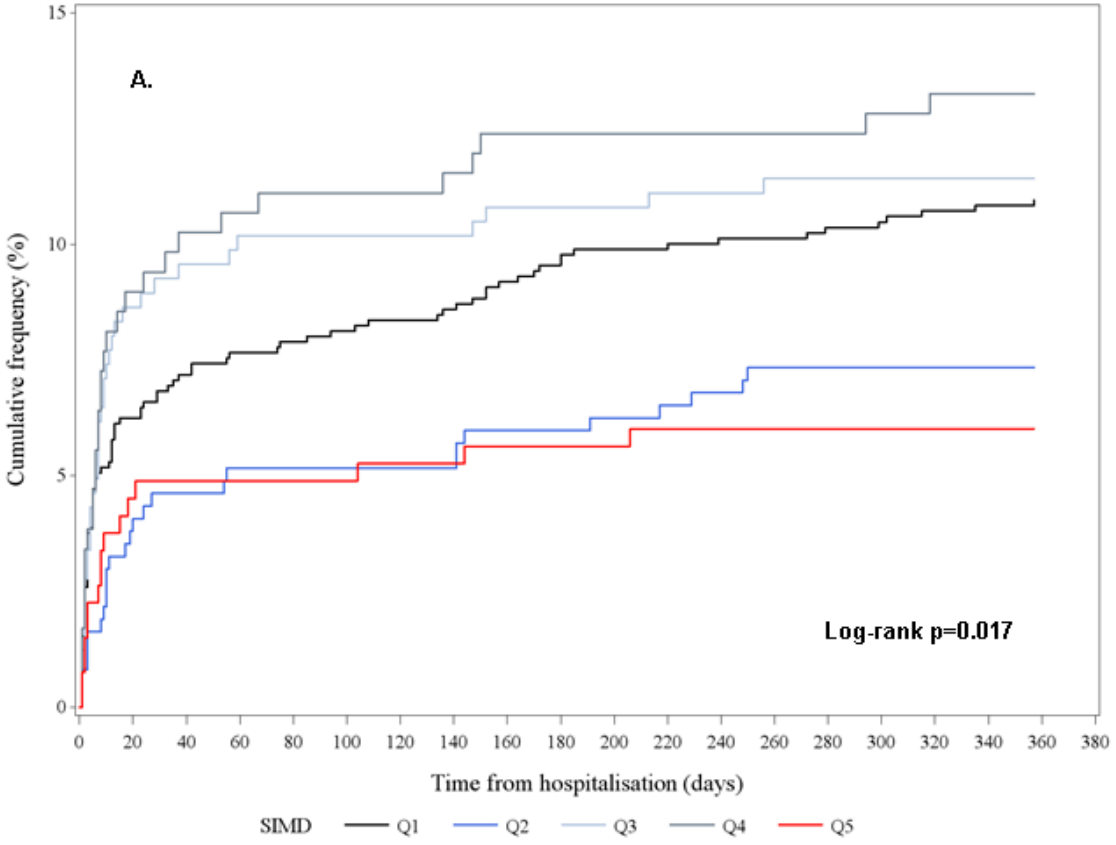
Similarly, after adjustment for baseline demographics, prognostic comorbidities and PCI, the association between socioeconomic status (SIMD) and all-cause mortality after NSTEMI/HA was not significant, while SIMD was an independent predictor of 1-year all-cause death after STEMI: SIMD quintiles 1, 3, and 4 had significantly higher mortality than quintile 5 (Table 3-26). With the additional adjustment of prescriptions preadmission and at discharge, only SIMD Q1 had statistically higher 1-year mortality than Q5 in STEMI patients.

Table 3-25. All-cause mortality all ACS, STEMI and NSTEMI/HA according to SIMD.

	All	SIMD Q1	SIMD Q2	SIMD Q3	SIMD Q4	SIMD Q5	P-value*
ACS	7876	3265	1418)	1126	993	1074	
30 days	386 (4.9%)	154 (4.7%)	61 (4.3%)	68 (6.0%)	55 (5.5%)	48 (4.5%)	0.218
1 year	861 (10.9%)	372 (11.4%)	146 (10.3%)	125 (11.1%)	117 (11.8%)	101 (9.4%)	0.325
STEMI	2041	849	368	324	234	266	
30 days	140 (6.9%)	58 (6.8%)	17 (4.6%)	30 (9.3%)	22 (9.4%)	13 (4.9%)	0.044
1 year	204 (10.0%)	93 (11.0%)	27 (7.3%)	37 (11.4%)	31 (13.2%)	16 (6.0%)	0.018
NSTEMI/HA	5381	2221	969	734	699	758	
30 days	120 (2.2%)	38 (1.7%)	27 (2.8%)	16 (2.2%)	18 (2.6%)	21 (2.8%)	0.238
1 year	469 (8.7%)	186 (8.4%)	95 (9.8%)	60 (8.2%)	61 (8.7%)	67 (8.8%)	0.726

P-value from chi-squared test.

Figure 3-13. Cumulative incidence curves for all-cause death A) STEMI and B) NSTEMI or HA patients stratified by SIMD



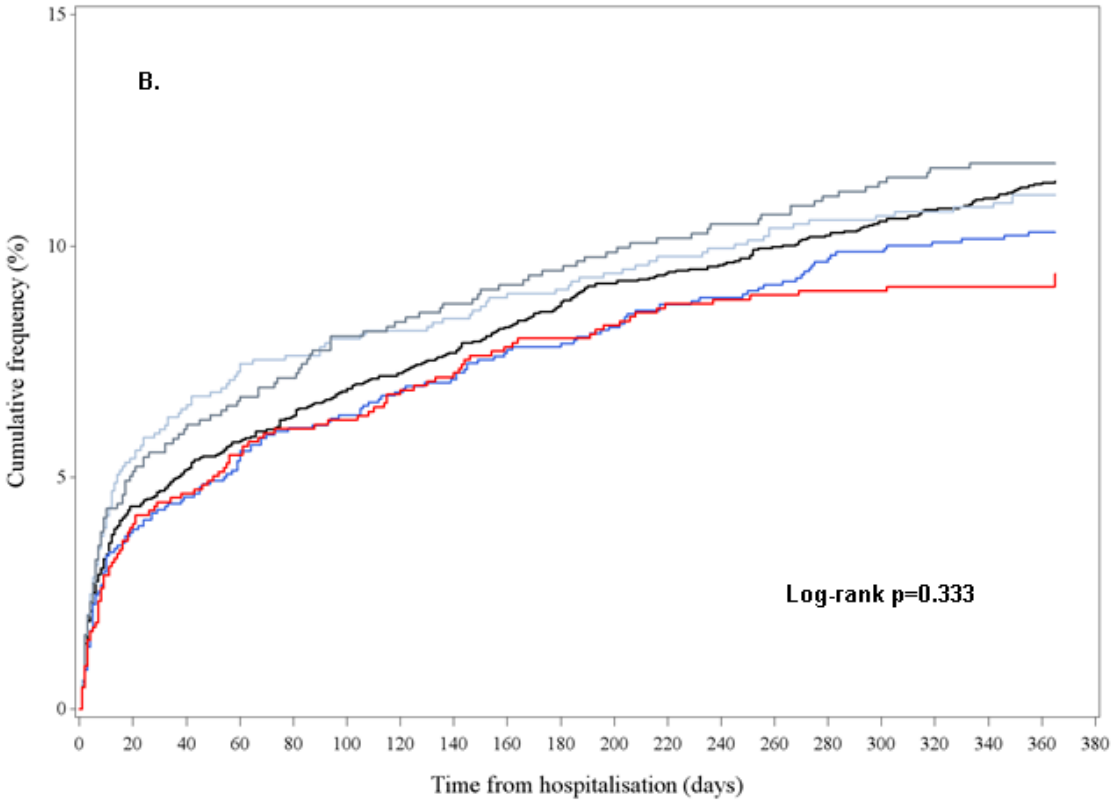


Table 3-26. Adjusted all-cause mortality before 1 year in STEMI and NSTEMI/HA patients by SIMD.

SIMD (vs Q5)	STEMI		NSTEMI/HA	
	HR (95%CI)	P-Value	HR (95%CI)	P-Value
Model 1		0.016		0.503
Q1	2.27 (1.32, 3.91)	0.003	1.06 (0.80, 1.42)	0.668
Q2	1.50 (0.81, 2.81)	0.200	1.21 (0.88, 1.66)	0.240
Q3	2.21 (1.22, 4.02)	0.009	0.92 (0.64, 1.30)	0.620
Q4	2.35 (1.28, 4.33)	0.006	0.99 (0.70, 1.41)	0.950
Model 2		<0.001		0.261
Q1	1.81 (1.03-3.18)	0.039	0.98 (0.73-1.30)	0.865
Q2	0.78 (0.41-1.49)	0.455	1.18 (0.86-1.62)	0.304
Q3	0.96 (0.51-1.78)	0.887	0.83 (0.58-1.19)	0.320
Q4	0.91 (0.48-1.73)	0.771	0.89 (0.62-1.26)	0.509

Adjusted hazard ratio and 95CI shown for each SIMD quintile vs the least deprived quintile (Q5). Model 1 adjusted for age, sex, shock, diabetes with complications, congestive heart failure, pulmonary edema, peripheral vascular disease, dementia, connective tissue disease, renal disease, lymphoma, solid tumour, hypertension, chronic pulmonary disease, psychoses and use of percutaneous coronary intervention. Model 2 adjusted for covariates in model 1 + preadmission and discharge uptake of statins, ACE/ARBs, beta-blockers and aspirin.

3.3.5.1 Predictors of adjusted mortality

Predicators of age and sex adjusted 1-year mortality among baseline characteristics, comorbidities, treatment quality and process of care measures identified previously as outcome measures, and prescription uptake by STEMI and non-STEMI patients were examined (Table 3-27).

Unsurprisingly, older patients have a higher risk of 1-year mortality (HR 1.06 in STEMI and HR 1.08 in non-STEMI per 1-year increase in age). Survival was worse for women than for men, but only in non-STEMI patients. ACS patients with comorbid shock, diabetes, pulmonary edema, cancer and psychoses have the greatest increase in likelihood of death at 1 year.

Out of all treatment quality and process of care measures, receipt of angiography and PCI within hospital, as well as receipt of statins, ACE/ARBs, beta-blockers and aspirin at discharge were associated with the lowest 1-year mortality.

Proportional hazards were checked for age, sex, SIMD and all predictors included in the age and sex adjusted cox regression models and violations were not detected for any of the significant predictors except for Shock and solid tumour without metastasis. The presence of both these conditions are low and although

the effect of SES on mortality are unaffected, they should be interpreted with care.

Table 3-27. Age and sex-adjusted hazard ratio for mortality within 1 year.

	STEMI		NSTEMI/ HA	
Variable	HR (95%CI)	P-Value	HR (95%CI)	P-Value
Age (1 yr)	1.06 (1.05, 1.07)	< 0.001	1.08 (1.07, 1.09)	<0.001
Male vs Female	0.84 (0.63, 1.12)	0.242	1.37 (1.14, 1.65)	0.001
SIMD (categorical) (vs Q5)		0.003		0.219
Q1	2.47 (1.45, 4.20)		1.28 (0.96, 1.69)	
Q2	1.40 (0.76, 2.60)		1.35 (0.99, 1.85)	
Q3	2.24 (1.24, 4.02)		1.06 (0.75, 1.50)	
Q4	2.27 (1.24, 4.15)		1.09 (0.77, 1.54)	
Prognostic Comorbidities				
Shock	13.94 (7.29, 26.65)	< 0.001	10.35 (4.27, 25.05)	<0.001
Diabetes with complications	2.46 (1.01, 5.99)	0.048	3.59 (2.49, 5.17)	<0.001
Congestive Heart Failure	2.54 (1.67, 3.88)	< 0.001	2.51 (2.06, 3.06)	<0.001
Pulmonary edema	4.35 (2.21, 8.55)	< 0.001	3.27 (2.31, 4.62)	<0.001
Peripheral vascular disease	1.36 (0.82, 2.28)	0.236	2.17 (1.70, 2.75)	<0.001
Dementia	2.04 (1.07, 3.91)	0.031	1.56 (0.99, 2.45)	0.054
Connective tissue disease	1.02 (0.42, 2.49)	0.970	2.12 (1.43, 3.16)	<0.001
Moderate/severe renal disease	2.39 (1.66, 3.43)	< 0.001	2.02 (1.65, 2.47)	<0.001
Lymphoma	2.70 (0.86, 8.43)	0.088	3.19 (1.58, 6.42)	0.001
Metastatic solid tumour	3.67 (1.72, 7.80)	< 0.001	5.58 (3.81, 8.19)	<0.001
Hypertension Uncomplicated	1.27 (0.91, 1.78)	0.155	1.11 (0.92, 1.35)	0.276
Chronic Pulmonary Disease	1.62 (1.13, 2.34)	0.009	1.69 (1.37, 2.09)	<0.001
Solid Tumour without Metastasis	2.45 (1.60, 3.75)	< 0.001	2.19 (1.70, 2.82)	<0.001
Psychoses	5.90 (0.82, 42.58)	0.079	8.58 (4.04, 18.23)	<0.001
Other clinically relevant comorbidities				
Atrial fibrillation	1.52 (0.99, 2.33)	0.055	1.26 (1.01, 1.58)	0.043
Cerebrovascular disease	1.48 (0.90, 2.45)	0.124	1.55 (1.19, 2.03)	0.001
Stroke	1.68 (0.79, 3.59)	0.178	1.66 (1.11, 2.48)	0.014
Myocardial infarction	1.28 (0.96, 1.71)	0.098	1.38 (1.15, 1.66)	<0.001
Depression	1.41 (0.58, 3.42)	0.454	0.86 (0.41, 1.82)	0.694
Service Delivery				
Admission Method (vs Non-emergency to local hospital)		<0.001		0.010
Emergency to Cath lab	2.29 (0.85, 6.22)		1.22 (0.57, 2.64)	
Non-emergency to Cath lab	3.48 (1.17, 10.35)		0.50 (0.31, 0.79)	
Emergency to local hospital	4.28 (1.56, 11.71)		0.76 (0.53, 1.07)	
Received CAG	0.38 (0.28 - 0.51)	< 0.001	0.35 (0.28, 0.45)	<0.001
Received PCI	0.50 (0.37 - 0.66)	< 0.001	0.49 (0.37, 0.65)	<0.001
Length of stay in hospital (days)	1.01 (1.00 - 1.02)	0.053	1.01 (1.01, 1.01)	<0.001
Length of episode (days)	1.00 (1.00 - 1.01)	0.349	1.01 (1.01, 1.01)	<0.001
Admission on weekday	1.02 (0.74 - 1.41)	0.908	0.83 (0.67, 1.02)	0.081
Treatment quality in those with CAG				
Received PCI	0.87 (0.54, 1.40)	0.5638	-	
Call to door (10 min increase)	1.04 (1.02, 1.06)	<0.001	-	
Call to balloon (10 min)	1.07 (1.04, 1.09)	<0.001	-	
Door to balloon (10 min)	1.01 (1.00, 1.02)	0.150	-	
Call time from 6am to 11pm	2.01 (1.00, 4.02)	0.050	-	
Door time from 6am to 11pm	1.09 (0.70, 1.69)	0.714	-	
Balloon time from 6am to 11pm	1.19 (0.74, 1.920	0.473	-	
Call time on weekday	1.20 (0.71, 2.04)	0.492	-	
Door time on weekday	1.00 (0.66, 1.49)	0.984	-	
Balloon time on weekday	0.98 (0.64, 1.50)	0.930	-	
Prescriptions *				
Statins				
Pre-admission	2.22 (1.45, 3.40)	< 0.001	1.30 (1.05, 1.61)	0.016
Initiation	0.28 (0.18, 0.43)	< 0.001	0.55 (0.45, 0.69)	<0.001
Continuation at 6 months	0.67 (0.28, 1.64)	< 0.384	0.99 (0.70, 1.40)	0.971
ACE inhibitor/ARB				
Pre-admission	1.41 (0.89, 2.23)	0.138	0.92 (0.75, 1.14)	0.465
Initiation	0.17 (0.11, 0.27)	< 0.001	0.49 (0.39, 0.60)	<0.001

Continuation at 6 months	0.41 (0.17, 1.03)	0.057	0.64 (0.45, 0.91)	0.012
Beta blockers				
Pre-admission	1.66 (1.04, 2.65)	0.035	1.35 (1.10, 1.66)	0.005
Initiation	0.33 (0.21, 0.51)	< 0.001	0.72 (0.58, 0.89)	0.003
Continuation at 6 months	0.59 (0.24, 1.43)	0.244	1.46 (1.03, 2.06)	0.035
Antiplatelets				
Aspirin				
Pre-admission	1.62 (1.02, 2.58)	0.042	1.35 (1.10, 1.66)	0.005
Initiation	0.28 (0.18, 0.43)	<0.001	0.68 (0.55, 0.84)	<0.001
Continuation at 6 months	0.53 (0.21, 1.29)	0.160	1.15 (0.82, 1.61)	0.419
Clopidogrel				
Pre-admission	1.75 (0.89, 3.45)	0.104	1.12 (0.83, 1.51))	0.466
Initiation	1.31 (0.81, 2.10)	0.271	1.10 (0.88, 1.38)	0.399
Continuation at 6 months	1.02 (0.33, 3.13)	0.978	1.20 (0.80, 1.80)	0.374
Ticagrelor				
Pre-admission	-	0.979	-	0.922
Initiation	0.15 (0.09, 0.26)	<0.001	0.66 (0.51, 0.85)	0.001
Continuation at 6 months	0.73 (0.24, 2.24)	0.585	0.86 (0.46, 1.61)	0.644
Mineralocorticoid Receptor Antagonists (MRA)				
Pre-admission	2.16 (0.53, 8.84)	0.285	2.32 (1.46, 3.68)	<0.001
Initiation	1.21 (0.61, 2.43)	0.586	1.22 (0.80, 1.86)	0.352
Continuation at 6 months	1.33 (0.31, 5.79)	0.702	1.11 (0.52, 2.39)	0.779
Oral Anticoagulants (OAC)				
Pre-admission	1.78 (0.72, 4.41)	0.215	1.39 (1.03, 1.89)	0.034
Initiation	1.10 (0.50, 2.40)	0.811	0.86 (0.61, 1.20)	0.368
Continuation at 6 months	0.65 (0.09, 4.88)	0.675	1.05 (0.63, 1.74)	0.861
Combinations				
Single anti-platelet therapy (SAPT)				
Pre-admission	1.80 (1.16, 2.81)	0.009	1.30 (1.05, 1.61)	0.014
Initiation	0.27 (0.18, 0.43)	<0.001	0.65 (0.52, 0.82)	<0.001
Continuation at 6 months	0.63 (0.26, 1.56)	0.319	1.07 (0.75, 1.51)	0.717
Dual anti-platelet therapy (DAPT)				
Pre-admission	1.27 (0.31, 5.19)	0.736	1.40 (0.92, 2.11)	0.115
Initiation	0.23 (0.15, 0.35)	<0.001	0.74 (0.60, 0.91)	0.005
Continuation at 6 months	0.63 (0.23, 1.75)	0.375	1.30 (0.86, 1.97)	0.208
OAC or SAPT				
Pre-admission	1.92 (1.24, 2.98)	0.004	1.54 (1.23, 1.94)	<0.001
Initiation	0.29 (0.18, 0.45)	<0.001	0.60 (0.47, 0.77)	<0.001
Continuation at 6 months	0.57 (0.23, 1.42)	0.228	1.18 (0.81, 1.72)	0.384
3 or more recommended medications				
3 or more pre-admission	1.66 (1.01, 2.72)	0.044	1.22 (0.99, 1.50)	0.065
Initiated 3 or more	0.25 (0.16, 0.38)	<0.001	0.53 (0.43, 0.66)	<0.001
Discontinuation of all medication after 90 days	2.92 (1.36, 6.30)	0.006	2.29 (1.57, 3.34)	<0.001
Discontinuation of all medication after 6 months	4.76 (1.69, 13.39)	0.003	4.03 (2.72, 5.96)	<0.001

***Include those that are alive at the follow up points.**

3.4 Discussions

3.4.1 Mortality

3.4.1.1 Summary

Overall, the risk of death at 1 year after admission to hospital differs by SIMD group within STEMI patients but not in non-STEMI patients, and there is no distinct linear trend within the SIMD quintiles. The increased risk of death in Q1, Q3, and Q4 compared to the least deprived Q5 is independent of age, sex, baseline comorbidities and PCI use, but may be mostly attributed to differences in prescription uptake. After also accounting for differences in prescriptions, excess mortality only remains in the most deprived patients compared to the least deprived quintile. Therefore, equal access to medication use could possibly have eliminated excess mortality between quintiles 2-5. This finding is in agreement with studies from Finland (Salomaa et al., 2001), Sweden (Wilhelmsen and Rosengren, 1996), and England (Greenwood et al., 1995a), which suggested less efficient secondary prevention as a contributing factor for worse one-year prognosis.

3.4.1.2 Discussion

Since in-hospital quality of care measures (such as call to balloon times etc.) did not differ between SIMD groups, other unmeasured risk factors that contribute to unequal mortality between patients residing in the most and least socioeconomically disadvantaged quintiles are at play.

Differences in survival may reflect higher prevalence of risk factors in the most deprived group that have not been considered. Modifiable behavioural risk factors such as BMI, smoking status, alcohol consumption and physical activity were not available. Quite a few studies have consistently found that among ACS patients, more socio-economically deprived patients exhibited less healthy lifestyle habits at baseline and lower propensities to modify to healthier behaviours after ACS diagnosis; such as more years of smoking (Notara et al., 2016b, Chan et al., 2008), more had failed to quit smoking and alcohol (Chan et al., 2008, Kotseva et al., 2009a, Tang et al., 2013), and are less physically active

(Gerber et al., 2011, Chan et al., 2008, Pitsavos et al., 2008, Ejlersen et al., 2017, Notara et al., 2016b) or made dietary modifications (Chan et al., 2008, Chow et al., 2010). In Scotland, alcohol-related hospital admission rates were 4 times higher in the most deprived areas compared to the least deprived in 2018 (Scottish Government, 2020).

Although there is no difference in call to balloon times between SES groups, the literature review also saw evidence of a delay in onset of symptoms to medical presence with low SES compared with high SES as a possible explanation for differences in case-fatality (Gibler et al., 2002, Heo et al., 2015, Park et al., 2012, Smolderen et al., 2010, Austin et al., 2014, Fournier et al., 2013a). The possibility of deprived patients suffering from greater risk of procedure-related complications and less frequent use of medication during PCI has been suggested but were not found (Schmucker et al., 2017, Jones et al., 2015, Biswas et al., 2019). However, procedure related differences warrant further attention as it has not been studied in detail in the UK.

Psychosocial factors such as stress have also been suggested as alternative risk factors (Tonne et al., 2005). It has widely been acknowledged by the ß-Blocker Heart Attack Trial that MI participants classified as being socially isolated and having a high degree of life stress had more than four times the risk of death of those with low levels of both stress and isolation three years post-MI (Ruberman et al., 1984). The study also found education to be inversely associated with stress and social isolation. More recent data suggest that on the contrary, socially & economically advantaged groups tend to be employed in more strenuous and demanding positions with less time to participate in outdoor recreational activities and therefore are at an increased risk of obesity and smoking (Notara et al., 2016b, Tsai, 2012). Combined, might explain the S-shaped association between prognosis and SES in STEMI patients, with the most (Q1) and lower-intermediate (Q3-Q4) deprived groups negatively affected by lifestyle- and psychosocial-related factors.

Although these factors could not be included in the analysis of this study, it is still worthy to keep in mind that health behaviours are major contributors of socioeconomic differences in health; while behaviours are heavily impacted by

culture norms as well (Yusuf et al., 2001, Stringhini et al., 2011). Therefore promoting a healthier lifestyle is a difficult long-term project with a need to shift culture norms.

It has been suggested that there may be a social class gradient in the ability to heal, as well as higher likelihood of death from illnesses in more socio-economically disadvantaged groups. In Glasgow for example, recovery from various surgical procedures for cancer is worse among people who are deprived after adjustment for stage of disease and treatment (Carnon et al., 1994). There are also significant social gradients for alcohol-specific mortality and all-cause mortality in the general population of Scotland (Scottish Government, 2020). Therefore, compared to the general population and other disease populations, the problem of health and healthcare inequalities is actually much better in those with ACS.

Using area-level measures of socioeconomic position inevitably leads to some misclassification of SES and may bias the results towards the null (Salomaa et al., 2001, McLoone and Ellaway, 1999). The intermediate quintiles likely contain a mixture of deprived and less deprived households, whereas comparing the most vs the least deprived quintiles better indicate the effect of SES as the extreme quintiles are “purer”. It has been suggested by the Scottish Government Office of the Chief Statistician and Performance that analysis focusing on the most deprived group would be appropriate (Scottish Government, 2013b) as the index works best at the most deprived end, and levels of deprivation drop off quite rapidly in the other groups (Scottish Government, 2013a), i.e. the differences in level of deprivation between the SIMD Q2-Q5 is very small. Therefore, it is not a surprise to see the highest mortality rate in SIMD Q1 and non-significant differences in mortality rates between Q2 to Q5 after adjusting for possible baseline risk factors.

Compared to the Glaswegian population 30 years ago, when SES was defined by the Carstairs and Morris deprivation score, there was no SES difference in 28-day case fatality after MI in the northern Glasgow MONICA coronary event register 1985-1991 (Morrison et al., 1997). Although it is possible that the inequality gap has indeed increased over the years, the inequalities seen in this study is also

possibly related to how SES is measured differently. Government reports show that the mortality gap between the most and least deprived areas, when defined by SIMD, exist not just for CHD, but for many other health indicators (Scottish Government, 2020). Since the Carstairs index is comprised of four indicators that represent material disadvantage (lack of car ownership, low occupational social class, overcrowded households and male unemployment) (Public Health Scotland, 2020), theoretically, this also support the notion that we should work on the different domains between SIMD index and the Carstaris index that may be the actual reason for inequalities but has been reflected as differences between SIMD and mortality.

It is possible that one or more of the social determinants of SIMD, including education, health, crime or geographical indicators, is taking its toll on the survival of the most deprived group. We should continue to make improvements to social exclusion issues that communities in SIMD Q1 embodies (i.e. the reasons why SIMD Q1 are the most deprived group, the specific challenges/domains reflected in the SIMD measure). Solving any public health inequality issues associated with SES may ultimately come down to closing the upstream socioeconomic gaps within society.

Finally, the number of ACS patients in the most deprived group is 3 times the number of other SES quintiles. This is comparable to the distribution of Glasgow's SIMD data zones (48%, 16%, 15%, 11% vs 10%): the national share of the most deprived group is highest in Glasgow. Regardless of any differences or the lack of differences in mortality in ACS patients, it is still important to decrease the SES gap measured by the SIMD index. The differences in mortality in ACS patients offers yet another reason for continued work in the most deprived areas. Any improvements made in Glasgow will benefit the whole of Scotland as well.

3.4.2 Comorbidities

3.4.2.1 Direct relationship with SES and mortality

According to the British Cardiovascular Intervention Society, although adverse outcomes will depend on the quality of care given and the timeliness of

treatment, the biggest predictor of mortality is how sick a patient is when they are treated, and almost invariably, a fatal outcome is a result of the patient's underlying disease, rather than due to the treatment one receives (Ludman et al., 2017).

The prevalence of most prognostic comorbidities did not differ by the SES group except for diabetes, dementia and chronic pulmonary disease in the ACS patients studied. Dementia was the only comorbidity to correlate with crude 1-year mortality rates (Q2 and Q5 has the lowest mortality rate and lowest prevalence of dementia). While only diabetes and CPD were clearly more common the in most deprived group. It is well established that diabetic MI patients have higher case fatality than the non-diabetic ones (Miettinen et al., 1998). Accordingly, the greater prevalence of diabetes may have contributed to higher crude mortality rates in the most deprived group.

3.4.2.2 As a confounder in the relationship between SES and outcomes

Risk adjusted analysis attempts to account for the differences in how sick patients are at admission, so that what remains of the variation in outcomes between SES groups might be explained by the care received. Accordingly, comorbidities are adjusted for whenever possible in the analyses. In general, despite the differences in comorbidities, patients' SES still independently predicted the 1-year prognosis of STEMI patients, suggesting that other factors, such as aforementioned unmeasured lifestyle choices, or disparities in treatment which are further investigated must explain this relationship. In addition, disparities in the distribution of comorbidities by SES level did not affect the significant association of SES with the provision of PCI in NSTEMI patients. However, it is possible the accumulation of multi-morbidities had effects on the outcomes of interest but cannot be accounted for.

3.4.3 Within hospital treatment measures

The present study is the only known cohort study that have investigated the relationship between SES and quality of disease management among ACS patients in Scotland.

3.4.3.1 STEMI

The Glasgow G&CC National Health Service is generally delivering equitable in-hospital cardiovascular treatment in STEMI patients regardless of SIMD deprivation group. Although there is some evidence that the rate of coronary angiogram (CAG) is higher in the most deprived group (OR 1.58 CI 1.02-2.45) compared to the least deprived group but the strict criteria and clear guidelines for the use of PCI eliminates any inequalities subsequent a CAG. NICE guidelines (QS68) recommend that STEMI patients receive PCI within 90 minutes from arrival at the PCI hospital. Compared to PCI hospitals across the UK, the GJH has the highest performance in terms of this criteria: almost 100% (Ludman et al., 2017).

3.4.3.2 NSTEMI

In non-STEMI patients, deprivation was an independent predictor of both CAG and PCI. Similar to most other studies detailed in the literature review, especially in hospitalised angina patients where invasive treatment is less urgent and more discretionary (compared to STEMI patients where guidelines for treatment are relatively well established) (Korda et al., 2009), patients living in the most deprived areas were less likely to receive CAG [adjusted OR 0.63, CI 0.52–0.75] and PCI [adjusted OR 0.67, CI 0.56–0.81] than the least deprived areas. The social gradient was not linear but S-shaped in non-STEMI patients, where SES Q1, Q2, Q4, but not Q3 were less likely to receive invasive care compared to Q5. In part this may be attributable to the difference in the type of hospital where the patient was initially admitted to. Those residing in more deprived areas were more often admitted to a local hospital first instead of the catheter lab directly and an investigation of service delivery by admission method found a similar S-shaped trend for patients with emergency admission to local hospital first but not for other admission methods. In other words, unequal use of CAG and PCI in particular SIMD groups were only seen among patients first admitted to local hospitals that do not provide these services on-site. On a higher level, patients first admitted to local hospitals were less inclined to be investigated and treated with invasive strategies after ACS compared to patients first admitted to hospitals that perform them on-site in general. Therefore, focusing on this particular admission group (those admitted to local hospital

first) and auditing local hospitals' performance in referring patients for invasive treatment should be noted as potential steps to advance care in ACS patients. These actions not only correct unequal treatment in non-STEMI patients, but also improve the overall prognosis for all non-STEMI patients.

The findings are consistent with the inverse equity hypothesis, which predicts that inequalities will appear when there is still a relatively low rate of use in the population (as in non-STEMI patients and in earlier studies where PCI were not used widely where the relatively 'well off' likely benefit with more marginal gains (Korda et al., 2009, Khaykin et al., 2002)), but will decrease as the intervention becomes more commonly used (as in STEMI patients, and with more recent data where PCI rates are high and recommended for management of all ACS types).

3.4.4 Secondary prevention

The overall use of medications with proven effect in secondary prevention is either higher than or comparable to previous studies in Scotland (Simpson et al., 2005), England (Hawkins et al., 2013) and other European countries (Kotseva et al., 2009b) with over 85% STEMI patients prescribed with 3 or more recommended drugs and 75% for non-STEMI at discharge. The slight decreasing trend in crude rates of secondary prevention therapy for patients less deprived might be reflective of the baseline need innate in the SIMD groups (trend for Q1-Q4). However, there were no difference between the most and least deprived SIMD quintiles (Q1 vs Q5) both before and after adjusting for confounding variables. In those that were prescribed with secondary medications after discharge, continuation at follow up times were usually not different between SIMD groups in STEMI patients and higher in the most deprived group in non-STEMI patients. Compared to other countries such as Finland (Salomaa et al., 2001) and the USA (Rathore et al., 2000, Bernheim et al., 2007) which saw consistently less prescriptions for patients of lower income. In Scotland, prescriptions have been free since April 2011. Thus, there is no surprise that we have achieved more equitable prescription rates across SES as the economic obstacles for obtaining necessary medications have been abolished.

In 14 435 Scottish primary care patients diagnosed with CHD from 1997 to 2002, the adjusted prevalence of receiving secondary preventive treatment at least once by year was unaffected by Carstairs deprivation quintile for all but statins in most years (Simpson et al., 2005). Although quite different in study set-up, these results are somewhat comparable with the continuation rates after discharge in this study. This analysis builds on this report, with more specific follow up times for each patient and accounting for severity of CHD through subgroup analysis. Similarly, little inequality is seen in similar healthcare systems where prescriptions for acute MI are either free (e.g. Italy (Cesana et al., 2001)) or largely subsidized (England: (Hawkins et al., 2013, Barakat et al., 2001) and France (Lang et al., 1998)).

It has been stated that participation in secondary prevention programs depends mainly on financial constraints (Notara et al., 2015). Since this is no longer an issue in Scotland, better compliance in the most deprived group in NSTEMI patients, reflected in higher prescription rates at 6 months and 1 year after discharge, is not as surprising. Something else contrary to financial constraints are at play and needs more investigation to aim for equal high participation in secondary prevention across all groups. In Scotland, NHS Boards have health promotion programmes (e.g. Health Promoting Health Service) that are sensitive to inequalities based on social deprivation. It could be that the most deprived group had benefited from these health promoting approaches and extra attention that we neglected less deprived groups.

3.4.5 Limitations

By using the newly built ACS registry and national registers, this is a comprehensive study of multiple risk factors, treatment in hospitals and secondary care measures in all ACS patients of GG&C (2013-2016) using a validated index of deprivation. Given the geographic scale and complexity of this regional secondary care network, observational research had not previously been possible. Despite this study being sufficiently large in size and detailed in nature, limitations of this study, other than the ones mentioned before (e.g. lack of data on unhealthy lifestyle habits, one of the main prognostic factors), should be acknowledged in order to better interpret the results.

The Scottish Index of Multiple Deprivation (SIMD) is produced and used by the Scottish Government to identify deprived areas in Scotland. The SIMD provides a relative measure of multiple deprivation, including indicators relating to not just material deprivation, but also social exclusion, and lack or access to resources. The SIMD score has been criticised for its complexity and for not relating to individual-levels but to geographical areas. Therefore, all the limitations of using area-level deprivation index applies (refer to discussion section in literature review chapter).

Touched on earlier is that areas are not internally homogenous: populations containing a mixture of deprived and less deprived households are likely to have middle ranking scores. Therefore, the SES effects are more likely to be underestimated (McLoone and Ellaway, 1999). As suggested by the Scottish government, in this study, comparisons are made between the most deprived end and the least wherever possible (Scottish Government, 2013b).

When looking at SIMD's association with mortality in cox-proportional hazard regressions, non-proportional hazards were detected in the SIMD Q2 group in STEMI patients and SIMD Q1 group in non-STEMI patients using the supremum test and check of the KM survival function. Since only one quintile violated the proportional hazards assumption, this non-proportionality is ignored. However, this does add to the conclusion that SES's association on mortality is not consistent over time and there is no associated linear trend within the SIMD quintiles. The only consistent outcome was that the least deprived (Q5) quintile consistently has one of the best outcomes.

As stated by ISD Scotland (Geography Population and Deprivation Team, 2020), one theoretical criticism of SIMD is that because it includes a health domain, its use to study deprivation patterns in health is invalid because the SIMD and the health indicator being studied are not independent of each other. However, the health domain is weighted to account for a relatively small part of the overall SIMD (14% of SIMD 2012), and analyses of health inequalities using SIMD 2004 were found to give similar results whether the health domain was included or excluded, because that domain was so highly correlated with the overall index.

Therefore, ISD Scotland's advice to analysts is that the full SIMD may be used for analysing health data.

In addition, the SIMD identifies deprived areas, not deprived individuals. Therefore, it is important to avoid the "ecological fallacy" when interpreting the statistical results. Ecological fallacy results from the false assumption that inferences about the nature of individuals can be deduced from inferences about the group to which those individuals belong. The SIMD's association with health outcomes and treatment may be explained by both an individual's personal experience of deprivation, and/or the effect of living in a deprived area. However, composite measures correlate reasonably with individual socioeconomic position (Leyland, 2005) and remains useful in capturing the contextual effects of living conditions (Hawkins et al., 2013) and identifying groups living in areas of greater need for support and intervention.

It is possible to dive deeper into inequalities analyses by looking at the individual deprivation domains and subdomains that makes up the SIMD measure. Although not all indicators have been published (mainly due to confidentiality rules), a variety of measures could be analysed further. In particularly, since this study found differences between SES and prescription rates, further analysis may look at the association between secondary prevention rates and drive time to GP, or the association between prescription rates and public transport travel time to retail centre. The SIMD measure provides a rich source of data for analyses as it is made up of 7 domains and 35 subdomains. Ultimately, helping policy makers to target improvements not just in the correct areas but also the specific cause of problems.

3.5 Conclusion

Recognising and tackling socioeconomic inequalities in health has long been emphasized by both the UK and Scottish government (Scottish Government, 2020). In this study of GG&C patients hospitalised with ACS, one-year prognosis varied by socioeconomic position in STEMI patients but not non-STEMI patients. Differences between the intermediate and least deprived groups can be attributed to differences in prescription rates of secondary prevention therapy;

data suggested that the use of medications with proven efficacy was not equal in different socioeconomic groups, especially lower in those residing in intermediate-deprived areas. Combined with the reassuring evidence that in-hospital cardiovascular care was equitable and of high standard regardless of SIMD deprivation group, the difference in prognosis between the most and least deprived STEMI patients irrespective of clinical characteristics and medication can only be explained by other unmeasured factors. This study represents a success for the hospital management of STEMI but there is no room for complacency. Continuation of high performance within hospitals and correcting the differences in secondary prevention treatment should be the first steps towards the reduction of excess case fatality due to socioeconomic disparities.

The burden of ACS is very high. It is estimated that the 1 year case-fatality rate is 11%, causing around 66,000 deaths in the UK each year (British Heart Foundation, 2018a). But it is important to not forget that like all other public health issues and socio-economic inequality issues, primary prevention and aiming to improve public goods/infrastructure reflected in the SIMD indicators (i.e. geographical access, education) may carry even more and wider benefits. In light of the possible coming of one of the greatest economic crisis in modern times due to COVID-19 pandemic, we potentially face more extreme socioeconomic inequalities and instabilities. In addition to the pursuit of cost-effective health services: and prevention is always more cost-effective than treatment to the public health system in the long term; emphasis should be placed on resisting widening deprivation gaps, strategically developing deprived areas and achieve regional balance in the SIMD dimensions. This would stimulate growth and be of benefit in many aspects: socially, economically and therefore positively influence the population’s health and wellbeing in the long term.

Chapter 4 Mind the gap 2: Healthcare disparities for women hospitalised with acute coronary syndrome

4.1 Introduction

Ischaemic heart disease persists as the leading global cause of death (Collaborators, 2018). Myocardial infarction (MI) accounts for a large proportion of death due to cardiovascular disease. Between 2007 and 2016, age-sex standardised mortality for MI in Scotland has fallen by 42.5% from 129 to 74 per 100,000 population (NHS Health Scotland Information Services Division, 2018b) – a trend also apparent in other countries (Dudas et al., 2012, Yeh et al., 2010). Despite improvements in survival, considerable disparities exist according to sex in terms of delivery of guideline-recommended treatments and outcomes following MI suggesting women may be disadvantaged (Wilkinson et al., 2019).

Use of high-sensitivity troponin assays with sex-specific thresholds increases the detection of MI in women (Shah et al., 2015). However, women are less likely to undergo percutaneous coronary revascularisation (PCI) and are more often subject to underutilisation of evidence-based secondary preventative pharmacotherapy (Wilkinson et al., 2019, Hvelplund et al., 2010, Bugiardini et al., 2011). Differences in adoption of invasive management may, in part, be explained by a perception held by clinicians and patients that outcomes are worse for women receiving PCI, as well as differences in symptoms and baseline risk profile which may impact clinical decision-making (Jacobs et al., 2002). Adverse events post-MI, including cardiogenic shock, heart failure and death, remain more common in women than in men, most notably in those with ST-elevation myocardial infarction (STEMI) (Velders et al., 2013, Lam et al., 2015). Whether sex remains an independent predictor of adverse events despite adjustments for the higher risk-profile of women, notably age, is less clear.

We hypothesised that sex-related differences in demographics and comorbidity underpin disparities in management and outcomes of women and men hospitalised with MI or angina. We investigated this hypothesis by analysis of a contemporary secondary care electronic registry (e-Registry) using electronic

patient records (EPRs) for patients admitted to a complex regional healthcare network (Findlay et al., 2018a).

4.2 Methods

4.2.1 Setting

Seven acute hospitals in the National Health Service (NHS) in Glasgow and the West of Scotland provide a complex healthcare system serving a population of approximately 1.2 million. The Golden Jubilee National Hospital is a regional cardiothoracic centre that provides invasive cardiology services for this population. EPRs were implemented across all secondary care clinical and administration systems in NHS Greater Glasgow and Clyde (GGC) and the Golden Jubilee National Hospital by June 2012 enabling capture of key components of hospital care. These EPRs have been combined into an e-Registry for quality improvement and research (Findlay et al., 2018a).

The Information Services Division is part of NHS National Services Scotland and holds a range of health-related administrative data, including information relating to medicines dispensed in the community within its Prescribing Information System (PIS) database, morbidity collected from all hospital admissions in the Scottish Morbidity Record 01 (SMR01) database and all deaths registered by National Records of Scotland (NRS). Once data were extracted, identifiers were removed and replaced with a pseudonymous identifier. The research team accessed these pseudonymised datasets within a Safe Haven analytical platform (NHS Greater Glasgow and Clyde Safe Haven).

4.2.2 Design and methodology

Data were extracted from EPRs for all admissions (01/10/13-30/06/16) with an International Statistical Classification of Diseases (ICD-10) diagnosis of angina (I200-I209), MI (I210-I229), other ischaemic heart disease (I240-I249), or heart failure (I50) to ensure complete capture of events. Data were deposited within an existing repository for electronic health data and linked to electronic referrals for cardiovascular procedures performed in the invasive centre. An executable system was developed to identify, link and classify these records into episodes of care as

detailed in a previous project (Findlay et al., 2018a). Patients with a final diagnosis of MI or angina were isolated and linked to PIS prescribing data, SMR01 data for comorbidities and mortality data from NRS. This linked dataset was analysed to look at patient characteristics, invasive cardiovascular procedures, service delivery metrics, drug treatment and mortality. The pre-specified primary outcomes were 30 day and 1 year all-cause mortality (from date of admission). The receipt of cardiac interventions and medical therapy at discharge, 6 months and 1 year post-discharge were the pre-specified secondary outcomes.

4.2.3 Statistical analysis

Baseline characteristics were described using means with standard deviations, total numbers with percentages, or medians with interquartile ranges. Where all patients were analysed, this included unspecified MI. Comparisons between men and women were made using appropriate statistical tests (t-test/Mann-Whitney/chi-squared/Fisher's exact). Deprivation status was identified based on home postcode and measured using quintiles of the Scottish Index of Multiple Deprivation (SIMD) 2012 measure (Scottish Government, 2016b). Quintile 1 represents the highest level of deprivation with quintile 5 representing the least deprived. The top 20% most deprived data zones in Scotland are in quintile 1, and the distribution of Glasgow's data zones is 49%, 19%, 13%, 10.5%, 8.5% (Q1-Q5)(Scottish Government, 2012). A Charlson comorbidity score was derived using standard procedures and ICD-10 codes included the hospital admission records (Quan et al., 2005). Pre-admission medical therapy and medical therapy at discharge were defined as fulfilment of prescription within 90 days pre-admission and post-discharge, respectively. Medical therapy at 6 months and at 1 year were defined as fulfilment of prescription at 6 months or 1 year post-discharge +/- 45 days.

To analyse the relationship between sex and medical treatment, three analyses using mixed effects logistic models were performed for each drug and drug combination: (1) for patients alive at discharge, fulfilling a prescription claim within 90 days of discharge, (2) for patients discharged with treatment and alive at 6 months post-discharge, fulfilling a prescription claim at 6 months post-discharge, (3) for patients discharged with treatment and alive at 1 year post-

discharge, fulfilling a prescription claim at 1 year post-discharge. Analyses were adjusted for age, SIMD, use of the respective drug within 90 days pre-admission, comorbidities and PCI. Furthermore, we adjusted for clustering at the discharge hospital level. When analysing the association of sex with use of drug combinations, pre-admission drug use was not adjusted for. Multivariable logistic regression was used to evaluate the association of sex and baseline factors with invasive management. Predictors of invasive management between men and women were assessed separately to detect any sex differences in comorbidities' association with invasive management. Any differences in predictors of invasive management were then confirmed by adding an interaction term with gender in the entire population. Cox proportional hazards regression was used to evaluate the association of sex with all-cause mortality by ACS diagnosis. The proportional hazard assumption for sex were assessed by adding time - dependent sex to the original models. Analyses were conducted using SAS Enterprise Guide (v5.1).

4.3 Results

4.3.1 Baseline characteristics

There were 7878 patients admitted with MI or angina between 1 October 2013 and 30 June 2016, including 3161 (40.1%) women (Table 4-1). Diagnosis of STEMI was made in 2042 (25.9%) patients, non-ST-elevation myocardial infarction (NSTEMI) in 3957 (50.2%) patients, hospitalised angina in 1425 (18.1%) patients, and in 454 (5.8%) patients the MI type was unspecified. Women were older than men (69.7 years vs 64.0 years, p<0.001) and were relatively more deprived (75.7% vs 72.5% in SIMD Q1-3, p=0.002). Diagnosis of STEMI was less common in women than men (20.3% vs 29.7%, p<0.001), but women had a higher proportion of NSTEMI (51.7% vs 49.2%, p <0.001) and hospitalised angina (21.4% vs 15.9%, p<0.001). Comorbidity differed according to sex both in terms of higher Charlson scores and an increased proportion of individual comorbid diseases in women, who more frequently had hypertension, atrial fibrillation, renal failure, respiratory disease, cerebrovascular disease, stroke, heart failure, dementia and depression. Compared to men, women were more often treated with statins (46.9% vs 43.2%, p=0.001), beta-blockers (34.9% vs 30.5%, p<0.001) and anticoagulants or antiplatelets (48.5% vs 42.1%, p<0.001) pre-admission.

Table 4-1. Baseline demographics and management for all patients according to sex

	All n=7878	Men n=4717	Women n=3161	P-value
Mean age ± SD - years	66.3 ± 13.7	64.0 ± 13.0	69.7 ± 13.9	<0.001
SIMD quintile - N(%)				<0.001
1 (most deprived)	3265 (41.5)	1865 (39.5)	1400 (44.3)	0.002*
2	1418 (18.0)	833 (17.7)	585 (18.5)	
3	1126 (14.3)	720 (15.3)	406 (12.8)	
4	993 (12.6)	623 (13.2)	370 (11.7)	
5	1074 (13.6)	675 (14.3)	399 (12.6)	
Diagnosis - N(%)				<0.001
STEMI	2042 (25.9)	1399 (29.7)	643 (20.3)	
NSTEMI	3957 (50.2)	2322 (49.2)	1635 (51.7)	
HA	1425 (18.1)	749 (15.9)	676 (21.4)	
Unspecified MI	454 (5.8)	247 (5.2)	207 (6.5)	
Comorbidities - N(%)				
Hypertension	1920 (24.4)	986 (20.9)	934 (29.5)	<0.001
Diabetes	1172 (14.9)	672 (14.2)	500 (15.8)	0.0547
Atrial fibrillation	822 (10.4)	431 (9.1)	391 (12.4)	<0.001
Renal failure	836 (10.6)	416 (8.8)	420 (13.3)	<0.001
Respiratory disease	1186 (15.1)	579 (12.3)	607 (19.2)	<0.001
Cerebrovascular disease	511 (6.5)	253 (5.4)	258 (8.2)	<0.001
Peripheral vascular disease	572 (7.3)	340 (7.2)	232 (7.3)	0.826
Heart failure	794 (10.1)	442 (9.4)	352 (11.1)	0.011
Previous MI	1571 (19.9)	967 (20.5)	604 (19.1)	0.130
Dementia	152 (1.9)	63 (1.3)	89 (2.8)	<0.001
Depression	165 (2.1)	68 (1.4)	97 (3.1)	<0.001
Charlson score				<0.001
0	4322 (54.9)	2701 (57.3)	1621 (51.3)	
1-3	2979 (37.8)	1708 (36.2)	1271 (40.2)	
≥4	577 (7.3)	308 (6.5)	269 (8.5)	
Pre-admission medical therapy - N(%)				
Statin	3523 (44.7)	2040 (43.2)	1483 (46.9)	0.001
ACE inhibitor or ARB	2739 (34.8)	1612 (34.2)	1127 (35.7)	0.177
Beta-blocker	2542 (32.3)	1440 (30.5)	1102(34.9)	<0.001
Antiplatelet				
Aspirin	2595 (32.9)	1524 (32.3)	1071 (33.9)	0.145
Clopidogrel	743 (9.4)	381 (8.1)	362 (11.5)	<0.001
Ticagrelor	110 (1.5)	66 (1.4)	52 (1.6)	0.379
Any APT	3134 (39.8)	1792 (38.0)	1342 (42.5)	<0.001
DAPT	312 (4.0)	173 (3.7)	139 (4.4)	0.104
MRA	145 (1.8)	86 (1.8)	59 (1.9)	0.889
Anticoagulant				
Warfarin	340 (4.3)	175 (3.7)	165 (5.2)	0.001
Any anticoagulant	463 (5.9)	239 (4.9)	224 (7.1)	<0.001
Combined therapy				
Anticoagulant or APT	3517 (44.6)	1984 (42.1)	1533 (48.5)	<0.001
Anticoagulant or DAPT	770 (9.8)	407 (8.6)	363 (11.5)	<0.001
Anticoagulant or anticoagulant + APT	463 (5.9)	239 (5.1)	224 (7.1)	<0.001
≥3 medications	2488 (31.6)	1483 (31.4)	1005 (31.8)	0.740
Type of admission - N(%)				
Emergency to invasive centre	1473 (18.7)	1035 (21.9)	438 (13.9)	<0.001
Non-emergency to invasive centre	997 (12.7)	636 (13.5)	361 (11.4)	0.007
Emergency to local hospital	4986 (63.3)	2783 (59.0)	2203 (69.7)	<0.001
Non-emergency to local hospital	422 (5.4)	263 (5.6)	159 (5.0)	0.292
Coronary angiography - N(%)				
All	4866 (61.8)	3219 (68.2)	1647 (52.1)	<0.001
PCI	3149 (40.0) (64.7)**	2192 (46.5) (68.1)**	957 (30.3) (58.1)**	<0.001 <0.001
Median length of stay (IQR) - days	4 (2-7)	4 (2-7)	5 (2-8)	<0.001

*** P-value for SIMD Q1-Q3 vs Q4-Q5**

**** Those who had PCI as a proportion of those who underwent coronary angiography**

4.3.2 Invasive management

Approximately 16% fewer women than men underwent coronary angiography (52.1% vs 68.2%, p<0.001) and PCI (30.3% vs 46.5%, p<0.001) (Table 4-1). Amongst those who had a coronary angiogram, women received PCI 10% less frequently than men (58.1% vs 68.1%, p<0.001). The difference in median duration of hospital stay was 1 day (5 days for women vs 4 days for men, p<0.001). In patients with STEMI, 6.2% fewer women than men were transferred for immediate invasive management (63.6% vs 69.8%, p=0.012) and the median door-to-balloon time was longer for women (23mins vs 21mins, p<0.001) (Table 4-2). We also examined the effect of age on door-to-balloon time; in those above 65 years, the median time was 3 minutes longer for women than for men (24mins vs 21mins, p<0.001), whereas no difference existed in those under 65 years (21mins vs 21mins, p=0.229).

The sex differences in demographic characteristics were similar for patients with STEMI and NSTEMI (Table 4-2 and Table 4-3). In patients hospitalised with angina, there were fewer differences although women were older and less frequently received invasive management (Table 4-4).

Table 4-2. Baseline demographics and management for STEMI patients according to sex

	All n=2042	Men n=1399	Women n=643	P-value
Mean age ± SD - years	62.7 ± 13.8	60.5 ± 12.8	67.3 ± 14.7	<0.001
SIMD quintile - N(%)				0.027
1 (most deprived)	849 (41.6)	553 (39.6)	296 (46.0)	
2	368 (18.0)	248 (17.7)	120 (18.7)	
3	324 (15.9)	237 (17.0)	87 (13.5)	
4	234 (11.5)	171 (12.2)	63 (9.8)	
5	266 (13.0)	189 (13.5)	77 (12.0)	
Comorbidities - N(%)				
Hypertension	283 (13.9)	173 (12.4)	110 (17.1)	0.004
Diabetes	166 (8.1)	107 (7.6)	59 (9.2)	0.241
Atrial fibrillation	102 (5.0)	68 (4.9)	34 (5.3)	0.681
Renal failure	109 (5.3)	61 (4.4)	48 (7.5)	0.004
Respiratory disease	200 (9.8)	112 (8.0)	88 (13.7)	<0.001
Cerebrovascular disease	80 (3.9)	47 (3.4)	33 (5.1)	0.055
Peripheral vascular disease	93 (4.6)	60 (4.3)	33 (5.1)	0.396
Heart failure	80 (3.9)	48 (3.4)	32 (5.0)	0.095
Previous MI	223 (10.9)	157 (11.2)	66 (10.3)	0.519
Dementia	30 (1.5)	13 (0.9)	17 (2.6)	0.003
Depression	32 (1.6)	14 (1.0)	18 (2.8)	0.002
Charlson score				0.001
0	1398 (68.5)	993 (71.0)	405 (63.0)	
1-3	566 (27.7)	360 (25.7)	206 (32.0)	
≥4	78 (3.8)	46 (3.3)	32 (5.0)	
Pre-admission medical therapy - N(%)				
Statin	559 (27.4)	370 (26.4)	189 (29.4)	0.166
ACE inhibitor or ARB	432 (22.6)	309 (22.1)	153 (23.8)	0.392
Beta-blocker	355 (17.4)	234 (16.7)	121 (18.8)	0.247
Antiplatelet				
Aspirin	354 (17.3)	238 (17.0)	116 (18.0)	0.569
Clopidogrel	102 (5.0)	51 (3.6)	51 (7.9)	<0.001
Ticagrelor	9 (0.4)	<9	<9	0.549
Any APT	436 (21.4)	276 (19.7)	160 (24.9)	0.008
DAPT	28 (1.4)	19 (1.4)	9 (1.4)	0.940
MRA	18 (0.9)	<18	<18	0.174
Anticoagulant				
Warfarin	36 (1.8)	19 (1.4)	17 (2.6)	0.040
Any anticoagulant	50 (2.4)	29 (2.1)	21 (3.3)	0.105
Combined therapy				
Anticoagulant or APT	479 (23.5)	299 (21.4)	180 (28.0)	0.001
Anticoagulant or DAPT	76 (3.7)	46 (3.3)	30 (4.7)	0.127
Anticoagulant or anticoagulant + APT	50 (2.4)	29 (2.1)	21 (3.3)	0.105
≥3 medications	293 (14.3)	204 (14.6)	89 (13.8)	0.657
Type of admission - N(%)				
Emergency to invasive centre	1386 (67.9)	977 (69.8)	409 (63.6)	0.005
Non-emergency to invasive centre	139 (6.8)	91 (6.5)	48 (7.5)	0.424
Emergency to local hospital	410 (20.1)	255 (18.2)	155 (24.1)	0.002
Non-emergency to local hospital	107 (5.2)	76 (5.4)	31 (4.8)	0.565
Coronary angiography - N(%)				
All	1804 (88.3)	1266 (90.5)	538 (83.7)	<0.001
PCI	1586 (77.7) (87.9)*	1134 (81.1) (89.6)*	452 (70.3) (84.0)*	<0.001 0.001
Median length of stay (IQR) - days	4 (3-6)	4 (3-6)	5 (4-8)	<0.001
Median treatment time (IQR) - mins				
Call-to-door	73 (60-94)	72 (60-91)	75 (62-101)	0.104
Missing - no. (%)	733 (35.9)	534 (38.2)	199 (30.9)	
Call-to-balloon	96 (82-120)	95 (82-116)	99 (83-129)	0.090
Missing - no. (%)	795 (38.9)	568 (40.6)	227 (35.3)	
Door-to-balloon	21 (18-27)	21 (17-27)	23 (19-28)	<0.001

Missing – no. (%)	459 (22.5)	312 (22.3)	147 (22.9)	

*** Those who had PCI as a proportion of those who underwent coronary angiography**

Table 4-3. Baseline demographics and management for NSTEMI patients according to sex

	All n=3957	Men n=2322	Women n=1635	P-value
Mean age ± SD – years	67.0 ± 13.4	64.8 ± 13.7	70.0 ± 13.8	<0.001
SIMD quintile – N(%)				<0.001
1 (most deprived)	1572 (39.7)	877 (37.8)	695 (42.5)	
2	733 (18.5)	416 (17.9)	317 (19.4)	
3	555 (14.0)	357 (15.4)	198 (12.1)	
4	503 (12.7)	302 (13.0)	201 (12.3)	
5	593 (15.0)	370 (15.9)	223 (13.6)	
Comorbidities – N(%)				
Hypertension	1063 (26.9)	546 (23.5)	517 (31.6)	<0.001
Diabetes	672 (17.0)	388 (16.7)	284 (17.4)	0.586
Atrial fibrillation	439 (11.1)	225 (9.7)	214 (13.1)	0.001
Renal failure	468 (11.8)	230 (9.9)	238 (14.6)	<0.001
Respiratory disease	608 (15.4)	293 (12.6)	315 (19.3)	<0.001
Cerebrovascular disease	256 (6.5)	127 (5.5)	129 (7.9)	0.002
Peripheral vascular disease	289 (7.3)	168 (7.2)	121 (7.4)	0.844
Heart failure	458 (11.6)	245 (10.6)	213 (13.0)	0.017
Previous MI	892 (22.5)	534 (23.0)	358 (21.9)	0.414
Dementia	69 (1.7)	31 (1.3)	38 (2.3)	0.019
Depression	82 (2.1)	34 (1.5)	48 (2.9)	0.001
Charlson score				0.007
0	2037 (51.5)	1241 (53.4)	796 (48.7)	
1-3	1606 (40.6)	913 (39.3)	693 (42.4)	
≥4	314 (7.9)	168 (7.2)	146 (8.9)	
Pre-admission medical therapy – N(%)				
Statin	1827 (46.2)	1037 (44.7)	790 (48.3)	0.023
ACE inhibitor or ARB	1480 (37.4)	837 (36.0)	643 (39.3)	0.036
Beta-blocker	1327 (33.5)	732 (31.5)	595 (36.4)	0.001
Antiplatelet				
Aspirin	1363 (34.4)	790 (34.0)	573 (35.0)	0.505
Clopidogrel	374 (9.5)	201 (8.7)	173 (10.6)	0.042
Ticagrelor	86 (2.2)	43 (1.9)	43 (2.6)	0.098
Any APT	1629 (41.2)	932 (40.1)	697 (42.6)	0.117
DAPT	186 (4.7)	98 (4.2)	88 (5.4)	0.089
MRA	75 (1.9)	43 (1.9)	32 (2.0)	0.811
Anticoagulant				
Warfarin	175 (4.4)	92 (4.0)	83 (5.1)	0.093
Any anticoagulant	234 (5.9)	122 (5.3)	112 (6.9)	0.036
Combined therapy				
Anticoagulant or APT	1818 (45.9)	1031 (44.4)	787 (48.1)	0.020
Anticoagulant or DAPT	418 (10.6)	218 (9.4)	200 (12.2)	0.004
Anticoagulant or anticoagulant + APT	234 (5.9)	122 (5.3)	112 (6.9)	0.036
≥3 medications	1320 (33.4)	779 (33.5)	541 (33.1)	0.762
Type of admission – N(%)				
Emergency to invasive centre	83 (2.1)	54 (2.3)	29 (1.8)	0.233
Non-emergency to invasive centre	787 (19.9)	501 (21.6)	286 (17.5)	0.002
Emergency to local hospital	2893 (73.1)	1650 (71.1)	1243 (76.0)	0.001
Non-emergency to local hospital	194 (4.9)	117 (5.0)	77 (4.7)	0.637
Coronary angiography – N(%)				
All	2837 (71.7)	1811 (78.0)	1026 (62.8)	<0.001
PCI	1476 (37.3)	997 (42.9)	479 (29.3)	<0.001
	(52.0)*	(55.1)*	(46.7)*	<0.001
Median length of stay (IQR) – days	5 (3-8)	5 (3-8)	6 (4-9)	<0.001

*** Those who had PCI as a proportion of those who underwent coronary angiography**

Table 4-4. Baseline demographics and management for HA patients according to sex

	All n=1425	Men n=749	Women n=676	P-value
Mean age ± SD - years	67.2 ± 12.6	65.8 ± 12.1	68.9 ± 12.8	<0.001
SIMD quintile - N(%)				0.511
1 (most deprived)	649 (45.5)	334 (44.6)	315 (46.6)	
2	236 (16.6)	122 (16.3)	114 (16.9)	
3	179 (12.6)	89 (11.9)	90 (13.3)	
4	196 (13.8)	112 (15.0)	84 (12.4)	
5	165 (11.6)	92 (12.3)	73 (10.8)	
Comorbidities - N(%)				
Hypertension	442 (31.0)	209 (27.9)	233 (34.5)	0.008
Diabetes	246 (17.3)	138 (18.4)	108 (16.0)	0.222
Atrial fibrillation	183 (12.8)	91 (12.1)	92 (13.6)	0.411
Renal failure	158 (11.1)	75 (10.0)	83 (12.3)	0.174
Respiratory disease	286 (20.1)	132 (17.6)	154 (22.8)	0.015
Cerebrovascular disease	117 (8.2)	55 (7.3)	62 (9.2)	0.209
Peripheral vascular disease	139 (9.8)	81 (10.8)	58 (8.6)	0.156
Heart failure	167 (11.7)	95 (12.7)	72 (10.7)	0.234
Previous MI	359 (25.2)	221 (29.5)	138 (20.4)	<0.001
Dementia	25 (1.8)	13 (1.7)	12 (1.8)	0.955
Depression	38 (2.7)	14 (1.9)	24 (3.6)	0.049
Charlson score				0.629
0	676 (47.4)	351 (46.9)	325 (48.1)	
1-3	630 (44.2)	339 (45.3)	291 (43.0)	
≥4	119 (8.4)	59 (7.9)	60 (8.9)	
Pre-admission medical therapy - N(%)				
Statin	929 (65.2)	504 (67.3)	425 (62.9)	0.080
ACE inhibitor or ARB	632 (44.4)	363 (48.5)	269 (39.8)	0.001
Beta-blocker	692 (48.6)	381 (50.9)	311 (46.0)	0.067
Antiplatelet				
Aspirin	722 (50.7)	401 (53.5)	321 (47.5)	0.023
Clopidogrel	210(14.7)	100 (13.4)	110 (16.3)	0.120
Ticagrelor	17 (1.2)	11 (1.5)	6 (0.9)	0.313
Any APT	871 (61.1)	469 (62.6)	402 (59.5)	0.223
DAPT	78 (5.5)	43 (5.7)	35 (5.2)	0.641
MRA	36 (2.5)	19 (2.5)	17 (2.5)	0.979
Anticoagulant				
Warfarin	103 (7.2)	52 (6.9)	51 (7.5)	0.661
Any anticoagulant	131 (9.2)	64 (8.5)	67 (9.9)	0.373
Combined therapy				
Anticoagulant or APT	978 (68.6)	517 (69.0)	461 (68.2)	0.736
Anticoagulant or DAPT	208 (14.6)	106 (14.2)	102 (15.1)	0.617
Anticoagulant or anticoagulant + APT	131 (9.2)	64 (8.5)	67 (9.9)	0.373
≥3 medications	723 (50.7)	403 (53.8)	320 (47.3)	0.015
Type of admission - N(%)				
Emergency to IC or local hospital*	1274 (89.4)	662 (88.4)	612 (90.5)	0.188
Non-emergency to invasive centre	67 (4.7)	41 (5.5)	26 (3.8)	0.147
Non-emergency to local hospital	84 (5.9)	46 (6.1)	38 (5.6)	0.677
Coronary angiography - N(%)				
All	183 (12.8)	113 (15.1)	70 (10.4)	0.008
PCI	72 (5.1) (39.2)**	51 (6.8) (45.1)**	21 (3.1) (30.0)**	0.001 0.001
Median length of stay (IQR) - days	2 (1-3)	2 (1-3)	2 (1-3)	0.285

*** Emergency groups combined due to small numbers in one group**

**** Those who had PCI as a proportion of those who underwent coronary angiography**

4.3.3 Predictors of coronary angiography and PCI

After adjusting for differences in age, deprivation and comorbidities, sex was an independent predictor of both coronary angiography and PCI in all patients (Table 4-5). For patients with STEMI, men were more likely to receive coronary angiography (adjusted OR:1.44 CI:1.05-1.97) and PCI (adjusted OR:1.62 CI:1.28-2.05). The same was true for patients with NSTEMI (coronary angiography adjusted OR:1.48 CI:1.26-1.75, PCI adjusted OR:1.52 CI:1.32-1.76).

Predictors of coronary angiography and PCI split by men, women and also combined are shown in Figure 4-1 and Figure 4-2. Several baseline characteristics were found to be independently associated with lower use of coronary angiography and PCI in patients with MI including older age, prior MI in STEMI, and heart failure in NSTEMI regardless of gender (Figure 4-1 and Figure 4-2). Subgroup analysis were performed to see if any differences in predictors of invasive care between men and women exist. There were few major sex differences within subgroups; most notably, in those with NSTEMI and renal failure men were less likely than women to receive PCI, and in those with NSTEMI and dementia women were less likely than men to receive coronary angiography and PCI. This was confirmed by adding an interaction term of all predictors with gender in the entire population: in those with STEMI, HF was a significant predictor of PCI in women but not in men (p-interaction 0.007), dementia's predictive value of CAG (p-interaction 0.038) and renal failure's predictive value of PCI (p-interaction 0.004) was significantly different in men and women with NSTEMI.

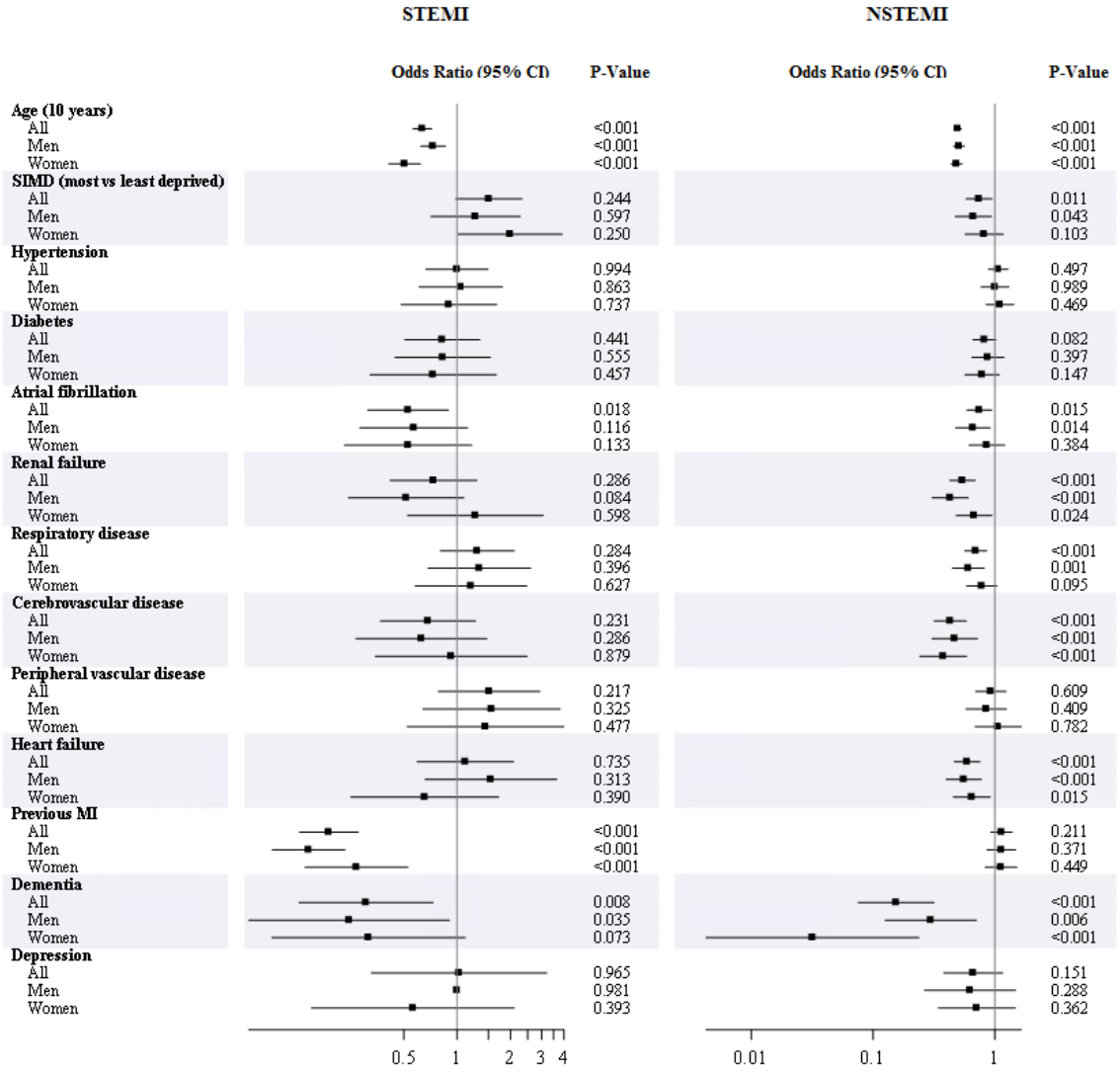
Table 4-5. Association of sex with coronary angiography and PCI according to diagnosis (odds ratio and 95% confidence interval shown for men vs women)

	Coronary Angiography		PCI	
	OR (95% CI)	P-value	OR (95% CI)	P-value
All				
Age-adjusted[a]	1.57 (1.42-1.73)	<0.001	1.70 (1.54-1.88)	<0.001
Fully adjusted[b]	1.52 (1.37-1.68)	<0.001	1.68 (1.52-1.86)	<0.001
STEMI				
Age-adjusted[a]	1.29 (0.96-1.73)	0.086	1.51 (1.21-1.89)	<0.001
Fully adjusted[b]	1.44 (1.05-1.97)	0.023	1.62 (1.28-2.05)	<0.001
NSTEMI				
Age-adjusted[a]	1.55 (1.33-1.81)	<0.001	1.57 (1.37-1.81)	<0.001
Fully adjusted[b]	1.48 (1.26-1.75)	<0.001	1.52 (1.32-1.76)	<0.001
HA				
Age-adjusted[a]	1.44 (1.05-1.99)	0.026	2.18 (1.30-3.68)	0.003
Fully adjusted[b]	1.43 (1.02-1.99)	0.037	2.25 (1.32-3.84)	0.003

[a] Adjusted for age only

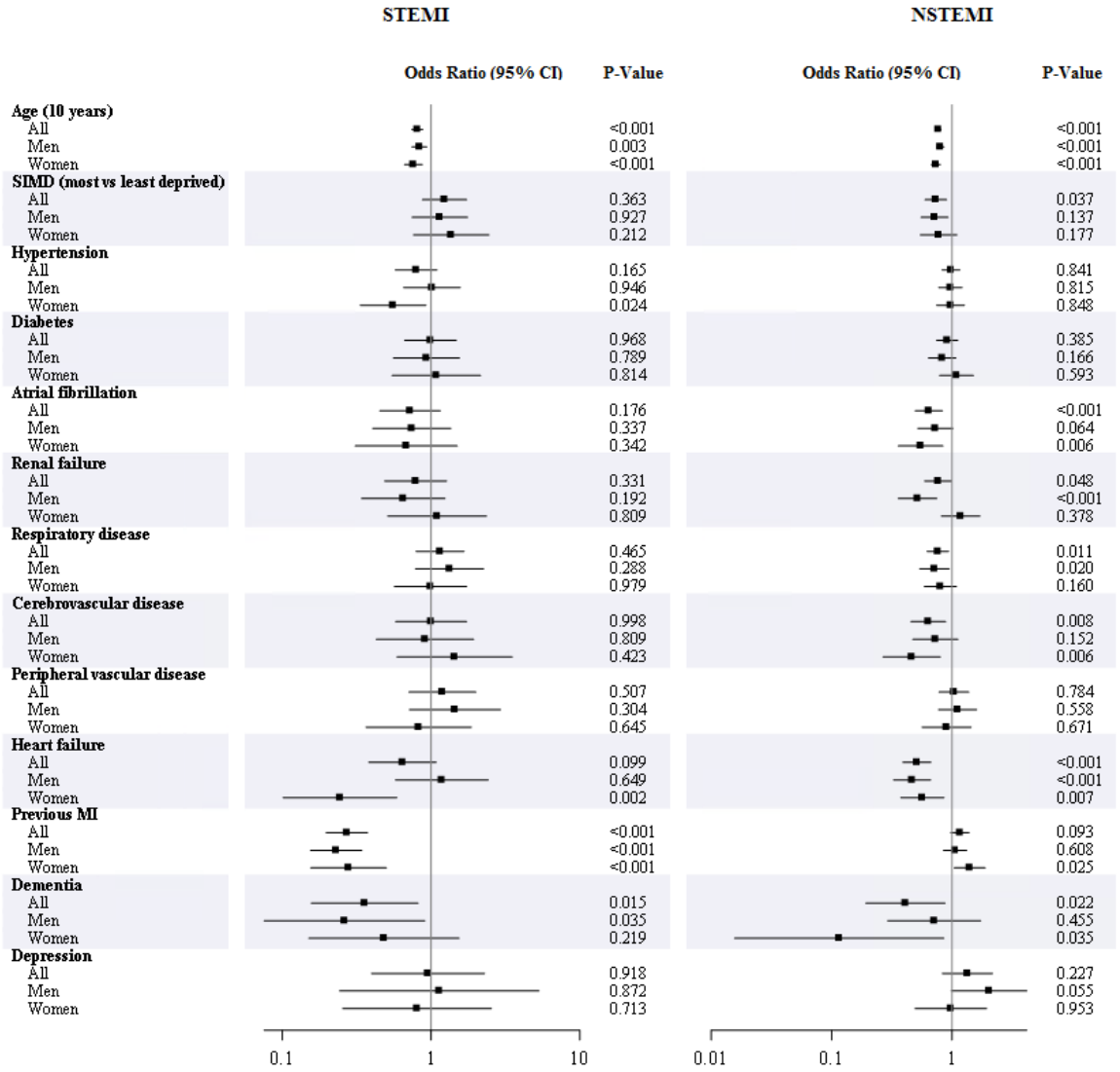
[b] Adjusted for age, Scottish Index of Multiple Deprivation quintile, hypertension, diabetes, atrial fibrillation, renal failure, respiratory disease, cerebrovascular disease, peripheral vascular disease, heart failure, previous MI, dementia, depression

Figure 4-1. Association of baseline characteristics with coronary angiography in all and split by sex for STEMI and NSTEMI



Adjusted odds ratio[a] and 95% confidence interval shown for each baseline characteristic: 10-year increase in age, most vs least deprived, presence vs absence of comorbidity. P-values for significance of predictor of interest in all patients and split by gender.
[a] Adjusted for age, Scottish Index of Multiple Deprivation quintile, hypertension, diabetes, atrial fibrillation, renal failure, respiratory disease, cerebrovascular disease, peripheral vascular disease, heart failure, previous MI, dementia, depression, plus sex in the 'all' group (excluding the variable being examined)

Figure 4-2. Association of baseline characteristics with PCI according to sex for STEMI and NSTEMI



Adjusted odds ratio[a] and 95% confidence interval shown for each baseline characteristic: 10-year increase in age, most vs least deprived, presence vs absence of comorbidity. P-values for significance of predictor of interest in all patients and split by gender.
[a] Adjusted for age, Scottish Index of Multiple Deprivation quintile, hypertension, diabetes, atrial fibrillation, renal failure, respiratory disease, cerebrovascular disease, peripheral vascular disease, heart failure, previous MI, dementia, depression, plus sex in the 'all' group (excluding the variable being examined)

4.3.4 Medical therapy post-MI

Women were less frequently treated with antiplatelets than men (with no greater treatment with anticoagulants), with a difference at 1 year of 2.8% (p=0.0368) (Figure 4-3). At 1 year, women were also less often prescribed statins (3.8% difference, p=0.005) and ACE inhibitors or ARBs (4.3% difference, p=0.003). A similar pattern was seen in the NSTEMI group (Figure 4-4). In this group, women were also less frequently treated with beta-blockers at 1 year.

Drug therapy was similar for men and women at 1 year in the STEMI and hospitalised angina groups, other than anticoagulants, with which fewer women than men were treated (Figure 4-3 and Figure 4-4). In patients with STEMI or hospitalised angina, sex was not an independent predictor of treatment with anticoagulants or antiplatelets, statins, ACE inhibitors or ARBs or beta-blockers at 1 year (Table 4-6). Conversely, in NSTEMI men were 20-32% more likely than women to be treated with statins, ACE inhibitors or ARBs, or beta-blockers at 1 year.

Figure 4-3. Medical therapy at discharge*, at 6 months and at 1 year** for all (upper panel) and STEMI (lower panel) patients by sex**

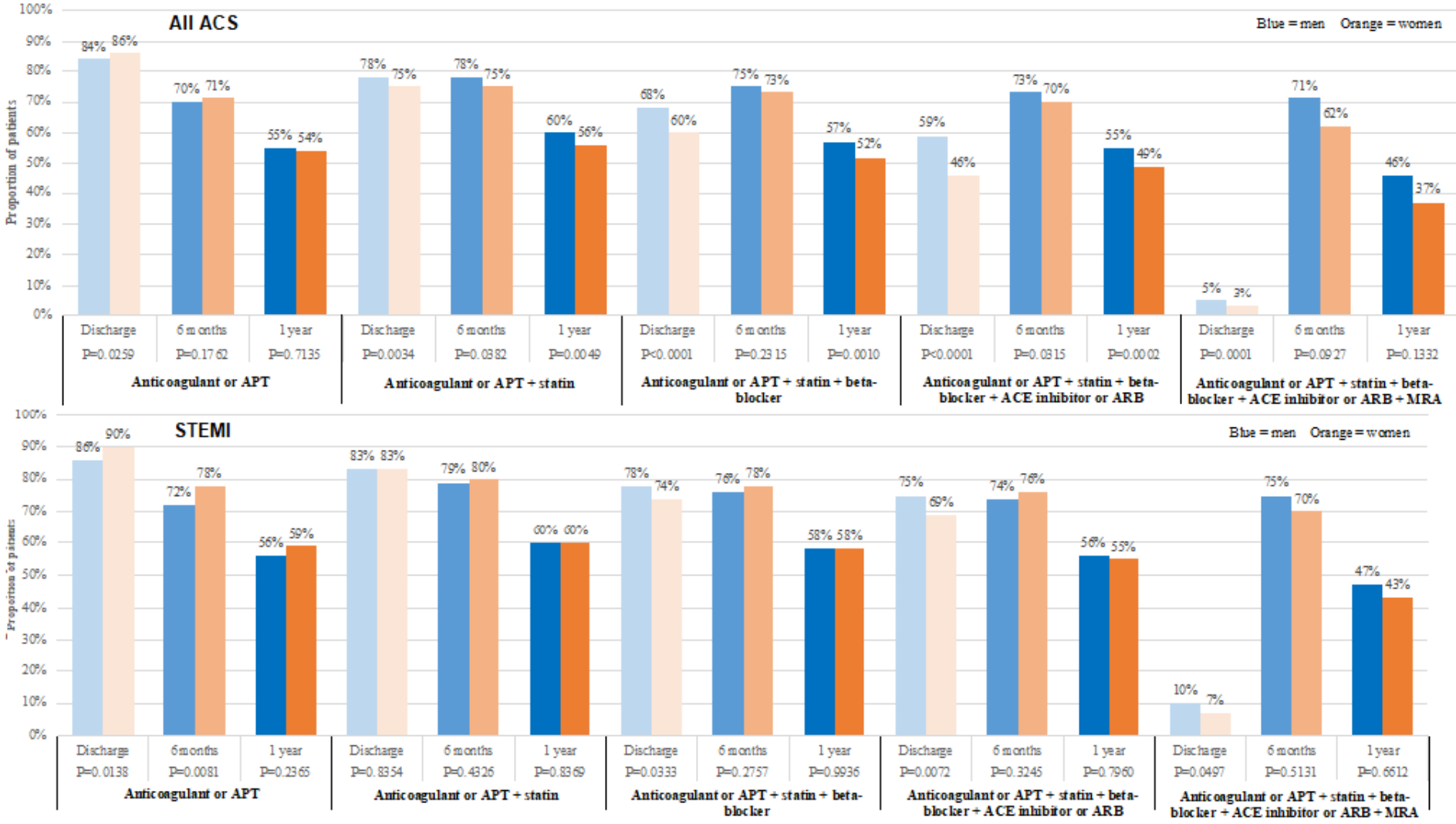


Figure 4-4. Medical therapy at discharge*, at 6 months and at 1 year** for NSTEMI (upper panel) and UA (lower panel) patients by sex**

*** At discharge within 90 days post-discharge. ** Proportions shown for 6 months and 1 year are of those on the drug(s) at discharge and still alive**

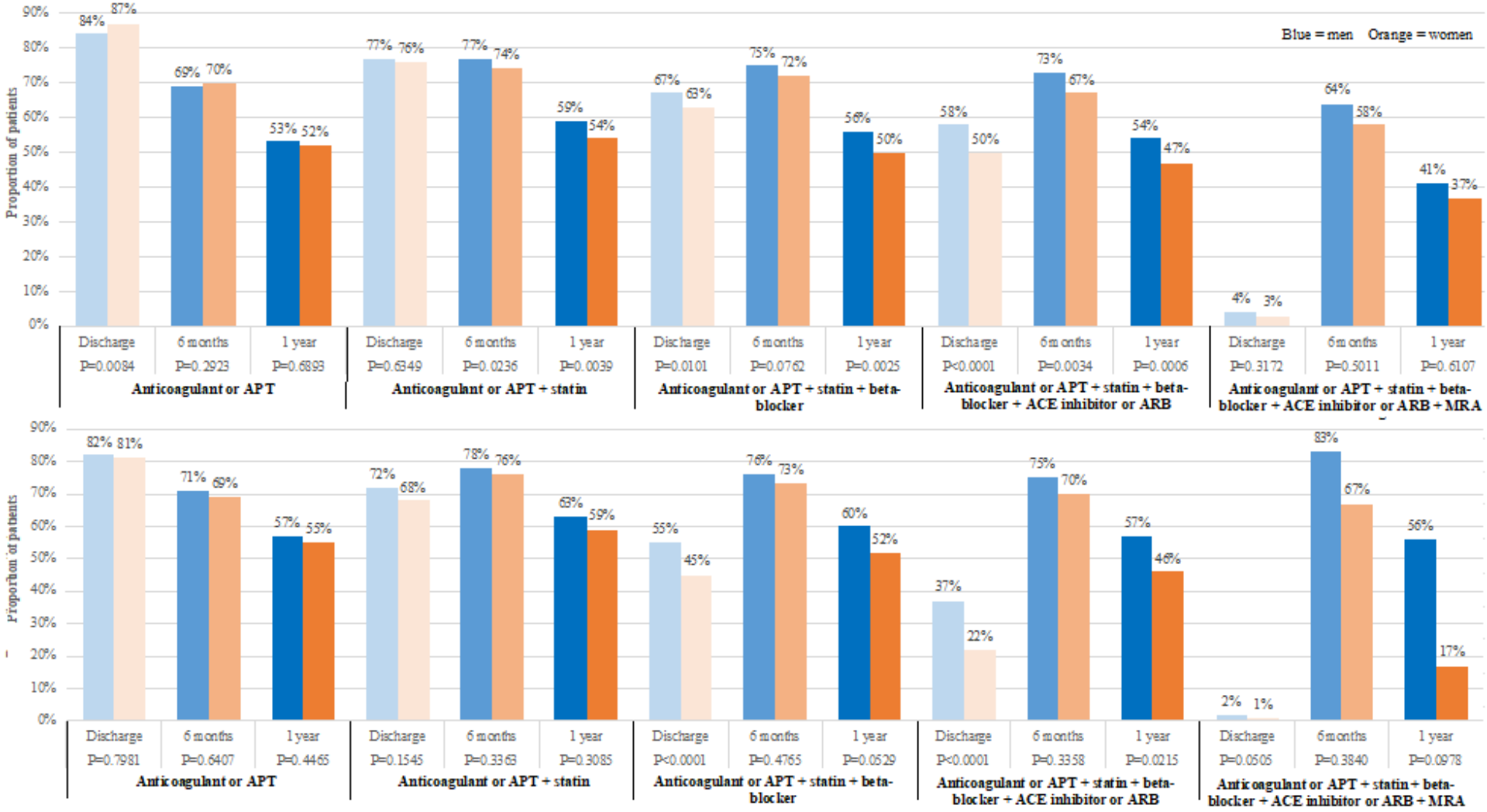


Table 4-6. Association of sex with medical therapy at discharge, 6 months and 1 year according to drug(s) and diagnosis for men vs women

	Discharge		6 months		1 year	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Antiplatelet						
Aspirin						
All	0.88 (0.78-0.99)	0.028	1.01 (0.88-1.15)	0.514	1.14 (1.01-1.28)	0.030
STEMI	0.68 (0.50-0.92)	0.012	0.78 (0.59-1.03)	0.083	1.00 (0.79-1.28)	0.981
NSTEMI	0.85 (0.72-1.00)	0.050	1.13 (0.95-1.35)	0.170	1.20 (1.02-1.41)	0.028
HA	0.91 (0.69-1.20)	0.504	0.84 (0.60-1.18)	0.311	1.01 (0.75-1.35)	0.956
Clopidogrel						
All	0.89 (0.79-1.01)	0.065	1.04 (0.85-1.28)	0.698	0.92 (0.73-1.16)	0.488
STEMI	0.88 (0.67-1.15)	0.355	0.87 (0.54-1.41)	0.577	0.62 (0.37-1.06)	0.083
NSTEMI	0.85 (0.72-1.00)	0.046	1.12 (0.85-1.48)	0.413	1.02 (0.74-1.42)	0.894
HA	1.46 (1.02-2.10)	0.038	1.03 (0.61-1.77)	0.902	1.04 (0.62-1.75)	0.876
Ticagrelor						
All	1.00 (0.90-1.12)	0.931	1.13 (0.96-1.33)	0.131	1.80 (1.21-2.69)	0.004
STEMI	0.93 (0.73-1.18)	0.564	0.96 (0.74-1.23)	0.727	1.96 (0.97-3.97)	0.060
NSTEMI	0.91 (0.79-1.05)	0.191	1.16 (0.93-1.45)	0.200	1.47 (0.89-2.43)	0.134
HA	1.17 (0.69-1.99)	0.554	2.88 (0.77-10.77)	0.114	-	-
Any APT						
All	0.86 (0.75-0.98)	0.022	1.05 (0.92-1.20)	0.439	1.07 (0.95-1.20)	0.252
STEMI	0.63 (0.45-0.90)	0.010	0.76 (0.57-1.02)	0.071	0.89 (0.70-1.13)	0.324
NSTEMI	0.84 (0.70-1.02)	0.072	1.17 (0.98-1.39)	0.082	1.14 (0.98-1.34)	0.092
HA	0.93 (0.69-1.24)	0.605	0.90 (0.65-1.23)	0.510	0.97 (0.74-1.27)	0.810
DAPT						
All	0.95 (0.85-1.05)	0.323	1.02 (0.89-1.17)	0.760	1.44 (1.12-1.86)	0.005
STEMI	0.77 (0.58-1.01)	0.062	0.85 (0.68-1.08)	1.187	1.56 (0.96-2.54)	0.072
NSTEMI	0.83 (0.72-0.96)	0.013	1.07 (0.89-1.29)	0.479	1.27 (0.91-1.76)	0.160
HA	1.57 (1.09-2.26)	0.016	1.50 (0.77-2.93)	0.231	2.02 (0.79-5.13)	0.139
Statin						
All	1.01 (0.89-1.14)	0.933	1.15 (1.01-1.32)	0.040	1.18 (1.05-1.33)	0.006
STEMI	0.90 (0.66-1.21)	0.474	0.83 (0.62-1.11)	0.204	0.94 (0.73-1.20)	0.591
NSTEMI	0.91(0.77-1.08)	0.295	1.26 (1.04-1.52)	0.017	1.30 (1.10-1.52)	0.002
HA	1.51 (0.84-1.57)	0.374	1.27 (0.92-1.74)	0.146	1.14 (0.86-1.51)	0.355
ACEi or ARB						
All	1.20 (1.07-1.34)	0.002	1.12 (0.97-1.30)	0.122	1.16 (1.02-1.32)	0.021
STEMI	0.82 (0.62-1.10)	0.188	0.73 (0.55-0.98)	0.036	0.87 (0.68-1.11)	0.263
NSTEMI	1.07 (0.91-1.25)	0.415	1.31 (1.08-1.59)	0.006	1.32 (1.11-1.56)	0.002
HA	1.99 (1.38-2.87)	<0.001	1.34 (0.88-2.03)	0.172	1.10 (0.77-1.58)	0.603
Beta-blocker						
All	1.10 (0.98-1.23)	0.107	0.96 (0.83-1.11)	0.610	1.11 (0.98-1.26)	0.062
STEMI	0.95 (0.73-1.25)	0.730	0.64 (0.47-0.87)	0.004	0.84 (0.65-1.08)	0.162
NSTEMI	1.02 (0.87-1.20)	0.801	1.10 (0.90-1.34)	0.347	1.20 (1.02-1.43)	0.033
HA	1.28 (0.97-1.69)	0.075	1.22 (0.87-1.73)	0.250	1.20 (0.89-1.62)	0.239
MRA						
All	1.32 (1.05-1.66)	0.017	1.21 (0.75-1.95)	0.438	0.99 (0.64-1.54)	0.957
STEMI	1.21 (0.85-1.71)	0.294	1.15 (0.50-2.65)	0.749	0.96 (0.46-2.04)	0.924
NSTEMI	1.33 (0.94-1.89)	0.112	0.78 (0.38-1.61)	0.494	1.01 (0.50-2.04)	0.983
HA	1.78 (0.68-4.69)	0.243	8.22 (0.30-226.05)	0.204	1.09 (0.18-6.74)	0.924
Anticoagulant						
All	1.02 (0.82-1.27)	0.849	0.99 (0.66-1.50)	0.974	1.17 (0.80-1.71)	0.422
STEMI	1.88 (1.13-3.14)	0.016	0.28 (0.07-1.15)	0.077	0.45 (0.14-1.53)	0.198
NSTEMI	0.72 (0.53-0.98)	0.035	0.86 (0.47-1.55)	0.608	0.91 (0.54-1.55)	0.728
HA	1.15 (0.64-2.03)	0.643	2.52 (0.99-6.41)	0.052	2.53 (1.08-5.92)	0.032
Anticoagulant or APT						
All	0.83 (0.72-0.95)	0.010	1.01 (0.88-1.15)	0.926	1.08 (0.96-1.21)	0.178
STEMI	0.64 (0.45-0.91)	0.014	0.74 (0.54-0.99)	0.044	0.89 (0.70-1.01)	0.099

NSTEMI	0.80 (0.65-0.97)	0.026	1.08 (0.90-1.30)	0.380	1.12 (0.96-1.32)	0.142
HA	1.00 (0.73-1.37)	0.987	1.04 (0.76-1.41)	0.814	1.04 (0.80-1.36)	0.745
Anticoagulant or APT + statin						
All	1.05 (0.93-1.17)	0.433	1.15 (1.00-1.31)	0.044	1.17 (1.04-1.31)	0.010
STEMI	0.91 (0.68-1.22)	0.540	0.84 (0.64-1.12)	0.237	0.95 (0.75-1.21)	0.702
NSTEMI	0.95 (0.81-1.12)	0.560	1.26 (1.05-1.50)	0.013	1.25 (1.07-1.47)	0.006
HA	1.18 (0.93-1.48)	0.172	1.17 (0.86-1.59)	0.324	1.13 (0.85-1.49)	0.395
Anticoagulant or APT + statin + beta-blocker						
All	1.20 (1.09-1.33)	<0.001	1.06 (0.92-1.21)	0.449	1.20 (1.06-1.36)	0.005
STEMI	1.10 (0.86-1.41)	0.452	0.79 (0.59-1.05)	0.100	0.93 (0.72-1.19)	0.547
NSTEMI	1.06 (0.92-1.22)	0.390	1.19 (0.98-1.43)	0.077	1.29 (1.08-1.54)	0.004
HA	1.49 (1.20-1.84)	<0.001	1.13 (0.79-1.61)	0.499	1.31 (0.95-1.81)	0.103
Anticoagulant or APT + statin + beta-blocker +ACE inhibitor or ARB						
All	1.35 (1.23-1.50)	<0.001	1.14 (0.98-1.32)	0.088	1.24 (1.07-1.42)	0.003
STEMI	1.08 (0.85-1.37)	0.518	0.80 (0.60-1.06)	0.120	0.94 (0.73-1.21	0.609
NSTEMI	1.18 (1.03-1.35)	0.020	1.33 (1.08-1.62)	0.006	)	0.002
HA	2.09 (1.64-2.66)	<0.001	1.19 (0.75-1.89)	0.467	1.34 (1.11-1.62)	0.095
					1.46 (0.94-2.28)	
Anticoagulant or APT + statin + beta-blocker +ACE inhibitor or ARB + MRA						
All	1.46 (1.15-1.87)	0.002	1.40 (0.83-2.36)	0.206	1.40 (0.82-2.40)	0.217
STEMI	1.35 (0.93-1.97)	0.117	1.30 (0.58-2.93)	0.528	1.24 (0.55-2.78)	0.607
NSTEMI	1.35 (0.94-1.94)	0.110	1.25 (0.55-2.85)	0.585	1.61 (0.66-3.94)	0.291
HA	2.33 (0.96-5.66)	0.062	-	-	-	-

Odds ratios adjusted for age, Scottish Index of Multiple Deprivation quintile, pre-admission use of respective drug, Charlson score, percutaneous coronary intervention

4.4 Death

Case-fatality at 30 days was 4.9% in all patients, 6.9% in STEMI patients and 2.9% in NSTEMI patients (Table 4-7). Case-fatality at 1 year was 10.9% in all patients, 10% in STEMI and NSTEMI patients and 5.1% in patients hospitalised for angina. Survival was worse for women than for men, driven by marked differences in outcomes in STEMI (Figure 4-5); in this group, 6.3% more women than men had died by 1 year (14.3% vs 8.0%, p<0.001). However, after adjustment for baseline demographics, comorbidities and PCI, the association between sex and mortality after STEMI was not significant and male sex emerged as an independent predictor of death in patients with NSTEMI (1 year HR:1.38 CI:1.12-1.69) (Table 4-7).

The proportional hazard assumption were assessed by adding time - dependent variables to the original models (i.e., product of sex and logarithm of time). If such variable is statistically significant then it can be concluded that the assumption of proportional hazards is not satisfied for the given covariate. However, time-dependent sex were not significant (p=0.196, P=0.513, P=0.130 and P=0.456 for all ACS, STEMI, NSTEMI, HA respectively).

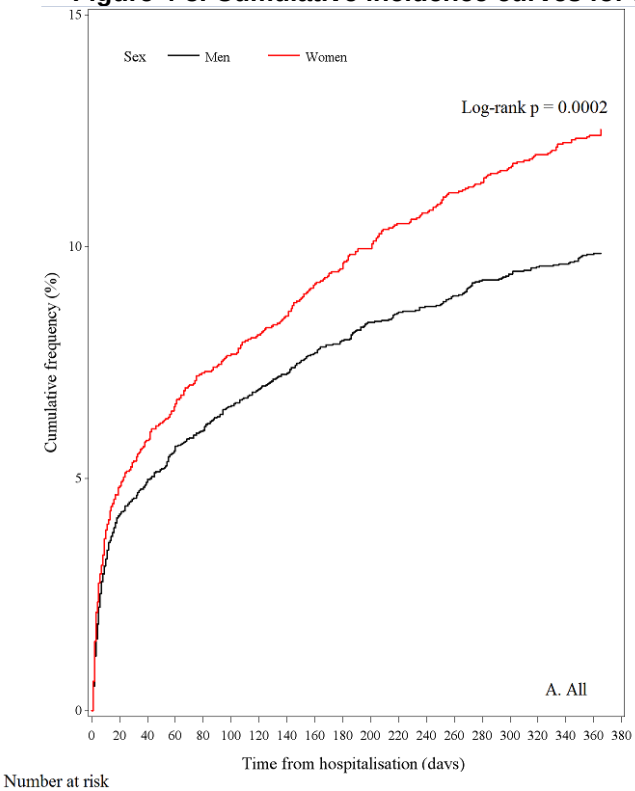
Table 4-7. All-cause death at 30 days and 1 year according to sex and diagnosis

	All	Men	Women	P-value	HR (95% CI)	P-value
All	n=7878	n=4717	n=3161			
All-cause death						
30 days	386 (4.9)	216 (4.6)	170 (5.4)	0.107	1.28 (1.04-1.57)	0.022
1 year	861 (10.9)	465 (9.9)	396 (12.5)	<0.001	1.21 (1.06-1.40)	0.006
STEMI	n=2042	n=1399	n=643			
All-cause death						
30 days	140 (6.9)	80 (5.7)	60 (9.3)	0.003	1.00 (0.70-1.43)	0.985
1 year	204 (10.0)	112 (8.0)	92 (14.3)	<0.001	0.95 (0.71-1.27)	0.713
NSTEMI	n=3957	n=2322	n=1635			
All-cause death						
30 days	111 (2.8)	66(2.8)	45 (2.8)	0.866	1.72 (1.16-2.56)	0.007
1 year	396 (10.0)	220 (9.5)	176 (10.8)	0.183	1.38 (1.12-1.69)	0.002
HA	n=1425	n=749	n=676			
All-cause death						
30 days	9 (0.6)	<9	<9	0.625	0.55 (0.13-2.31)	0.416
1 year	73 (5.1)	39 (5.2)	34 (5.0)	0.880	1.19 (0.74-1.91)	0.486

***N (%) or* adjusted hazard ratio[a] (95% confidence interval) shown for men vs women);**

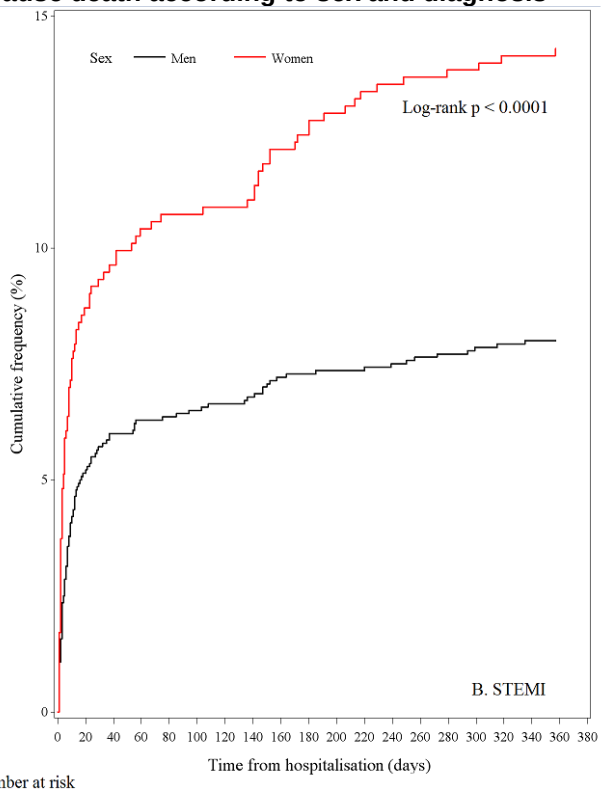
[a] Adjusted for age, Scottish Index of Multiple Deprivation quintile, hypertension, diabetes, atrial fibrillation, renal failure, respiratory disease, cerebrovascular disease, peripheral vascular disease, heart failure, previous MI, dementia, depression, percutaneous coronary intervention

Figure 4-5. Cumulative incidence curves for all-cause death according to sex and diagnosis



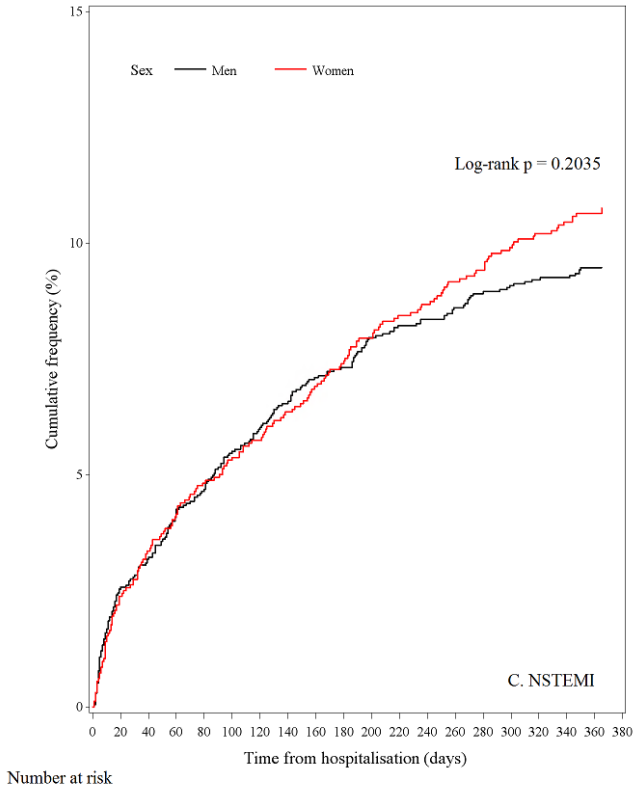
Number at risk

Men:	4717	4340	4251
Women:	3161	2859	2768



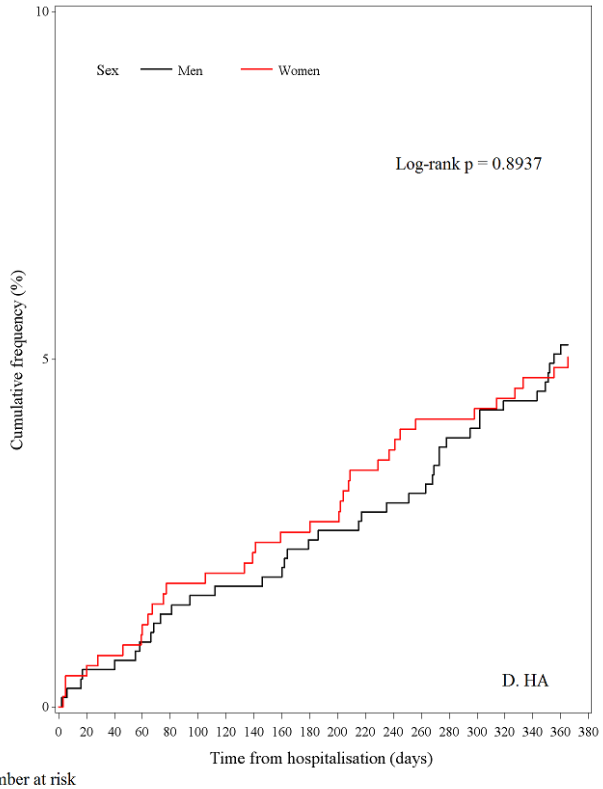
Number at risk

Men:	1399	1296	1286
Women:	643	562	550



Number at risk

Men:	2322	2151	2101
Women:	1635	1513	1459



Number at risk

Men:	749	730	709
Women:	676	658	612

4.5 Discussion

In this study of 7878 patients with hospitalised with MI or angina from 2013-2016 we found that women had a higher crude rate of death but, after accounting for baseline risk factors, men were more likely to die following NSTEMI, with no difference for patients with STEMI or hospitalised angina. After taking account of baseline risk factors, there remain sex disparities for patients with MI related to treatment times, invasive management and use of secondary prevention therapies. Our findings highlight the need for renewed focus on achieving health equity for women and men through prioritisation of guideline-directed management.

Our analysis serves evidence of the persistently high crude mortality event rate in women, particularly with STEMI. We found that death from any cause was 2.6% more common amongst women than men at 1 year, driven predominantly by deaths in the STEMI population for whom the crude difference was in excess of 6%. The survival curves for men and women with STEMI separate almost immediately, and this is reflected in the 3.6% mortality difference as early as 30 days. In this study, the crude differences were explained by the older age of women compared to men, greater burden of comorbidity, higher relative degree of deprivation and reduced access to coronary angiography and PCI.

We have included a comprehensive indicator of social deprivation which measures deprivation across seven weighted domains. In our study, women were more often from deprived socioeconomic groups. Socioeconomic deprivation is strongly linked with poorer outcomes in MI and in women the effect is more prominent (Macintyre et al., 2001). In Scotland, rates of coronary revascularisation have increased across all deprivation categories over the past 10 years with the exception of the least deprived (NHS Health Scotland Information Services Division, 2018b).

Important sex differences in cardiovascular risk factors are evident; diabetes and hypertension are more common in women (particularly younger women), and they may increase risk more in women than men (Yusuf et al., 2004). There are a number of other risk factors specific to women, including hypertensive disorders

of pregnancy and pregnancy-related diabetes mellitus, which are associated with a higher later cardiovascular risk (Fraser et al., 2012). We evaluated additional important comorbidities, notably dementia and depression. Although we must interpret the results with caution due to small numbers of patients identified with each condition, the presence of dementia was associated with a lower likelihood of coronary angiography. Dementia likely serves as a disincentive for clinicians and the families of affected patients to adopt invasive management. It's rising prevalence and emergence as a leading cause of death in women in several countries will increase the magnitude of this disparity (National Records of Scotland, 2017, Public Health England, 2017). Large trials to investigate the appropriate treatment strategy for older patients with MI, including those with dementia, are underway (ClinicalTrials.gov, 2017, ClinicalTrials.gov, 2014).

We found that an invasive strategy was used less often in the management of women with MI than it was for men, and this mirrors existing literature (Wilkinson et al., 2019, Hvelplund et al., 2010, Anand et al., 2005, Lansky et al., 2005). Women were less likely to undergo coronary angiography and PCI. Our analyses suggest that this factor may, in part, explain why crude survival is worse for women than it is for men. There are several reasons why this discrepancy may exist. There were notable differences in route of admission to hospital, with fewer women than men taken directly to the catheterisation laboratory irrespective of MI type. This will incur delays to revascularisation and may reduce the likelihood of coronary angiography altogether. Differences in admission route may be explained by greater diagnostic uncertainty amongst women, who report non-specific or atypical symptoms more often than men (Canto et al., 2012). Data on the time between symptom onset and first contact with medical services would highlight delays in presentation, when the benefits of emergent coronary revascularisation are less certain. Finally, emergency care decisions regarding coronary angiography and PCI in women may be influenced by smaller coronary anatomy, more technically challenging vascular access (the excess door-to-balloon time seen in older women in this study may also reflect this), and greater risk of procedure-related complications and post-procedural mortality (Lansky et al., 2005). Although bleeding complications remain more prevalent in women despite accounting for age, comorbidity and medication use, major adverse

cardiac events are largely explained by baseline factors such as these (Lansky et al., 2005, Hess et al., 2014).

A further important finding of our study is that male sex was independently associated with a higher risk of death in patients with NSTEMI. This association has been recognised previously and highlights the importance of evaluating subtypes of MI separately (Berger et al., 2009, Champney et al., 2009). The reason for this is likely multifactorial. One possible explanation is that women have less obstructive coronary artery disease than men and, in post-menopausal women, more efficient vascular tissue repair (Vaccarino et al., 2011). Differences in provision of primary preventative medical therapy may also contribute towards the findings. Finally, we lack data on cigarette smoking. In MI, smoking is not only more prevalent in men than in women (Anand et al., 2005, Wilkinson et al., 2019), but is also thought to be associated with different pathologic mechanisms – predominantly plaque rupture and acute thrombosis in men, and plaque erosion with superimposed thrombosis in women (Ambrose and Barua, 2004).

Our study has a number of limitations. In addition to those that are inherent to the retrospective design, we were unable to include several important prognostic variables, including haematological and biochemical bloods tests, biomarkers, haemodynamic, left ventricular systolic function, coronary anatomy and extent of disease. We lack information regarding rates of prior PCI, subsequent coronary artery bypass grafting and symptom-burden after the event. However, women are less likely than men to undergo coronary artery bypass grafting and, even in the absence of adjusting for this, the crude association between female sex and death was removed. A further confounder is lack of data on sex of the treating physician; female patients with MI treated by male physicians are less likely to survive than if treated by female physicians, and greater male physician-experience in treating female patients is linked to better outcomes (Greenwood et al., 2018).

4.6 Conclusion

Survival at 30 days and 1 year following STEMI is worse for women than for men. However, this is explained by relative differences in baseline characteristics

such as older age, greater deprivation, more prevalent comorbidity and lower rates of coronary angiography and PCI. Differences in the use of evidence-based drug therapy following MI also exist, with women at a disadvantage. Amongst patients with NSTEMI, male sex is an independent predictor of mortality. Efforts to address these sex disparities should be directed towards better understanding the differences in baseline risk and care pathways in order to highlight areas that would benefit from target, sex-specific intervention.

Chapter 5 An exploration of mediation models in acute coronary syndrome health disparities

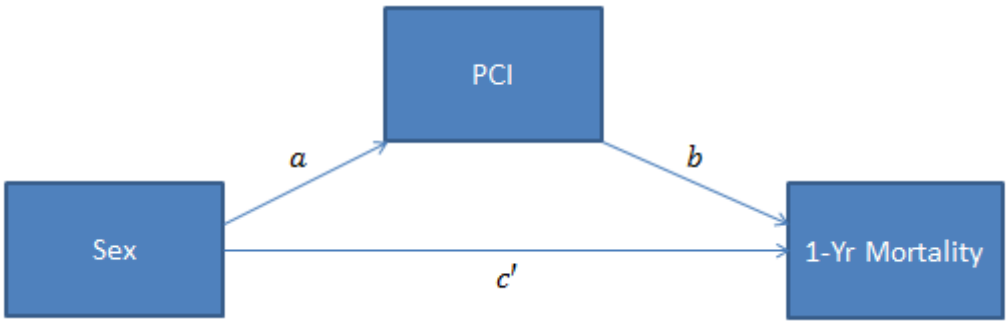
5.1 Introduction

In the previous chapters, we have explored the relationships between sex (and socio-economic status (SES)) on access to cardiac procedures such as percutaneous coronary interventions (PCI), medications uptake, and mortality in patients with acute coronary syndromes (ACS). We separately modelled the association between sex (or SES) and each of these outcomes, sometimes adjusting for earlier outcomes (i.e. PCI use adjusted when the outcome is mortality). What is also interesting but less known is how sex became associated with mortality. Does the association between sex and the provision of PCI translate into effects on mortality, or is the association between sex and mortality solely independent of PCI use? Similarly, does SES exert its effect on mortality through differences in the initiation of recommended drugs and continuation of drugs? This is where mediation analysis comes into place.

When looking at the association between sex and rate of PCI in patients with ACS, we find a significant association after adjustment for possible confounding factors. Men, on average, receive more guideline recommended therapy (OR=1.68, CI:1.52-1.86, p<0.001). However, men have a higher mortality rate after consideration of differences in guideline recommended therapy (HR=1.21, CI:1.05-1.40, p=0.006). In other words, if men and women didn't differ in treatment, then the male sex is associated with higher mortality. But since men and women do differ in treatment rates, does the difference due to PCI between men and women impact sex's association with mortality? Are the differences in treatment by sex transferred to differences in mortality by sex? If so, by how much? From previous Chapters, we only know the relationship between sex and mortality when PCI rate is controlled for. We are unsure if lower treatment in females actually leads to a mortality difference between men and women. These are reasonable questions to ask. And answers to these questions are important. How much does unequal treatment in women translate to unequal mortality? A closer look using mediation analysis will help us better understand this relationship.

In this section, the association between sex (or SES) and mortality is separated into its direct association and indirect association through possible mediators such as PCI and medications use. We are interested in whether lower rates of PCI and medication use in women has any additional effect on mortality, after controlling for any sex effects that operate through baseline characteristics.

Figure 5-1. A simple mediation model.



Consider the simple mediation model in Figure 5-1. The relationships between sex, the use of cardiac procedures and mortality are modelled so that the provision of the procedure is an intermediate variable that lies on the causal pathway between sex and mortality. Sex may then be both directly and indirectly associated with mortality. The primary aim of this chapter is to estimate and interpret these separate associations for different mediators.

Mediation was initially developed for and primarily used in the field of psychology (Nathanson and Fries, 2014, Newheiser and Barreto, 2014, Banks et al., 2014, Dubois-Comtois et al., 2014, Nelson et al., 2014, Windgassen et al., 2016, Wiedemann et al., 2009). A well-known example of mediation analyses in clinical psychology found that exposure to the thin ideal body image by mass media is not directly but indirectly associated with body dissatisfaction in women through the mediator: internalisation of this thin-as-ideal image (Lopez-Guimera et al., 2010, Grabe et al., 2008, Levine and Murnen, 2009, Cafri et al., 2005). Simple mediation models are also increasingly being applied in women's studies (Mittal et al., 2013), education research (Coetzee, 2014, Paige et al., 2014), political science (Wohl and Branscombe, 2009, de Moore, 2015), and health (Blashill and Vander Wal, 2010, Doue and Roussiau, 2016, Walker et al., 2016) literature, among many other disciplines. No existing analysis looks for these separate effects for sex, invasive or medical treatment and mortality,

while Hagen et. al. (Hagen et al., 2015) is the only study found that attempts to differentiate between these two types of effects on survival for SES with use of PCI as a mediator. Understanding which healthcare factors mediates inequalities in mortality and the strengths of the associations is critical for prioritizing approaches aimed at eliminating disparities in health for cardiac patients. The main contribution of this chapter to existing literature not only includes simple mediation models that look at how sex and SES disparities relate to mortality through their effects on use of PCI, but also more complex modelling that includes medication use and multiple mediators in serial and parallel.

This chapter is organised as follows. Section 2 provides a quick summary of findings from Chapters 3&4, which is also background information on the effects of PCI on mortality and variations in the provision of PCI and medication uptake, by sex and SES. Section 3 provides a brief theoretical discussion of mediation analysis and Section 4 describes the models explored. The primary goal of the analysis is to explore the possible paths where sex (and SES) is associated with mortality indirectly through mediators. These mediators include both in-hospital invasive treatment and after-discharge medications uptake. Ultimately, we are able to estimate if the effects of inequalities (both sex and SES) in access to treatment translate into higher mortality. Section 5 and 6 comprise of the main results and discussions respectively.

5.2 Background

5.2.1 Association between PCI and mortality

Currently, percutaneous coronary interventions are the preferred treatment for narrowed arteries of the heart. A review of 23 randomised trials that compared PCI to the next best treatment, in-hospital thrombolytic therapy, have shown significant improvement in mortality for acute MI patients (Keeley et al., 2003).

In this group of ACS patients in West of Scotland, the risk of death in those who received PCI was almost halved compared to those who did not receive PCI, after adjustment for risk factors (See Chapters 3, 4).

5.2.2 Sex and socioeconomic disparities in utilisation of PCI

PCI is more applicable to less severe cases of ACS, which tends to favour groups that are younger and with fewer comorbidities. Therefore, there is often a substantial reduction in the association between sex (or SES) and PCI after adjustment for comorbidities and risk factors.

In this sample of ACS patients, it was shown that men on average, received more invasive treatment (OR=1.68, CI: 1.51-1.86) after adjusting for age, SIMD, and comorbidities (See Chapter 4).

The differences in crude PCI rate between the SIMD quintiles were not statistically significant. And there does not seem to be a trend in the provision of PCI and SES. However, the most deprived group was less likely to receive PCI compared to the least deprived group after adjusting for age, sex, and comorbidities (OR=0.81, CI: 0.69-0.94). This relationship was only apparent when considering all ACS patients together (See Chapter 3).

5.2.3 Sex and socioeconomic disparities in prescriptions after discharge

In this group of ACS patients, women were associated with higher unadjusted use of statins, beta-blockers, antiplatelets and OACs prior to admission. And the most deprived SIMD group was associated with higher unadjusted rates of pre-admission use of statins and antiplatelets compared to other groups. Considering that the most deprived SIMD group are composed of more women and women are older and have more comorbidities, the use of medical therapies pre-admission likely reflects the conditions of the underlying patient characteristics rather than any differences in pre-admission treatment. It is therefore important to adjust for comorbidities or pre-admission medical therapy in all analyses, including mediation analysis.

After adjusting for age, SIMD, comorbidities and PCI, men on average were more likely to receive medical therapy at discharge, and this association persisted after 1 year (See Chapter 4).

Although there was no linear trend between SES and medications uptake at discharge and after 1 year, quintiles 2-4 were less likely to receive medications compared to Q1 and Q5 at discharge, after adjusting for age, sex, comorbidities and PCI (See Chapter 3).

5.2.4 No need to show existing association between sex (or socioeconomic status), mediators and outcomes to look for mediating affect

In this chapter, we are interested in estimating the mediating effect of these treatment inequalities between sex and between SES groups on mortality. On the surface, it seems that the existence of an association between sex (or SES) and mortality would be a reasonable precondition of trying to explain the underlying effect of sex (or SES) on mortality. Following on from this logic, it would also seem reasonable that an effect of sex on the treatment mediators and mediators on outcome are criterions to be met in order to test for mediating effects of treatments. This is called a causal steps approach and was popular due to the publication of an influential article by Baron and Kenney (Baron and Kenny, 1986). However, such preconditions are no longer advocated and "there is a growing awareness of and appreciation that such thinking is misguided and outdated" (Hayes and Ebooks Corporation Limited., 2013, Zhao et al., 2010, Cerin and Mackinnon, 2009). So regardless of our findings of an association between sex (or SES) on treatment and mortality in previous Chapters, it is still appropriate and useful to conduct mediation analysis. An effect that doesn't exist can still be mediated.

5.3 Theoretical background

Going back to the findings in Chapter 4, which looked at sex's association with mortality while holding PCI rate and other covariates constant. It was found that men have excess mortality in NSTEMI patients but not so in STEMI patients regardless of treatment rate, and the rates of PCI are higher in men for both NSTEMI and STEMI patients.

It is tempting to conclude that there is no indication that the less aggressive intervention strategy in women leads to any harm compared to men for STEMI

patients and that maybe men with NSTEMI are over-treated, leading to excess mortality in this group compared to women. But this cannot be concluded. From the main results of Chapter 4, we only know that:

1. Women have less aggressive intervention (less PCI).

2. After controlling for interventions in models, there are no differences between sexes in mortality in STEMI patients, while men have higher mortality rates in NSTEMI patients, as well as in all ACS patients.

Mediation analysis will allow us to decipher if less aggressive intervention in women leads to any harm. To decrease health disparities in ACS patients, information on this mechanism is valuable. This section contains a discussion of the statistical background for mediation analysis. For a better and more detailed discussion of mediation analysis, see Hayes (2018) (Hayes, 2018).

5.3.1 Simple mediation

Mediation analysis is a statistical method used to evaluate *how* some initial variable *X* is related to a consequent variable *Y*. In terms of this study, what is the mechanism, through which type of treatment (invasive or prescriptions), by which sex or SES influences mortality? Is sex (*X*) associated with mortality (*Y*) because women get undertreated, less likely to fulfil their prescriptions, which in turn reduces the effectiveness of the treatments and lowers mortality? Potential mediators such as undertreatment (*M*) represent a possible mechanism by which sex relates to death at 1-year.

To assist in this reasoning, consider the simple mediation model in Figure 5-1 again. As can be seen, this model contains two dependent variables (where an arrow points): (PCI) and ($Mortality$) and two independent variables (where an arrow starts): (Sex) and (PCI). Sex influences both provision of PCI and 1-year mortality, and PCI influences mortality.

In such a model, there are two pathways by which sex (X) can influence mortality (Y):

1. One pathway, c', leads from sex (X) to mortality (Y) without passing through PCI use (M) and is called the "direct effect" of sex on mortality.

2. The second pathway from X to Y is the "indirect effect" of X on Y through M. It first passes from sex (X) to dependent variable PCI use (M) and then from PCI use to mortality (Y). This is denoted as a and b. As sex is believed to have an impact on the provision of PCI, the indirect effect represents whether sex' influence on the probability of receiving PCI to such an extent that it carries on to mortality.

To estimate the direct and indirect effects of sex on mortality through PCI use, the following regression models are fitted. These models correspond to Figure 5-1 as well:

Equation 5-1 $$\boldsymbol{PCI = i_{pci} + a(Sex) + \varepsilon_{pci}}$$

Equation 5-2 $$\boldsymbol{Mortality = i_{mortality} + b(PCI) + c'(Sex) + \varepsilon_{mortality}}$$

where i_{pci} and $i_{mortality}$ are regression constants, ε_{pci} and $\varepsilon_{mortality}$ are errors in the estimation of PCI use and 1 year mortality, respectively, and a, b, and c' are the regression coefficients given to the independent variables in the model in the estimation of the dependent variables.

The effects of the different paths are estimated by the following coefficients in Equation 5-1 and Equation 5-2 (Table 5-1).

Table 5-1. Estimation of effects of different paths

Effect	Coefficient	Analysed in previous chapters
The direct effect of sex on mortality	c'	✓
The direct effect of sex on PCI	a	✓
The direct effect of PCI on mortality	b	✓
The indirect effect of sex on mortality	$a * b$	✘

Note the individual "direct effects" in mediation analysis is about statistically modelling relationships that, in reality, may or may not be causal, although the term "effect" is used. No distinction is made between "association" and

"effect" or "cause of" and "predictor of" when looking at the individual "direct effects".

However, the mediation process, or the indirect association in mediation analyses are assumed to be part of a causal process, hence the name "effect" in the terms used in mediation analyses. It must be assumed that *X* causes *M*, which in turn causes *Y*. *M* cannot possibly carry *X*'s effect on *Y* if *M* is not located *causally* between *X* and *Y*. Although most of the data used cannot afford causal interpretation, Hayes (2018) argued that "so long as we couch our causal claims with the required cautions and caveats given the nature of the data available, we can apply any mathematical method we want to understand and model relationships between variables" (Hayes, 2018). Mediation analysis is merely a tool that provides possibilities when trying to discern process that may be at work. The results do not justify causal claims, inferences that are made about cause is only one interpretation of the associations and results should be interpreted with care when used in observational studies.

5.3.1.1 The direct effect of sex (*X*) on mortality (*Y*)

In Equation 5-2, c' yield the direct effect of sex on mortality. c' estimates the difference between the two sexes in mortality holding PCI use constant. A generic interpretation of the direct effect is that two cases that differ by one unit on X but are equal on *M* are estimated to differ by c' units on Y.

Note, the direct effects are what researchers usually report, and are what I have reported as the main results in previous chapters.

5.3.1.2 The indirect effect of sex (*X*) on mortality (*Y*)

In Equation 5-1, a estimates the direct effect of sex on PCI and b in Equation 5-2 estimates the direct effect of PCI on mortality. The indirect effect of sex on mortality is the product of $a\ and\ b$. In generic terms, the indirect effect consists of two components: the effect of X on M as well as the effect of M on Y. It tells us that two cases that differ by one unit on X are estimated to differ by $a * b$ units on Y as a result of the effect of X on M which, in turn, affects Y. It is the indirect effects that we are interested in dissecting out in this chapter.

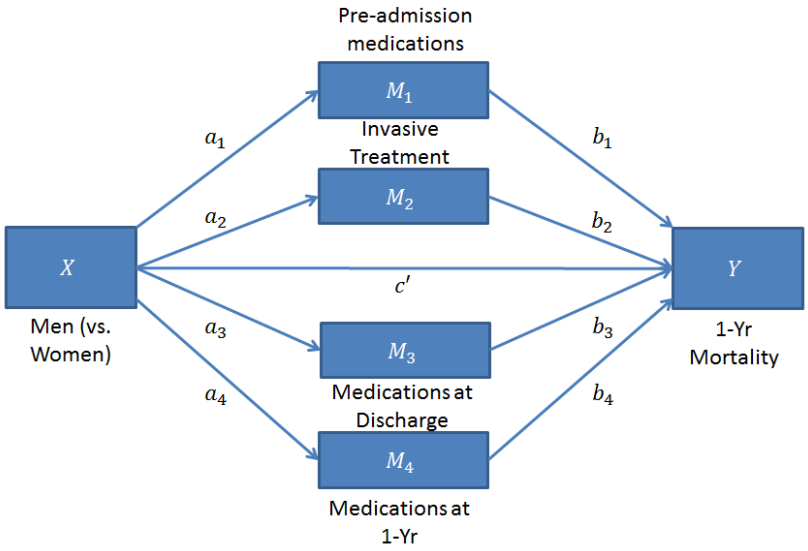
5.3.2 Mediation with more than one mediator

For pragmatic purposes, the fundamentals of statistical mediation analysis were explained using a simple mediation model involving one mediator in the section above. The principles of a simple mediation model can be extended to more complex models involving more than one mediator as well. Two forms of multiple mediator models are explored to explain the complicated treatment regimens patients face after hospitalisation with ACS. The mediators can be linked together in a causal chain (the serial multiple mediator model) or are merely allowed to correlate with but not causally influence one another (the parallel multiple mediator model). A third type is also explored which mixes the two types of processes.

5.3.2.1 The parallel multiple mediator model

In a parallel multiple mediator model, predictor variable X is modelled as influencing outcome Y directly as well as indirectly through two or more mediators, with the condition that the mediators do not influence each other. This is not to say that the mediators are assumed to be independent, they are allowed to be correlated. In hospitalised ACS patients, Figure 5-2 below depicts an example with multiple treatment mediators in parallel between sex and mortality that will be investigated later.

Figure 5-2. A parallel multiple mediator model



In this model of 4 mediators in parallel, 5 equations are needed:

Equation 5-3 $$M_1 = i_{M1} + a_1\mathrm{X} + \varepsilon_{M1}$$

Equation 5-4 $$M_2 = i_{M2} + a_2\mathrm{X} + \varepsilon_{M2}$$

Equation 5-5 $$M_3 = i_{M3} + a_3\mathrm{X} + \varepsilon_{M3}$$

Equation 5-6 $$M_4 = i_{M4} + a_4\mathrm{X} + \varepsilon_{M4}$$

Equation 5-7 $$Y = i_Y + b_1M_1 + b_2M_2 + b_3M_3 + b_4M_4 + c'\mathrm{X} + \varepsilon_Y$$

In Equation 5-3 to Equation 5-6, $a_1 - a_4$ quantify the amount by which two cases that differ by one unit on X are estimated to differ on $M_1 - M_4$, respectively. In Equation 5-7, b_1 estimates the amount by which two cases that differ by one unit on M_1 differ on Y holding $M_2 - M_4$, and X constant. Similarly, b_2 estimates the amount by which two cases that differ by one unit on M_2 differ on Y holding $M_{1,}M_3, M_4$ and X constant, and so on. Finally, c' estimates the amount by which two cases that differ by one unit on X differ on Y holding all mediators constant.

Similar to a simple mediator model, the direct effect of X is estimated by c' in Equation 5-7. In a multiple mediator model, the indirect effects are referred to as *specific indirect effects*. Thus, a model with k mediators has k specific indirect effects. For a parallel multiple mediator model, one indirect effect is through M_1 ($X \rightarrow M_1 \rightarrow Y$), one through M_2 ($X \rightarrow M_2 \rightarrow Y$), and so forth, up through M_k ($X \rightarrow M_k \rightarrow Y$). As in a simple mediation model, the indirect effect of X on Y through a given mediator M_i is quantified as the product of paths linking X to Y through M_i. In the above example, the first specific indirect effect of sex on mortality is modelled through the use of pre-admission medication. This is estimated as $a_1 * b_1$ from Equation 5-3 and Equation 5-7. The second specific indirect of effect of sex on mortality through use of invasive treatment is estimated as $a_2 * b_2$ from Equation 5-4 and Equation 5-7. And so forth. When added together, the specific indirect effects yield the *total indirect effect* of X on Y through all mediators in the model.

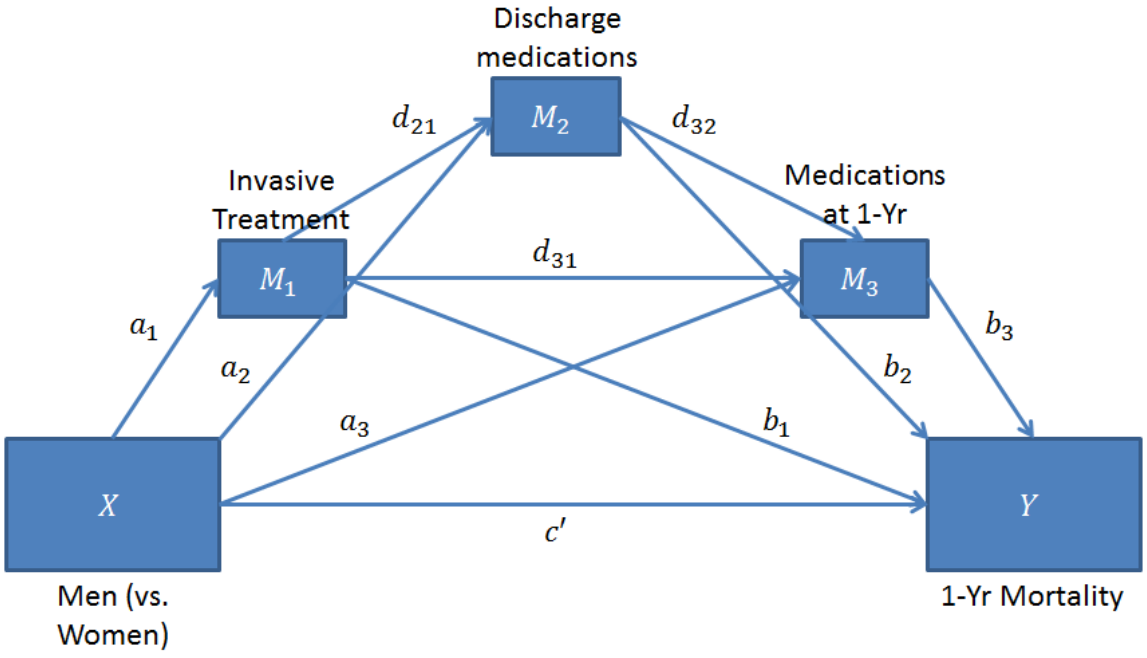
The interpretations of the direct effect and specific indirect effects in a parallel multiple mediator model are just as in the simple mediation model, except with the addition of "controlling for all other mediators in the model".

5.3.2.2 The serial multiple mediator model

The serial multiple mediator model can investigate the direct and indirect effects of X on Y by modelling a process in which X causes M_1, which in turn causes M_2, and so forth, with Y as the final outcome in the pathway.

For example, Chapter 4 results showed that in ACS patients, men relative to women have higher rates of invasive treatment, those that received a PCI are also associated with higher medications uptake after discharge, and those that take more medications after discharge are associated with better adherence, measured as use of medications 1-year after discharge, which could translate to an effect on mortality rates. The diagram in Figure 5-3 depicts these 3 mediators in a serial model in which sex is modelled as affecting mortality through 8 pathways: 1 direct and 7 indirect.

Figure 5-3. A serial multiple mediator model



The indirect effects include three passing through only a single mediator ($X \rightarrow M_1 \rightarrow Y$, $X \rightarrow M_2 \rightarrow Y$, $X \rightarrow M_3 \rightarrow Y$), three passing through two mediators in

serial ($X \rightarrow M_1 \rightarrow M_2 \rightarrow Y$, $X \rightarrow M_1 \rightarrow M_3 \rightarrow Y$, $X \rightarrow M_2 \rightarrow M_3 \rightarrow Y$), and one through all three mediators in serial ($X \rightarrow M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow Y$), with each of the mediators affecting the next in sequence. The 4 equations representing the 3 mediator serial multiple mediator model are:

Equation 5-8 $$M_1 = i_{M1} + a_1 \mathrm{X} + \varepsilon_{M1}$$

Equation 5-9 $$M_2 = i_{M2} + d_{21} M_1 + a_2 \mathrm{X} + \varepsilon_{M2}$$

Equation 5-10 $$M_3 = i_{M3} + d_{31} M_1 + d_{32} M_2 + a_3 \mathrm{X} + \varepsilon_{M3}$$

Equation 5-11 $$Y = i_Y + b_1 M_1 + b_2 M_2 + b_3 M_3 + c' \mathrm{X} + \varepsilon_Y$$

The direct effect is as always, estimated by c'. It is the estimated difference in Y between two cases that differ by one unit on X but that are equal on all mediators and covariates in the model.

The specific indirect effects are all constructed by multiplying the regression coefficients corresponding to each step in an indirect pathway. And they are all interpreted as the estimated difference in Y between two cases that differ by one unit on X through the causal sequence from X to mediator(s) to Y. In the example of 3 serial mediators, the specific indirect effects are: $a_1 b_1$, $a_2 b_2$, $a_3 b_3$, $a_1 d_{21} b_2$, $a_1 d_{31} b_3$, $a_1 d_{32} b_3$, $a_1 d_{21} d_{32} b_3$.

A combination of parallel mediators and serial mediators will also be explored.

5.3.2.3 Advantages of multiple mediator models

A search through existing literature did not find anything that included more than one mediator looking at healthcare disparities in patients with ACS. But doing so comes with advantages. First, it would seem obvious that a simple mediation model oversimplifies the complex dynamics through which any X influences Y in real processes that researchers study. Each of the direct effects in a simple mediation model ($X \rightarrow Y, X \rightarrow M$, $M \rightarrow Y$) could be partitioned into further direct and indirect components linked by some other mediator that's not included in the model. Given the treatment regimens an ACS patient likely

follows, we have strong reasons to believe that any predictor's effect (SES or sex) on outcome operates through multiple mechanisms with multiple mediators.

In addition, by including more than one mediator in a model simultaneously, it is possible to compare the size of the indirect effects with each other. For instance, theory A may postulate that the effect of healthcare inequalities in women on mortality is transmitted primarily through disproportionate use of PCI as the mediator, whereas theory B stipulates that inequalities in medical therapy is the conduit through which healthcare inequalities in women affects mortality. Inclusion of both (or more) mediators in an integrated model can show which indirect effect is the strongest.

In a multiple mediator model, it is also possible to talk about the indirect effect of X on Y summed across all mediators. This is the total indirect effect. It is interesting to know, for example, the total indirect effect of sex differences in mortality as a result of the effect of sex differences in medication uptake at both discharge and differences at 1 year.

5.4 Methods

It is not difficult to find examples of mediation analysis, or papers and books that promote our understanding and appreciation of this field (Hayes and Ebooks Corporation Limited., 2013, Baron and Kenny, 1986, Alderman et al., 2012, Preacher and Hayes, 2004, Valeri and Vanderweele, 2013, VanderWeele, 2016, VanderWeele and Vansteelandt, 2014, Vanderweele and Vansteelandt, 2010). However, this method is primarily used in the field of psychology, and has not been applied much in public health, such as the study of healthcare inequalities. The reasons for this might be largely due to the complicated treatment pathways and the complex nature of patients of pragmatic studies. Therefore this chapter will be exploratory and methodological in nature. The mediation models to be analysed are a bit like "data mining", it is more discovery oriented and results of the section should deepen our understanding of health and healthcare disparities in ACS patients, but may also shed new light on a different story than expected.

To make complete use of the data available and to examine the role of invasive and medical treatment as a mediator of mortality between the sexes, different indirect relationships between sex and mortality are tested. The following mediation pathways are theoretically plausible.

First, following on from results of previous chapters, a set of simple models (Table 5-2) based on the diagram in Figure 5-4 are examined to explain the mechanisms at work that leads to differences in 1-year mortality (Y) between men and women (X). Note the covariates adjusted follows the previous chapters: continuous age, categorical SIMD and Charlson score (0, 1-3, +4). Sensitivity analyses was performed using categorical age (<55, 55-65, 65-75, 75+) instead of continuous age for the final model.

Figure 5-4. Path diagram A, simple mediation

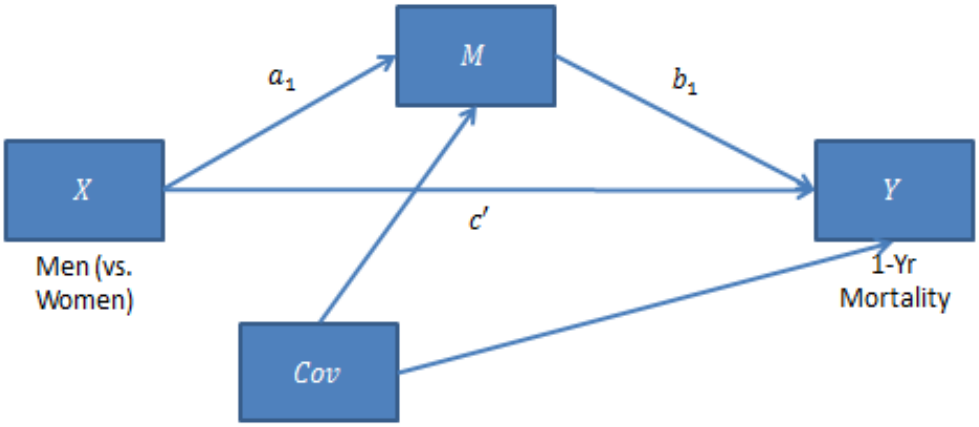


Table 5-2. Specific path analysis models A

Model	Path	Mediator (M)	Covariates	Population
1	A	Invasive treatment	Age, SIMD, Charlson score	All
2	A	Number of medications (out of OAC or APT, statin, beta-blocker, ACE inhibitor or ARB) at discharge	Age, SIMD, Charlson score and PCI	Discharged alive
3	A	Number of medications (out of OAC or APT, statin, beta-blocker, ACE inhibitor or ARB) at 1 year	Age, SIMD, Charlson score and PCI	

Also, more complicated alternative proposals to the process are considered. Models with mediators in parallel are detailed in Figure 5-5 and Table 5-3. Models with mediators in serial are detailed in Figure 5-6 and Table 5-4.

As described before, establishing an indirect effect of X on Y through M through a simple mediation analysis does not imply that M is the only mechanism at work linking X to Y. Estimation of indirect effects in multiple mediator models would allow for a simultaneous test of each mechanism while accounting for the associations between them.

Figure 5-5. Path diagram B, parallel mediation

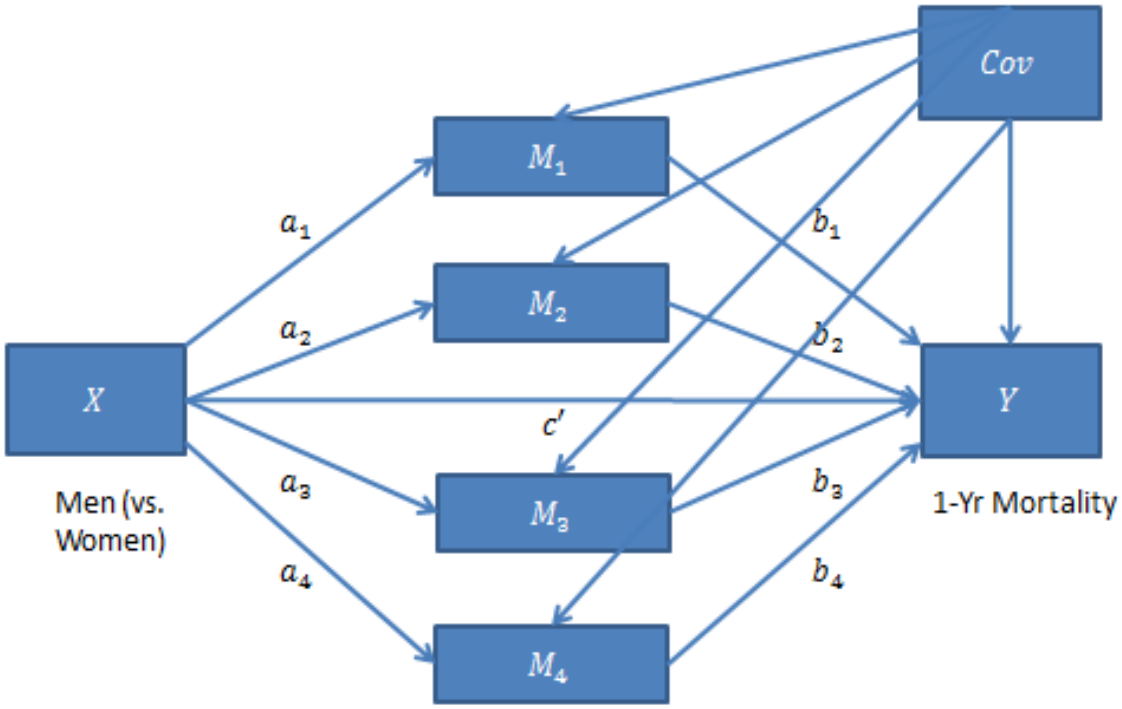


Table 5-3. Specific path analysis models B

Model	Path	Mediators	Covariates	Population
4	B	M_1 = Medications at discharge M_2 = Medications at 1 yr	Age, SIMD, Charlson score and PCI	Discharged alive
5i	B	M_1 = Pre admission medications M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, SIMD, Charlson score and PCI	Discharged alive
5ii	B	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, SIMD, Charlson score	All
6	B	M_1 = Pre admission medications M_2 = Invasive treatment M_3 = Medications at discharge M_4 = Medications at 1 yr	Age, Charlson score	All

Table 5-4. Specific path analysis models C

Model	Path	Mediators	Covariates	Population
7	C-I	M_1 = Medications at discharge M_2 = Medications at 1 yr	Age, SIMD, Charlson score and PCI	Discharged alive
8i	C-II	M_1 = Pre admission medications M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, SIMD, Charlson score and PCI	Discharged alive

8ii	C-II	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, SIMD, Charlson score	All
9	C-III	M_1 = Pre admission medications M_2 = Invasive treatment M_3 = Medications at discharge M_4 = Medications at 1 yr	Age, SIMD, Charlson score	All

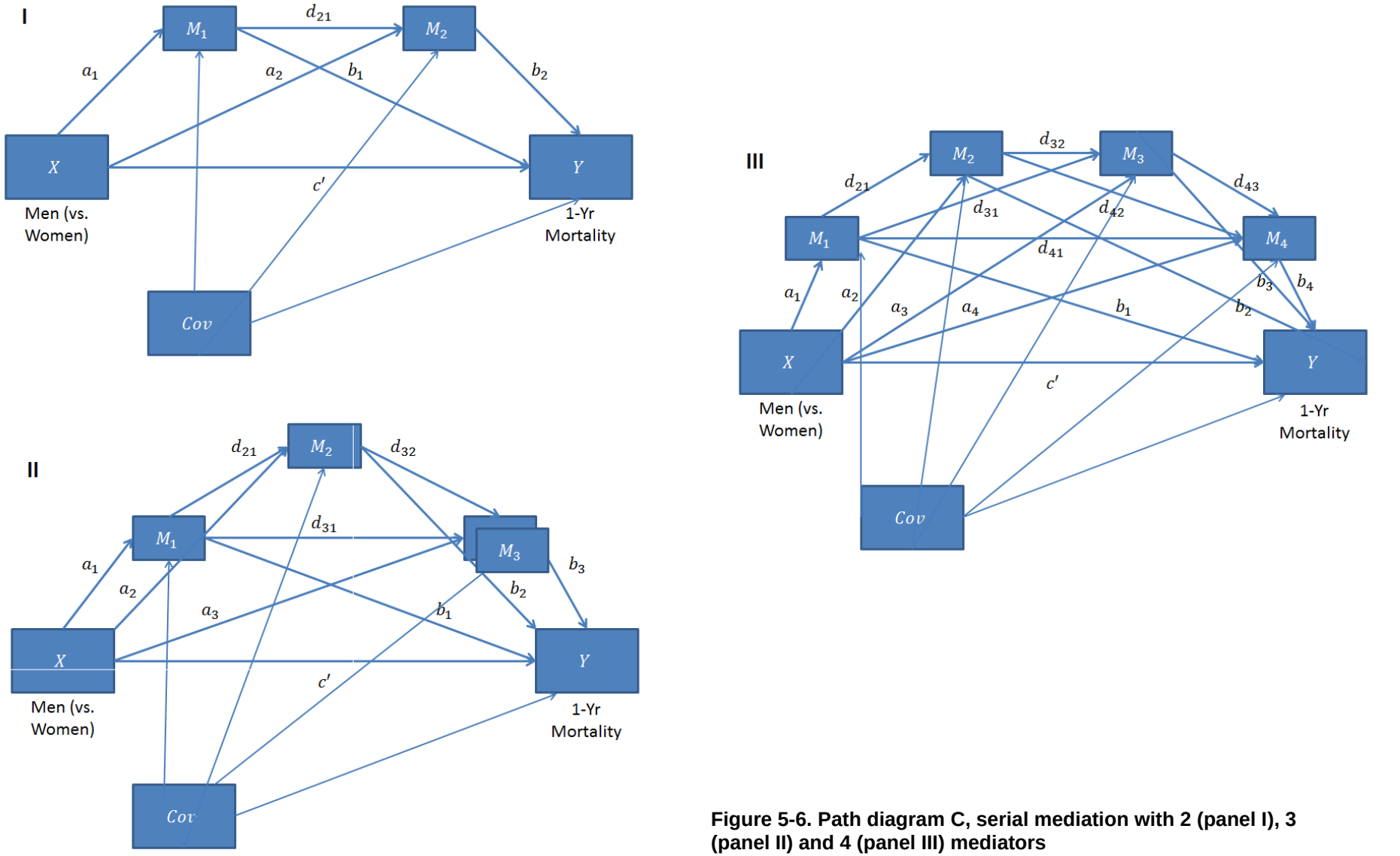


Figure 5-6. Path diagram C, serial mediation with 2 (panel I), 3 (panel II) and 4 (panel III) mediators

Finally, alternative models that combined parallel and serial mediation are explored (Table 5-5 and Figure 5-7).

Figure 5-7. Path diagram D, combination of serial and parallel mediation

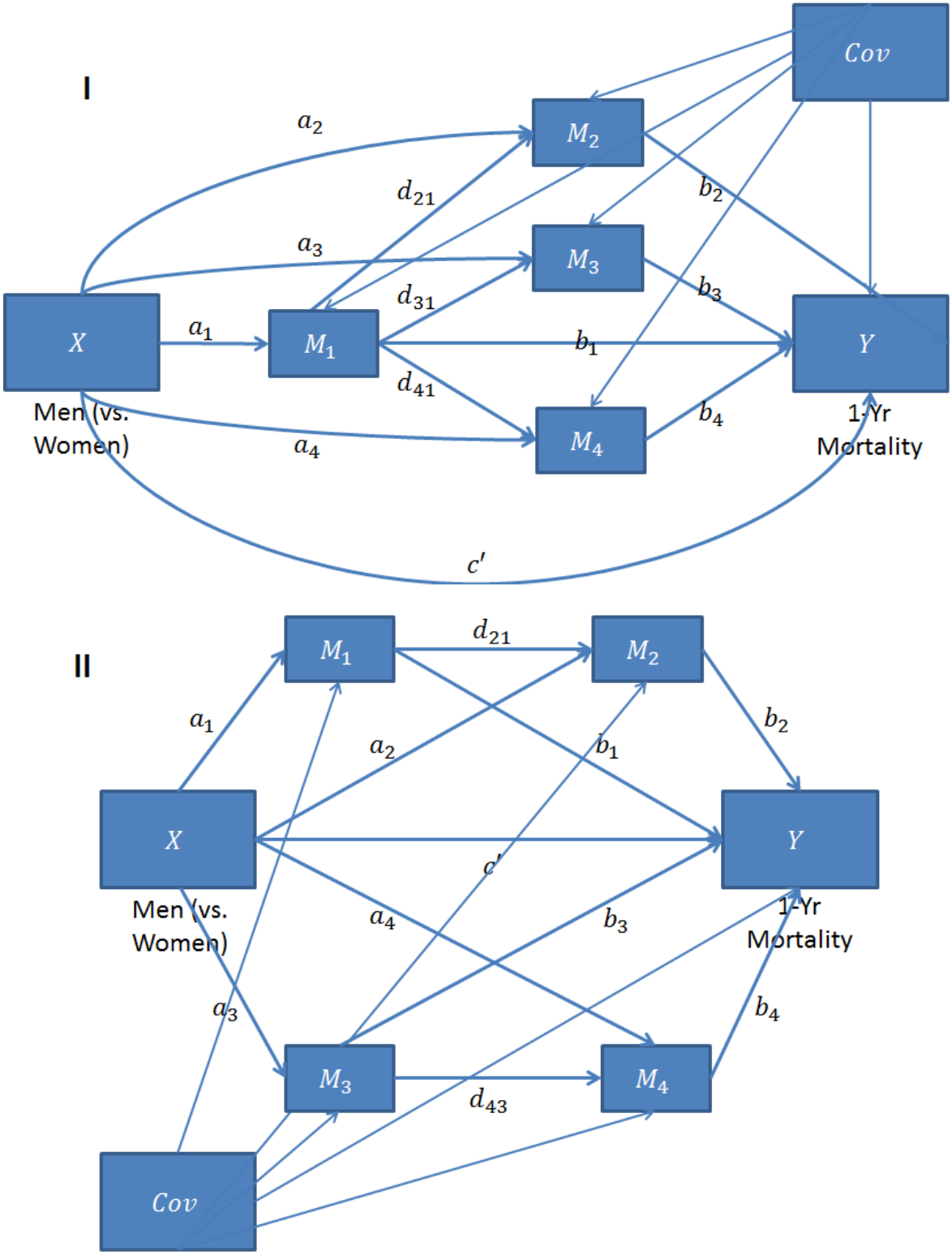


Table 5-5. Specific path analysis models D

Model	Path	Mediators	Covariates	Population
10i	D-I	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, SIMD, Charlson score	All
10ii	D-I	M_1 = Pre admission medications M_2 = Invasive treatment M_3 = Medications at discharge M_4 = Medications at 1 yr	Age, Charlson score	All
11	D-II	M_1 = Medications at discharge M_2 = Medications at 1-yr M_3 = Pre admission medications M_4 = Invasive treatment	Age, Charlson score	All

The medication mediators, the number of medications at different time points, range from 0 to 4. They are measured as the number of items out of the following list of filled prescriptions: OAC or APT, statin, beta-blocker, ACE inhibitor or ARB. Invasive treatment takes the following values: 0 = none, 1 = coronary angiography (CAG) only, and 2 = CAG and percutaneous coronary intervention (PCI). The primary outcome measure was all-cause mortality at 1 year.

The effects of the different paths are estimated by fitting models 1 to 11. The regression coefficients of interest in the diagrams (Figure 5-4 to Figure 5-7), the direct and indirect effects and their associated 95% confidence intervals are reported. The statistical background section introduces mediation in the simplest case: when all the variables are continuous, but the same concepts apply when outcomes are binary (Vanderweele and Vansteelandt, 2010, Valeri and Vanderweele, 2013). Therefore, the coefficients c' and b are computed using logistic regression, whereas linear ordinary least-squares regression is used for coefficients a and d. The coefficient a can be interpreted as the difference in receiving number of treatments (M) in women compared to men and d measures the relationship between mediators. Since c' and b are computed using logistic regressions, the odds ratios of the relationships are reported by exponentiation of the regression coefficients. The indirect effects are also reported as odds ratios, comparing the odds of 1 year mortality between women and men through the mediators. The recommended type of inferential test (Preacher et al., 2007, Hayes, 2018): the 95% bootstrap confidence intervals (using 3000 samples) for

the indirect effects are estimated using the PROCESS macro for SAS (Hayes, 2018).

As shown in the diagrams, all models are adjusted for baseline characteristics which are allowed to affect the individual mediators and mortality. Hence, the direct and indirect effects estimate the influence of sex on the mediators and mortality after removing the possible confounding effects of these baseline variables. In models with multiple mediators, the specific indirect effects are compared against each other (test of differences) with 95% bootstrap CIs shown where appropriate.

The same direct and indirect effects are estimated for SES inequalities as well, by replacing X=sex with X=SES in a subgroup of the least deprived group and the most deprived group. Analyses are conducted using SAS Enterprise Guide (v5.1).

5.5 Results

5.5.1 Treatment disparities in women compared to men

5.5.1.1 Simple mediation

The association between women (vs men) and mortality at 1 year after discharge, directly as well as indirectly through invasive or medical treatment are estimated through simple mediations models 1-3. Figure 5-8 provides the regression coefficients, and Table 5-6 contains the main results of the path analysis.

Table 5-6. Path analysis models 1-3. Effects are for women compared to men.

Model	Mediator	Direct Effect, OR (95%CI)	Indirect Effect, OR (95%CI)
1	Invasive treatment	0.76 (0.65-0.89)	1.10 (1.07-1.13)
2	Number of medications at discharge	0.78 (0.66-0.93)	1.03 (0.98-1.08)
3	Number of medications at 1 year	0.80 (0.67-0.95)	1.15 (1.00-1.36)

What researchers usually show, and what we showed in Chapter 4 were the direct effect of sex on mortality. It quantifies the difference in mortality

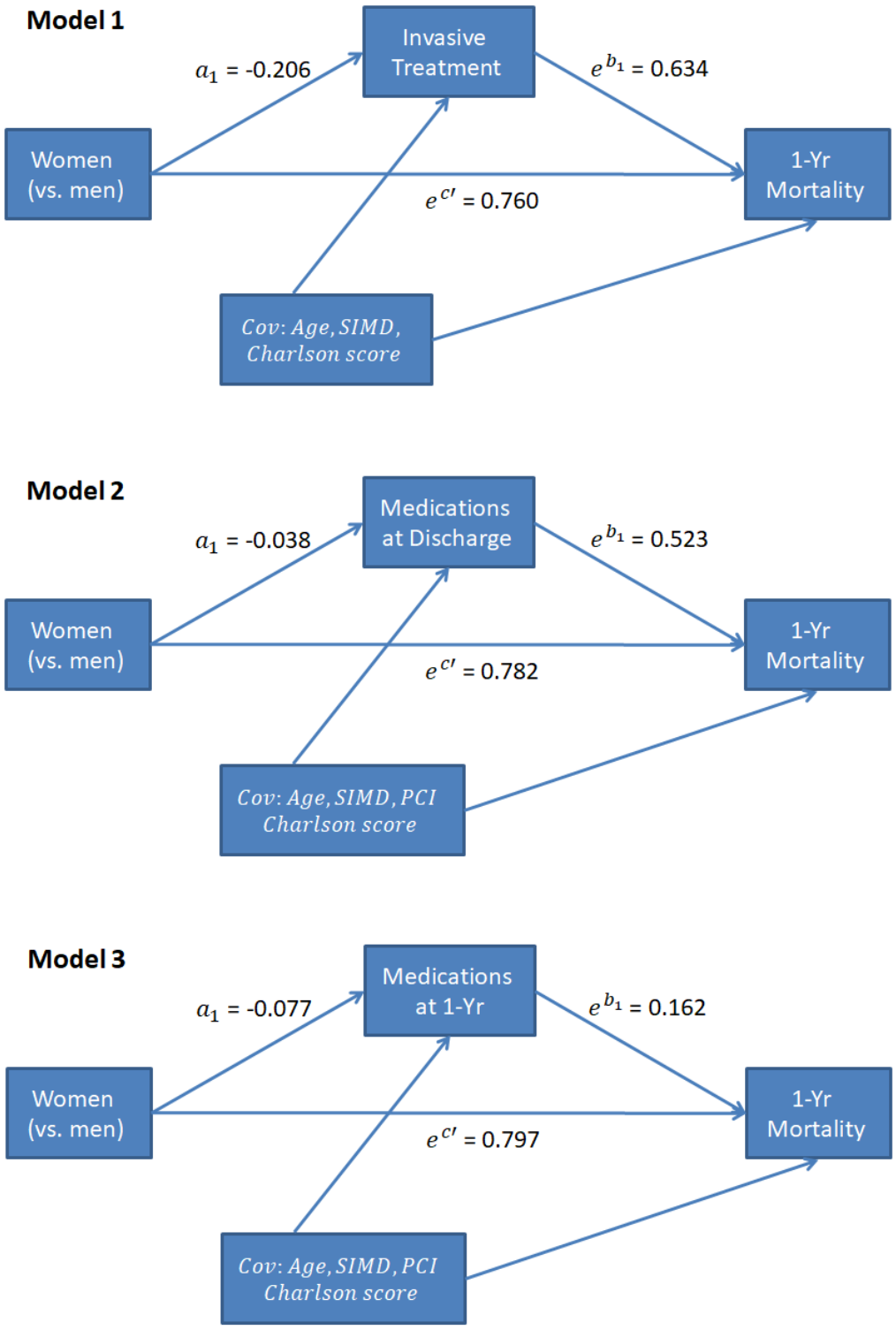
between women and men that are equal on invasive treatment rate. Independent of the effect of treatment inequalities, male sex was an independent predictor of higher all-cause mortality in patients with ACS (women are associated with lower risk of death by 24%, independent of PCI use). However, the effect of lower invasive treatment rates in women has carried over to mortality (the indirect effect), increasing the relative mortality rate in women compared to men (women associated higher risk of death by 10% due to less aggressive intervention). Given that crude survival was significantly worse for women than for men (from Chapter 4: 12.5% vs 9.9%, p=0.0002), reducing healthcare disparities for women would significantly reduce the case-fatality rate in women. On the other hand, from a health service perspective for men, who are at higher risk if treatment rates were the same between men and women, this might be seen as a success: with limited resources, treatments are preferentially given to those at higher risk (men) to maximise benefits. Except a balance was not achieved, women who had lower risk compared to men now are at higher risk due to this preferential treatment.

In more detail, let's first look at the indirect effect (Figure 5-8). Similar to previous findings, after adjusting for differences in age, deprivation category and comorbidities, women are associated with lower likelihood of receiving invasive treatment (a=-0.206) compared to men. While the provision of PCI is protective and associated with lower mortality (OR=e^{b_1}=0.632). The indirect effect is quantified as the product of the effect of sex on invasive treatment (a) and the effect of invasive treatment on mortality when sex is held fixed (b). The indirect effect of sex on mortality as a result of sex's influence receiving invasive treatment is statistically significant (OR=1.10; CI: 1.07-1.13). So relative to men, women were 10% higher in their likelihood of death at 1 year as a result of the effect of lower invasive treatment rates which, in turn, putatively affected patients' mortality rate at 1 year.

The estimated direct effect of sex on likelihood of death at 1 year is also statistically significant but of the opposite direction (OR=0.76; CI: 0.65-0.89). This matches the main findings of Chapter 4: that all cause death at 1 year is higher in men compared to women when equal on baseline demographics, comorbidities and PCI.

That is, male sex is an independent predictor of higher mortality, and invasive treatments are preferentially given to them in this ACS population, ultimately reversing their mortality risks compared to females.

Figure 5-8. Statistical diagrams of simple mediations models for (1) invasive treatment, (2) number of medications at discharge and (3) at one-year after discharge.



According to Models 2 and 3, even though we find that being female was associated with taking fewer medications at discharge (-0.038 and -0.077) (Figure 5-8), the indirect effects on mortality along these pathways are not significant when accounting for differences in baseline characteristics, comorbidities and PCI rate. Hence, the effects of sex on medical therapy barely carry over to mortality. Differences in the number of medications taken do not serve as a mediator of the effect of sex on mortality.

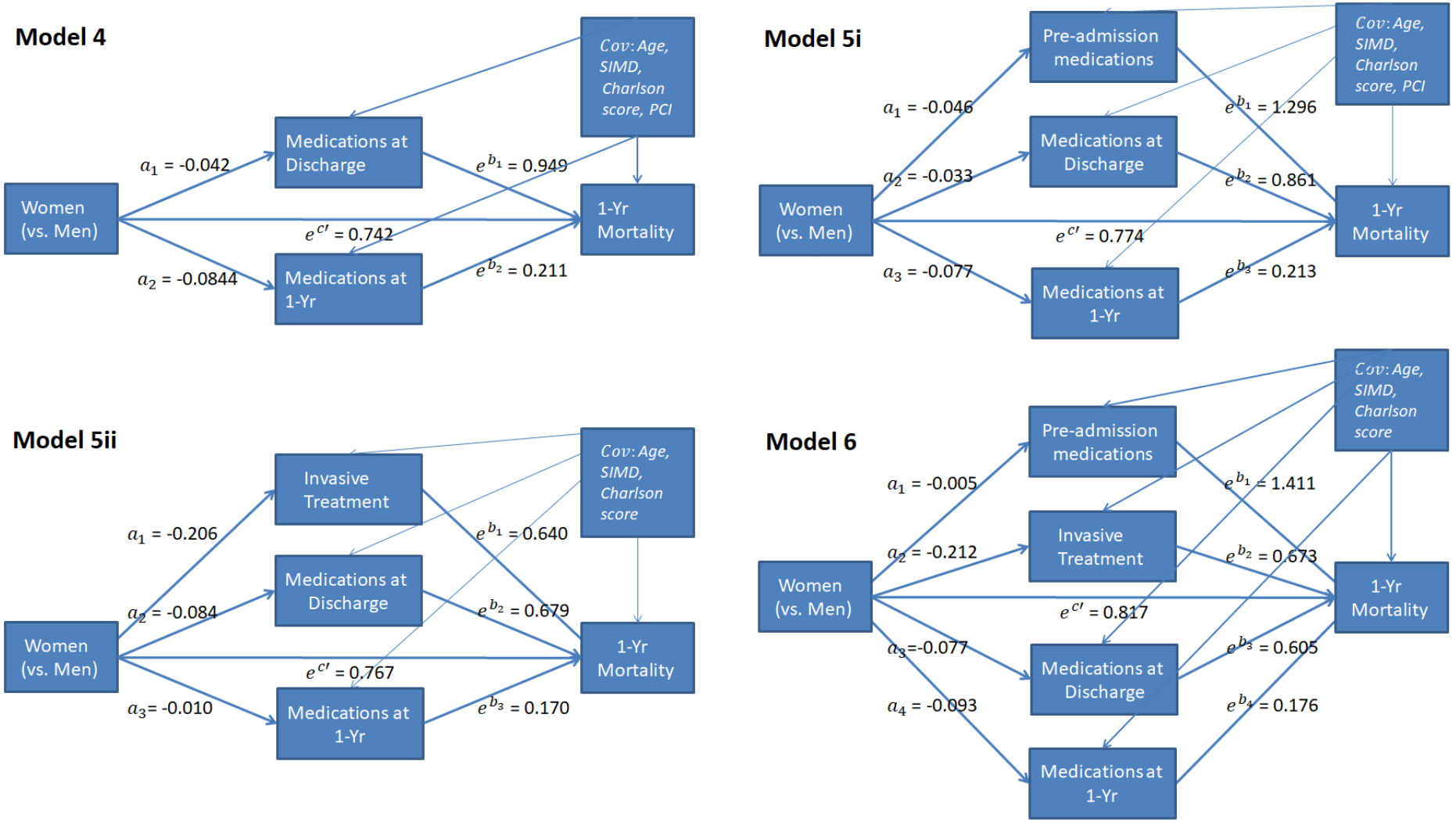
5.5.1.2 Multiple mediators in parallel

Results for Models 4-6 with multiple mediators in parallel are summarized in Table 5-7, model coefficients are superimposed in Figure 5-9's statistical diagrams.

Table 5-7. Path analysis models 4-6. Effects are for women compared to men.

Model	Mediators	Direct Effect, OR (95%CI)	Specific Indirect Effects, OR (95%CI)	
4	M_1 = Medications at discharge M_2 = Medications at 1 yr	0.74 (0.60-0.92)	M_1 M_2 Total M_1- M_2	1.00 (1.00-1.01) 1.14 (0.96-1.40) 1.14 (0.96-1.42) 0.88 (0.71-1.02)
5i	M_1 = Pre admission medications M_2 = Medications at discharge M_3 = Medications at 1 yr	0.77 (0.63-0.96)	M_1 M_2 M_3 Total M_1-M_2 M_1-M_3 M_2-M_3	0.99 (0.97-1.01) 1.00 (1.00-1.01) 1.13 (0.99-1.28) 1.12 (0.98-1.27) 0.98 (0.96-1.00) 0.88 (0.76-1.00) 0.89 (0.78-1.01)
5ii	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	0.77 (0.64-0.92)	M_1 M_2 M_3 Total M_1-M_2 M_1-M_3 M_2-M_3	1.10 (1.07-1.14) 1.03 (1.01-1.06) 1.19 (1.04-1.44) 1.35 (1.16-1.66) 1.06 (1.02-1.10) 0.92 (0.76-1.05) 0.87 (0.72-0.98)
6	M_1 = Pre admission medications M_2 = Invasive treatment M_3 = Medications at discharge M_4 = Medications at 1 yr	0.82 (0.68-0.98)	M_1 M_2 M_3 M_4 Total M_1-M_2 M_1-M_3 M_1-M_4 M_2-M_3 M_2-M_4 M_3-M_4	1.00 (0.97-1.02) 1.09 (1.06-1.12) 1.04 (1.01-1.08) 1.18 (1.02-1.42) 1.33 (1.11-1.61) 0.92 (0.88-0.95) 0.96 (0.91-1.00) 0.85 (0.70-0.99) 1.05 (1.00-1.10) 0.92 (0.78-1.06) 0.88 (0.76-1.01)

Figure 5-9. Statistical diagrams of models 4-6 with mediators in parallel



Model 4 - Similar to simple mediation analysis Models 2 and 3, when medication use was specified as the mediator of the effect of sex on mortality, there was no evidence of such a process at work when accounting for baseline characteristics, PCI use and comorbidities. A bootstrapped CI for the indirect effect (OR=1.00 for medications at discharge and OR=1.14 for medications at 1 year) included one indicating no evidence of a mediating effect. However, having multiple mediators in parallel in a single model allows a comparison of the two different specific indirect effects. There are no differences between the specific indirect effects as the 95%CI straddles one (OR=0.88, CI: 0.71-1.02).

In a parallel multiple mediator model, it is also possible to talk about the indirect effect of sex on mortality summed across all mediators. This is the total indirect effect. The total indirect effect sex on mortality as a result of the effect of sex differences in medication uptake at both discharge and at 1 year is not significant as its 95%CI contained one (Model 4). Hence, the sex differences in medication uptake at discharge and at 1 year do not add to sex difference in mortality.

Model 5i - When a third mediator of pre-admission number of medications is added to the model, still, none of the indirect effects through medication use are significant.

Model 5ii & 6 - Recall Model 1, the simple mediation model that placed PCI use as the mediator intervening between sex and mortality. That is, women are less inclined to receive PCI relative to men, so women have higher mortality (higher than would be expected without considering inequalities in PCI). In Models 5ii and 6, invasive treatment and medications uptake at different time points are all included as mediators. All mediators included (except pre-admission medications) significantly increase the chance of death at one year for women through inequalities in healthcare, which in turn results in higher mortality.

However, note in model 5ii and 6, the relationship between PCI and medications uptake are not accounted for (Equation 5-3 to Equation 5-6 only includes X and no other mediators). Therefore, the specific indirect effects tested are independent of other mechanisms. It is likely that the indirect effect through

medications seen could be due to an epiphenomenal association between medication uptake and the "true" mediator provision of PCI. As Chapter 4 and others (Setoguchi et al., 2007) have shown, they are highly correlated. The next section, on the estimation of indirect effects using serial multiple mediators models allow for simultaneous test of each mechanism while accounting for the association between invasive procedures and medications uptake.

5.5.1.3 Multiple mediators in serial

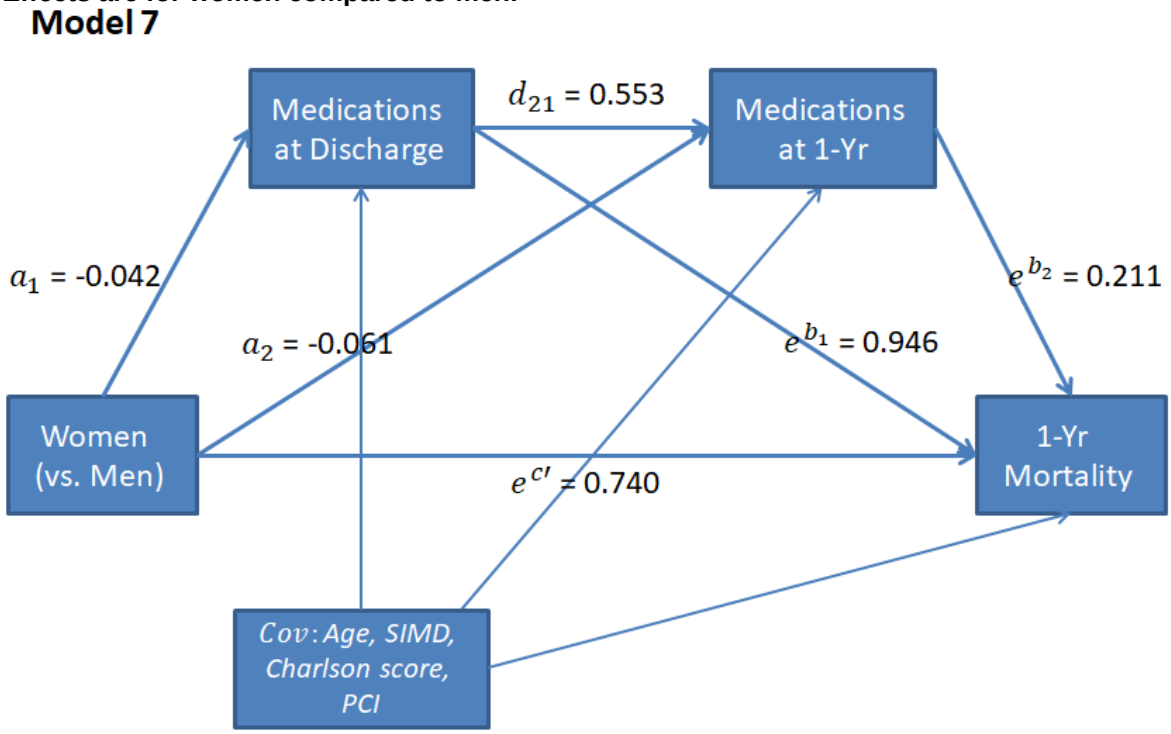
The parallel multiple mediator models estimated above assumes no causal association between the mediators. Although plausible, it is perhaps more plausible that receipt of medications at 1 year are going to be influenced by the receipt of medications before that as well as the provision of PCI in hospital. From Model 8ii, the association between use of PCI and medications at discharge is estimated using Equation 5-9 and is statistically significant (d_{21} = 0.277, CI: 0.239-0.315), with those who received invasive treatment more likely to received medications at discharge. Medications at 1 year is also associated with medications at discharge (d_{32} = 0.553, CI: 0.528-0.577), estimated using Equation 5-10. Therefore models with mediators in serial more appropriately reflect the treatment paths being modelled by accounting for the causal association between the mediators.

Model coefficients of serial multiple mediator models 7-9 are in the statistical diagrams in Figure 5-10 to Figure 5-13. The direct effect and specific indirect effect of sex on mortality through multiple mediators in serial are summarised in the tables below the diagrams. The models tell the same overall story: when invasive and medical treatments are equal between the two sexes, the mortality rate in women is lower than men (evident from the direct effects). However, women end up have higher odds of death at 1 year through the combined effect of lower invasive and medical treatment compared to men. In addition, the effect through lower invasive treatment is stronger than that through medical treatment.

Each model is explained in detail, followed by a general discussion.

Model 7 - The simplest serial multiple mediator with two mediators: medication at discharge and medication at 1-year. This model has 3 specific indirect effects and 1 direct effect. The first specific indirect effect (M_1) of the female sex on mortality through disparities in medications at discharge is not statistically significant (OR=1.00; CI% 1.00-1.01). Same with the specific indirect effect (M_2) through medications at 1-year and the specific indirect effect ($M_1 \rightarrow M_2$) through medications at discharge then at 1-year in serial. Women are less likely to take medication at both time points (because a_i's are negative), and medications are protective (OR=e^{b_i}'s are below 1) regardless of time of uptake. Those taking medications at discharge are also more likely to take medications at 1 year (d_{21} is positive). Combined, the three indirect effects sum to the total indirect effect of gender on mortality through medication use. As can be seen in table, the total indirect effect increased relative mortality risk in women, but is not statistically significant (OR=1.14, 95% 1.00-1.13).

Figure 5-10. Statistical diagrams and path analysis of model 7 with mediators in serial. Effects are for women compared to men.



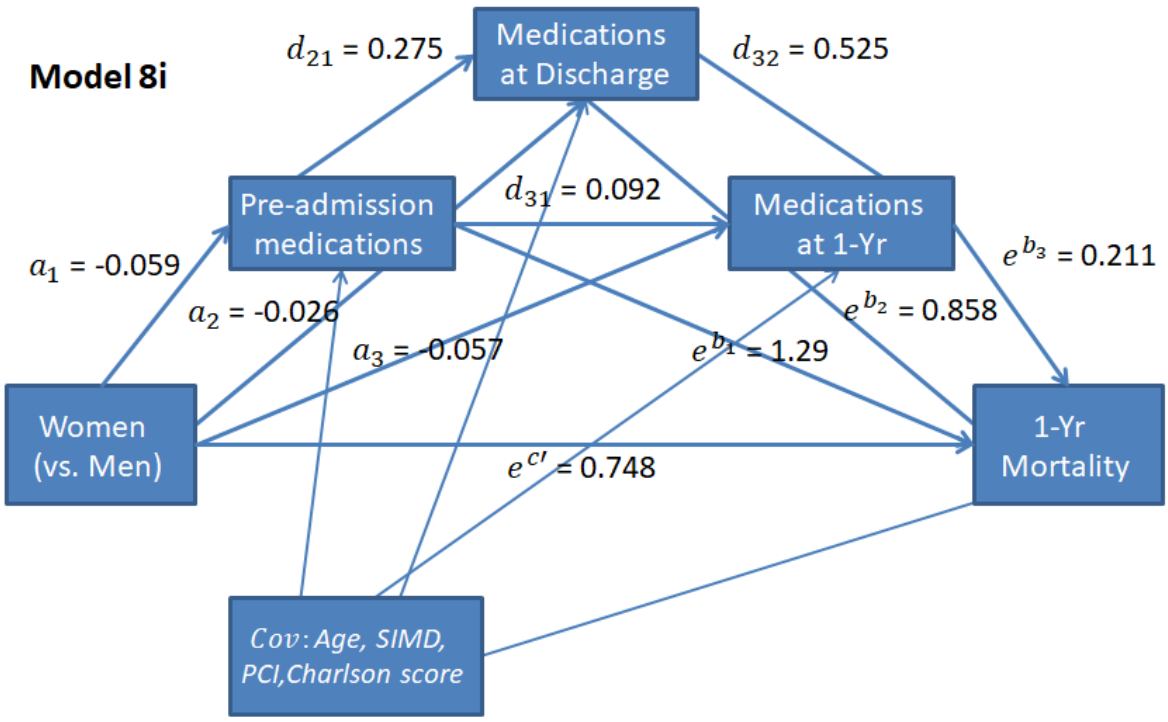
Model	Mediators	Direct Effect OR (95%CI)	Specific Indirect Effects, OR (95%CI)	
7	M_1 = Medications at discharge M_2 = Medications at 1 yr	0.74 (0.60-0.91)	M_1 M_2 $M_1 \rightarrow M_2$ Total	1.00 (1.00-1.01) 1.10 (0.98-1.25) 1.04 (0.99-1.10) 1.14 (1.00-1.33)

The direct effect is the same as that in the parallel mediator model (Model 4) as the model for the direct effect on the outcome does not change for different

mediator models. As in the parallel mediator models, women have lower death risk (OR=0.74) independent of the effect of medication use at discharge and at 1-year.

Model 8i – A third mediator on pre-admission medication use is added on top of the ones in model 7. However, the newly modelled relationships are not statistically significant. Like medication use at discharge and at 1 year, pre-admission use is not a mediator between sex and mortality. The combined sex differences in medication uptake adds to sex differences in mortality to little or no extent (OR=1.13; 95%CI 0.98-1.31).

Figure 5-11. Statistical diagrams and path analysis of model 8i with mediators in serial. Effects are for women compared to men.



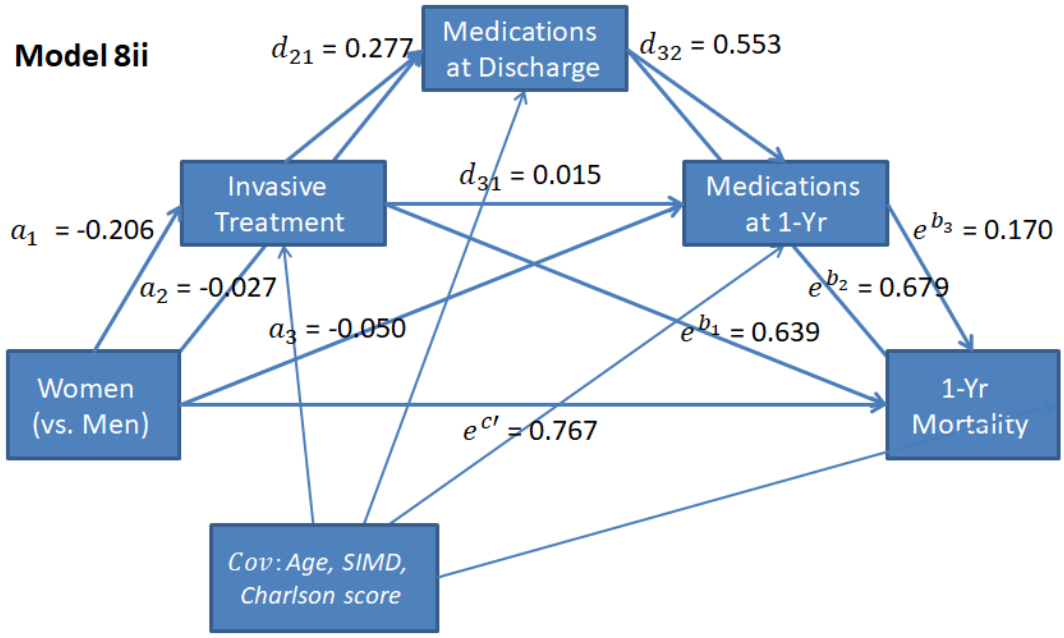
Model	Mediators	Direct Effect OR (95%CI)	Specific Indirect Effects, OR (95%CI)	
8i	M_1 = Pre admission medications M_2 = Medications at discharge M_3 = Medications at 1 yr	0.75 (0.61-0.92)	M_1	0.99 (0.97-1.00)
			M_2	1.00 (1.00-1.01)
			M_3	1.09 (0.97-1.25)
			$M_1 \rightarrow M_2$	1.00 (1.00-1.01)
			$M_1 \rightarrow M_3$	1.01 (1.00-1.02)
			$M_2 \rightarrow M_3$	1.02 (0.97-1.07)
			$M_1 \rightarrow M_2 \rightarrow M_3$	1.01 (1.00-1.03)
			Total	1.13 (0.98-1.31)

Model 8ii – Invasive treatment is considered as a mediator, alongside medication use after discharge and at 1-year in serial. In this model, the first indirect effect of gender on mortality through provision of PCI (M_1) is significant (OR=1.10; CI%

1.07-1.14). Women are less likely to receive PCI compared to men (because a_1 is negative), and treatment is associated with a decreased mortality (e^{b_1} is below 1) independent of medication use. Less invasive treatment in women is translated into higher mortality by 10%. The other indirect effects through medication uptake are similar to the ones detailed for Model 7 and not statistically significant.

Overall, there is no indirect effect through medications uptake only (regardless of time), but a negative indirect effect through lower PCI only, as well as through invasive treatment and then medication use in serial. The sum of all the specific indirect effects through treatment disparities is statistically significant at OR=1.35 (CI: 1.16-1.66). In this model, women have 35% higher odds of death at 1 year through the combined effect of lower invasive and medical treatment compared to men.

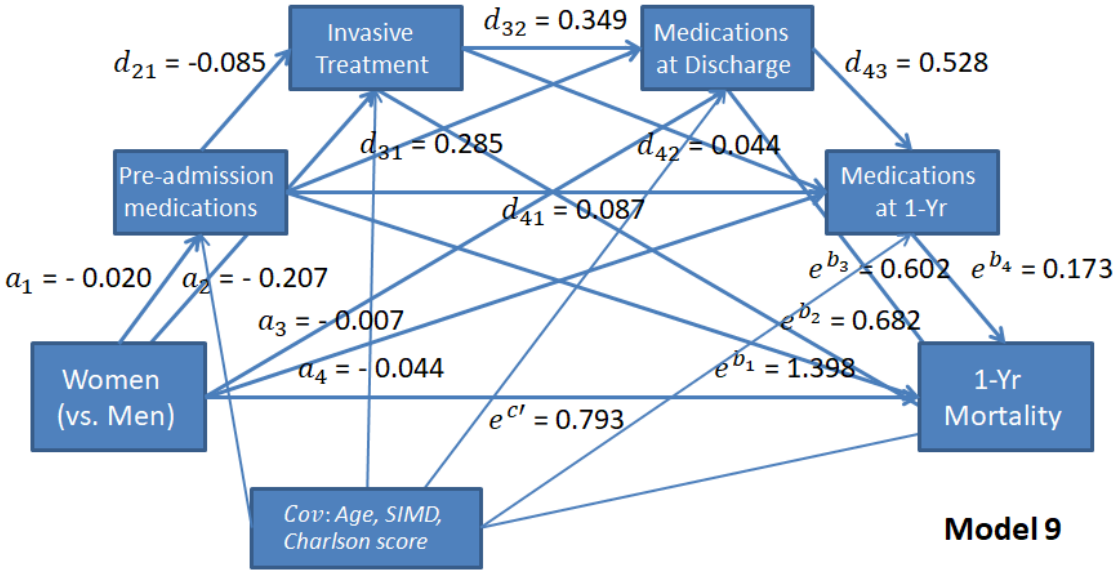
Figure 5-12. Statistical diagrams and path analysis of model 8ii with mediators in serial. Effects are for women compared to men.



Model	Mediators	Direct Effect OR (95%CI)	Specific Indirect Effects, OR (95%CI)	
8ii	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	0.77 (0.64-0.92)	M_1	1.10 (1.07-1.14)
			M_2	1.01 (0.98-1.04)
			M_3	1.09 (0.96-1.28)
			$M_1 \rightarrow M_2$	1.02 (1.02-1.03)
			$M_1 \rightarrow M_3$	1.01 (0.99-1.02)
			$M_2 \rightarrow M_3$	1.03 (0.96-1.10)
			$M_1 \rightarrow M_2 \rightarrow M_3$	1.06 (1.04-1.09)
			Total	1.35 (1.16-1.66)

Model 9 – Four mediators are considered in serial: (1) pre-admission medications, (2) Invasive treatment, (3) medications at discharge and (4) medications at 1 year. The total indirect effect indicates that women have 34% higher odds of death at 1 year through the combined effect of lower invasive and medical treatment compared to men. The direct effect indicates that when invasive and medical treatments are equal between the two sexes, the mortality rate in women is lower than men (OR= 0.82, CI: 0.68-0.98).

Figure 5-13. Statistical diagrams and path analysis of model 9 with mediators in serial. Effects are for women compared to men.



Model	Mediators	Direct Effect OR (95%CI)	Specific Indirect Effects, OR (95%CI)	
9	M_1 = Pre admission medications M_2 = Invasive treatment M_3 = Medications at discharge M_4 = Medications at 1 yr	0.82 (0.68-0.98)	M_1	0.99 (0.97-1.02)
			M_2	1.08 (1.06-1.12)
			M_3	1.00 (0.97-1.03)
			M_4	1.08 (0.95-1.25)
			$M_1 \rightarrow M_2$	1.00 (1.00-1.00)
			$M_1 \rightarrow M_3$	1.00 (0.99-1.01)
			$M_1 \rightarrow M_4$	1.00 (0.99-1.01)
			$M_2 \rightarrow M_3$	1.04 (1.03-1.05)
			$M_2 \rightarrow M_4$	1.02 (1.00-1.04)
			$M_3 \rightarrow M_4$	1.01 (0.94-1.07)
			$M_1 \rightarrow M_2 \rightarrow M_3$	1.00 (1.00-1.00)
			$M_1 \rightarrow M_2 \rightarrow M_4$	1.00 (1.00-1.00)
			$M_1 \rightarrow M_3 \rightarrow M_4$	1.01 (0.99-1.02)
			$M_2 \rightarrow M_3 \rightarrow M_4$	1.07 (1.05-1.10)
			$M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow M_4$	1.00 (1.00-1.00)
			Total	1.34 (1.15-1.65)

Summary of serial models

The *direct effect* of sex on mortality through multiple mediators in serial is exactly the same as those through multiple mediators in parallel because whether the mediators are modelled as causally influencing each other or not does not change the equations used to estimate the direct effect (Equation 5-11 and Equation 5-7). For all models 4-9, the direct effect of the female sex on

mortality at 1 year is around OR=0.8 and statistically significant independent of the effect of invasive and medical treatment.

All the *specific indirect effects* in Models 7-9 with number of medications used as the involved mediators are not statistically significant. This means that even though it was found that women had lower likelihood of taking medications compared to men, gender differences in mortality was not influenced by disparities in medical treatment between the genders.

The *specific indirect effect* of the female sex on mortality through disparities in invasive treatment is significant. Lower PCI rates in females (a_1 = -0.206 in Model 8ii and a_2 = - 0.207 in Model 9) increases mortality in females by around 10% (not accounting for pre-admission medications in Model 8ii is OR=1.10, CI: 1.07-1.14; accounting for pre admission medications in Model 9 is OR=1.08, CI: 1.06-1.12).

Since patients who received invasive treatment were more likely to receive medications at discharge, the *serial specific indirect effects* of female sex on mortality through provision of PCI and number of medications taken in serial, with PCI modelled as affecting medication use, which in turn influences mortality (i.e., $Sex \rightarrow PCI \rightarrow Medications \rightarrow Mortality$) are slightly less than the indirect effect through disparities in PCI use alone but still significant. For example, in model 9, the specific indirect effect through invasive treatment, medications at discharge and at one year ($M_2 \rightarrow M_3 \rightarrow M_4$) is estimated to be OR=1.07 (CI: 1.05-1.10). Relative to men, women are less likely to receive invasive treatment (a_2 = - 0.213), but the provision of PCI was associated with an increase in the number of medications taken at discharge (d_{32} = 0.347), while patients taking more medications at discharge were also more likely to be taking medications at discharge (d_{43} = 0.528), and taking more medications at 1 year is linked to lower mortality (e^{b_4} = 0.176). So even considering the protective effects of increased medication use after PCI, the lower PCI rates in women increased their mortality rates compared to men.

From model 9, the sum of all the specific indirect effects through treatment disparities is statistically significant at OR=1.34 (CI: 1.15-1.65). In other words,

women have 34% higher odds of death at 1 year through the combined effect of lower invasive and medical treatment compared to men. On the other hand, if invasive and medical treatments are equal between the two sexes, the mortality rate in women should be lower than men (OR= 0.82, CI: 0.68-0.98). Therefore, even though women have lower mortality than men when treated the same, the net result of these treatment disparities is that women currently have higher mortality than men overall, as the overall crude association between sex and mortality is OR=1.31 (CI: 1.14-1.51).

5.5.1.4 Multiple mediators in serial and parallel

Models that combined the properties of parallel and serial mediators were also examined and detailed in Figure 5-14. The results are similar to those found before: lower rates of invasive treatment increased mortality in women, but disparities in medications did not function as a mediator if accounting for their associations with the provision of PCI.

From the results of Models 1-9, it seems model 8ii or 9 are the most appropriate at modelling the relationships between sex, treatments and mortality. The models that consider mediators in parallel may be mis-specified as it does not account for the relationships between them.

5.5.1.5 Sensitivity analysis adjusting for categorical age

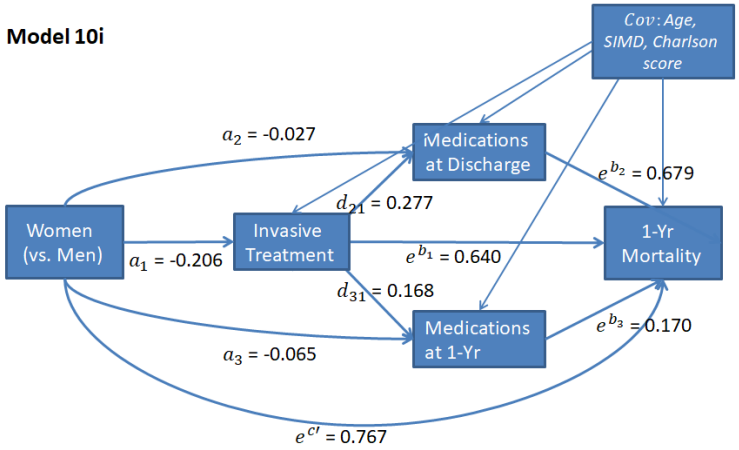
Sensitivity analysis adjusting for categorical age instead of continuous was for model 8ii (as deemed most appropriate at modelling the relationships between sex, treatment and mortality) did not change the significance of the direct or indirect effects but increased the magnitude of the indirect effects.

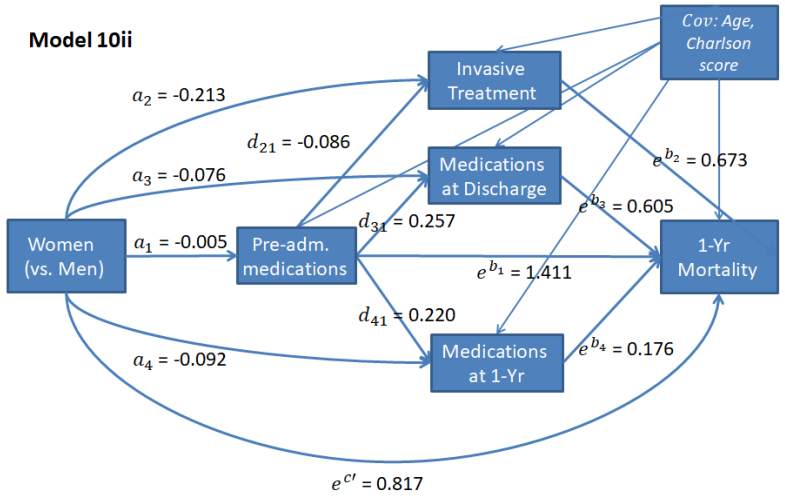
In the sensitivity analysis, women have 52% higher odds of death at 1 year through the combined effect of lower invasive and medical treatment compared to men (compared to 35% when adjusting for continuous age). On the other hand, if invasive and medical treatments are equal between the two sexes, the mortality rate in women is still lower than men but not as extreme as before (OR= 0.87, CI: 0.73-0.96, compared to OR 0.77 CI: 0.64-0.92).

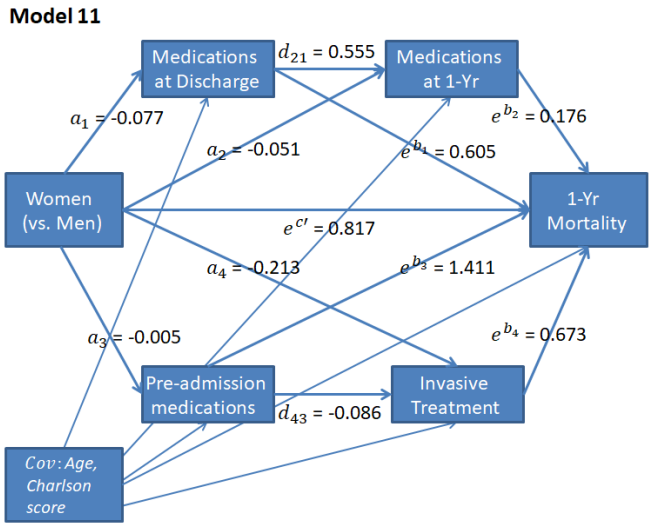
Table 5-8. Sensitivity path analysis of model 8ii with mediators in serial. Effects are for women compared to men.

Model	Mediators	Covariates	Direct Effect, OR (95%CI)	Indirect Effects, OR (95%CI)	
8ii	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	Categorical Age, SIMD, Charlson score	0.87 (0.73-0.96)	M_1	1.15 (1.11-1.20)
				M_2	1.02 (0.98-1.04)
				M_3	1.12 (0.99-1.31)
				$M_1 \rightarrow M_2$	1.03 (1.02-1.04)
				$M_1 \rightarrow M_3$	1.01 (0.99-1.03)
				$M_2 \rightarrow M_3$	1.04 (0.97-1.11)
				$M_1 \rightarrow M_2 \rightarrow M_3$	1.07 (1.05-1.11)
				Total	1.52 (1.30-1.90)

Figure 5-14. Statistical diagrams and path analysis of models 10 and 11, mediators in parallel and serial. Effects are for women compared to men.







Model	Mediators	Direct Effect OR (95%CI)	Specific Indirect Effects, OR (95%CI)	
10i	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	0.77 (0.64-0.92)	M_1	1.10 (1.07-1.14)
			M_2	1.01 (0.98-1.04)
			M_3	1.12 (0.98-1.34)
			$M_1 \rightarrow M_2$	1.02 (1.02-1.03)
			$M_1 \rightarrow M_3$	1.06 (1.04-1.10)
			Total	1.35 (1.16-1.66)
10ii	M_1 = Pre admission medications M_2 = Invasive treatment M_3 = Medications at discharge M_4 = Medications at 1 yr	0.82 (0.68-0.98)	M_1	1.00 (0.97-1.02)
			M_2	1.09 (1.06-1.13)
			M_3	1.04 (1.01-1.07)
			M_4	1.17 (1.02-1.40)
			$M_1 \rightarrow M_2$	1.00 (1.00-1.00)
			$M_1 \rightarrow M_3$	1.00 (0.99-1.01)
			$M_1 \rightarrow M_4$	1.00 (0.98-1.03)
			Total	1.33 (1.11-1.61)
11	M_1 = Medications at discharge M_2 = Medications at 1-yr M_3 = Pre admission medications M_4 = Invasive treatment	0.82 (0.68-0.98)	M_1	1.04 (1.00-1.08)
			M_2	1.09 (0.95-1.26)
			M_3	1.00 (0.98-1.02)
			M_4	1.09 (1.06-1.12)
			$M_1 \rightarrow M_2$	1.08 (1.01-1.17)
			$M_3 \rightarrow M_4$	1.00 (1.00-1.00)
			Total	1.33 (1.12-1.61)

5.5.2 Treatment disparities in socio-economically deprived

5.5.2.1 Simple mediation

From simple mediation analyses conducted using path analyses, differences in invasive treatment between the least deprived group and the most deprived group indirectly influenced mortality at one year.

As can be seen in Model 1 of Figure 5-15 and Table 5-9, ACS patients in the least deprived group are more likely to receive invasive treatment during hospitalisation than the most deprived group (a = 0.140 is positive), and patients that underwent PCI have a lower mortality rate (OR = e^{b_1} = 0.632). A 95% bootstrap confidence interval for the indirect effect (OR = e^{a*b}=0.94) based on 3000 bootstrap samples was below one (0.90 to 0.97). Therefore, even though the mortality rate is much lower in the least deprived group ($e^{c'}$ = 0.618, CI: 0.48 to 0.70 from direct effect) if the two SES groups did not differ in the rate of PCI, unequal invasive treatment rates contributed additional inequalities that favoured the least deprived group. Closing this treatment gap would alleviate the overall mortality difference between the two SES groups.

SES is not associated with mortality indirectly through its effect on number of medications taken at discharge, as seen from Models 2 and 3.

Figure 5-15. Statistical diagrams of models 1 to 3 for the least deprived vs most deprived group

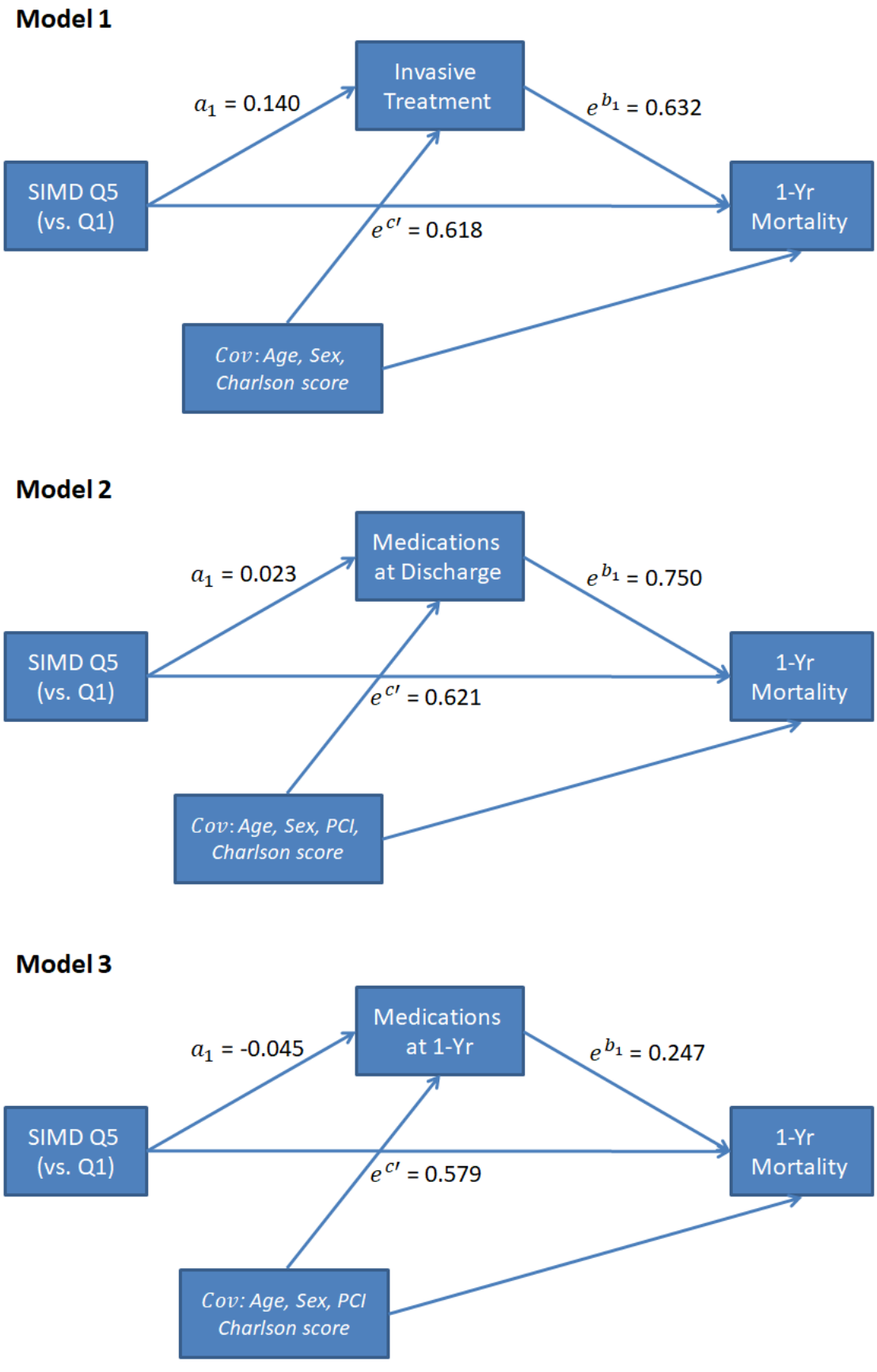


Table 5-9. Path analysis models for SES and mortality. Effects are for SIMD Q5 vs Q1 (the least deprived compared to the most deprived group)

Model	Path	Mediators	Covariates	Population	Direct Effect, OR (95%CI)	Indirect Effects, OR (95%CI)	
1	A	M = Invasive treatment	Age, sex, Charlson score	All	0.62 (0.48-0.79)	0.94 (0.90-0.97)	
2	A	M = Number of medications at discharge	Age, sex, Charlson score and PCI	Discharged alive	0.62 (0.45-0.85)	0.99 (0.97-1.02)	
3	A	M = Number of medications at 1 year	Age, sex, Charlson score and PCI	Discharged alive	0.58 (0.42-0.81)	1.06 (0.87-1.29)	
4	B	M_1 = Medications at discharge M_2 = Medications at 1 yr	Age, sex, Charlson score and PCI	Discharged alive	0.58 (0.42-0.81)	$\boldsymbol{M_1}$ $\boldsymbol{M_2}$ Total $\boldsymbol{M_1}$- $\boldsymbol{M_2}$	1.00 (0.99-1.01) 1.06 (0.87-1.29) 1.06 (0.87-1.28) 0.94 (0.77-1.13)
5i	B	M_1 = Pre admission medications M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, sex, Charlson score and PCI	Discharged alive	0.60 (0.43-0.84)	$\boldsymbol{M_1}$ $\boldsymbol{M_2}$ $\boldsymbol{M_3}$ Total $\boldsymbol{M_1}$-$\boldsymbol{M_2}$ $\boldsymbol{M_1}$-$\boldsymbol{M_3}$ $\boldsymbol{M_2}$-$\boldsymbol{M_3}$	0.97 (0.94-0.99) 1.00 (0.98-1.01) 1.06 (0.87-1.27) 1.03 (0.87-1.29) 0.97 (0.94-0.99) 0.91 (0.74-1.10) 0.94 (0.76-1.14)
7	C-I	M_1 = Medications at discharge M_2 = Medications at 1 yr	Age, sex, Charlson score and PCI	Discharged alive	0.58 (0.42-0.81)	$\boldsymbol{M_1}$ $\boldsymbol{M_2}$ $\boldsymbol{M_1 \rightarrow M_2}$ Total	1.00 (0.99-1.01) 1.08 (0.90-1.33) 0.98 (0.91-1.05) 1.06 (0.87-1.28)
8i	C-II	M_1 = Pre admission medications M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, sex, Charlson score and PCI	Discharged alive	0.60 (0.43-0.84)	$\boldsymbol{M_1}$ $\boldsymbol{M_2}$ $\boldsymbol{M_3}$ $\boldsymbol{M_1 \rightarrow M_2}$ $\boldsymbol{M_1 \rightarrow M_3}$ $\boldsymbol{M_2 \rightarrow M_3}$ $\boldsymbol{M_1 \rightarrow M_2 \rightarrow M_3}$ Total	0.97 (0.94-0.99) 0.99 (0.98-1.00) 1.05 (0.86-1.27) 1.00 (1.00-1.01) 1.03 (1.01-1.06) 0.96 (0.89-1.02) 1.02 (1.01-1.04) 1.03 (0.83-1.25)
8ii	C-II	M_1 = Invasive treatment M_2 = Medications at discharge M_3 = Medications at 1 yr	Age, sex, Charlson score	All	0.59 (0.43-0.79)	$\boldsymbol{M_1}$ $\boldsymbol{M_2}$ $\boldsymbol{M_3}$	0.95 (0.92-0.98) 0.98 (0.94-1.02) 1.08 (0.91-1.28)

						$\boldsymbol{M_1 \rightarrow M_2}$	0.98 (0.97-0.99)
						$\boldsymbol{M_1 \rightarrow M_3}$	1.00 (0.99-1.01)
						$\boldsymbol{M_2 \rightarrow M_3}$	0.96 (0.89-1.05)
						$\boldsymbol{M_1 \rightarrow M_2 \rightarrow M_3}$	0.96 (0.93-0.97)
						Total	0.91 (0.74-1.15)
9	C-III	M_1 = Pre admission medications M_2 = Invasive treatment M_3 = Medications at discharge M_4 = Medications at 1 yr	Age, sex, Charlson score	All	0.61 (0.46-0.82)	$\boldsymbol{M_1}$	0.95 (0.92-0.98)
						$\boldsymbol{M_2}$	0.96 (0.93-0.98)
						$\boldsymbol{M_3}$	0.96 (0.92-1.01)
						$\boldsymbol{M_4}$	1.05 (0.89-1.26)
						$\boldsymbol{M_1 \rightarrow M_2}$	0.99 (0.99-1.00)
						$\boldsymbol{M_1 \rightarrow M_3}$	1.02 (1.01-1.03)
						$\boldsymbol{M_1 \rightarrow M_4}$	1.04 (1.01-1.06)
						$\boldsymbol{M_2 \rightarrow M_3}$	0.98 (0.96-0.99)
						$\boldsymbol{M_2 \rightarrow M_4}$	0.99 (0.98-1.01)
						$\boldsymbol{M_3 \rightarrow M_4}$	0.94 (0.87-1.01)
						$\boldsymbol{M_1 \rightarrow M_2 \rightarrow M_3}$	1.00 (0.99-1.00)
						$\boldsymbol{M_1 \rightarrow M_2 \rightarrow M_4}$	1.00 (1.00-1.00)
						$\boldsymbol{M_1 \rightarrow M_3 \rightarrow M_4}$	1.03 (1.01-1.05)
						$\boldsymbol{M_2 \rightarrow M_3 \rightarrow M_4}$	0.96 (0.93-0.98)
						$\boldsymbol{M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow M_4}$	0.99 (0.99-1.00)
						Total	0.87 (0.71-1.09)

5.5.2.2 Multiple mediators

Since medication uptake at different time points are related to each other and to the provision of PCI, the multiple mediator models that account for these (Models 4, 5i, 7, 8, 9) are presented.

Consistent with simple mediation analysis, as can be seen in Models 8ii and 9 in Table 5-9, the odds of death at 1 year were lower in the least deprived group by around 5% through the mediation of increased use of PCI in the least deprived group (Figure 5-16).

Similar to medical treatment variations between men and women, SES differences in medication uptake at discharge or at 1 year did not add to SES differences in mortality. While the data revealed a significant indirect effect of SES on mortality through pre-admission medications uptake (OR=0.97, CI: 0.94-0.99 for least vs most deprived group). Pre-admission medications, mainly an indicator of frailty, were negatively associated with the least deprived group (Figure 5-16 and Figure 5-17: a_1 negative in Models 5, 8i, 9). In other words, patients of the least deprived SES group are less likely to be taking cardiovascular drugs at baseline, and since less pre-admission medications is associated with better outcomes (less frail), the mortality rate in the least deprived group is further decreased by 3% through lower pre-admission medications.

Together, through both better invasive and medical treatment access in the least deprived group, the odds of death at 1 year was 13% lower in least deprived SES group (total indirect effect OR=0.87, CI:0.71-1.09) compared to the most deprived group. This further exacerbates the already unequal survival rates in the two groups (direct effect OR=0.61; CI: 0.46-0.82) under equal treatment conditions.

Figure 5-16. Statistical diagrams of models 4 and 5i for the least deprived vs most deprived group

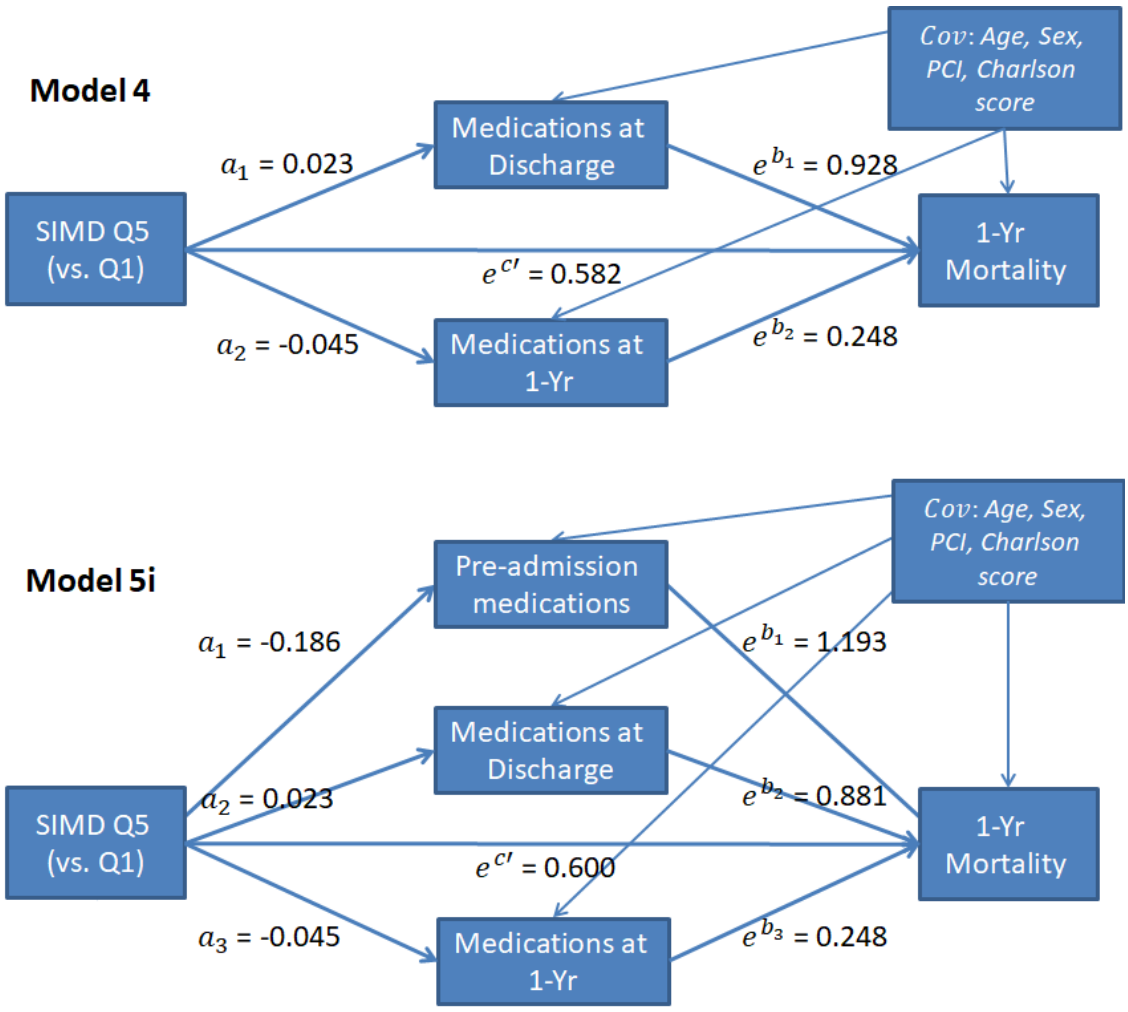
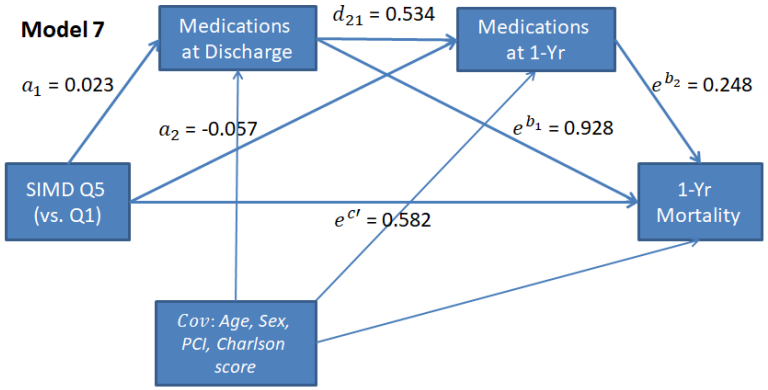
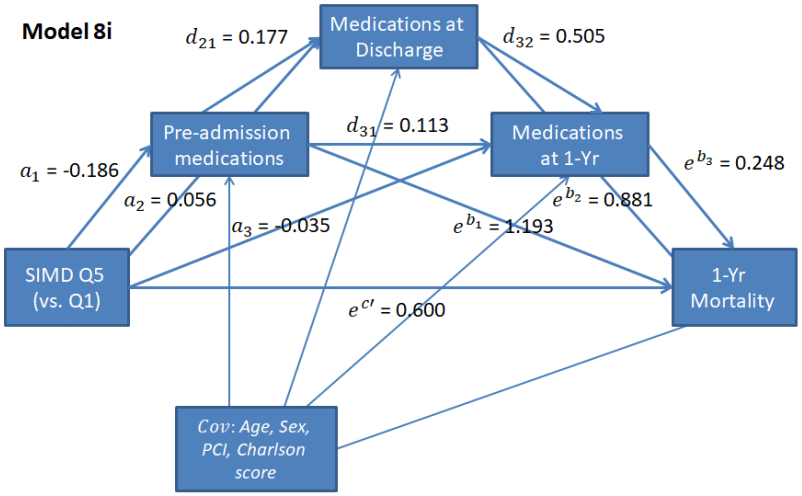
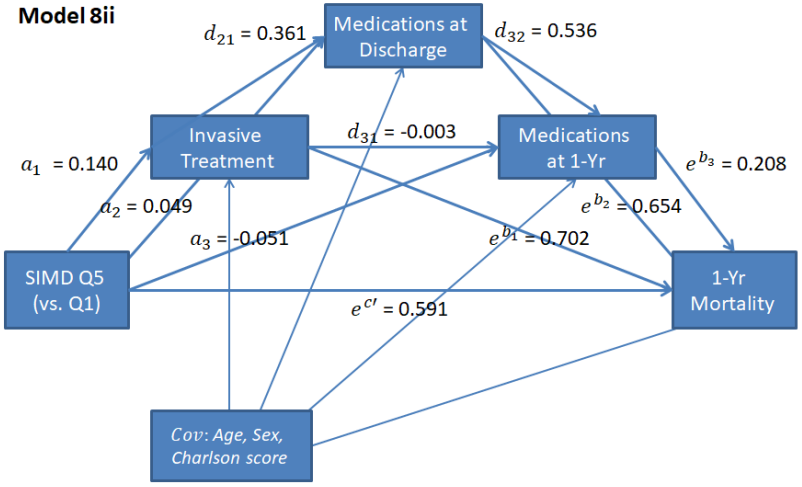
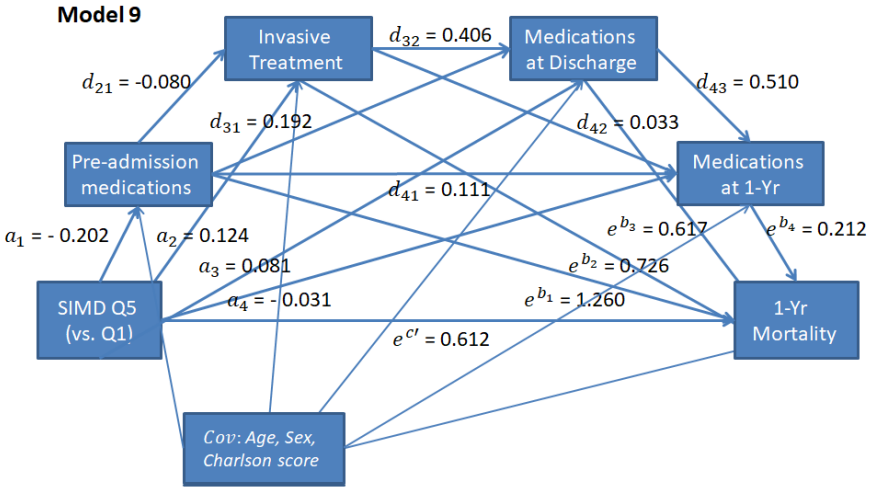


Figure 5-17. Statistical diagrams of models 7-9 for the least deprived vs most deprived group









5.6 Discussion

5.6.1 Summary

In previous chapters, we looked at the existence of treatment inequalities by sex and by SES in ACS patients, but little is known about the effect of these treatment inequalities on mortality and the most efficient mechanisms that might facilitate decreasing the mortality gap between the sexes (or SES groups). This chapter examined the mediating effect of healthcare inequalities on the relationship between sex (or SES) and 1-year all-cause mortality.

Models that tested mediation effects of mediators one at a time in simple mediation models and multiple mediators in serial in complex models were performed. All models adjusted for the effects of baseline characteristics: age, sex, SIMD, and comorbidities.

Inequalities in the provision of PCI mediated the relationship between sex and mortality at 1 year for ACS patients. This indirect effect alone increased mortality by around 10% in women compared to men. Inequalities in recommended medications uptake alone were more subtle and did not mediate the effect of sex on mortality. The combined indirect effect of reduced invasive and medical treatments increased women's mortality by 34% compared to men. Similar associations were found for SES, treatment inequalities and mortality. The findings suggest that women and patients of lower SES received less invasive treatment, which in turn reduced their 1-year survival rates after ACS admission compared to their counterparts. Even though women have lower risk compared to men when treated the same, treatment disparities reversed this mortality risk: women currently have higher mortality than men overall. For the most deprived group, who are already at increased risk when treated the same, lower treatment rates exaggerated the unequal risk of death compared to the least deprived group. Of particular importance in this analysis was that most of mediating effect on mortality was through unequal PCI rates, while the indirect effect on mortality though likelihood of medications were minor. Hence, reducing treatment inequalities by increasing PCI rates in women and deprived

groups would most effectively diminish the survival gap seen between the sexes, and SES groups.

5.6.2 Limitations

5.6.2.1 Alternative explanations

This study represents a first attempt to understanding the mechanisms of health disparities between men and women, and by SES in patients hospitalised with ACS with a number of mediation models. By estimating the different magnitudes of association between sex and mortality through different treatment disparities, the current research extends prior studies. However, when interpreting the results, it is important to keep in mind that the mediation models proposed are exploratory and their results should be interpreted with caution. As highlight by Hayes (2018), "all models are wrong to some extent, and no model will completely and accurately account for all influences of the variable of interest" (Hayes, 2018, MacCallum, 2003). Mediation analysis was a mathematical procedure used to answer some questions that came up as a result of our findings from previous chapters on healthcare inequality. The models proposed are tools to help us understand the data, and they can provide insights that are only approximations of reality. Alternative explanations abound, for at least some of the relationships observed. A few other important factors associated with prognosis after ACS and sex were not measured in the present study, such as smoking history, vessel diameter, and CAD severity. Alternative interpretations and confounding variables may exist, but I have done my best to account for as much data that is available into the analysis. Some would argue that the effect of recommended medications on mortality should not be estimated in pragmatic studies such as this one because reasons for not taking these recommended medications are sometimes due to adherence on the patient's side but more likely, guided by the medical conditions of each patient. These reasons are usually complex, involve contraindications and not recorded. However, it is imperative that certain conditions are met for these factors to allow an alternative explanation for our findings: these unmeasured factors would have to be associated with both the independent variable (X) and the mediator (M) in the models.

For pragmatic purposes, analysis on the relationship between SES, use of recommended treatment and mortality is shown only for the least deprived compared to the most deprived group. Results of Chapter 3 indicated that although the most and least deprived (SIMD Q1 and Q5 respectively) did not differ in medications uptake after discharge, SIMD quintiles 2-4 were less likely to receive medications compared to Q1 and Q5 at discharge after adjusting for baseline characteristics. A sensitivity analysis was performed to test the indirect relationship between SIMD Q3 vs Q1 and mortality through use of PCI and medications at different time points. Results from model 8ii showed that the odds of mortality at 1 year was indirectly increased through lower medication uptake at discharge in SIMD Q3 compared to SIMD Q1 by 16% (OR=1.16, CI: 1.10-1.22). This indirect effect was larger in magnitude than the indirect effect through inequalities in PCI use. The indirect effects through medications at 1 year were not statistically significant.

5.6.2.2 Methods

Mediation was initially developed for and primarily used in the field of psychology where most outcomes are continuous measures. Therefore linear regression was the foundation on which mediation models were built on. In this analysis, the outcome (mortality) is binary so logistic regression was used to model mortality. The mediators are counts data, or can be treated as binary (e.g. yes/no PCI, yes/no statins), but ordinary least squares regression were used to estimate the mediators. This violates the normality assumption, therefore it is not ideal for modelling mediators. However, this is not uncommon or entirely inappropriate (Hagen et al., 2015, Hayes and Ebooks Corporation Limited., 2013). As pointed out by Hayes (2018), the "advantages of OLS regression far outweigh some of the costs of abandoning it for other perhaps better but much more complicated and less well-understood methods" (Hayes, 2018). When the mediator M is dichotomous and logistic regression is used to model M, then the analytic formulas for the direct and indirect effects no longer take quite as simple a form (Vanderweele and Vansteelandt, 2010), while methods with count mediators have not been developed yet. Software to estimate indirect effects with binary mediators is available for simple mediation models (Valeri and Vanderweele, 2013), while the individual and combined

specific indirect effects of multiple mediators in serial have not been adapted for use yet, only the total and indirect effects of multiple mediators in parallel have been theorised (VanderWeele and Vansteelandt, 2014, Tchetgen Tchetgen, 2013). In addition, a mix of continuous and binary mediators in serial would bring even more unnecessary complications to the models. Sensitivity analyses were performed with the provision of PCI as a binary mediator using both logistic and OLS regression to model this measure with simple mediation. Although model coefficients a and b were different due to the scale of the measure, the indirect effects did not differ from findings here (logistic indirect effect OR=1.08; OLS with PCI=1 if PCI performed and PCI=0 if PCI not performed indirect effect OR=1.10). This means that inference of indirect effects using invasive procedures as a dichotomous measure would be similar to the findings in this Chapter.

5.6.3 **Other concerns**

Statistical significance of individual pathways in the path analysis models (i.e. a's and b's in statistical diagrams) were not shown. As explained in Section 5.2.4, these are not necessary conditions for calculating the indirect effect. It is possible that there is no evidence of an association between X and the proposed mediator, but evidence of an indirect effect through this mediator, and vice versa. Modern thinking about mediation analysis does not require evidence of a simple association between X and M or X and Y in order to estimate and test hypotheses about indirect effects (Hayes, 2018, Hayes, 2009).

As we are interested in healthcare inequalities, it was also not within the scope of this chapter to investigate the total effect of sex (or SES) on mortality, which usually accompanies mediation analysis. This is simply the overall effect of X on Y (without adjustment for mediators' effect) and can be decomposed into either the sum of the direct and indirect effects when outcomes are continuous (Baron and Kenny, 1986) or the product (VanderWeele and Vansteelandt, 2014) on the odds ratio scale when outcome is binary.

In addition, the "degree of mediation" or "proportion mediated" is also not shown. This measure is defined as the ratio of the indirect effect to the total

effect when the outcome is continuous; or can also be calculated on the risk difference scale when the outcome is binary using a transformation of the odds ratios (Valeri and Vanderweele, 2013, Vanderweele and Vansteelandt, 2010). This concept has been applied in abundance in mediation analyses but has recently been discouraged (Hayes, 2018) for the following reasons:

1. It is possible for an indirect effect to exist without evidence of a total effect. However, the degree of mediation cannot be calculated in such circumstances since the total effect (denominator) would be zero.

2. As the denominator (total effect) approaches zero, even tiny indirect effects will explode in size relative to the total effect.

3. Contrary to what the concept implies, a mediator that completely mediates the effect of X on Y does not preclude the existence of other mediators and does not mean the model is perfect. Similarly, findings of only partial mediation do not mean it is incomplete or "mis-specified".

4. This measure is too sample size dependent. It is possible to limit the sample size such that there is just enough power to be able to claim that M is a mediator, but not enough to detect the direct or total effect. This is because tests of indirect effects are generally higher in power than tests on total effects of the same size, in other words an indirect effect of a given size is sometimes easier to detect than a comparably sized total effect.

Consequently, although a very popular measure in mediation analysis, it was not implemented.

5.6.4 Further work

Regarding the use of mediation models in analysing healthcare inequalities, much more can be explored, and the models could be extended. For example, subgroup analysis could be performed by ACS type. However, since the difference in PCI rate between men and women are similar by ACS type (Chapter

4), it will be very likely that the indirect effect of sex on mortality through PCI use do not differ by subgroup.

Other indicators of treatment quality such as admission lengths can be explored as a possible mediator. In addition, quantifying the impact of pre-existing conditions on mortality through different paths related to quality of care could be of interest.

5.7 Conclusion

Mediation models as described in this chapter are statistical tools to help guide the story we tell from the data we have collected. In this chapter, some of the most sensible causal processes for differences in sex and SES in mortality are tested and quantified. To my knowledge, this is first study to apply mediation analysis to quantify and compare the effect of healthcare inequalities by sex on health outcomes. The models applied were also more elaborate and complex than prior research.

Although the use of PCIs and availability of treatment facilities have increased during the past two decades for treating AMI (Setoguchi et al., 2008, Hagen et al., 2015), the rates between sex and between SES groups are not equal within this group of ACS patients (Chapter 3 and 4). Such findings are consistent with previous findings and with the inverse-equity hypothesis (Korda et al., 2011) which predicts an increase in inequalities of coverage for new interventions due to preferential uptake by the most advantaged groups. Not surprisingly, results from this Chapter suggest that inequalities in treatment have translated into inequalities in outcome by a significant amount. More specifically, the indirect effect of inequalities in the provision of PCI alone increased 1-year mortality by around 10% in women compared to men in ACS patients, while inequalities in recommended medications uptake alone were more subtle and did not mediate the effect of sex on mortality. Similar associations were found for SES, treatment inequalities and mortality. These data should encourage clinicians to close this social gap in the use of proven therapies in the management of ACS patients. Policies for reducing health disparities for ACS patients of the Greater

Glasgow and Clyde Health board should pay particular attention to reducing inequalities in the provision of PCI.

Appendices

Appendix Document. Copyright clearance for Chapter 4

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Appendix Table. Summary of assessed studies for literature review.

Study, Publication year	Country	SES measure	Endpoints	Population	Measure (lowest vs highest SES)*	Adjustments in analysis
Abbasi et al., 2015	Iran	Education and occupation (<=5 yrs education and unemployed vs >5 yrs education and employed)	In-hospital mortality	6246 (All first time ACS admissions)	OR 3.29 (1.02-10.64)	Age, sex, BMI, comorbidities, ACS type
Abrams et al., 2010	USA	Access (URH code: highly rural, rural, urban; RUCA code: isolated town, town, urban)	Revascularization (PCI or CABG) within 30 days of admission	15870 (All veterans admitted with AMI)	OR 1.13 (0.96-1.31)	Age, sex, race, marital status, comorbidities, location of AMI, lab tests (stepwise) final model not shown
			30-days morality		HR 0.84 (0.53-1.31)	
Agarwal et al., 2014	USA	Median household income of neighbourhood (residential zip code quartiles)	In-hospital mortality	372984 (All STEMI admissions)	OR 1.11 (1.06-1.17)	Age, sex, comorbidity index, hospital characteristics
			Timely reperfusion (PCI) on day 0		OR 0.80 (0.74-0.88)	
Ahmadi et al., 2014	Iran	Education (Yrs: 0, 11-5, 6-9, 10-12, >12)	In-hospital mortality	20750 new MI admissions	HR 1.27 (1.06-1.52)	Age sex, comorbidities, type of MI, thrombolytic therapy and PCI
Alter et al., 1999	Canada	Median neighbourhood income (every 10000$ decrease)	Angiography within 6 months	51591 AMI admissions, total length of hospital stay<4 days discharged alive and transfers from another acute care facility excluded	HR 0.85 (0.82-0.89)	Age, sex, comorbidity index, attending physician, hospital characteristics (volume, distance, type)
			Mortality at 1 year		HR 1.11 (1.06-1.16)	
			Waiting time for angiography		Additional 9.2 days	
Alter et al., 2004	Canada	Household income	Mortality between 30 years and 1 year	2256 AMI through emergency departments, excluded deaths within 1 month, discharged or transferred early	RR 1.25 (0.68-2.31)	Age, sex, race, comorbidities, hospital type, patient rural/urban
		Education			RR 0.88 (0.51-1.50)	
Alter et al., 2005	Canada		In-hospital mortality		OR 1.05 (1.03-1.06)	Age, sex, age*sex

		Neighbourhood median household income (10000$ decrease)	Revascularisation at 30 day	139484 AMI patients, excluded those with hospital stay less <3 days	OR 0.99 (0.96-1.02)	stepwise
		Neighbourhood education < 9 years (10% increase)	In-hospital mortality		OR 1.06 (1.03-1.10)	
			Revascularisation at 30 days		OR 0.87 (0.82-0.92)	
Alter et al., 2006	Canada	Household income	2-year mortality	3407 hospitalized for MI through emergency departments, excluded deaths within 1 day, discharged or transferred early	HR 1.22 (0.87 – 1.69)	Age, sex, race, cardio comorbidities, social support, no- cardio comorbidities, revascularisation, attending physician specialty
Ambugo et al., 2015	Norway	Education (primary vs tertiary)	1-year mortality	9412 first AMI patients hospitalised for AMI and discharged alive	OR 1.18 (0.92- 1.49)	Age, sex, other SES, AMI type, minutes to nearest PCI facility, PCI, length of stay, comorbidities
		Income (1890 kroner decrease)			OR 1.11 (0.91 – 1.14)	
		Marital status (unmarried vs married)			OR 1.18 (1.03-1.35)	
Austin et al, 2014	England	Marital status (unmarries vs married)	Mortality (of entire fu: median 545 days)	2297 STEMI patients with PPCI	HR 1.33 (0.95-1.89)	**Age, sex, other SES, path (self-presentation vs direct), comorbidities**
			Symptom to first medical contact >30 min		OR 1.30 (1.03 – 1.62)	
			Total ischemic time (Call to balloon +STFC time) >180min		OR 1.25 (1.01 – 1.54)	
		Access (based on distance to nearest ER) (driving time >20min vs <=10 min)	Mortality (of entire fu: median 545 days)		HR 0.85 (0.54-1.35)	
			Symptom to first medical contact >30 min		OR 1.25 (1.01 – 1.54)	
			Total ischemic time (Call to balloon +STFC time) >180min		OR 1.30 (0.97-1.74)	
Bang et al.,2014	USA	Education (<12 yrs vs >=16 yrs)	Mortality (of entire fu)	637 patients with MI	HR 0.93 (0.55-1.57)	Age, sex, comorbidity index, type of MI, PTCA, CABG, statin, beta blocker, aspirin

Barakat et al.,2001	England, UK	Carstairs deprivation score (Area-level SES index, a composite for social class of head of household, overcrowding, car ownership and unemployment)	30 day mortality	1417 patients admitted with AMI to coronary care unit of 1 hospital	HR 1.63(1.01-2.62)	Age, sex, race, diabetes, acute thrombolysis and aspirin, left ventricular failure; + discharge drugs (aspirin and beta blockers)
			31 days to 1 year mortality		HR 0.79(0.41-1.53)	
Bergstrom et al.,2015	Sweden	Area-level SES tertiles (aggregate of income and education)	Mortality (of entire fu: mean 1720 days)	10895 patients hospitalised for AMI	HR primary adjustment only: 1.17 (1.09-1.26) HR additional adj: 1.12 (1.03-1.20)	Primary adjustments: age sex, comorbidities, revascularisation, STEMI, calendar year Additional adjustments: propensity scores for additional patient characteristics and medical treatment at discharge
			Likelihood of reperfusion		RR 0.95 (0.86-1.06)	
Bernheim et al.,2007	USA	Self-reported household income (<10000, 10000-29000, 30000-49000, 50000-69000, >70000)	1 year mortality	2141 patients hospitalised with AMI within 24 hours of symptom onset	Unadjusted HR: 2.80 (1.37 – 5.72) Adjusted: 1.19 (0.54-2.62) Additional quality adjustments: 1.07 (0.48, 2.35)	Age, sex, race, insurance status, and clinical factors; quality measures: medicine, timely reperfusion, reperfusion
Blais et al.,2012	Canada	Area-level deprivation index quintiles (2 dimensions: material and social). Material based on education, employment and average income; social on living alone, marital status and single-parent family.	1 year-mortality	50242 Patients with a first AMI, excluding those discharged within 3 days	Material: 1.16 (1.08 – 1.25) Social: 1.13 (1.05 – 1.21)	Age sex, comorbidity index (OAMPR), geography of residence, hospital characteristics; + PCI of CABG for mortality
			6 month access to coronary revascularization		Material: 0.99 (0.94 – 1.05) Social: 0.94 (0.89-0.99)	
Cacciani et al., 2017	Italy	Education (None, lower secondary, upper	Access to PCI within 2 days	14013 hospitalised for STEMI (analysis split into 2 five-year	2001-07: 0.74 (0.62 – 0.86) 2007-12: 1.15 (0.95-1.38)	Age, sex, birthplace, comorbidities

		secondary, >post-secondary)	30 day mortality	periods: 2001-07, 2007-12)	2001-07: 1.05 (0.78-1.42) 2007-12: 1.59 (1.14 – 2.23)	
Cafagna et al., 2017	Italy	Education (<middle school, middle school, >high school)	30-day mortality	12409 patients hospitalised for AMI, age<=75	OR 1.49 (1.06 – 2.13)	Age, sex, comorbidities, hospital characteristics
				10993 patients hospitalised for AMI, age>75	OR 1.39 (1.05 – 1.85)	
Capewell et al., 1996	Scotland, UK	Deprivation score by Carstairs and Morris	30-day mortality	39876 admission with AMI	OR 1.06 (0.98 – 1.15)	Age, sex, co-morbidities
Capewell et al., 2000	Scotland, UK	Deprivation score by Carstairs and Morris	30-day mortality	117718 admission with first AMI, 69563 males, 49155 females	Male OR 1.10 (1.03- 1.18) Female OR 1.04 (0.97 – 1.11)	Age, prior admission to hospital as comorbidity indicator
			30-day to 10 year mortality		Male HR 1.27 (1.21-1.33) Female HR 1.15 (1.09-1.21)	
Casale et al., 2007	USA	Neighbourhood median household income quintiles	Use of primary PCI on same day of admission	16985 STEMI (first of study period) admission to hospitals with PCI capability	OR 0.87 (0.80 – 0.95) Women less likely to undergo primary PCI	Age, sex, prior PCI, comorbidities, ethnicity, insurance, hospital characteristics
Cesana et al., 2001	Italy	Occupation (Erikson-Goldthorpe-Portocarero social class scheme based on employment status, work setting, job titles)	28-day mortality	1063 MI events in males age 35-64, women excluded due to low employment rate and events	OR 2.46 (1.44-3.72) Additional cov (treatments) cannot explain observed differences, exact numbers not given	Age Additional cov: within hospital Anti-platelet, beta blockers, Ca blockers, thrombolytic therapy, angiography, PCI, CABG
Chan et al., 2010	USA	Neighbourhood median income (per quartile decrease)	Statin adherence (fully adherent when filled prescriptions covered >80% of days within 1 year)	14257 privately insured patients prescribed a statin	OR 0.88 (0.85-0.93)	Age, gender, comorbidities, insurance payment type, physician characteristics
Chang et al., 2007	Canada	Neighbourhood median household income (per $10000 decrease)	1-year all-cause morality	5622 patients with initial AMI presented to emergency department	HR 1.20 (1.06-1.36)	Age, sex, comorbidities, hospital characteristics
					HR 1.06 (1.02-1.09)	Age, sex, comorbidities, hospital characteristics and revascularisation

					SES interacted with revascularisation significantly (P=0.03) SES effect was largely confined to non-revascularised patients.	Age, sex, comorbidities, hospital characteristics, revascularisation, SES*revascularisation interaction term
			1-year revascularisation		OR 0.94 (0.91-0.96) NS after adj for hospital charac.: lower trt rate due to access issue, more likely to be hospitalised in rural area without rev facilities.	Age, sex, comorbidities; +hospital characteristics
Coady et al., 2014	USA	Individual education (< high school, high school vs > collage),	30-day mortality	8043 women and 7929 men over 66 with first MI patients with Medicare	Female HR 1.07 (0.84-1.37) Male HR 1.07 (0.87-1.31)	Age, race, comorbidities, PCI-CABG at hospitalisation, year of MI
			30-day to 1-year mortality		Female HR 1.07 (0.87-1.32) Male HR 1.00 (0.85-1.17)	
		Area median income quintiles	30-day mortality		Female HR 1.05 (0.86-1.28) Male HR 1.06 (0.84-1.33)	
			30-day to 1-year mortality		Female HR 1.02 (0.86-1.22) Male HR 1.24 (1.04-1.48)	
Consuegra-Sanchez et al., 2015	Spain	Individual Education	Long term mortality (median 8.5 yrs)	5797 admitted to coronary care unit for AMI within 24 hours of symptom onset	HR 1.18 (1.02-1.35)	Age, sex, bmi, comorbidities, PCI, time to admission
Coory et al., 2002	Australia	Neighbourhood level SES index based on education and employment quintiles	Rate of invasive coronary procedures (angiography, PCI)	3531 admitted for first AMI (30-89), excluding those with <4 day stay and discharged alive to reduce # of false positives	Angiography RR 0.34 (0.31-0.39) PCI RR 0.53 (0.35-0.79)	Age, sex, location of residence, admitting doctor, comorbidities
Davies et al., 2010	Scotland, UK	Neighbourhood level SES index (Carstairs)	Mortality from day 1 -28, excludes those that died on day of event	375848 first AMI >30 yrs	Men<60 1.37 (0.99-1.90) Men>60	Age, sex, year of admission

					1.05 (0.94-1.17) Women<60 0.86 (0.51-1.45) Women>60 0.99 (0.90-1.09)	
Donyavi et al., 2011	Iran	Individual education (yrs: illiterate, 1-5, 6-9, 10-12, >12)	In hospital mortality	664 hospitalised with MI	OR 1.51 (0.87-6.31)	Age, PCI, bmi, comorbidities, marital status
Fabreau et al., 2014	Canada	Neighbourhood median household income quintiles (lowest vs highest)	Access to catheterization within 2 days of admission	9995 men and 4017 women admitted with ACS >18yrs (2004-2011)	Men 1.03 (1.02-1.05) Women 0.99 (0.93-1.06)	Age, type of ACS, comorbidities, hospital characteristics, year
			30-day mortality		Men 1.05 (0.95-1.15) Women 1.14 (1.01-1.28) Sex modified aSES and 30-day mortality	
			1-year mortality		Men 1.05 (0.98 - 1.14) Women 1.01 (0.93-1.09)	
Foraker et al., 2008	USA	Neighbourhood household income (tertile)	Pre-hospital delay (time from symptom onset to hospital arrival: <2 hrs, 2-12, 12-72hrs)	6746 AMI aged 35-74, excluding events with delay times > 3 days, hospital transfers	Long vs short delay OR: 1.46 (1.09-1.96) Medium vs short delay OR: 1.43 (1.12-1.81)	Age, sex, race, comorbidities, pathway of admission, distance to hospital, year of AMI event
Foraker et al., 2010	USA	Neighbourhood household income (tertile)	Receipt of medications: aspirin, beta blockers, ACE inhibitors, optimal therapy (>=2 trt) received during hospitalization or at discharge	9608 AMI cases	Beta blockers: 0.93 (0.87-0.98) Ace inhibitors: 1.13 (1.04-1.22) For other outcomes, exact numbers not given as not statistically significant	Age, gender, race, study community, year of MI, hospital type, comorbidities
Fournier et al., 2013	Switzerland	Individual education (low vs high)	Delay: symptom to first medical contact time (medians), door to needle time	222 Patients with STEMI undergoing PCI in tertiary hospital, excludes patients with time delay >12 hr, previous fibrinolytic trt	Symptom to contact: 123.5 (80.0-264.0)min vs 101.0 (58.5-159.0) Door to needle time NS	None
		Marital status(unmarried vs married)			Symptom to contact: 118.0 (68.3-273.5)min vs 105.0 (60.5-174.0)	

				or immediate CABG referral	Door to needle time NS	
Gerber et al., 2008	Israel	Individual level income	Mortality (entire follow up mean 12 yrs)	1521 patients discharged from AMI (not dead within hospital)	Less than 12 yrs of education: HR 1.78 (1.13-2.21) More than12 yrs of education: 1.26 (0.79-2.03)	Age, sex, comorbidities, acute management and medication
Gerber et al., 2008 (a)	USA	Neighbourhood level median income (tertile)	Long term mortality (Median fu 13 months)	705 hospitalised with MI	HR 2.10 (1.42-3.12)	Age, sex, race, comorbidities, hospital trt (PCI, CABG, medications), the other SES factor
Gerber et al., 2010	Israel	Neighbourhood level SES index developed by Israel Central Bureau of Statistics tertiles (summary of demographics, education, standard of living, unemployment, social benefits)	All-cause mortality (entire follow up median 13.5 yrs)	11179 hospitalised with first ever MI and discharged alive	HR 1.47 (1.05-2.06) Without adjusting for other individual SES factors: 1.75 (1.28-2.40)	Age, sex, comorbidities, individual SES measures (income, education, employment), PCI/CABG within 45 days
		Individual income			HR 1.07 (0.75-1.54) Not adjusted for other SES factors: 1.59 (1.14-2.20)	
		Education (every 3 yrs decrease)			HR 1.10 (1.01-1.19) Not adjusted for other SES factors: 1.17 (1.08-1.28)	
		Unemployment			HR 1.74 (1.31-2.31) Not adjusted for other SES factors: 2.04 (1.56-2.68)	
		Living with a partner			HR 1.51 (1.14-2.04) Not adjusted for other SES factors: 1.69 (1.27-2.27)	
Gerward et al., 2006	Sweden	Area level SES index (rate of migration,	28 day mortality	5533 Admission with first MI	OR 1.25 (1.03-1.52)	Age, sex (Also adj for area-level cardio risk score, but

		foreign residence%, social welfare%, %unemp)				didn't change significance, exact # not shown)
Gerward et al., 2010	Sweden	Marital status (No vs Yes)	28 day mortality	3035 with first coronary event 27-61 yrs (admission for AMI, or died of IHD without reaching hospital)	Exact # not reported for 28 days, use 1st day mortality est: Men 2.14 (1.63-2.91) Women 2.32 (0.93-5.79)	Age, comorbidities, lab measures
		Occupational groups			Occupation not related to mortality OR 1.25 (0.90-1.73) (men only), similar finding in women but without precise data.	
Gibler et al., 2002	USA	Individual education	Delays to hospital arrival and trt with fibrinolytic therapy (<2 hrs, 2-4, >4 hours)	4744 with STEMI enrolled in thrombolysis trial	Patients with higher education levels or not living alone are associated with earlier response to symptoms and experienced more rapid treatment	None
		Living alone				
Gnavi et al., 2014	Italy	Individual education (>13 yrs, 8-12, <8)	Rate of revascularisation	Patients hospitalised with first STEMI (n=3506) or NSTEMI (n=2286)	STEMI Angio OR 0.58 (0.40-0.83) STEMI PCI OR 0.59 (0.45-0.79) NSTEMI Angio OR 0.70 (0.47-1.04) NSTEMI PCI OR 1.04 (0.78-1.38)	Age, sex, comorbidities index, hospital characteristics
			30-day mortality		STEMI OR 1.31 (0.85-2.00) NSTEMI OR 0.85 (0.42-1.71)	
			In-hospital to 1 year mortality		STEMI RR 1.29 (0.79-2.10) NSTEMI RR 0.92 (0.55-1.54)	
Greenwood et al., 1995	England, UK	Social support (marital status, social contacts)	Long term mortality (median fu 5.6 yrs)	3458 patients with suspected AMI that completed baseline	HR 1.33 (0.95-1.77)	Age, sex, city, comorbidities, discharge medication (using forwards stepwise selection)

				questionnaire and alive 7 days after event	Lack of social contact or being unmarried NS associated with survival	
Grey et al., 2014	New Zealand	Area based measure combing 9 variables (NZDep2006)	28-day mortality 29 day to 1-yr mortality	42920 ACS patients	HR 1.18 (1.05-1.33) HR 1.14 (0.73-1.79)	Age, sex, race, ACS type, CVD comorbidities and revascularisation
Hagen et al., 2015 *****pathway analysis******	Finland and Norway	Individual income (quartile)	Access to PCI within 14 days; Mortality at 14 days, 15days-1 year Quantify both direct SES effect and indirect effect mediated by cardiac procedures Total effect (SES on mortality) Direct effect (adjust for trt) Indirect =Total-Direct or Direct (SES on PCI)*Direct (PCI on mortality)	10522 Norway and 8256 Finland patients admitted to hospital with AMI	% change (p-value) for SES effect on 14 day mortality Norway: Total effect: 1.5 (0.05) Direct: 1.3 (0.07) PCI: -3.6 (SS) Indirect: 0.2(0.02) Finland Total: 2.6 (0.01) Direct: 2.3 (0.02) PCI: -5.3 (SS) Indirect: 0.3 (0.01) % change (p-value) for SES effect on 15-1yr mortality: Norway: Total effect: 1.7 (0.11) Direct: 1.5 (0.16) PCI: -3.6 (SS) Indirect: 0.2(0.03) Finland Total: 3.1 (0.01) Direct: 2.7 (0.03) PCI: -5.3 (SS) Indirect: 0.4 (0.01)	Age, sex, type of AMI, travel distance, other SES factor, and comorbidities
Hassan et al., 2009	Canada	Place of residence (metropolitan, urban, rural)	Cardiac catheterization rate (within 6months)	7351 hospitalised with acute MI	HR 0.75 (0.67-0.84)	Age, sex, comorbidities, type of AMI, neighbourhood level median income, receipt of thrombolytic therapy

			Wait times		Extra 10.8 days (p<0.0001)	None
Hawkins et al., 2013	England, UK	UK IMD - Weighted composite of 7 area-level deprivation domains	Use of aspirin, ACEi/ARB, beta-blocker, Clopidogrel	51755 MI patients with hospital discharge	2003 RR Aspirin: 1.00 (0.96-1.04) ACEi/ARB: 1.00 (0.92-1.10) beta-blocker: 1.00 (0.94-1.06) Clopidogrel: 0.94 (0.70-1.25) 2007 Aspirin: 0.98 (0.97-1.00) ACEi/ARB: 1.08 (0.98-1.19) beta-blocker: 1.05 (0.96-1.14) Clopidogrel: 0.96 (0.93-1.00) No SE gradient apparent in trt	Age
Hayes et al., 2016	England, UK	Marital status (Single vs Married)	Length of hospital stay (measure of efficiency in the use of hospital resources)	929552 New diagnosis of ACS	2.12 (1.05-3.20) mean days longer	Age, sex
			Mortality (max fu 3 yrs)		HR 1.16 (1.07-1.25)	
Heo et al., 2015	South Korea	Individual education (completion of elementary, high school, bachelor)	Time to reperfusion (prehospital delay: symptom to door; inhospital delay: door to balloon)	8222 STEMI patients referred for reperfusion	Symptom to door: 59.1min (27.6-90.7) longer Door to balloon: NS	Age, sex, season, day of week, EMS use; stratified by days from symptom onset to door
Hetemaa et al., 2004	Finland	Individual family income tertile	Invasive coronary procedure rate (within 2 years)	5172 hospitalized with first MI, excluded those discharged alive after <4 days of stay	Men HR 0.75 (0.64-0.89) Women HR 0.59 (0.44-0.78)	Age, comorbidities; by sex
		Education (<9 vs >10)			Men 0.87 (0.77-0.98) Women 0.93 (0.72-1.20)	
		Occupational class			White-collar employees receive more procedures among men; no significant relationship in women. Men: 0.76 (0.66-0.87) Women 0.92 (0.72-1.18)	

Ho et al., 2006	USA	Individual education (< high school)	Discontinuation of all medication at 1 month after MI hospitalisation	1521 patients discharged with all 3 medications: aspirin, beta blockers and statins	OR 1.76 (1.20-2.60)	Age, sex, race, comorbidities, marital status, revascularisation during hospitalisation, type of MI, psychosocial variables (stepwise)
Hong et al., 2014	South Korea	Location: counties vs Capital, Metropolitan, cities	Invasive management within 30 days: angiography, PCI	95616 hospitalised with AMI	Angio OR 0.14 (0.12-0.15) PCI OR 0.21 (0.19-0.23)	Age, sex, insurance type, comorbidities
			30-day mortality		3.09 (2.85-3.45) After adjustment for trt 1.47 (1.35-1.61)	
			Medical management: aspirin, beta-blockers, statins		Total medical management: 0.12 (0.11-0.13) Aspirin: 0.13 (0.11-0.14) Beta-blocker: 0.27 (0.25-0.30) Cholesterol-lowering: 0.22 (0.19-0.24)	
Hvelplund et al., 2011	Denmark	Distance from home to invasive centre (tertiles: <21 km, 21-64, >64km)	Angiography and revascularisation (PCI or CABG) rate within 60 days	24910 admitted with first ACS, excluded discharge of admission	Angiography HR long vs short :0.74 (0.72-0.77) In those with angio, HR: PCI 0.86 (0.88-0.90)	Age, sex, comorbidity, SES
Igland et al., 2014	Norway	Individual Education (basic vs secondary, uni)	28-day mortality	111993 Hospitalised for new AMI	Age 36-69 HR 1.38 (1.20-1.58) Age 70-94 HR 1.05 (0.99-2.12) Without PCI adjustment: Age 36-69 HR 1.43 (1.25-1.64) Age 70-94 HR 1.09 (1.02-1.16)	Age, sex, year, comorbidities, PCI within 28 days
Jakobsen et al., 2012	Denmark	Individual level income (tertiles)	30-day mortality	7385 STEMI treated with PCI (STEMI patients are almost exclusively treated with PCI in Denmark)	HR 1.15 (0.79-1.67)	Age, sex, comorbidities, mutual SES factors+ procedure related (drugs, stent)+ drugs during fu
			1-year mortality		HR 1.15 (0.85-1.56)	
			30-day mortality		HR 0.68 (0.45-1.03)	

		Individual level education (primary vs higher, secondary)	1-year mortality		HR 0.79 (0.57-1.09)	(clopidogrel, b-blocker, ace, diuretics, nitroglycerin)
		Employment status (unemployed vs employed)	30-day mortality		HR 1.13 (0.68-1.87)	
			1-year mortality		HR 0.94 (0.61-1.45)	
		Income, Education, employment status	Max follow-up mortality		Income: 1.27 (1.04-1.54) Education: 0.79 (0.57-1.09) ES: 1.11 (0.84-1.45)	
Jin et al., 2014	China	Individual level: Income (low vs high)	Not taking any recommended medication at fu	469 ACS without another episode during fu (1.5-2 yrs)	OR in age >65: 0.68 (0.22-1.51) Age <65: 3.97 (1.47-10.75)	Age, sex, mutual SES factors, insurance, comorbidities, # of prescribed medication at discharge
		Education (< high school, vs >high school)			OR in age >65: 3.93 (1.65-9.32) age<65: 2.69 (0.86-8.46)	
Jones et al., 2015	England, UK	English IMD (neighbourhood level index)	Long-term mortality (median fu 3.7 yrs)	13770 After PCI	HR 1.93 (1.38-2.69)	Age, sex, race, comorbidities, ACS vs non ACS, procedure related characteristics
Khafaji et al., 2012	6 Middle East countries	Marital status (single vs married, widowed vs married)	1-month mortality	5334 hospitalised with ACS	Single OR1.35 (0.46-3.99) Widowed OR 1.97 (1.23-3.18)	Age, sex, BMI, comorbidities
Khaykin et al., 2002	Canada	Median neighbourhood income level	Use of coronary angiography within 6 months	146364 hospitalised with AMI excluded those with stay <3 days and discharged alive	Trend shows widening inequalities in SE related access to angio over 1992-1999, despite increased funding and supply. Higher SES used angio more significantly. Exact numbers not given.	Age, sex, severity of illness, hospital factors
Kim et al., 2014	South Korea	Individual education (<6, 7-12, >13)	3 year mortality	2358 with AMI who underwent PCI	HR 1.93 (1.16-3.20)	Age, sex, comorbidities

		Neighbourhood deprivation index (% living instability, elderly, education, social class, households without cars, living alone)			HR 1.12 (0.88-1.43)	AMI severity, PCI characteristics
Kirchberger et al., 2014	Germany	Individual education	Mortality during fu (median 6.1 yrs,)	2574 men and 844 women hospitalised with first-time AMI who survived longer than 28 days	HR in: Young <65: 0.88 (0.55-1.40) Older: 1.44 (1.05-1.98) Total: 1.16 (0.90-1.50)	Age, sex, living alone, comorbidities, AMI type, any reperfusion therapy+backward selection
Kitzmiller et al., 2013	USA	Neighbourhood household income (tertiles)	Lipid lowering medications received during hospitalisation or at discharge	3546 MI events	Prevalence ratio: 0.91 (0.81,1.03)	Age, sex, race, community, year of MI, hospital type, comorbidities
Korda et al., 2009	Australia 2001-2003	Neighbourhood level deprivation index: SEIFA (population-based quintiles)	Receipt of angiography, PCI within 1 yr	5539 admitted for AMI and 7401 for angina	Males, HR: Angio: 1.05 (0.92-1.20) PCI: 0.99 (0.83-1.18) Female: Angio: 1.10 (0.85-1.41) PCI: 0.93 (0.65-1.33)	Age, sex, marital status, race, country of birth, area of residence (remoteness/ accessibility index), hospital area (urban vs rural), comorbidities
Kulkarni et al., 2013	USA	Regional density of cardiologists/ access (# of cardiologists divided by population aged>65 within hospital referral regions, categorised into quintiles)	30-day mortality	171126 Hospitalisation for AMI compared with pneumonia, age >65	OR 1.20 (1.13-1.27)	Age, sex, comorbidities, other neighbourhood level SES measures: unemployment rate, race, median household income. (these are highly collinear with each other and with density of cardiologists, so omitted)
			1-year mortality		OR 1.11 (1.05-1.17)	
Lammintausta et al., 2014	Finland 1993-2002	Marital status (unmarried vs married)	28 day mortality	15330 ACS cases	Men 1.58 (1.11-2.25) Women 2.05 (1.32-3.19)	Age, stratified by sex
			1 year		Men 1.58 (1.12-2.21) Women 1.87 (1.24-2.83)	
			Rate of PCI or CABG		Use of reperfusion did not differ.	

			Treatment seeking times (proportion of patients with a treatment-seeking time of less than 4 hours)		Event rate (%, 95%CI): Delay <4 hours rate: Men: 54 (47–61) vs 62 (58–67) Women: 18 (12–24) vs 24 (17–31) Not significant in either group	
Lee et al., 2013	Singapore	Individual education (None vs university or higher) Marital status (single vs married)	Symptom to balloon time	374 STEMI hospitalisations within 12 h after symptom onset	Median Education: +35.6 (-43.0-114.2) min MS: +67.4 (29.2-105.6)	Age, sex, citizenship, race, comorbidities, education, marital status
Machon et al., 2012	Spain 1999-2000	Neighbourhood level deprivation index quintiles (%unemployment, education, low level comfort housing)	28-day mortality	2003 Hospitalised AMI	Men HR 0.94 (0.55-1.62) Women 0.82 (0.46-1.44) SES effect reduced significantly after adjusting for comorbidities, trt in hospital, AMI severity.	Age + sex, comorbidities, AMI characteristics, trt including medications during hospitalisation and discharge
Macleod et al., 1999	Scotland, UK 1991-1993	Neighbourhood Carstairs deprivation quintiles (overcrowding, unemployment rate, car-ownership, occupational social class distribution)	Angiography, PCI within 2 yrs	36838 admitted with AMI	Angiography OR 0.70 (0.58-0.85) PCI OR 0.70 (0.43-1.16)	Age, sex, area of residence
Martensson et al., 2016	Denmark 2001-2009	Individual education (tertiles)	Time from admission to angiography/PCI within 30 days	First time admission for NSTEMI (n=16625) or UA (n=8800) and discharged alive with CAG/PCI/CABG within 30 days	NSTEMI HR Angio: 0.78 (0.74-0.83) PCI: 1.00 (0.91-1.10) UA HR Angio: 0.89 (0.83-0.96) PCI: 0.98 (0.86-1.13)	Age, sex, comorbidities, CAG and time to CAG (for mortality as outcome)
			30-day mortality		NSTEMI 1.21 (0.74-2.10) UA 2.25 (0.80-9.40)	
			1 year		NSTEMI 1.61 (1.15-2.32) UA 2.13 (1.17-4.37)	
Mehta et al., 2011	Canada, New Zealand, USA, UK, Germany, Sweden,	Individual education (per year)	Day 8 to 1-year mortality	11326 STEMI who presented within 6 h after symptom onset, excludes hypertensive patients	HR 1.37 (1.18-1.59) Effect is different between countries, NS in New Zealand, Poland and Australia. Also found that the prognostic importance of education is	Age, severity, MI location, SBP, country

	Italy, Poland, Australia				second to age based on the model chi-square.	
Molshatzki et al., 2011	Israel	Individual income (high/low)	Long term mortality (13-yr fu)	1178 discharged after MI	HR 1.33(1.01-1.74)	Age, sex, comorbidities, severity, other SES measures
		Education (/5 yrs)			HR 1.16 (1.02-1.33)	
		Unemployment (y/n)			HR 1.87 (1.44-2.43)	
		Living alone (y/n)			HR 1.62 (1.21-2.17)	
		Neighbourhood SES index (tertiles)			HR 1.49(1.08-2.06)	
Morrison et al., 1997	Scotland, UK (1985-1991)	Neighbourhood level index: Carstairs and Morris deprivation score (quarters)	28-days case fatality in hospital	3627 admissions with MI	Men OR 0.94 (0.70-1.26) Women OR 1.07 (0.68-1.68) However, SES affects event rates, community deaths (before or after hospitalisation) and chance of admission.	Age, sex
Notara et al., 2016	Greece	Education (<9 yrs vs 9-14, >14 yrs)	10-year mortality	2172 ACS hospitalised patients	HR 2.08 (1.14-3.84)	Age, sex, comorbidities, physical activity, adherence to medication
O'Shea et al., 2002	USA, Canada, UK, Italy, Germany, Australia, Sweden, Poland, New Zealand	Living alone (y/n, as measure of social isolation)	30-day mortality	13095 with STEMI	OR 0.93 (0.78-1.11)	Age, SBP, HR, severity, infarct location
			1-year mortality		OR 1.02 (0.91-1.15)	
Osler et al., 2015	Denmark	Individual education (<9 years, high school, >high school)	30-day mortality	29583 admitted first time ACS patients	HR 1.28 (1.17-1.39)	Age, sex, comorbidities, depression
			1-year mortality		HR 1.34 (1.23-1.41)	
Park et al., 2012	South Korea	Individual Education (< high school vs > high school)	Pre-hospital time delay (onset-to-door) (short: <180min or long)	423 presented with STEMI to emergency	OR 1.66 (1.08-2.56) Delay is more frequent in patients with low education levels.	Day/night, referral hospital transport vehicle (after backwards selection)
Patil et al., 2014	Norway	Education (basic, secondary, university)	28-day mortality	111993 new AMI hospitalisation, 2001-2009	<69 HR 1.24 (1.07–1.44) >70 HR 1.04 (0.97–1.11)	Age, sex, year, comorbidities, PCI within 28 days (for 28 day mortality)

			29-day to 1-yr mortality		<69 HR 1.29 (1.05-1.59) >70 HR 1.18 (1.09-1.28)	or PCI/CABG within 8 weeks for 29-365 day mortality, individual income
Perelman et al., 2009	USA, Belgium, Canada	Neighbourhood level median income	Angio, PCI	1701557 admission with AMI, age 65-99, excludes those with stay <3 days and discharged alive, 1993-1998	Lowest vs highest quintile: Exact numbers not shown, relatively lower cardiac procedure rates in patients from the lowest-income areas, but within 2% difference. But significant difference when not accounting for distances between patient and hospital: richer areas closer to cath lab, therefore any inequality largely related to location.	Age, sex, year, distance to cath lab, comorbidities
Philbin et al., 2000	USA	Neighbourhood level household income	Invasive cardiac procedures: Angio, PCI	28698 discharged with AMI, 1995	Angio OR 0.85 (0.77-0.94) Angio+PCI OR 0.61 (0.52-0.71)	Age, sex, race, insurance type, comorbidities, hospital characteristics
Pierce et al., 1998	USA	Access: distance from cardiac referral centre (> 60 miles vs 30-59 or <30 miles)	Rates of Angio, PCI within 90 days	1658 discharged with AMI of rural residence > 65 age with Medicare, 1991	Angio 0.55 (0.40-0.75) PCI0.68 (0.47-0.98)	Age, sex, race
			30-day mortality		OR 0.99 (0.70-1.41)	
			1-year mortality		OR 0.91 (0.67-1.23)	
Pilote et al., 2003	Canada	Neighbourhood level index (median family income (low vs high), avg rent, distance to cath lab)	Invasive cardiac procedures: angio, PCI, CABG within 90 days	62364 admitted with first AMI, 1985-1995	Estimated % difference low vs high SES: Angio: Men: -14 (-35,7) Women: -29 (-52, -7) Angio+PCI: Men:2 (-12, 15) Women: -8 (-34, 15)	Age, sex, year, comorbidities, other SES variables (education, housing), distance to cath lab
Pilote et al., 2007	Canada	Neighbourhood level indicators for education, average gross rent, % rented dwelings, employment rate, median family income, average family income, % low-income housholds	Medications within 90 days; Invasive cardiac procedures within 90 days; 30 and 1 yr mortality	145882 admission for AMI 1996-2001	Across 3 provinces and various SES indicators, no SS association between SES and access to b-blockers, statins, or ACE inhibitors or invasive cardiac procedures: angio, pci, CABG or 30-day or 1-year mortality.	Age, sex, comorbidities, hospital characteristics

Quinones et al., 2014	Germany	Marital status/ Cohabitation status	Long term mortality (median 5.3 yrs)	3766 first AMI survivors alive 28 days after MI (2000-2008)	MS HR: 1.20 (0.99-1.47) Stratified analyses revealed strong protective effects in <60 yrs with hyperlipdemia. Substitution of MS with co-habitation status (living alone vs with s/o) confirmed effect, HR 1.92 (1.16-3.23).	Age, sex, recruitment day, PCI, hyperlipidaemia, comorbidities
Randall et al.,2013	Australia, 2000-2008	Neighbourhood level index Quintile	Rate of revascularisation (PCI or CABG) within 30 days	59282 admissions for AMI	HR 0.95 (0.89-1.01)	Age, sex, AMI type, comorbidities, private health insurance. ethnicity
		Remoteness of residence index (based on road distance to 5 categories of service centers as a proxy for availability of services, quartiles)			HR 1.05 (0.88-1.25)	
Rao et al., 2004	USA, 1994-1996	Neighbourhood level median income (deciles)	30-day mortality	132130 elderly (65+) Medicare beneficiaries hospitalised for AMI	RR 1.22 (1.11-1.32)	Age, sex, lab results, severity of MI, comorbidities, refusal of thrombolytic agents, hospital characteristics
			30-day to 1-year mortality		RR 1.14 (1.03-1.25)	
			In-hospital revascularisation procedure use		Lowest vs highest tertile: Unadjusted revascularisation rate similar among income groups: less than 1% difference	None
			Use of aspirin during hospitalisation and discharge; beta-blockers at discharge		Lowest vs highest tertile: Aspirin in hospital: 77.1% vs 79.1% Aspirin at discharge: 69.7 vs 68.6% Beta blocker at discharge: 33.3 vs 42.7%	
Rasmussen et al., 2006	Denmark 1995-2002	Individual-level income (tertiles)	30-day mortality	37560 hospitalised for first time AMI	<65 RR 1.54 (1.36-1.79) >65 RR 1.27 (1.15-1.41)	Age, sex, comorbidities, cohabitation status, other SES factor; effect of age and income on mortality interacted so analyses stratified into 2 age groups
			30-day to entire fu mortality (last date 2003)		<65 RR 1.65 (1.45-1.85) >65 RR 1.38 (1.27-1.50)	
			30-day mortality		<65 RR 1.24 (1.03-1.50) >65 RR 1.09 (0.94-1.28)	

		Individual-level education (yrs, tertiles)	30-day to entire fu mortality (last date 2003)		<65 RR 1.33 (1.11-1.59) >65 RR 1.07 (0.94-1.22)	
Rasmussen et al., 2007	Denmark, 1996-2004	Individual-level income (tertiles)	Rate of revascularisation (PCI or CABG) within 6 months	38803 hospitalised for first time AMI, exclude those died within 1st day	Acute PCI (within 2 days) HR: 0.98 (0.92-1.05) PCI after 3rd day: 0.85 (0.80-0.90) Total revas: 0.89 (0.85-0.93)	Age, sex, living alone, previous PCI/CABG, admitting hospital type, comorbidities, drug use within 1 yr prior to AMI.
		Individual-level education (yrs, tertiles)			Acute PCI (within 2 days) HR: 1.09 (1.00-1.18) PCI after 3rd day: 0.95 (0.88-1.03) Total revas: 1.01 (0.95-1.06)	
Rasmussen et al., 2007_2	Denmark, 1995-2001	Education (yrs, tertiles)	Use of statins and beta-blockers (initiation: claim of prescriptions within 6 months of discharge and long-term refill persistency: first break in trt lasting at least 90 days and re-initiation)	30078 surviving first hospitalisation for AMI,	Age 30-64: Statin initiation: 0.89 (0.83-0.95) Risk of break in statin: 1.26 (1.11-1.45) Statin re-initiation: 0.93 (0.78-1.12) Beta blockers initiation: 0.93 (0.88-0.97) BB break: 0.92 (0.85-0.99) BB re-initiation: 1.12 (1.00-1.28) Age 65-74: Initiation statin: 0.81 (0.72-0.90) Risk of break in statin: 0.88 (0.71-1.07) Statin re-initiation: 0.87 (0.65-1.16) Beta blockers initiation: 0.94 (0.88-1.02) BB break: 0.91 (0.81-1.02) BB re-initiation: 1.16 (0.95-1.43)	Age, sex, living alone, drug use before admission, comorbidities, admitting hospital type, revascularisation
		Individual-level income (tertiles)			Initiation statin: 0.78 (0.74-0.83) Risk of break in statin trt: 1.41 (1.27-1.56) Reinititation: no trend 0.97 (0.84-1.12)	

					Beta blockers initiation: 0.87 (0.85-0.92) BB break: 0.96 (0.90-1.03) opposite direction as statin BB reint: 1.12 (1.01-1.25)	
Rathore et al., 2000	USA	Neighbourhood level index of poverty (poor vs nonpoor, using median household income <15 percentile vs other)	Discharge aspirin, beta-blockers	169079 medicare beneficiaries >65 treated for AMI (1994-1996)	RR Aspirin 0.98 (0.96-1.00) BB: 0.95 (0.91-0.99)	Race, sex, age, AMI severity, physician speciality, geographic and hospital characteristics
Rhudy et al., 2016	USA 2010	Neighbourhood level geographical IC access (interventional cardiology) (%), defined as residential location > 60 min drive time to IC vs < 60 min	In-hospital mortality	3126 unique AMI events	OR 1.29 (0.88-1.88) In NSTEMI: 1.22 (0.96-1.97) In STEMI: 1.41 (0.75-2.66) Delayed access was associated with increased unadjusted in-hospital mortality	Age
Ringback et al., 2008	Sweden	Individual level Education (<9 yrs, 9-11 yrs, >12 yrs)	Drug trt according to national guidelines (1-2 yrs after AMI): prescribed and dispensed ASA, b-blockers, lipid-lowering, ACE inhibitors (i.e. adherence to drugs 1-2 yrs after hospitalisation)	28168 incident cases of AMI (2003-2004)	OR ASA: 1.09 (1.01-1.18) b-blocker: 1.06 (0.99-1.15) Statins: 0.91 (0.85-0.98) ACE-in: 1.01 (0.94-1.08)	Age, sex, country of birth, comorbidities
Rosvall et al., 2008	Sweden	Cumulative household income in 2 separate years: (1975 & 1990) (quartiles for each year added up: 8 categories)	Use of revascularisation (CABG or PCI) within 1 month	46407 alive 28 days after first AMI hospitalisation (1993-1996)	Revascularisation: SS, numbers not shown. Lowest cumulative income had around 2-8 times less procedures. Only 2-3% had a revascularisation in this population	Age sex, comorbidities, type of hospital
			5 yr mortality after recovery from AMI		HR Men 1.99 (1.79-2.21) Women: 2.24 (1.69-2.97)	Age
Salomaa et al., 2001	Finland 1983-1992	Individual level income (tertiles)	2-27-day mortality (hospitalised alive)	6485 men and 1942 women with first MI	Men HR 2.01 (1.45-2.80) Women 1.62 (0.90-2.91)	

			28-365-day mortality	(includes non-hospitalised patients)	Men 2.68 (1.78-4.04) Women 3.08 (1.21-7.88)	Age, study area, urban/rural residence, study period; stratified by sex
		Individual level education (binary: basic vs secondary+)	2-27-day mortality (hospitalised alive)		Men 1.25 (0.95-1.65) Women 1.22 (0.75-1.99)	
			28-365-day mortality		Men 1.23 (1.91-1.68) Women 1.30 (0.69-2.44)	
Shimony et al., 2010	Israel 2004-2006	Neighbourhood level socioeconomic index (average income, %care owners, family size, age, welfare recipients, employment status and educational parameters), tertiles	Medication: aspirin and clopidogrel adherence (days of continuous trt, considered to be taking medication until a schedules refill is delayed by >15 days), adherence to guidelines recommended therapy	1391 patients that underwent PCI	Continuous treatment days for aspirin: 453+/- 326 for low vs 585+/-336 for high Clopidogrel:94+/-81 vs 301 +/-225	None
Smolderen et al., 2010	USA 2005-2008	Marital status	Prehospital Delay (>6 hrs, 2-6 hrs, <2 hrs) in seeking hospital care for AMI	3721 hospitalised for AMI	0.98 (0.86-1.11)	Age, sex, race, residential area, comorbidities, other SES factors, MI severity and type, time of hospital arrival, social and psychological factors
		Education			1.27 (1.00-1.62)	
Spatz et al., 2014	USA 2003-2004	Usual source of care (duration and familiarity with any doctor/ care provider)	1-year mortality	2454 AMI patients hospitalised	1.92 (1.19-3.12)	Age, sex, race, marital status, education, financial situation, medication, comorbidities, severity of AMI
Stirbu et al., 2012	Netherlands 2003-2005	Individual level-Income (quintiles)	28-day mortality	15416 admitted with first AMI	Men HR 1.20 (0.98-1.48) Women 1.25 (0.93-1.68)	Age, sex, comorbidities
			1-year mortality		Men HR 1.23 (1.04-1.46) Women 1.39 (1.09-1.76)	
			PCI rate (no time limit)		OR 0.79 (0.71-0.89)	
			PCI/CABG		OR 0.82 (0.74-0.91)	
			Long term mortality (1-4 yrs)		Men HR 1.39 (1.19-1.62) Women 1.37 (1.11-1.69)	
Thorne et al., 2015	Wales, 2004-2011	Neighbourhood level index: WIMD quintiles	30-day mortality	30663 Emergency admission for AMI	OR 1.25 (1.12-1.40)	Age, sex, comorbidities

		(Welsh Index of Multiple Deprivation)	1-year mortality		OR 1.20 (1.08-1.32)	
Tofler et al., 1993	USA	Individual Education (< vs >high school)	In-hospital mortality	816 with AMI and evaluated < 18 hours of symptom onset.	13% vs 5% p<0.001	Age, sex, race, comorbidities risk index
Tonne et al., 2005	England, UK	Neighbourhood level SEP (median income, % living in poverty, % with education< high school, crowding, and a composite index measure)	Long term mortality after discharge (fu range from 1-7 yrs)	3423 AMI admissions surviving hospitalisation	HR 1.38 (1.13-1.67)	Age, sex, hospital, comorbidities, age*sex
Tyden et al., 2002	Sweden	Neighbourhood level SES index (based on migration rate, % with foreign citizenship, % with social welfare support, rate of employment) (tertiles)	Long term mortality (full fu mean 4.9 yrs)	2931 male and 2083 female patients with MI discharged for the first time at a single cath lab	HR <65: 1.67 (1.23-2.27) 65-74: NS (exact numbers not given) >74: NS (exact numbers not given)	Age, sex
Van Oeffelen et al., 2012	Netherlands 1998-2007	Standardized disposable income on household level (can assume as individual level)	28-day mortality	60498 with first AMI, with income data available	OR All: 1.22 (1.13-1.32) Men <55: 0.98 (0.75-1.30) 55-64: 1.19 (0.97-1.48) 65-74: 1.40 (1.17-1.68) 75-84: 1.26 (1.06-1.50) >85: 1.36 (0.99-1.85) Total: 1.28 (1.17-1.41) Women <55: 1.35 (0.87-2.12) 55-64: 0.96 (0.65-1.42) 65-74: 0.98 (0.75-1.29) 75-84: 1.23 (0.99-1.52) >85: 1.02 (0.76-1.35) Total: 1.11 (0.98-1.26)	Age, race, marital status, degree of urbanization, comorbidities index (charlson)
Xavier et al., 2008	India	Individual level SES index: education, occupation, family income, properties (quintile)	30 day mortality	20468 volunteered participants hospitalised with AMI, and admitted directly (not transferred), and	OR Adj for risk factors: 1.57 (1.12-2.20) + location of infarct: 1.44 (1.03-2.02)	Age, sex, comorbidities; trt: type of hospital, time to hospital, time to thrombolysis, drugs in

				available for 30 day FU at enrolment.	+ trt 0.90 (0.43-1.88)	hospital, interventional procedures
Yong et al., 2014	USA 2008-2011	Neighbourhood level income(median household income, quartiles)	Angiogram, catheterisation (24 hrs for STEMI, 48 hours NSTEMI)	835070 hospitalisations for ACS	STEMI Angio within 24 hrs: 0.79 (0.68-0.91) NSTEMI Angio within 48 hours: 0.86 (0.74-0.93) ACS (includes UA): Angio: 0.82 (0.70-0.96) PCI: 0.82 (0.74-0.91)	Age, sex, race, comorbidities, insurance type, hospital clustering
			In hospital mortality		STEMI 1.17 (1.11-1.25) Add adjustment for time to reperfusion in STEMI: 1.14 (1.07-1.21) NSTEMI 1.02 (0.99-1.05) ACS (includes UA): Mortality: NS, exact numbers not given	

*Transformed to lowest SES (most deprived) vs highest SES group (least deprived) if necessary.Greyed out studies/outcomes not included in meta-analysis.

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