Time trends in incidence, treatment, and clinical outcomes according to socioeconomic position in patients with acute coronary syndrome

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BY
AMALIE HELME SIMONI

DISSERTATION SUBMITTED 2023

AALBORG UNIVERSITY
DENMARK

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Amalie Helme Simoni, Aalborg 2023

ENGLISH SUMMARY

Acute coronary syndrome (ACS) is defined as an acute presentation of coronary atherosclerosis, including myocardial infarction and unstable angina pectoris and represents a leading cause of mortality. Socioeconomic disparities in the ACS epidemiology, care, and clinical outcomes have been reported for at least 40 years across multiple countries. However, an up-to-date overview of the evidence in incidence treatment and clinical outcomes reflecting current clinical practice is unavailable. In addition, no thorough evaluation has been performed on temporal trends in socioeconomic disparities in incidence and clinical outcomes within the Danish universal healthcare setting during decades with changes in both medical care and epidemiology of ACS. The aim of this thesis was to review the scientific literature from 2009 to 2021 regarding socioeconomic disparity in the incidence and prevalence of ACS, as well as the ACS-related medical care and all-cause--mortality among ACS patients; and to investigate 20-year temporal trends in socioeconomic disparities in incidence and clinical outcomes in patients with an incident ACS admitted to a hospital in Denmark during 1998-2017.

The thesis consists of a systematic literature review and two Danish nationwide cohort studies. PubMed and Embase was searched for relevant literature published from 2009 until July 2021, according to predefined methods. Results from the identified studies were extracted and presented according to outcomes, exposures, and the risk of bias. Results from the identified studies were extracted and presented according to outcomes and exposures, and the risk of bias. Socioeconomic disparities were elucidated according to educational level, income level, occupation status, health insurance status, and composite indicators of socioeconomic position (SEP). The two Danish cohort studies included the entire adult Danish population and all patients admitted to the Danish hospitals with an incident ACS diagnosis from 1998 to 2017, accessed through the Danish national registers. In these studies, socioeconomic disparities were evaluated based on personal equivalized disposable income and educational level. The primary outcomes were incidence of ACS and major adverse cardiac events (MACE) 30- and 365-days after the primary ACS admission. Temporal trends were evaluated based on interaction analyses.

The systematic literature search and screening of papers resulted in 181 studies included in the systematic review. Most of the studies were conducted in high-income countries, and most identified an association between a lower SEP and an increased ACS incidence or prevalence or receiving less optimal ACS-related medical care or higher mortality after the ACS. The studies which represented a lower risk of bias were more likely to identify a disparity in favor of those with a higher SEP than the studies with higher risk of bias. The two cohort studies identified a decrease in the incidence rates of ACS and subsequent MACE within all investigated income and educational levels. However, the incidence rates remained higher in the lowest income quartile and educational level. The interaction analyses showed only a minimal decrease in the disparity of incidence of ACS and no change in the disparity in MACE.

Across all the studies identified from the last decade, lower SEP was generally associated with a higher risk of ACS, less care and higher mortality risk among the ACS patients. In particular, the studies with a lower risk of bias identified this association. Furthermore, despite the incidence of ACS and the subsequent clinical outcomes have decreased substantially over the last decades, the socioeconomic disparity in ACS persisted in the Danish welfare state.

DANSK RESUME

Akut koronart syndrom (AKS) er defineret som en akut præsentation af aterosklerose i form af myokardieinfarkt eller ustabil angina pectoris og repræsenterer en førende global dødsårsag. Socioøkonomisk ulighed i epidemiologien af AKS, inklusive behandling og prognose er blevet rapporteret på tværs af lande i mindst 40 år. Imidlertid mangler der fortsat et opdateret overblik over evidensen for social ulighed i incidens, behandling og prognose for AKS baseret på nutidig klinisk international praksis. Derudover er der ikke blevet udført nylige evalueringer af tendenserne i socioøkonomisk ulighed i incidens og prognose for AKS i det danske sundhedsvæsen gennem årtier, hvor behandlingen og epidemiologien af AKS i høj grad er blevet forbedret. Formålet med denne afhandling var at gennemgå den videnskabelige litteratur fra 2009 til 2021 vedrørende social ulighed i incidens og prævalens af AKS, samt behandling og dødelighed blandt patienter med AKS. Derudover var formålet at undersøge 20-års tendenser i social ulighed i incidens af AKS og prognose blandt patienter med AKS indlagt på danske hospitaler fra 1998 til 2017.

Afhandlingen er baseret på et systematisk litteraturstudie og to danske nationale kohortestudier. Litteratursøgningen blev udført i PubMed og Embase, og inkluderede alle relevante studier publiceret fra 2009 til juli 2021, i henhold til en foruddefineret og publiceret metode. Resultater fra de identificerede studier blev samlet og præsenteret i henhold til udfald, eksponering og risiko for bias. Socioøkonomisk ulighed blev således belyst i henhold til uddannelsesniveau, indkomstniveau, beskæftigelsesstatus, sundhedsforsikringsstatus og kompositte mål for socioøkonomisk position. De to danske kohortestudier inkluderede hele den danske voksne befolkning og alle patienter, som var indlagt på et dansk hospital med en AKS diagnose fra 1998 til 2017. Dette blev tilgået ved hjælp af danske administrative nationale registre. I kohortestudierne blev socioøkonomisk ulighed evalueret på baggrund af personlig ækvivaleret disponibel indkomst og uddannelsesniveau. De primære endepunkter i disse studier var incidens af AKS og *major adverse cardiac events* (MACE) 30- og 365-dage efter indlæggelse for det oprindelige AKS. Tendenser blev evalueret ved brug af interaktionsanalyser.

Den systematiske litteratursøgning og screening af studierne resulterede i inklusion af 181 studier i det systematiske review. De fleste af de identificerede studier var udført i højindkomstlande og de fleste identificerede en socioøkonomisk ulighed, hvor lavere socioøkonomisk position var associeret med højere AKS incidens eller prævalens, mindre optimal behandling eller højere mortalitet blandt AKS patienterne. Studierne som repræsenterede en lavere risiko for bias, havde højere tilbøjelighed til at identificere denne sammenhæng. De to kohortestudier fandt et fald i incidensen af både AKS og efterfølgende MACE i alle de undersøgte indkomst- og uddannelsesniveauer. Dog forblev incidensraten højest blandt dem med lavest indkomst og uddannelse, og interaktionsanalyserne viste kun et minimalt eller ingen fald i uligheden i incidens af AKS og efterfølgende MACE.

På tværs af de identificerede studier fra det sidste årti, var lav socioøkonomisk position generelt associeret med en højere risiko for AKS og mindre optimal efterfølgende behandling samt mortalitet blandt AKS patienterne. Særligt studier med en lav risiko for bias identificerede denne association. Selvom incidensen af AKS og den efterfølgende prognose er blevet markant forbedret i løbet af de sidste årtier, så er omfanget af den socioøkonomiske ulighed i AKS i den danske velfærdsstat vedblivende.

PAPERS IN THE THESIS

Study I

Simoni, Amalie H; Frydenlund, Juliane; Kragholm, Kristian H; Bøggild, Henrik; Jensen, Svend E; Johnsen, Søren P: **'Socioeconomic inequity in incidence, outcomes and care for acute coronary syndrome: A systematic review'**, *International Journal of Cardiology: June 2022 – Volume 356 – p 19-29 doi: 10.1016/j.ijcard.2022.03.053.*

Study II

Simoni, Amalie H; Kragholm, Kristian H; Bøggild, Henrik; Jensen, Svend E; Valentin, Jan B; Johnsen, Søren P: '**Time Trends in Income-related inequity in Incidence of Acute Coronary Syndrome'**, *[Manuscript submitted]. 2022*

Study III

Simoni, Amalie H; Valentin, Jan B; Kragholm, Kristian H; Bøggild, Henrik; Jensen, Svend E; Johnsen, Søren P: '**Temporal trends in socioeconomic disparity in clinical outcomes for patients with acute coronary syndrome'**, *[Manuscript submitted]. 2022*

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
ARBs	Angiotensin II receptor blockers
CABG	Coronary artery bypass grafting
CAG	Coronary angiography
CCI	The Charlson Comorbidity Index
CI	Confidence interval
CRS	The Danish Civil Registration System
DNPR	The Danish National Patient Registry
DRCD	The Danish Register of Causes of Death
HR	Hazard rate ratio
ICD	International Classification of Diseases
IQR	Interquartile range
IR	Incidence rate
IRR	Incidence rate ratio
ISCED	The International Standard Classification of Education
MACE	Major adverse cardiac events
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
OECD	Organization for Economic Cooperation and Development
OR	Odds ratio
PCI	Percutaneous coronary intervention
SEP	Socioeconomic position
STEMI	ST-segment elevation myocardial infarction
UAP	Unstable angina pectoris

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CHAPTER 1. INTRODUCTION

Acute coronary syndrome (ACS) is an acute presentation of coronary atherosclerosis, including myocardial infarction (MI) and unstable angina pectoris (UAP). ACS ranks as the leading cause of mortality globally, leading to about one-third of all deaths in the adult population.[1–3] Changes in the epidemiology of ACS across high-income countries during the last decades emphasize that ACS is widely preventable.[4–6] Hence, targeting the traditional risk factors, including smoking, hypertension, diabetes, inactivity, obesity, hypercholesterolemia, and family history of premature coronary artery disease has led to a reduction of the burden of ACS in Europe and worldwide, despite an increasing incidence of obesity and diabetes.[4,7,8] For around 35 years, it has been reported that cardiovascular morbidity and mortality, including ACS, is higher among people with low education, income, or social class, those with manual labor, without private health insurance, or living in or living in socioeconomic deprived areas.[4,7–10] These disparities counteract the individual's ability to live the free life they value and are an economic burden to society resulting in large groups of subjects having to poor health to contribute to societal production.[11] Thus, targeted efforts are necessary to eliminate or at least reduce the disparity in incidence, care, and clinical outcomes of ACS. However, considering the continuing changes in the epidemiology of ACS and the increased focus on interventions aiming to reduce disparities in morbidity and care, a contemporary overview of the socioeconomic disparity in ACS incidence, medical care, and outcomes in a clinical settings is essential to enable targeting of future efforts to reduce this disparity.[7,12–14] Furthermore, more extensive insight into the current temporal trends of ACS incidence and clinical outcomes is essential. This thesis examined the extent and progress of socioeconomic disparity in ACS in the contemporary international literature and temporal trends in the Danish healthcare setting.

1.1. SOCIOECONOMIC DISPARITY IN HEALTH

Health disparities are systematic differences in the health status across the population, which have significant social and economic costs both on individual and society levels.[11,15,16] The socioeconomic disparity in health essentially originates from socioeconomic stratification, based on mechanisms such as social mobility, social distribution of resources, and social resource benefits.[11,17,18] Hence, socioeconomic factors, including education, income level, occupation, sex, and ethnicity, have an important influence on how healthy a subject is.[15] Variations over time, within, or between countries, in any of these factors may give rise to variations in health disparities.[17] The World Health Organization reports that socioeconomic position (SEP) influence patients' treatment of illness as well as their health condition.[13] Within all countries, there are comprehensive disparities in health status according to the social groups. And although, there is some heterogeneity in the characteristics of the disparities, it most often presents as lower SEP being associated with a higher risk of poor health.[15,16] Generally, the age-adjusted mortality risk is two to three times higher for those with the lowest SEP than those with the highest.[18] It is unknown to what degree it is possible to prevent the health-related consequences of socioeconomic disparity. However, socioeconomic health disparities are barely advantageous to the societal productivity or the individual, but a rather large financial burden if groups of subjects have to poor health to contribute to societal development.[11,15,16]

The mechanisms behind socioeconomic disparities in health are complex, and part of the disparities originate from relations sustaining through generations.[16,19–21] In general, social determinants of health represent a comprehensive context, in which the value of each indicator represents individual pathways for the health disparity (e.g. differences in attitude, personal resources, knowledge, power, prestige, or network) and the value of each indicator change during the lifetime.[16–20,22] Hence, an unequal socioeconomic distribution of these resources may result in an unequal socioeconomic distribution of risk factors for disease or healthcare resources, resulting in socioeconomic disparity in health and disease in specific groups within the society *(Figure 1-1).*[16,18,23]

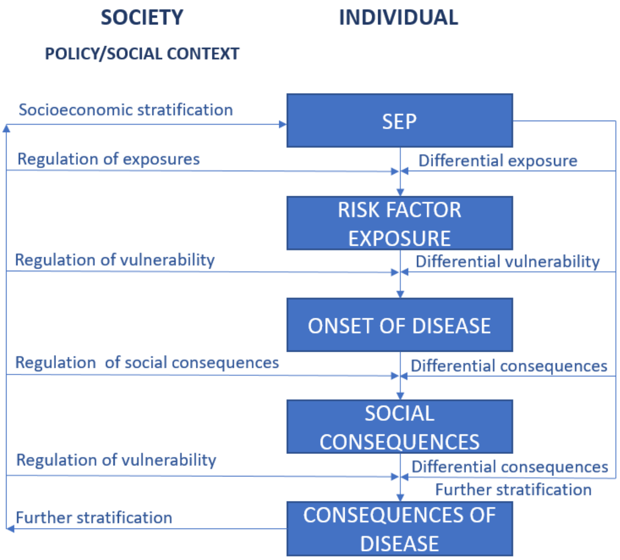

Figure 1-1 Central mechanisms in health disparity.
A modified figure of Finn Diderichsen's model of health disparity.[11,24] *SEP affects the onset and consequences of disease both through individual and societal pathways, including modulation of risk factors and vulnerability, which may again affect the SEP, for example, through a change in employment after the onset of chronic or acute disease. Abbreviations: SEP: socioeconomic position.*

1.1.1. SOCIOECONOMIC DISPARITY IN HEALTH BEHAVIOUR

It is important to acknowledge, that material improvements do not automatically improve the health disparities. Over the last decades, health disparity in Western Europe seems to have persisted or widened, despite improvements in material well-being and welfare policies.[17,21] In high-income countries, health improvements mainly derive from collective behavior change, including lifestyle changes and use of preventive or curative healthcare. These changes may imply health disparity since the behavior change possibly present a socioeconomic stratification, which explains a part of the socioeconomic disparity in mortality from circumstances that could have been prevented or treated.[16,17,19,20] Overall, Western Europe welfare policies during the last decades have contributed making the more affluent lifestyles more affordable.[17] However, paradoxically this could have contributed to a widening of health disparities by distributing the immaterial factors for health more socially unequal.[16,17,19,20]

It may be discussed whether stratification of personal health according to social status is a free choice rather than a public health problem.[11] It is clear that the distribution of risk factors have an effect on the disparity in health. However, the terminology of the so-called "lifestyle diseases," reflecting most non-communicable disorders, propose that the choice of a certain lifestyle solely results in the vulnerability of a specific disease.[11] However, most individuals would probably not voluntarily select extensive obesity or addiction to alcohol consumption or smoking.[11,23] Rather, the choice of these lifestyles is affected by social conditions and availability. Since humans from biology are of social nature and therefore adapt their behavior according to the surroundings, resisting the easy access to these cultural goods, including cigarettes, alcohol, high-calorie foods, and physical inactivity, requires at least some personal resources.[11,23] Generally, it is expected that health behavior itself accounts for around a quarter of the socioeconomic disparity in health.[11,23]

1.1.2. SOCIOECONOMIC POSITION

Socioeconomic disparities can be evaluated in various ways. The terminology varies, e.g., the terms social class, social stratification, social determinants of health, social or socioeconomic status are often used interchangeably, despite differences in the theoretical interpretations.[16,19] In this thesis, SEP refers to the socioeconomic factors influencing the position of an individual or group within the structure of society. This terminology target coverage of the intentional concepts of health disparity, acknowledging that different measures of SEP provide additional information on the distribution of disease and identifying specific explaining mechanisms of the progress and persistence of health disparity *(Figure 1-2)*.[16,19,20,23,25] It is central to acknowledge that although SEP is accessed at personal level, it is still determined by the structure and opportunities within the society. [16,19] Area-based indicators of SEP can be attained from aggregation of individual-level measures of SEP. These include indicators (often composite) of the proportion of unemployed, proportion with high education, and average area-income.[16,19] In general, studies using area-measures find a relatively small independent neighborhood effect on various health outcomes and health behaviors compared to studies using individual-level SEP indicators.[16,19,20] All SEP indicators used in this thesis were selected according to the principles from Galobardes et al. 2006.[19] These indicators, represent different influences on health and health behavior and are not interchangeable.[19,23] The strengths and weaknesses of these indicators of SEP will be elaborated on in the following sections.

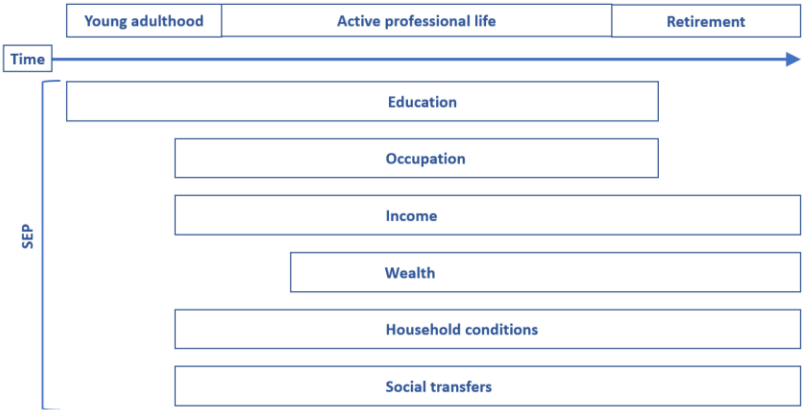

Figure 1-2 Relevance of indicators for SEP during adult life.
A modified model of life cause SEP from Galobardes.[16,19] In this thesis, household conditions and social transfers (if not measured as income) were only included if part of a composite SEP measure. Abbreviations: SEP: socioeconomic position

1.1.2.1 Income and wealth

In epidemiological studies, income and wealth are the indicators of SEP that measure the distribution of material resources most directly. Although income alone is not likely to directly affect most health outcomes, many possible pathways can describe the association between income disparity and health disparity, including affordability of assessing health-promoting environments, lifestyle, and healthcare.[16,22] It is important to understand that reverse causality may exist in the association between income and health outcomes, meaning that income may change a lot on short-term basis, and poor health may lead to a decreased income.[16,19,20] To estimate the health-relevant income, the household size should ideally be taken into account, assuming an even distribution of the income according to the needs within the household. Furthermore, a measure of disposable income optimally reflects the available resources.[16,19,20,26] However, gross income is often the only available measure, and it could even be described as a simple measure of above or below the poverty threshold.[16,19,20] Optimally, the income measure should include income from any source, including jobs, social security benefits, retirement benefits, unemployment benefits, income from rental units, child support, and any unofficial income.[16,19,20] If income is collected using questionnaires, the willingness to disclose accurate data was lower than for educational and occupational data.[16,19,20] Income disparity can be measured using the Gini-coefficient, representing the most commonly used index of the disparity wideness. The Gini-coefficient is represented as a number from 0 to 100. A Gini-coefficient of 0 indicates completely equal income distribution, whereas, when the Gini score approaches 100, this indicates an income distribution where a larger part of the total income accumulates in a smaller group of individuals. [11,25–27] Material resources can also be measured as wealth, capturing more resources than just income (including value of houses, cars, investments, and any savings). During the life course the wealth measure gets more relevant at older ages due to the effect of lifetime accumulation of finances and decreasing income at retirement.[16] However, the choice of wealth or income as indicator of SEP for adults aged 50 or more, does not seem to have a great impact regarding healthcare use.[28]

1.1.2.2 Educational level

In epidemiological studies, educational level is often used as a generic SEP indicator, aiming to capture the distribution of knowledge-related personal resources.[16] The personal attained level of education describes the individual's social, structural, and intellectual opportunities and abilities regarding education, influencing future socioeconomic circumstances, including employment and income. Generally, the educational level is the SEP indicator, which is most strongly associated with health behavior.[11,23] The advantages of educational level as an indicator of SEP include: it is rather easy to measure, self-administered questionnaires tend to have a high response rate to educational questions, it can be attained independent of age or working situations, and educational level seems to have life lasting impact on the risk of disease.[16,19,20] Educational level may be summarized in various ways, including years or level of attained education. In the early 1970’s, the United Nations Educational, Scientific and Cultural Organization (UNESCO) designed the International Standard Classification of Education (ISCED) to enable comparable statistics of education on a national and international level.[29] The ISCED is the international classification reference for education and qualifications by levels and fields, from early childhood education to doctoral or equivalent educational level.[29,30] The ISCED was updated in 2011 and has been implemented in all data collections in the European Union since 2014.[30]

1.1.2.3 Occupation and employment

In epidemiological studies, occupation- or employment-based indicators of SEP are widely used, and traditionally social stratification was widely defined based on occupation.[16,19,20] Both occupation and employment measures capture different aspects of SEP and are dynamically linked to income, suggesting that the association between occupation or employment and health could also indicate a direct association between material resources and health.[16,20] Furthermore, occupations and employment reflect social status and could associate with health outcomes because of specific job-related advantages such as direct access to high-quality healthcare. Furthermore, indicators of occupation could contain more specific occupation-related health factors, including toxic, pollutive, or physically working conditions.[16,19,20] However, some of the traditional indicators of occupation may not capture the contemporary occupational structures. Especially in high-income countries, the proportion of so-called manual and low-level occupations has decreased tremendously. Hence the traditional classifications of occupations into these groups may have lost some of the structural logic.[16,19,20,24] Furthermore, unemployed individuals, students, and people in unpaid or illegal jobs are often excluded from these traditional measures of occupation, resulting in possible underestimation of the socioeconomic disparity. Within the life course framework, the value of measuring current occupation or employment status declines when approaching the general retirement age *(Figure 1-2).*[16,19,20]

1.1.2.4 Health insurance

In epidemiological studies, health insurance coverage could be used as a measure of SEP.[31,32] Insurance status correlates with several other measures of SEP, including income, education, and occupation, and has been found to explain some of the disparity in health, especially in countries where access to care is not universal since insurance then represents a direct indicator for the affordability of healthcare or quality of the care offered to the patients.[31,32] However, health insurance coverage also associates with general health behavior.[31] Health insurance coverage may have a greater effect on disease outcomes and mortality after onset, than on disease incidence, since fewer preventive resources are allocated through insurance.[31] An advantage of health insurance as a SEP indicator is, that it is available across a large number of studies, with large reliability, since it is often the source of payment for healthcare interventions. A disadvantage is that it may introduce confounding by indication regarding disparity in medical care if the insurance status affects the services offered to the patients.[31,32]

1.1.2.5 Composite socioeconomic position

Composite measures of SEP using aggregates of several indicators can also be used to describe socioeconomic disparities. These composites may be computed on a personal level, combining multiple indicators for SEP, including, income, educational level, and occupation.[33,34] However, often composite measures of SEP are applied as area-based so-called deprivation indices, characterizing subjects on a scale from deprived to affluent based on their address.[16,19,20] Area-based composite indicators may be based on a variety of different measures, including the proportion of unemployed unskilled and semi-skilled manual occupations, households without a car, proportions of rental households and households with more than one person per room, single-parent households, proportions living in poverty, proportions with long-term illness in an area and geographical access to different services. The versions without health components are preferable for research on health outcomes. The area-based measures are especially relevant when investigating geographical disparities for political implementations, serving to allocate public resources to specific areas.[16,19,20] Deprived areas often present a higher proportion of fast-food restaurants, liquor-, and cigarettes-selling stores, and have fewer large grocery stores selling healthy fresh foods, which associates with more unfortunate health behavior. However, this association may also represent reverse causality, since grocery stores and restaurants sell the food and groceries in the highest demand.[23] Furthermore the area-based composite indexes may be easier to access according to data authorities, since data is not on individual-level, and in some cases are publicly available, and can be linked to any dataset if postal-codes for small geographical areas are available.[16,19,20]

1.1.3. TEMPORAL TRENDS IN SOCIOECONOMIC DISPARITY

A key objective of measuring SEP-related disparities in health is to define and detect changes over time to estimate if the policy targets aiming to diminish the health disparities have been fulfilled.[16] The challenge of health disparities has been described and discussed by the World Health Organization since the beginning of the 1980'ties, and the income disparity, measured using the Gini-coefficient, has been increasing in most Organization for Economic Cooperation and Development (OECD) countries since.[35–37] However, effectively decreasing the socioeconomic health disparities represents a great challenge for public health, even in the developed welfare states, despite being a high policy-maker priority in many European countries.[37–39] Temporal trends can improve the understanding of changes in the mechanisms that link SEP to health behaviors. Knowledge of specific avoidable risk factors may affect the health behavior pathways according to SEP, which have been found to increase the disparity in, e.g., smoking and diet patterns during the years.[23] Studies have generally shown a worrisome lack of progress on health disparity or even generally widening during the past 25 years both in Europe and the United States.[18,39,40] Furthermore, the substantial disparity in health and mortality in the Nordic advanced welfare states also persists despite relatively low material disparities.[17] Some healthcare regulations, including stronger regulations of public smoking, may have led to a tendency towards an increasing disparity in smoking habbits.[17,41]

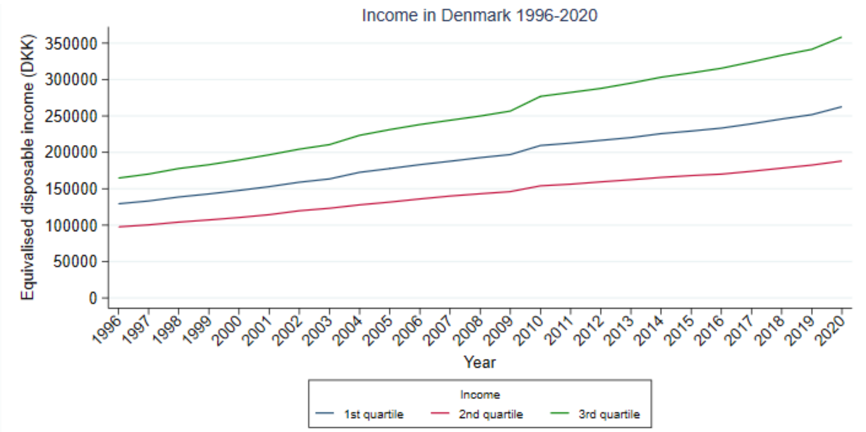

Figure 1-3 Income over time in Denmark.
Median and interquartile ranges for personal equivalent disposable income in Denmark 1996-2020.[42,43]

1.1.3.1 Trends in socioeconomic disparity in Denmark

Denmark (Adult population N=4.8 million 2022)[44] is well-known for egalitarian policies and its welfare societal model characterized by universal access to income transfers including social pension, user-free education, and unemployment benefit.[11,45] From 2005 to 2015, life expectancy in Denmark increased from 77.9 years to 80.6 years.[46] However, the population is still faced with a disparity in health and mortality, and the socioeconomic disparity in mortality has even been increasing for decades, partly facilitated by smoking and alcohol consumption.[11,45,47–50] Furthermore, the income disparity has widened during the last decades *(Figure 1-3)*. The Gini-coefficient, based on equivalent disposable income has increased from 23.8 in 1998 to 29.3 in 2017 *(Figure 1-4)*. However, how this reflects in health disparities has not been systematically examined.[42,43] Moreover, the distribution of education according to the ISCED 2011 definition has been changing, with a larger proportion of the population having attained a higher level of education and lower proportions having attained a lower or medium level of education, especially among employed individuals *(Figure 1-5)*.[42,51]

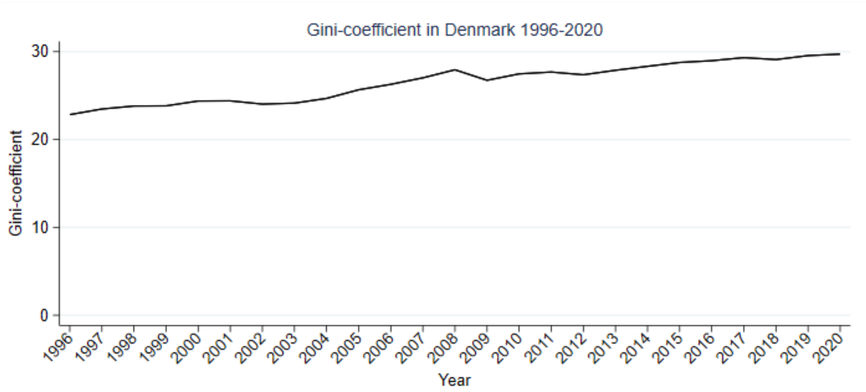

Figure 1-4 Income disparity over time in Denmark.
The Gini-coefficient based on the personal equivalent disposable income in Denmark 1996-2020.[42,43]

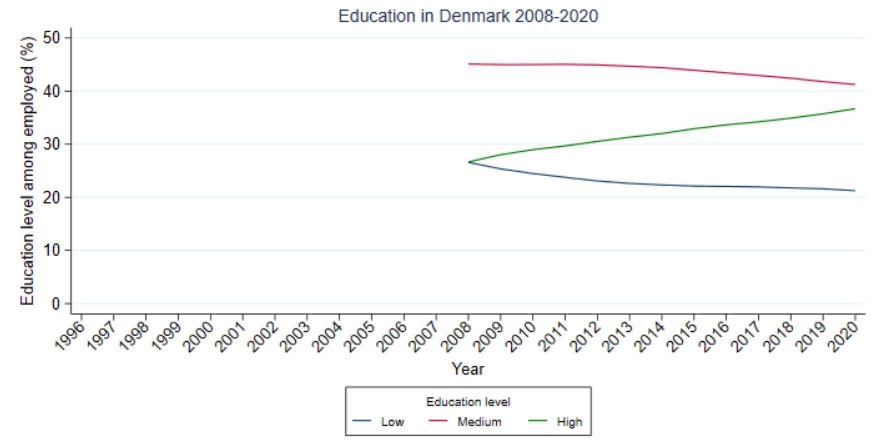

Figure 1-5 Educational level over time in Denmark among employed individuals aged 15 to 69 years.
The proportion of individuals within three levels of attained education among those aged 15 to 69 years with employment in Denmark. The education is estimated on the 30th of September each year. Educational level is available from 2008.[42,43] *Low education is defined as the ISCED 2011 level 0-2, medium as level 3, and high as level 5-8. ISCED level 4 is not used in the Danish education system.*[30,51] *Abbreviations: ISCED: International Standard Classification of Education.*

1.2. ACUTE CORONARY SYNDROME

A substantial global alteration in the distribution of diseases related to morbidity and mortality has occurred during the last century.[52,53] The industrialization and following advances in public health have implied a major increase in life expectancy, especially in Europe and North America.[18,52,53] Unfortunately, the improvements of general material wealth during industrialization and urbanization also implied a considerable change in lifestyle behavior. This included increased consumption of calories from dietary fat, smoking, physical inactivity, and obesity.[52] Overall, these lifestyle changes led to an acceleration in the progression of hypertension, hypercholesterolemia, diabetes, and metabolic syndrome, possibly causing coronary atherosclerosis, often presenting as acute events, i.e., ACS. ACS has emerged as the leading global cause of death among adults, accounting for approximately 30% of all deaths. [2,18,52–54]

ACS is the acute clinical presentation of coronary atherosclerosis causing cardiac ischemia, including MI and UAP.[2,55,56] The global incidence of ACS persists above 20 million cases yearly,[2,57] every year more than 7,000 Danish citizens suffer an incident MI, and ACS result in up to 21,000 admissions to Danish hospitals every year. [1,2,58,59] The most common pathophysiological mechanism of ACS is a rupture of an atherosclerotic plaque, resulting in partial or total occlusion of a coronary artery.[52,60] The plaque rupture exposes subendothelial collagen, activating the platelets and the coagulation cascade, generating a thrombus, which implies complete or partial coronary occlusion.[60] The coronary occlusion reduces the blood flow in the coronary artery resulting in cardiac ischemia and symptoms, typically chest pain.[52,60] The chest pain is often described as deep and prolonged, possibly radiating into one of the arms or armpits, jaw, tongue, teeth, or neck. Other symptoms may include dyspnea, nausea and vomiting, diaphoresis, and unexplained fatigue.[60] Adjustable patient risk factors, including lifestyle behavior are expected to play a large role regarding the risk of ACS.[52,60] However, non-adjustable risk factors, such as age, sex, and genetics also play a role in coronary atherosclerosis facilitated by systemic inflammation, platelet hyperreactivity, and prothrombotic conditions.[52,60] An ACS is diagnosed based on presentation of clinical symptoms and an electrocardiogram. The MI diagnosis further includes the presentation of biomarkers (i.e., troponin).[52,60] If ACS is suspected, an electrocardiogram should be completed and evaluated immediately after hospital arrival.[52,60] Cardiac troponin level above the 99th percentile of the standard range indicates necrosis in the myocardium and has generally substituted the use of other biomarkers. However, it may take up to six hours following the onset of myocardial necrosis for troponin to become elevated. Hence, a negative test should be repeated after six to nine hours. Complete occlusion of a coronary artery generally presents as an ST-segment elevation MI (STEMI) on the electrocardiogram, whereas partial occlusion of the coronary arteries generally presents without ST-segment elevation but may present other changes, such as ST-segment depression or T wave inversions, suggesting myocardial ischemia.[52,56,60–63] These patients are diagnosed with non-ST-segment elevation MI (NSTEMI) or UAP, depending on whether the biomarker evaluation presents elevation in troponin as evidence of myocardial necrosis indicating a MI.[52,56,60–63]

1.2.1. MEDICAL CARE IN ACUTE CORONARY SYNDROME

ACS patients are at high risk of mortality and morbidity on shorter and longer terms. Hence achieving the most efficient medical care on time are of major relevance for the patient outcome. Achieving rapid reperfusion is the basis of STEMI treatment. Urgent reperfusion therapy, by thrombolytics, used to be the preferred treatment to reestablish the blood flow in the occluded coronary artery, reducing patient mortality. For the last 20 years, urgent reperfusion with invasive treatment using primary percutaneous coronary intervention (PCI) has been preferred in Denmark.[60,64–69] Primary PCI is most effective in restoring the coronary blood flow, reducing mortality, recurrent MI, and stroke compared to thrombolytics in patients with STEMI, and only very few patients are not eligible for primary PCI. However, only 25% of hospitals in the United States have a PCI capacity.[60,65,66] Treatment for patients presenting to a hospital without the capability to perform primary PCI includes thrombolysis or transfer to a hospital with PCI capability. However, the benefit of primary PCI compared to thrombolytics is lost when the PCI is delayed more than 60 minutes from the first hospital admission. Thus, the guidelines recommend on-site thrombolysis for all eligible STEMI patients if transfer to a PCI center cannot be completed within 90 minutes.[60,65,66] Thrombolytics are associated with 25% decreased short-term mortality in STEMI patients. However, almost 40% of all patients undergoing thrombolysis may not attain the anticipated reperfusion in the infarcted coronary artery, and additionally 10% experience a recurrence of symptoms during hospitalization despite an initially effective reperfusion. Subsequent PCI is the best option for these patients. Hence, STEMI patients initially treated with thrombolysis would preferably also be relocated to a hospital with available PCI facilities.[60]

In contrast to the patients with STEMI, most patients with NSTEMI and UAP are preferably stabilized with medical therapy and referred for subacute invasive evaluation and treatment, with no need for thrombolytics in these patients.[60,62] Patients with NSTEMI or UAP should receive a combination of medical care and invasive evaluation to secure medical stabilization and coronary risk evaluation, aiming at minimizing the risk of recurrent events of ACS.[60,62,70] High-risk patients should undergo coronary angiography (CAG) within 24-48 hours after hospitalization to identify the appropriateness of revascularization using PCI or coronary artery bypass grafting (CABG) based on patient risk factors and the number of vessels affected by severe atherosclerosis, whereas low-intermediate risk patients can undergo invasive evaluation within 48-72 hours. Low-risk patients may undergo pharmacological care only.[60,62,70]

Recurrent ACS events and mortality after ACS are significantly reduced by the use of antiplatelets therapy (e.g., aspirin and/or thienopyridines/P2Y12-inhibitors) statins, β-blockers, angiotensin-converting enzyme inhibitors (ACEi), or angiotensin II receptor blockers (ARBs).[52,70,71] Therefore initiatives have focused on improving adherence to these guideline pharmacotherapies, to improve patient outcomes after incident ACS. However, studies report a so-called risk-treatment paradox, where patients at high risk are less probable to use these guideline-recommended medications.[70,72] Furthermore, it is of major importance for the patient mortality and morbidity to encourage the patients to actively take action to live a healthy life after an incident ACS and to comply with recommended medical treatment. Cardiac rehabilitation initiatives include interventions intended to at improve the physical and psychological functions in cardiac patients and has a major effect on the patients ability to return to a satisfying life.[73–75] Cardiac rehabilitation programs include lifestyle interventions, exercise programs, and other strategies aiming at reducing the risk factors for atherosclerosis. This includes dietary, physical, and psychosocial counseling emphasizing the importance of management of hypertension, hypercholesterolemia, diabetes, overweight, and smoking cessation, in addition to the appropriate use of cardiovascular guideline pharmacotherapies.[73–75]

1.2.2. TEMPORAL TRENDS IN ACUTE CORONARY SYNDROME

The total age-adjusted incidence and mortality of ACS have decreased across high-income countries since the 1980es.[5,6,12,52,54,57,58,76] The demographics of ACS patients have evolved, with a large decline in the incidence of STEMI patients and a rise in NSTEMI patients. The aging of the population has contributed to this change because elderly individuals are more likely present with NSTEMI than the younger. Furthermore, clinical outcomes after ACS have advanced significantly following a progressive improvement of the evidence-based therapies including the more widespread use of primary PCI treatment in MI around the early 2000s.[52,77] This improvement also includes improved sensitivity and specificity of the biomarkers defining MI, which have affected the epidemiology of ACS.[52,78] The European Society of Cardiology and the American College of Cardiology of incorporated troponin level into the definition of MI in 2000, because of the evidence for its prognostic value.[52,60,62] However, this was not included in the universal definition of MI until 2007.[52] As expected, following the introduction of more sensitive biomarkers with greater diagnostic accuracy, an increased the incidence of NSTEMI presented in the following years was seen along with a decrease in incidence of patients diagnosed with UAP.[52] Additionally, the increasing use of preventative medications (aspirin, statins, β-blockers, ACEi, and/or ARBs) in patients with identified atherosclerosis, hypertension, or other cardiovascular diagnoses before hospital admission with incident ACS is associated with extensive reductions in the risk of STEMI due to the anti-inflammatory, antithrombotic, and plaque-stabilizing effects.[52] Hence, comprehensive strategies have been improved, including optimization of clinical guidelines and treatment of ACS, to ensure optimal medical care according to the specific diagnosis, and ultimately to reduce the burden and consequences of ACS.[62,71,79,80] Thus, the overall ACS incidence and subsequent short-and long-term major adverse cardiac events (MACE), including mortality, recurrent ACS, and urgent need for revascularization, have decreased during the last four decades.[52,81–84]

1.2.3. DISPARITIES IN ACUTE CORONARY SYNDROME

Cardiovascular diseases, including ACS and stroke, has the highest influence on disparity in life expectancy, causing 20-30% of the disparities.[85,86] Low SEP, measured in occupation, social network, or education, predicts a 2-3 times increased risk of death caused by cardiovascular disease, highest among men.[87–89] As for other disease outcomes, part of this association can be explained by lifestyle patterns and heath behavior, since multiple risk factors are associated with ACS, including hypertension, hypercholesterolemia, diabetes, family history of coronary artery disease, and smoking habits.[11,16–20] SEP is a known proxy associated with increased cardiovascular disease onset, as well as subsequent differences in medical care, and mortality, even in countries with user-free universal healthcare systems.[11,12,18,90,91] Hence, persons with more resources according to SEP may both maintain a more healthy lifestyle and receive better medical care.[11,18] A meta-analysis Manrique-Garcia et al., 2011 identified a higher incidence of MI among individuals with the lowest level of various SEP measures compared to those with the highest SEP. Seventy original studies were included, resulting in a total population of 3,869,270 individuals of whom 28,629 had a MI. Individuals from the lowest income-, education-, or occupation levels presented a 71%, 34%, and 35% higher risk of a MI, than individuals from the highest SEP level, respectively.[92] The same pattern was identified, in a systematic review by Coughlin et. al., 2020. This review included 17 original studies, specifically demonstrating the association between low area-based SEP and higher incidence of MI and higher subsequent mortality, compared to high area-based SEP.[93] Furthermore, previous systematic reviews have identified an association between lower SEP and absence of prescription or consumption of guideline-recommended pharmacotherapies and lower involvement in cardiac rehabilitation programs among ACS patients, compared to patients with a higher SEP.[7,94] However, these studies do not consider the general association between a wide variety of SEP indicators, and reperfusion therapy or CAG, and mortality among patients with ACS. [7,92–94] Considering the ongoing change in the epidemiology of ACS and the attention aimed at reducing health and care disparities, an internationally contemporary overview on the socioeconomic disparity in ACS incidence, prevalence, medical care, and outcomes would be valuable.[7,12,13] However, studies indicate that the improved treatment of hypertension and atherosclerosis could have led to a reduced disparity in heart disease.[11,23] Still, the disease burden of ACS among persons with lower SEP is a major challenge for modern healthcare systems, especially with the demographic changes in the society.[54]

1.3. THE DANISH HEALTHCARE SYSTEM

The Danish healthcare system is characterized by tax-supported healthcare for the entire population, financing approximately 85% of all healthcare costs including general practitioners, hospitals, outpatient specialty clinics, and partial reimbursement of expenses for prescription medications.[46,95–97] The universal healthcare includes preventive services offered to all citizens (e.g., preventive health examinations at a general practitioner, cancer screening programs, and vaccination programs). Furthermore, preventive policy regulations concerning public smoking, environmental conditions, traffic safety, occupational circumstances, and food content, are also universal.[11,23,46] In total, 10.6% of the Danish gross domestic product was spent on the universal healthcare system (in 2014), which exceeds the OECD country average of 9.0%.[46,97] The Danish healthcare system is categorized according to primary healthcare (general practitioners and healthcare in the municipalities), holding the obligation for health promotion, prevention, and rehabilitation, and secondary healthcare (hospitals) holding the obligation for the more specialized medical treatment (i.e. inpatient and outpatient care).[98] The Danish Health Authorities targeted to ensure proper health for everyone, and it has been part of all political plans for the Danish healthcare system for the last 50 years to decrease the health disparity.[22,99,100] Still, health and diseases are unevenly distributed within society and the socioeconomic disparity in mortality is of a particular magnitude.[45,47,48] The progression of life expectancy has increased less in Denmark than in other OECD countries during recent years and the disparity in mortality has increased.[101,102] Thus, the healthcare system has a special responsibility regarding equal treatment of all patients, despite SEP. Most important the healthcare system is obligated not to enhance the disparity.[48,99] The challenge of ensuring uniform high-quality care to all patients in the Danish healthcare system, independently of SEP, was further emphasized in a critical report from the Danish *Rigsrevision* from January, 2019.[14] The socioeconomic disparity seems to present both in regard of prevention, early detection, treatment, and rehabilitation.[99] However, continuous monitoring and evaluation are lacking to identify whether the disparity in specific diseases and treatment changes for the better or the worse.[47]

1.3.1. STRATEGIES IN THE DANISH HEALTHCARE SYSTEM

The Danish welfare system was founded already in the eighteenth century, including efforts focusing on the provision of healthcare for the poor, established at the town and county levels. The system of sickness was established in 1892 for lower-income groups but changed extensively over the years to include all Danish citizens.[100] Since the 1940'ties, there has been a wide political agreement that healthcare should be available to everyone, independent of the place of residence and economic resources.[22] The decentralization partly still exists even in today's healthcare service, which is mostly public and organized across three levels of administration, including the state, five regions, and 98 municipalities, last reorganized in 2007, where 14 counties were reduced to five regions which retain the local responsibility for the Danish healthcare. This was done to generate a sufficient population base for the development of a more specialized regional hospital system.[22,97,100] Since 2007, the full responsibility for all non-hospital bases prevention, health promotion, and rehabilitation lies within the 98 municipalities. This was previously a shared responsibility.[46,100,103]

Denmark has had a national strategy on quality of care since 1993.[97,104] However, the focus and methods of the strategy have changed over the years.[97,105] In 2002 the Danish Accreditation Model was introduced with mandatory participation for public hospitals. This was based on standard principles of accreditation and includes continuous monitoring of the quality of the provided care.[97,104,105] Part of the concept of improving the general quality of care is also to secure that all patients receive the best care available. However, the model was phased out in 2015 by the Ministry of

Health because dissatisfaction among healthcare professionals was increasing, including protesting against the heavy burden of bureaucracy.[97] At that time, all hospitals had completed two cycles of accreditation.[46,97] In 2016, the Danish Healthcare Quality Program was introduced, representing a new way of addressing quality in healthcare to all patients, serving as a driving force for regional and local quality improvements.[46,105,106] The strategy is based on 8 national goals, aiming to improve and align care, pathways, treatment, survival, patient involvement, efforts for the chronically ill, and healthy life years, as well as efficiency of the healthcare.[46,97] Over the years, Denmark has established an advanced data infrastructure with approximately 130 health registries and 85 clinical quality registries collecting the disease-specific quality of care, as well as numerous national surveys, all evaluating the pathways for national quality improvement.[97,106] The attention to the disparity in the Danish healthcare system has increased in the recent years, including accessibility and quality of diagnostics, treatment, and rehabilitation. [14,46,48] The major reforms and political initiatives which have substantially impacted the Danish healthcare system and patient access to equal healthcare are presented in *Table 1-1*.

Table 1-1: Timeline for the major reforms and policy initiatives which have shaped the concurrent Danish healthcare system, 1998-2017.[97,104]

Year	Description
1999	Introduction of DRG payments to finance hospitalization outside the patient home county (1998 budget agreement)
2002	Introduction of the Danish Accreditation model
2002	The waiting time guarantee, including an extended free choice of hospitals, was introduced. Thus, patients with >2 months waiting time could select a treatment at several private facilities including facilities abroad
2003	The 1999 DRG reform was expanded to activity-based financing in all hospitals from 2004
2005	Establishment of the Danish Institute for Quality and Accreditation in Healthcare
2005	The structural reform was presented, and a new Health Act stated the objectives, general purposes, and instruments of the healthcare sector was formally combined within one comprehensive check. This was previously based on 15 separate checks on healthcare legislation. The Health Act was passed in 2005 and executed in 2007
2007	The waiting time guarantee was shortened from 2 to 1 month
2007	The structural reform was implemented: the previous 14 counties were replaced by 5 regions. Municipalities were merged from 271 to 98. New distribution of responsibilities of decisions, financing, and tasks between state, regions, and municipalities
2007	The entire hospital sector was restructured and modernized (ongoing process), including establishment of joint acute wards, to secure specialized staff in all settings
2008	Establishment of mandatory clinical pathways packages for cancer and heart diseases
2009-2011	The Danish Healthcare Quality Program was established
2010-2011	Implementation of National specialty planning for hospitals
2015	Withdrawal of the Danish Accreditation model
2016	Introduction of the new National Quality Program

Abbreviations: DRG: diagnosis related group.

1.3.1.1 Danish strategies regarding disparity in healthcare

Danish health policy goals for improving public health and reducing socioeconomic disparity in health have been expressed for decades.[11,101,107–109] This includes the Government's Public health program 1999–2008 representing a goal regarding reduced social disparity in health, [107] and the Health package from 2009 proposing funds on projects that strengthen preventive interventions and better guidance material to lifestyle changes, including smoking cessation on recruitment and motivation among individuals with lower SEP.[11,109] However, as seen in across many other countries, the Danish national strategy on quality of care has generally been uncoordinated regarding indicators of health disparities.[11,99,101] The national goals have mainly focused on delivering the same quality across the regions rather than across different patient groups (e.g., levels of SEP, age, and sex).[47] Monitoring disparities across different patient groups was the lately suggested by an expert group in 2020, including the introduction of new indicators across the Danish quality registers. However, this has still not been introduced in practice.[47]

Table 1-2: Timeline for initiatives that have had a substantial impact on the healthcare of patients with ACS in Denmark 1998 – 2017. [63,66,104,110,111]

Year	Description
1998	Establishment of the Danish Heart Registry to monitor the Danish Heart Plan
2000	Introduction of troponins as biomarker for MI in Denmark
2003	Implementing primary PCI as standard treatment for all relevant patients with STEMI
2007	Joint acute wards were established to secure that e.g., ACS patients were meet by a cardiologist independent of representation other acute symptoms
2008	Establishment of “the heart packages” as national clinical pathways

Abbreviations: ACS: acute coronary syndrome, MI: myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction.

1.3.1.2 Danish strategies regarding acute coronary syndrome

The number of invasive treatments were significantly lower in Denmark compared to other Northern European in the mid-1990s. Hence, a comprehensive nationwide initiative (the Heart Plan) was established to improve the diagnosis and treatment of cardiovascular disease, implying an increase in the use of coronary diagnostics and interventions.[111,112] The Danish strategies regarding the treatment of ACS are based on the guidelines from the European Society of Cardiology.[62,80] Since 2003, all patients with STEMI have been transferred directly to a specialized cardiac center for evaluation and primary PCI, as a national revascularization strategy in Denmark.[65–69] Continuity of the quality of care has been regulated by comprehensive, standardized treatment programs (the “Heart packages”) focusing on four national clinical pathways for cardiovascular disease including one for patients with ACS, introduced in 2008.[68,104,110,111] Furthermore, national planning of the specialty distribution across hospitals has increased the patient pathways and specification of hospital staff, including the establishment of “joint acute wards”.[46,104] From 2000 to 2014, the number of CAG and PCI increased by 231% and 193%, respectively.[111] Denmark has presented the largest decline in cardiac-related mortality within the OECD countries, with a 69% decline from 2005 to 2012.[46,113] The most important initiatives that have had a substantial impact on ACS care in the Danish healthcare system are presented in *Table 1-2.*

CHAPTER 2. AIMS OF THE THESIS

2.1. OVERALL OBJECTIVE

The overall objective of this thesis was, to examine 20-year temporal trends (1998-2017) in socioeconomic disparities in incidence and clinical outcomes in patients with an incident ACS admitted to a hospital in Denmark; and to review the scientific literature (2009-2021) regarding socioeconomic disparity in incidence and prevalence of ACS, as well as medical care and all-cause-patient-mortality. Socioeconomic disparities were elucidated based on different indicators across the studies, including educational level, income level, occupation status, health insurance status, and composite indicators of SEP. This was evaluated within three studies. The aims of the individual studies are listed below.

2.1.1. AIM STUDY I

To examine the literature published from 2009 to 2021 regarding the association between SEP and the incidence and prevalence of ACS, as well as the association between SEP and subsequent ACS-related medical care and all-cause mortality among ACS patients. This was separated into the four aims; to investigate the association between SEP and:

1) the incidence of ACS
2) the prevalence of ACS
3) the medical care after ACS
4) the mortality after ACS.

2.1.2. AIM STUDY II

To investigate temporal trends in income-related disparity in the incidence of hospitalized ACS and out-of-hospital fatal ACS, in Denmark from 1998 to 2017.

2.1.3. AIM STUDY III

To investigate temporal trends in socioeconomic disparity in MACE within 30- and 365-days after the ACS diagnosis among patients with incident ACS in Denmark from 1998 to 2017.

CHAPTER 3. METHODS

This chapter describes the methods of the systematic review (Study I) and the two nationwide registry-based cohort studies (Study II-III), which is included in this thesis. Some details are not presented here, but may be identified in the specific studies in *Appendix I-III.*[114–116] Graphical abstracts for Study I-III are presented in *Supplemental Figure S1-S3.* The systematic review was conducted to identify and analyze all relevant peer-reviewed literature regarding the association between SEP and the incidence and prevalence of ACS, as well as the association between SEP and the medical care and mortality in the ACS patients, published in the last decade.[114] The two cohort studies were conducted to identify temporal trends of socioeconomic disparity in the incidence of hospitalized ACS and out-of-hospital fatal ACS, and socioeconomic disparity in MACE including all-cause mortality, within 30- and 365-days after ACS among patients with incident ACS, in Denmark from 1998 to 2017.[115,116] The main characteristics of the three studies are presented in *Table 3-1.*

Table 3-1 Overview of the study characteristics in study I-III.

	Study I	**Study II**	**Study III**
Objectives	To analyze the literature on the association between SEP and incidence and prevalence of ACS, and medical care and mortality in the ACS population	To investigate temporal trends in income-related disparity in the incidence of hospitalized ACS and out-of-hospital fatal ACS	To investigate temporal trends in socioeconomic disparity in MACE within 30- and 365-days after the incident ACS diagnosis
Setting	Studies published 2009-2021	Denmark 1998-2017	Denmark 1998-2017
Data sources	PubMed and Embase	CRS, DNPR, DRCD, and IND	CRS, DNPR, IND, RMPS, PER, RAS, and DHR
Study population	General population (aim 1-2) and patients with ACS (aim 3-4)	The entire Danish population aged ≥20 years	All patients with ACS aged ≥18 years admitted to a hospital in Denmark
Exposures		SEP:	
	Income, education, insurance, occupation, and composite indicators of SEP	Equivalized personal income quartile	Equivalized personal income quartile and highest attained educational level
Outcomes	Incidence and prevalence of ACS and medical care and patient mortality after the ACS	Incident ACS admission to a Danish hospital or out-of-hospital death from incident ACS	30- and 365-day MACE, i.e.: mortality, recurrent ACS, revascularization, stroke, or cardiac arrest
Method of analyses	Narrative data synthesis, summary of key features, and graphical illustrations stratified according to SEP exposures and Cochrane risk of bias	Yearly ACS IR per 100,000-py and IRR, standardized to age, sex, and year. Temporal trends identified from random effects meta-regression analysis	MACE IRs and HRs were computed with the highest SEP as reference. Trends identified from interaction analyses of HRs according to time

Abbreviations: ACS: acute coronary syndrome, CRS: the Danish Civil Registration System, DHR: the Danish Heart Registry, DNPR: the Danish National Patient Registry, DRCD: the Danish Register of Causes of Death, HR: hazard rate ratio, IND: the Personal Income Register, IR: incidence rate, IRR: incidence rate ratio, MACE: major adverse cardiac events, PER: the Danish Population's Education Register py: person-years, RAS: the Register-based Labor Force Statistics, RMPS: the Register of Medicinal Products Statistics, SEP: socioeconomic position.

3.1. SYSTEMATIC SEARCH STRATEGY

To identify all relevant studies on socioeconomic disparity in ACS and outcomes after ACS from the last decade (Study I), a systematic literature search was performed in PubMed[117] and Embase[118], using Medical subject heading (MeSH) terms, Emtree terms, and keywords.[119] The terms were based on two blocks, according to the generated PICO (Patient/population, Intervention, Comparison and Outcomes) diagram: 1) the indicators of SEP and 2) the ACS diagnosis. The search was limited to original studies and studies in press, published from 2009 to 2021 in English, Danish, Norwegian, or Swedish. The literature search was initially accomplished at the 10th of July 2020 and rerunned the 5th of July 2021.[114] Furthermore, reference lists of the included studies were manually hand-searched and the studies were cross-referenced in the Web of Science.[114]

The identified literature was double-screened for eligibility with the four study aims, by two independent researchers, using the blinding function in Rayyan QCRI.[120] A selection tool with specific in- and exclusion criteria on population, exposure, outcome, and study design, under the four aims of the study, was established to facilitate the screening process. First titles and abstracts were screened for eligibility, then full-text versions of studies, identified as possibly relevant, were read to decide final in- or exclusion.[114] To be included in the review, the studies should consider the ACS incidence or prevalence as the outcome in a general population, or consider an outcome regarding medical care or patient mortality in an ACS population, according to an indicator of SEP *(Table 3-2)*. Studies, where the ACS diagnosis was combined with other diagnoses, were excluded if separate results on ACS were not possible to extract. The studies were also excluded if presented as letters, case-reports, editorials, practice-guidelines, reviews, or conference abstracts.[114,121]

Table 3-2: Overview of the populations, outcomes and SEP exposures in Study I-III.

Study:	Population	Outcome	SEP
I (aim 1)	General population	ACS incidence	Education, income, occupation, insurance, or composite SEP
II (trends)			Personal income
I (aim 2)		ACS prevalence	Education, income, occupation, insurance, or composite SEP
I (aim 3)	ACS Population	Medical care	
I (aim 4)		Mortality	
III (trends)			Personal income, educational level
III (trends)		MACE	Personal income, educational level

Abreviations: ACS: acute coronary syndrome, MACE: major adverse cardiac events, SEP: socioeconomic position.

3.2. SETTINGS FOR THE NATIONWIDE COHORT STUDIES

The two nationwide, population-based, cohort studies (Study II-III) were conducted in Denmark.[44] Detailed clinical anonymized data on patient contacts to somatic hospital departments in Denmark were linked to sociodemographic data, accessed through the Danish Health Data Authorities and Statistics Denmark.[115,116] The Danish Health Data Authority and Statistics Denmark are state institutions, containing individual-level data from multiple administrative registers and governmental agencies [42,122] The accessed databases are presented in *Table 3-3*.

Table 3-3: Databases used in the three studies.

Database	Study	Information	Time
PubMed	I	Archive of biomedical and life sciences peer-reviewed literature, hosted by the United States National Institutes of Health's National Library of Medicine[117]	2009-2021
Embase	I	Database of biomedical and pharmacological published literature, hosted by Elsevier[118]	2009-2021
CRS	II & III	Data on age, sex, and vital status. Support linking across all registers from ten-digit personal identification numbers of all Danish citizens [44,95,123,124]	1977-2018
DNPR	II & III	Detailed clinical data on patient comorbidities from contacts to somatic hospital-, ambulatory- and emergency departments, based on nationally tax-supported healthcare of Danish citizens[96,124]	1977-2018
DRCD	II	Information on the cause of death, using ICD-10 codes, and codes for unknown reason of death (R999, R961, and R989) or registrations of death certificates never received (R990)[125]	1998-2017
IND	II & III	Data on tax-based annual equivalent income on personal level[122,126]	1997-2016
RMPS	III	ATC-code information on prescription pharmacotherapies within one year before the ACS diagnosis, used to define comorbidity[127]	1997-2017
PER	III	Data on personal highest attained educational level[128]	1998-2016
RAS	III	Data on personal employment status ultimo November[51]	1997-2016
DHR	III	Data on nationwide activity and quality of invasive diagnostic and treatment strategies in patients with ACS. From 2003 the completeness of procedures has been reported as >90%[111]	2000-2017

Abreviations: ACS: acute coronary syndrome, ATC-code: the Anatomical Therapeutic Chemical codes, CRS: the Danish Civil Registration System, DNPR: the Danish National Patient Registry, DHR: the Danish Heart Registry, DRCD: the Danish Register of Causes of Death, ICD: International Classification of Diseases, IND: the Personal Income Register, PER: the Danish Population's Education Register, RAS: the Register-based Labor Force Statistics, RMPS: the Register of Medicinal Products Statistics.

3.2.1. DATA SOURCES

The Danish Civil Registration System (CRS) is an administrative register established in 1968, containing individual-level information on all Danish residents, allowing individual-level-linkage across the Danish administrative registers. Daily updated information on migration-, civil-, and vital status allows the conduction of nationwide cohort studies with almost complete follow-up on emigration and death.[44,95,123,124]

The Danish National Patient Registry (DNPR) holds data on morbidity, co-morbidity, and hospital-based activities for all inpatients discharged from Danish somatic hospitals since the establishment of the database in 1977. Additionally, DNPR contains information from contacts to emergency departments and outpatient specialty clinics since 1995.[96,124] For each patient contact, one primary and optionally secondary diagnoses are recorded and classified according to the International Classification of Diseases 10th revision (ICD-10) since 1994 and the 8th revision (ICD-8) since 1977.[96,124]

The Danish Register of Causes of Death (DRCD) holds information on the cause of death, reported using ICD-10 codes, since 1994.[125] The coding is based on the medical information on the death certificates, and the status for collection of the certificates is recorded as well. To accelerate the updating of the statistics, the principles for coding were updated in 2002 to scanned information, and since 2007, death certificates have been submitted in electronic form. Thus, discontinuities in trend-specific mortality appear, partly caused by changes in collecting the specific causes of death.[125]

The Register of Medicinal Products Statistics holds information on all dispensed prescription pharmacotherapies according to the Anatomical Therapeutic Chemical classification system[127,129]. Data on pharmacotherapies dispensed in Danish community pharmacies and hospital-based outpatient pharmacies are available on an individual-level in a rather complete form since 1995.[127]

The Danish Heart Registry is a registry on medical and administrative data of patients referred for heart surgery and invasive cardiological procedures from 2000 in the Danish Clinical Registries. Invasive procedures are described by unique variables, including prognostic factors, operative data, procedure-related complications, and demographic characteristics. Data from 2003 is considered complete and valid.[111]

Socioeconomic variables were retrieved from statistics Denmark on an individual level. Income data was collected form the personal income register, which holds information on tax-based annual income on personal level.[122,126] Furthermore, the personal income statistics, on aggregated level are published and public available on the Statbank website, including median and interquartile ranges (IQR) according to sex, age, and year.[42] Education data was collected from the Danish Population's Education Register.[128] The Danish Population's Education Register holds data on the highest completed level of education for each individual, including administrative data on education and training completed in Denmark, and self-reported information on completed education for individuals completing education before 1974 and for immigrants with no Danish schooling records.[128] The Register-based Labor Force Statistics is the register on individual level labor market attachment ultimo November each year. The registry holds data on employment status, defined as employed, unemployed or outside the labor force.[51]

3.3. STUDY POPULATIONS

3.3.1. GENERAL POPULATION

The study population for Study I (aim 1-2) and Study II was defined as the general population *(Table 3-2)*.[114,115] In Study I this could include any specifically defined population, based on availability, living in specific investigated countries or areas, answering a specific survey, or defined as a control population to a population with the ACS outcome.[114] In Study II, the population was defined as the general Danish population aged ≥20 years from 1998 to 2017, with available aggregated tax-based income data in the Statbank at Statistics Denmark, including sex, age, and yearly personal equivalent income.[42,115,122]

3.3.2. ACS POPULATION

Across all three studies in this thesis, ACS was defined as the acute presentation of coronary atherosclerosis, including MI or UAP.[114–116] The study population for Study I (aim 3-4) and Study III was defined as a population with incident ACS *(Table 3-2)*.[114,116] In Study I, ACS was defined as diagnoses from ICD-10, ICD-9, ICD-8, doctors' decision, characteristic ACS symptoms, self-reporting, or similar indications were accepted *(Table 3-4)*.[114]

In Study III the incident ACS more specifically had to be based on an ICD-10 diagnosis, at a Danish hospital between January 1st, 1998, and December 31st, 2017, available in the DNPR. Only the first admission within the period was included for patients with multiple admissions, and patients with ACS diagnoses (including ICD-8) since 1977 were excluded *(Table 3-4)*. Furthermore, the patients with ACS had to be aged ≥18 years and living in Denmark, to be included.[116]

Table 3-4: Diagnosis codes for acute coronary syndrome in Study I-III.

ACS	ICD-8	ICD-9	ICD-10
Study I	410*,411*, or 413*	410*, 411.1, or 411.81	I21*, I24*, or I200*
Study II-III	410*,411*, or 413* (Used for exclusion of previous ACS)	-	I21* or I200*

*Abreviations: ICD: International Classification of Diseases, ACS:acute coronary syndrome, *:including all sub-codes.*

3.4. SOCIOECONOMIC POSITION

The SEP exposures across all three studies were pre-defined based on the principles from Galobardes et al. 2006, *(intro-section 1.1.2, and Figure 1-2)*.[19] In the systematic literature review (Study I), several indicators for education, income, occupation, insurance status, or a composite indicator of SEP were accepted, if only they were reliable and categorized.[12,114,130–132] The income indicator also included studies using indicators of wealth, and the occupation indicators also included indicators of employment. SEP indicators based on individual-, household-, or area-level information, were all accepted.[114] However, SEP indicators according to childhood, parental, or partner factors were excluded.[114,121] All three studies (Study I-III) intended to compare the lowest SEP level and the highest as an indicator of socioeconomic disparity, regardless of the number of SEP categories reported.[7,19,114–116]

For the two nationwide cohort studies (Study II-III) the indicators of SEP were more specifically selected. In both studies, income was applied, as equivalent disposable personal income quartiles.[115,116] This was based on nominal prizes on a modified scale from the OECD, which redistributes the disposable income equally among all household members, allowing comparability between different household sizes.[26,122] The personal equivalized disposable income the year before the incident ACS diagnosis was accessed in the personal income register through Statistics Denmark. Year- age- and sex-specific equivalents income median and IQR were accessed in the Statbank, to calculate income quartiles according to the entire Danish population to reduce the impact of inflation and demographic changes.[42,122,126]

In study III, SEP was also retrieved as the personal level of highest educational attainment.[116] The highest completed level of education for each patient before the incident ACS was obtained from the PER in statistics Denmark.[116,128] Education was categorized into three levels based on the ISCED 2011: 1) Low educational level (ISCED level 0-2) including early childhood, primary, and lower secondary educational level, 2) medium educational level (ISCED level 3) including general upper secondary education and vocational and upper secondary education, 3) high educational level (ISCED level 5-8) short-cycle tertiary education, medium-length tertiary and bachelor's-level educations or equivalent, second-cycle, master's-level or equivalent and PhD-level education.[30,116,128]

3.5. STUDY OUTCOMES

The primary outcomes of this thesis include the socioeconomic disparity in the incidence and prevalence of ACS, and the medical care and mortality in the ACS population.[114] Furthermore, the outcomes included temporal trends of socioeconomic disparity in the incidence of hospitalized ACS or out-of-hospital fatal ACS, or MACE or mortality within 30- and 365-days after the incident ACS.[115,116]

3.5.1. INCIDENCE OF ACS

Incidence is ascertained by counting the number of new cases occurring during a period e.g., one year.[54] Incidence of ACS was defined as a new diagnosis of ACS as defined above *(section 3.3.2)*, within a specific period. Thus, a wide range of definitions was accepted for the incidence of ACS in Study I (aim 1).[114]

Temporal trends in disparity in the incidence of ACS was the main outcome in Study II. The incidence of ACS in Study II was defined based on ICD-10 codes at a Danish hospital between January 1st, 1998, and December 31st, 2017, (as defined in Study III, presented in *section 3.3.2*). Furthermore, to identify whether possible changes in incidence were caused by changes in procedures for hospital admissions or registration of ACS, subjects who died from 1998 to 2017 without previous ACS diagnoses, with death registered as caused by ACS or with sudden death without any registered reason of death were included as possible ACS incidence as secondary outcomes in Study II.[115]

3.5.2. PREVALENCE OF ACS

Prevalence of ACS (Study I, aim 2) was defined as an ACS diagnosis, which could not be defined as new onset. The ACS diagnosis included the same range of definitions as for the ACS population *(section 3.3.2)* and the incidence of ACS in Study I (aim 1).[114] The prevalence outcome was included, to incorporate published studies, where the burden of ACS was investigated in cross-sectional settings since this could possibly have been accomplished at lower costs, thus; presenting different population settings possibly from lower-income countries.[133]

3.5.3. MEDICAL CARE

The medical care outcome in Study I was defined and categorized into three categories after the incident ACS: 1) reperfusion (thrombolysis, PCI, or CABG) or CAG during the index admission, 2) use of or adherence to cardiovascular pharmacotherapy (anti-platelet, lipid- or blood-pressure-lowering pharmacotherapies, or a combination), 3) invitation to attend or attendance in cardiac rehabilitation programs.[114] Furthermore, composite medical care was included if it was defined as a combination of these medical care categories. Suboptimal medical care was defined as receiving only part of a medical care outcome, receiving a medical care late after the hospitalization, or not receiving the specific medical care outcome.[114]

3.5.4. MORTALITY

In Study I, mortality was defined as case-fatality, all-cause-, or cardiac mortality after the incident ACS, including both in- and outpatient mortality, and stratified into short- (≤30 days after ACS) and long-term mortality (>30 days after ACS).[114]

Furthermore, temporal trends in socioeconomic disparity in mortality after ACS was a secondary outcome in Study III. Here, time to all-cause mortality after ACS was defined based on vital status data (i.e., date of death) from the CRS. All-cause mortality was accessed within 30- and 365-days after the incident ACS, and included in the composite MACE outcome.[116]

Table 3-5: Events and codes for major adverce cardiac events in Sudy III.

MACE	ICD-10	SKS code	CRS code
All-cause mortality			Status: 90
ACS	I21* or I200*		
PCI		KFNG* or specified as 05A or 02A	
CABG		KFNA*-KFNE*	
Stroke	I61, I63, I64, I69.3, or I69.4		
Cardiac arrest	I46.9		

*Abreviations: ACS: acute coronary syndrome, CABG: coronary artery bypass grafting, CRS: the Civil Registration System, MACE: major adverce cardiac events, PCI: percutaneous coronary interventions, SKS: the healthcare clasification system, *:including all sub-codes.*

3.5.5. MAJOR ADVERSE CARDIAC EVENTS

The main outcome of Study III was temporal trends in the socioeconomic disparity in MACE within 365-days after the incident ACS. MACE have been investigated in cardiovascular research using several definitions.[134–137] In Study III, 30- and 365-day

MACE was defined as composite endpoints of the first event of all-cause mortality after the ACS diagnosis, recurrent ACS, revascularization (PCI or CABG), stroke (hemorrhagic or ischemic), or cardiac arrest registered ≥7 days after the hospital discharge from the incident ACS admission *(Table 3-5)*.[116,137]

3.6. COVARIATES

In the systematic literature review (Study I), results from the identified studies were extracted in unadjusted or the least adjusted form available, to achieve comparability of the results across the studies.[114,121] However, adjusting for relevant prognostic covariates, was part of the quality assessment according to the Cochrane tools to access the risk of bias for cohort-, case-control-, and cross-sectional studies, applied in Study I. [138–141] If the presented results were only available in a stratified form, data were extracted for all stratified levels of age, sex, or ethnicity. However, if the results were stratified according to calendar time, the results from the last period were extracted.[114]

In Study II, the available covariates were limited to those available on an aggregated level in the Statbank data.[42] These included income-year, sex (male or female), and age-group (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, or ≥80 years).[42,122] A causal diagram was constructed, to identify whether the standardization using the available covariates was expected to imply confounding *(Supplemental Figure S4)*.[115] In Study III, available covariates included age, sex, employment, migrant status, civil status, and comorbidity level. Employment status was categorized from information in the Register-based Labor Force Statistics, defined as employed, retired (including early retirement), or unemployed. Migrant status was defined based on place of birth (Danish-born, or immigrant/descendant). Civil status was categorized as Married or cohabiting, or Unmarried or single living.[116] Comorbidities were evaluated using the Charlson Comorbidity Index (CCI), calculated from the ICD-8 and ICD-10 diagnoses based on 19 disease categories within ten years before the ACS.[142] Patients were categorized according to three levels of CCI: a score of 0 (low), given to patients with no disease record; a score of 1–2 (medium); and a score of 3 or more (high). In Study III, the covariates were selected for adjustment based on two causal diagrams *(Supplemental Figure S5-S6)*.[116,143]

3.7. DATA HANDLING

Statistical analysis and graphs for the three studies were performed in Stata v. 16.0 and 17.0 (Stata Corp. 2019) and Microsoft Excel 365 (Microsoft Corp. 2017).[114–116] All individual-level data for Study II-III was handled in anonymized form at a restricted server at statistics Denmark.

3.7.1. DATA EXTRACTION AND DATA SYNTHESIS

Data were included in the literature review (Study I) based on data extraction, using standardized forms based on the study aims.[114] If available, the following information was extracted from the included studies and summarized in a table: primary author, publication year, country of origin, study design (cohort, case-control, or cross-sectional study), population characteristics (age and sample size), specific ACS diagnosis (STEMI, NSTEMI, or UAP), applied SEP indicator(s) and the categories, outcome(s) (according to the four aims), follow-up and study results (defined as an association between highest/lowest SEP and outcome). If no risk measures were presented, an estimate and confidence interval (CI) were calculated based on the available data. Since the definitions of the SEP exposures were so diverse, it was found inappropriate to perform a meta-analysis. Thus, the data synthesis in the study was performed as a narrative synthesis, presenting all findings in summary tables. Furthermore, study results were summarized in diagrams as proportions, presenting whether each study found an association (and the direction of the association) stratified according to SEP exposure and outcomes.[114] Finally, the identified study results were presented according to the risk of bias, identified from the Cochrane tools to assess the risk of Bias for cohort studies, case-control studies, or cross-sectional studies.[114,138–140]

3.7.2. STATISTICAL ANALYSES

In the cohort studies, individual baseline characteristics for the primary ACS population, including available covariates, were presented as medians and IQR or frequencies and percentages where appropriate. This was presented according to year (Study II-III), income quartile (Study III), and educational level (Study III).[115,116] In Study II, direct standardized incidence rates (IR) were calculated using cell-specific equivalent income quartiles for the year before the incident ACS.[115] The income quartiles were standardized, according to year, sex and age-group.[42] Thus, yearly direct standardized IRs were presented as ACS cases pr. 100,000 person-years according to income quartile.[115,144] Standardized incidence rate ratios (IRR), were computed and graphically illustrated, using individuals in the highest-income quartile as the reference.[115] CIs at 95% were estimated using a method by Julious et al., 2001.[145] The analyses were repeated, including patients who died from 1998 to 2017 without previous ACS diagnoses, with death registered as caused by ACS or with sudden death without any registered reason of death.[115]

In Study III, two follow-up periods were applied (30- and 365-days). Thus, MACE IRs were computed, and cox-proportional hazards regression was used to estimate the cause-specific hazard rate ratio (HR) for MACE, with the lower income and educational level compared to the highest. Analyses were repeated for income and educational level in three levels of adjustment: univariable, simple-, and complex-adjusted, using inverse-probability of treatment weights. The simple-adjusted analyses were adjusted for age using cubic splines, sex, and migrant status. The more complex-adjusted analyses were also adjusted for the patient’s civil status, employment status, and CCI, as well as income or educational level (conditional on the exposure). Data were trimmed, and balance diagnostics were performed after the propensity score weightings.[146] The cox-proportional hazards regressions were adjusted using the Doubly robust method, to compensate for the imbalance following IPTW.[147]

3.7.2.1 Temporal trends

In Study II, the standardized IRs for ACS were compared for change in differences over time between the lowest- and the highest-income quartile by interaction analysis using random effects meta-regression, to account for the standard errors within the aggregated data.[115] In Study III, interaction analyses were applied for the HRs to identify temporal trends in socioeconomic disparities over the five-year periods in regard to income and education.[116]

3.7.2.2 Stratified analyses

Both in Study II and III, the analyses were stratified in multiple levels to identify possible effect modifications.[115,116]

3.8. ETHICS, REGISTRATION, AND REPORTING

Pre-defined methods for the systematic literature review (Study I) were pre-registered in the International Prospective Register of Systematic Reviews (registration no.: CRD42020197654).[114,121] The cohort studies (Study II-III) were approved and registered at the local institutional review board (Journal number: 2019-899/10-0429) according to Danish law.[115,116] Reporting of all three studies conforms to the relevant Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines.[148–152]

CHAPTER 4. RESULTS

This Chapter summarizes the results from the three studies. Further details, such as baseline characteristics of the patients with ACS, stratified results, and interaction analyses, may be found in the individual studies *(Appendix I-III)*.

4.1. STUDY AND POPULATION SELECTION

In the systematic search in the literature review (Study I), 4,573 unique studies were identified from the initial literature search in PubMed and Embase. After the screening of titles and abstracts, 322 studies were read in full-text, and finally, 171 studies met all eligibility criteria and were included in the study *(Figure 4-1)*. Furthermore, 10 studies were identified by the hand search or cross-referencing, resulting in a total of 181 studies.[114] In total, these studies included general populations of more than 120 million adults (up to 35 million adults per study) and populations of more than 16 million patients with ACS (up to 6.6 million per study).[114]

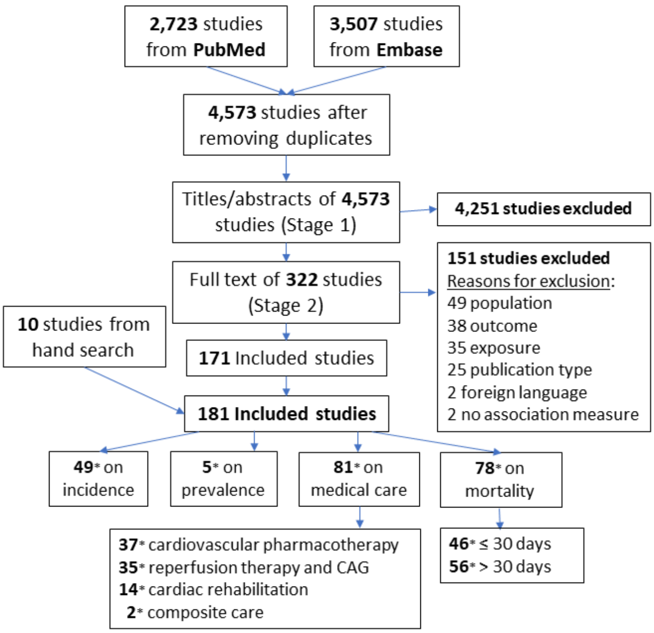

Figure 4-1 Flowchart Study I.
*Systematic selection of the identified studies in Study I. Abbreviations: CAG: coronary angiography, *: some studies presented results on multiple outcomes and/or sub-outcomes.*[114]

In Study II, the general Danish population aged ≥20 years from 1998 to 2017 was collected based on aggregated tax-based income data in the Statbank at Statistics

Denmark and address in Denmark. The flow from subject selection until study outcome is presented in *(Figure 4-2, Study II)*. Over the 20 years from 1998 to 2017, 220,070 patients with incident ACS were identified, based on the defined diagnosis criteria.[115] In Study III, 220,887 patients with an incident ACS diagnosis from 1998 to 2017, aged ≥18, living in Denmark the year before diagnosis, were included in the study population *(Figure 4-2, Study III)*.[116]

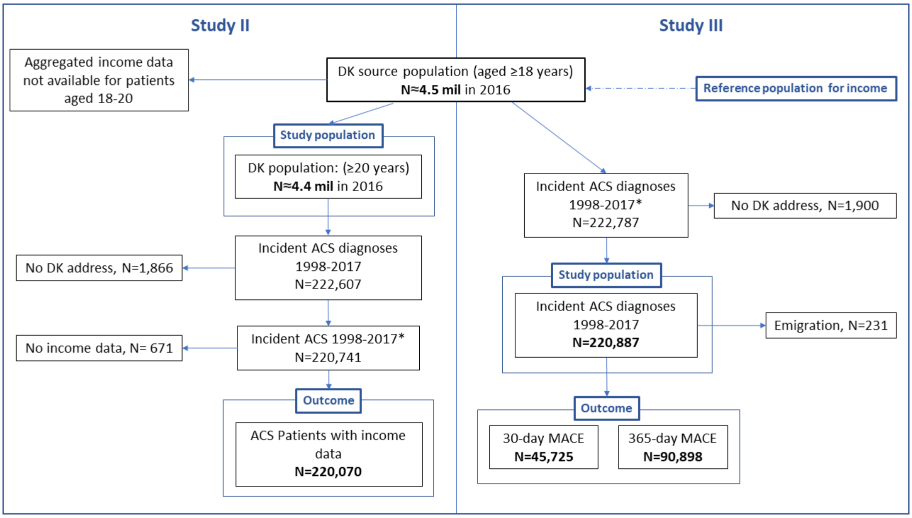

Figure 4-2 Flowchart Study II-III.
Flowchart of the selection of the study populations and outcomes for Study II-III. The actual DK population was dynamic and not constant N=4.5 as in 2016. This was accounted for in the analyses. Abbreviations: ACS: acute coronary syndrome, DK: Danish, mil: millions, N: number of individuals.

4.2. STUDY AND BASELINE CHARACTERISTICS

The included studies in Study I, were 155 cohort studies, 16 cross-sectional studies, and 10 case-control studies.[114] When categorized according to the World Bank assignment of income levels for world economies 2021,[153] 81% of the included studies were performed in high-income countries, 15% in upper-middle-income countries, 1% in lower-middle-income countries, 3% were multi-national, and none were performed in low-income countries.[114] The composite indicators of SEP varied to a great extent: including income, education, occupation, employment, area crime, crowding, household possessions, social benefits, rental or owned homes, and/or single-parent families.[154–158] Moreover, the exposures varied substantially according to the information level across all of the SEP indicators. In 66% of the studies, an individual-level indicator was used, in 12% a household indicator was used, and in 36% an area-based indicator was used.[114]

Baseline characteristics for the study population for Study II were only available in aggregated form Statbank in Statistics Denmark, thus, it could not be summarized in a baseline table.[42,115,122] However, 49% of the population in 2016 were males, and the median yearly personal equivalent income in 2016 was 233,300 DKK.[115] In the study population in Study III, the patients with an incident diagnosis of ACS in Denmark from 1988-2017, presented as 61% males and with a median age of 70 years (IQR: 59-79). The mean follow-up time was 243 days. Among the included patients with ACS, 43,832 (21%) died within the 365-days and 92,522 (42%) had a registered MACE.[116]

4.3. DISPARITY IN INCIDENCE OF ACS

The systematic literature review (Study I) identified 49 studies investigating socioeconomic disparity in the incidence of ACS published from 2009 to 2021. Most of the identified studies (89%) found an association between the lowest SEP level and a higher incidence of ACS, compared to the highest SEP level, independent of the specific SEP indicator *(Figure 4-3A)*.[114] The IRR ranged from 1.1 to 4.7. Few of the identified studies found no association or a lower incidence of ACS among individuals with a lower SEP.[6,33,162–171,34,172–181,131,182–191,154,192–200,157–161] The studies classified with a lower risk of bias, according to the Cochrane tools, were more likely to identify a socioeconomic disparity in the incidence of ACS.[114]

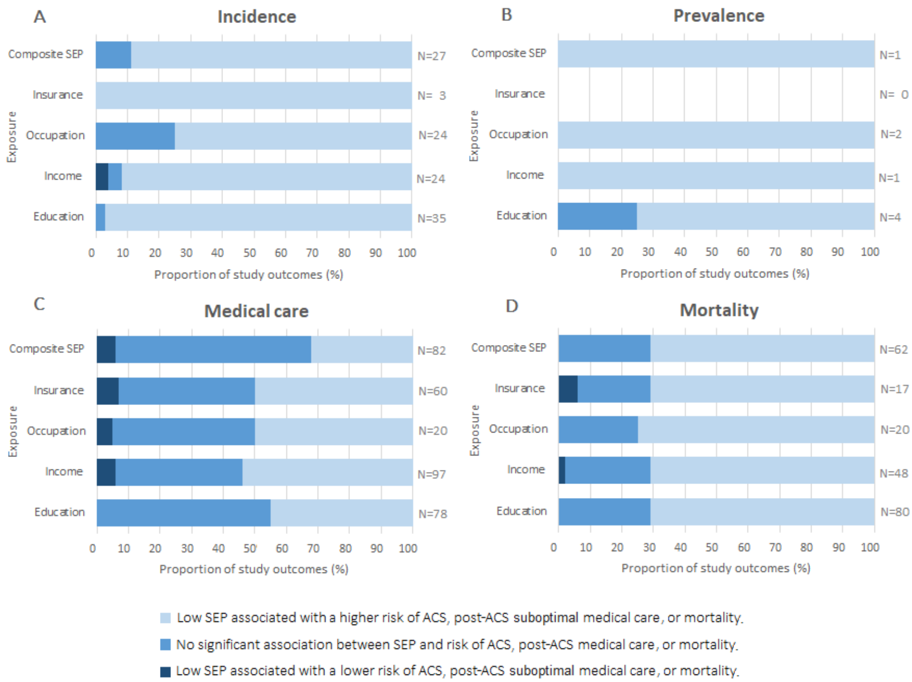

Figure 4-3 Incidence and prevalence of ACS, and medical care and mortality after ACS, according to the SEP. *The associations identified across all the included studies according to the different exposures and A) incidence, B) prevalence, C) medical care, and D) mortality. Abbreviations: ACS: acute coronary syndrome, N: number of study outcomes (some studies reported multiple outcomes). SEP: socioeconomic position.*[114]

In the results from Study II, the income-related disparity in the incidence of hospitalized ACS was presented across the investigated period, with an IR of 325 [95% CI: 322-27] pr. 100.000-person-years among patients from the lowest income quartile, and an IR of 217 [95% CI: 215-219] pr. 100.000-person-years among patients from the highest income quartile. When comparing patients from the lowest income quartile with those from the highest, the IRR was 1.50 [95% CI: 1.48-1.51].[115]

4.3.1. TEMPORAL TRENDS IN DISPARITY IN INCIDENCE OF ACS

Among the studies on the socioeconomic disparity in the incidence of ACS identified in the systematic literature review (Study I), eight studies investigated time trends in socioeconomic disparity in the incidence of ACS in Norway, Sweden, the United Kingdom, the Netherlands, and Germany. More specifically, the studies investigated temporal trends in socioeconomic disparity in the incidence of hospitalized MI and out-of-hospital fatal MI, according to income, education, occupation, or composite indicators, and most of the studies identified no significant improvements, or even an increased disparity over the period from 1987 to 2012.[6,131,168,171,175,181,191,193] Also, no significant change was identified in socioeconomic disparity in the incidence of UAP.[191] However, one study found a small decline in the income disparity from 2006-2015 in the incidence of MI among men, but not among women.[171] The results from the identified studies on temporal trends in the disparity of ACS incidence are presented in *Supplemental Table S1*.

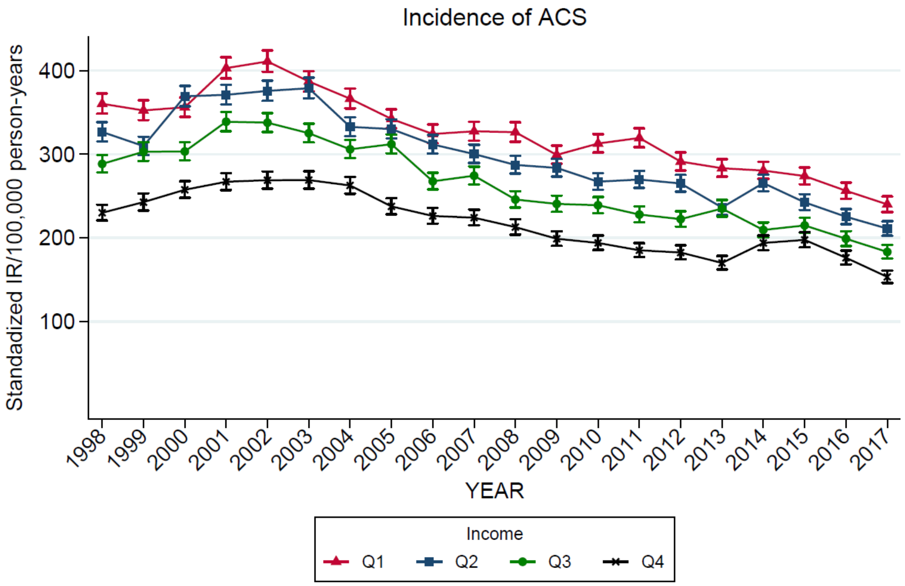

Figure 4-4 Standardized incidence rates of ACS in Denmark according to income quartile
Analyses were standardized according to year, sex, and age-group, and the results are presented with 95% confidence intervals. Abbreviations: ACS: acute coronary syndrome, IR: incidence rate, Q: income quartile from low (1) to high (4), based on the income the year before the diagnosis.[115]

When investigating income-related disparity in the Danish population from 1998-2017 (Study II), the income-related disparity in the standardized IRs and IRRs of ACS was present over the entire period *(Figures 4-4 and 4-5)*. The interaction analysis showed that the income-related disparity in the incidence of ACS decreased from 1998 to 2017 when comparing any lower-income quartiles to the highest-income quartile. However, the disparity only decreased with one to three cases pr. 100.000-person pr. year. The income-related disparity was primarily found in MI incidence, when stratifying to MI and UAP diagnoses.[115] When including the out-of-hospital fatal ACS events (independent of which of the applied definitions) income-related disparity in the incidence of ACS was also present in the entire period, and interaction analyses showed a maximum decrease in the disparity of one to five ACS cases pr. 100.000-person pr. year. [115]

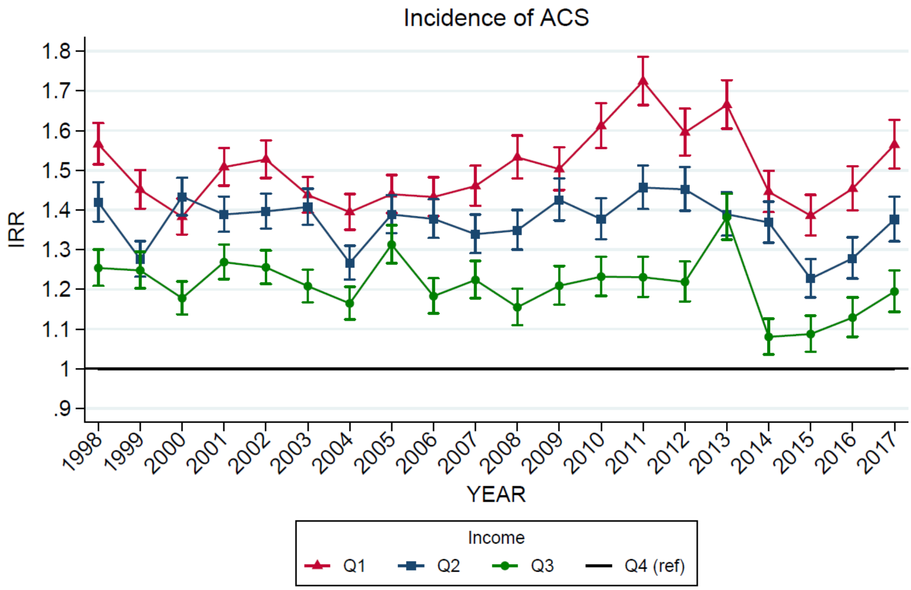

Figure 4-5 Standardized Incidence rate ratios of ACS in Denmark according to personal income quartile. *Analyses were standardized according to year, sex, and age-group, and the results are presented with 95% confidence intervals. Abbreviations: ACS: acute coronary syndrome, IRR: incidence rate ratio, Q: income quartile from low (1) to high (4), which is the reference group, based on the income the year before the diagnosis, Ref: reference group.*[115]

4.4. DISPARITY IN PREVALENCE OF ACS

The systematic literature review (Study I) identified five studies on the socioeconomic disparity in the prevalence of ACS, which were all cross-sectional. Overall, 88% of these studies found that a lower SEP (education, income, composite indicator, or occupation within construction) was associated with higher odds of having had a MI than having a higher level of SEP or occupation within management *(Figure 4-3B)*.[114] The odds ratios (ORs) were ranging from 1.8 to 3.9.[201–205] The studies classified with a lower risk of bias, according to the Cochrane tools, were more likely to identify socioeconomic disparity in the prevalence of ACS.[114] None of the identified studies investigated temporal trends in socioeconomic disparity in the prevalence of ACS.

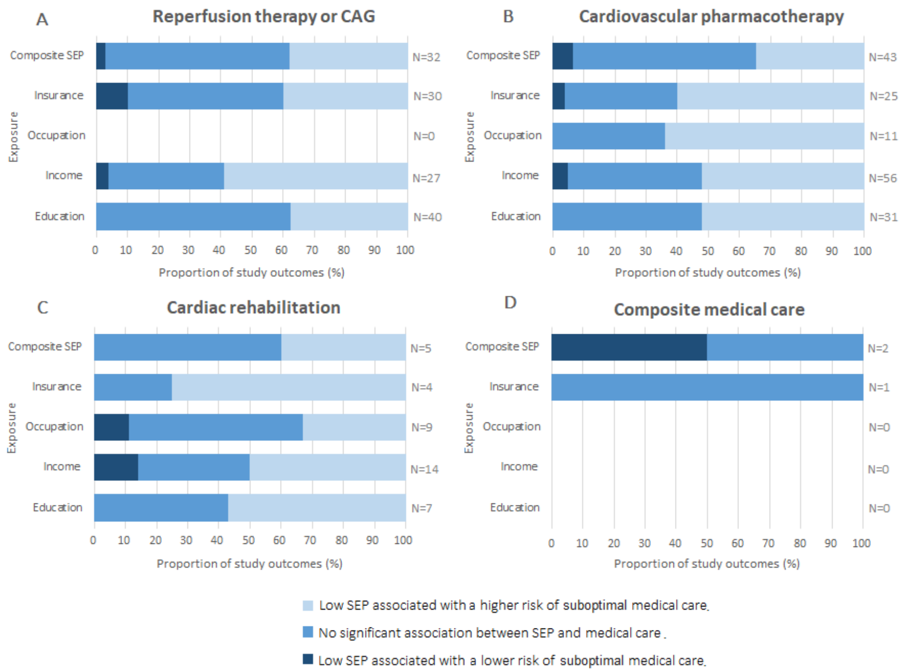

Figure 4-6 Medical care categories after ACS according to the SEP indicator.
The figure illustrates the associations identified from the included studies according to exposure and A) reperfusion therapy or CAG, B) cardiovascular pharmacotherapy, C) cardiac rehabilitation, and D) composite medical care. Abbreviations: ACS: acute coronary syndrome, CAG: coronary angiography, N: number of study outcomes (some studies reported multiple outcomes). SEP: socioeconomic position.[114]

4.5. DISPARITY IN MEDICAL CARE IN ACS PATIENTS

The systematic literature review (Study I) identified 81 studies on the disparity in medical care in patients with ACS. In 46% of the analyses in the studies, low SEP was associated with suboptimal medical care, compared to high SEP. The ORs ranged from 1.1 to 10.0. In 49% no association between SEP and medical care was identified *(Figure 4-3C)*.[114] Furthermore, 5% of the studies found that lower SEP was associated with a lower chance of suboptimal medical care. Overall, the same tendency towards socioeconomic disparity, favoring those with higher SEP was found when medical care outcomes were stratified into different types of care. Hence, 44%, 53%, and 51% of the studies found an association where low SEP was associated with receiving reperfusion therapy or CAG, cardiovascular pharmacotherapy, or CR, respectively, compared to high SEP *(Figure 4-6)*. This tendency was not presented in the studies focusing on composite indicators of medical care.[8,12,213–222,197,223–232,206,233–242,207,243–252,208,253–262,209,263–272,210,273–282,211,283,212] The studies classified with a lower risk of bias, according to the Cochrane tools, were more likely to identify socioeconomic disparity in medical care, in favor of those with a higher SEP.[114] Four of the identified studies investigated temporal trends in medical care in the United Kingdom, Italy, Australia, and Denmark.[220,243,256,260] More specifically, the studies investigated temporal trends in reperfusion therapy or use of cardiovascular pharmacotherapy after ACS, according to educational level or composite SEP indicators, identifying both increases, decreases, and no changes in the socioeconomic disparity (*Supplemental Table S2).*[220,243,256,260]

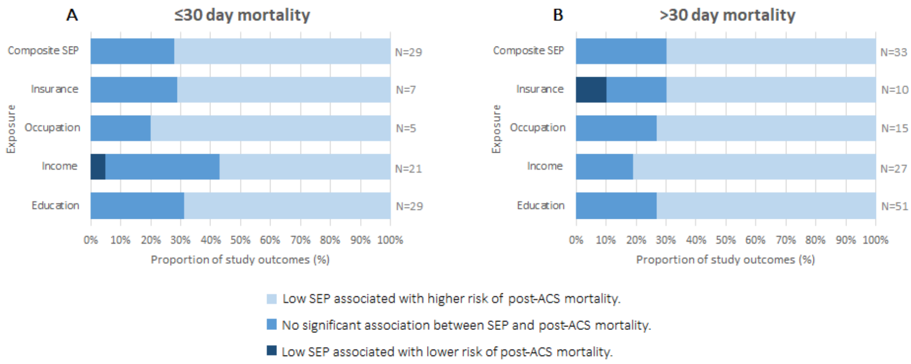

Figure 4-7 Short- and long-term mortality in patients with ACS according to SEP indicator.
The figure illustrates the associations identified from the included studies according to exposure and A) ≤30-day mortality, or B) >30-day mortality. Abbreviations: ACS: acute coronary syndrome, N: number of study outcomes (some studies reported multiple outcomes). SEP: socioeconomic position.[114]

4.6. DISPARITY IN MORTALITY IN ACS PATIENTS

The systematic literature review (Study I) identified 78 studies on the disparity in mortality after ACS. Most of the analyses (71%) in the studies found that a lower SEP was associated with a higher mortality after ACS, compared to a high SEP *(Figure 4-3D).*[114] The HR ranged from 1.1 to 4.13. The socioeconomic disparity in mortality in favor of those with higher SEP was presented in most studies, both regarding 30-day mortality (70%) and mortality within more than 30 days after ACS (73%) *(Figure 4-7).*[12,33,177,197,199,207,209,212,214,216,218,220,55,225,229,232,235,238,240,257,260–262,59,267,269,279,284–290,134,291–300,136,301–310,156,311–320,160,321–324,163,176] The studies classified with a lower risk of bias, according to the Cochrane tools, were more likely to present socioeconomic disparity in the mortality after ACS.[114]

In the results from Study III, socioeconomic disparity in all-cause mortality within 30- and 365-days after ACS, were presented both according to income and educational level.[116] The 30-day mortality HR was 1.46 [95% CI: 1.39-1.51] for patients in the low- compared to the high-income quartile, and 1.34[95% CI: 1.26-1.42] for patients with low- compared to high educational level.[116] The 365-day mortality HR was 1.46 [95% CI: 1.42-1.50] for patients in the low- compared to the high-income quartile 1.41 [95% CI: 1.35-1.47] for patients with low compared to high educational level.[116]

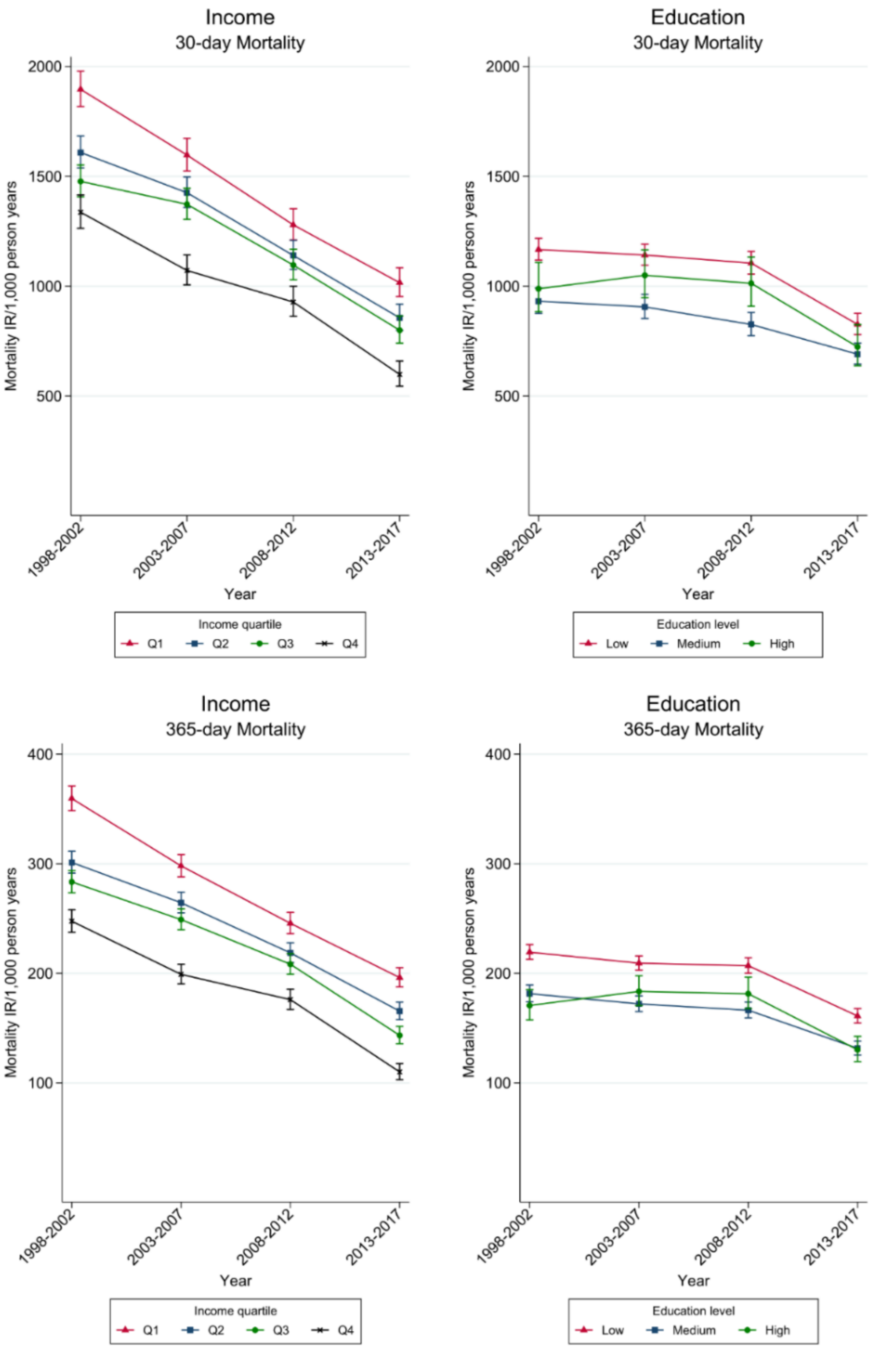

Figure 4-8 Adjusted incidence rates for 30-and 365-day mortality after ACS in Denmark, according to income and education. *The presented results were adjusted for age, sex, and migrant status, and the results are presented with 95% confidence intervals. Abbreviations: ACS: acute coronary syndrome, IR: incident rate, Q: income quartile (1: low, 2: medium-low, 3: medium-high, 4: high).*[116]

4.6.1. TEMPORAL TRENDS IN DISPARITY IN MORTALITY AFTER ACS

Among the studies on the socioeconomic disparity in the mortality among patients with incident ACS identified in the systematic literature review (Study I), four studies investigated temporal trends in mortality after ACS in Italy, the United Kingdom, Sweden, and Denmark. More specifically, the studies investigated temporal trends in socioeconomic disparity according to educational level, occupation, or composite indicators of SEP, and reported persistence or small increases in the socioeconomic disparity in the period 1988-2012 (*Supplemental Table S3)*.[220,260,293,309]

Study III also investigated temporal trends in income and educational disparity in all-cause mortality within 30- and 365-days after ACS. The socioeconomic disparity was present across the entire period when comparing patients from the lowest income quartile or educational level to those from the highest *(Figure 4-8)*. Within all levels of income and education, the incidence of all-cause mortality within 30- and 365-days after ACS decreased from 1998 to 2017. However, interaction analyses showed no significant changes and the disparity according to income, and educational level remained.

4.7. DISPARITY IN MACE IN ACS PATIENTS

The socioeconomic disparity in MACE after ACS was not included as an outcome in the systematic literature search (Study I)[114]. However, previous studies have investigated and identified socioeconomic disparity in clinical outcomes after ACS, including recurrent ACS, stroke, need for revascularization, and the composite MACE up to 10 years after the ACS diagnosis.[134,300,303,314] A summary of the study characteristics and results from these previous findings are presented in *Supplemental Table S4-S5.*

In the results from Study III, socioeconomic disparity in MACE within 30- and 365-days after an ACS diagnosis at a Danish hospital were presented both according to equivalent disposable personal income quartile and level of educational attainment.[116] The 30-day mortality HR was 1.24 [95% CI: 1.20-1.27] for patients in the low-compared to the high-income quartile, and 1.19 [95% CI: 1.15-1.23] for patients with low compared to high educational level.[116] The 365-day mortality HR was 1.23 [95% CI: 1.20-1.25] for patients in the low- compared to the high-income quartile 1.23 [95% CI: 1.20-1.26] for patients with low compared to high educational level.[116]

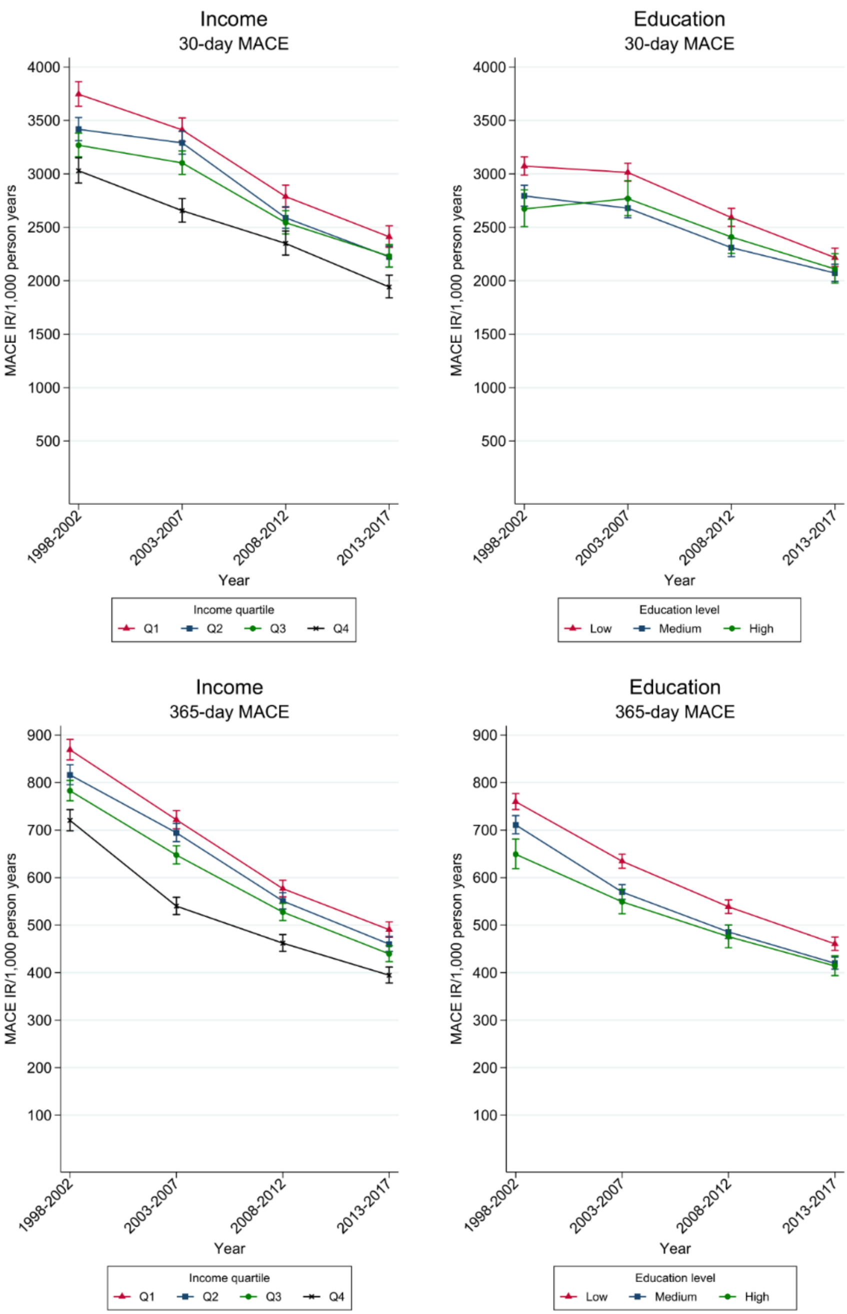

Figure 4-9: Adjusted incidence rates for 30-and 365-day MACE after ACS in Denmark, according to income and education. *The presented results were adjusted for age, sex, and migrant status, and the results are presented with 95% confidence intervals. Abbreviations: ACS: acute coronary syndrome, IR: incident rate, MACE: major adverse cardiovascular events, Q: income quartile (1: low, 2: medium-low, 3: medium-high, 4: high).*[116]

4.7.1. TEMPORAL TRENDS IN DISPARITY IN MACE AFTER ACS

None of the identified previous studies on the socioeconomic disparity in MACE after ACS investigated temporal trends in socioeconomic disparity in MACE after ACS. In Study III income and educational disparity in MACE within 30- and 365-days after ACS was present across the entire period when comparing patients from the lowest income quartile or educational level to those from the highest *(Figure 4-9)*. Within all levels of income and education, the incidence of MACE within 30- and 365-days after ACS decreased from 1998-2017. However, interaction analyses showed no significant changes, and the income and educational disparity remained. This finding was the same across all explorative stratified or restricted analyses.[116]

CHAPTER 5. DISCUSSION

The research presented in this thesis elucidates 20-year temporal trends in socioeconomic disparities in incidence and clinical outcomes in patients with an incident ACS in Denmark (1998-2017); and examines the scientific literature regarding socioeconomic disparity in the incidence and prevalence of ACS, as well as medical care and all-cause-patient-mortality (2009-2021). This chapter provides a presentation and discussion of the main findings in relation to the existing literature and implications. Finally, methodological considerations related to the presented research are presented and discussed.

5.1. KEY RESULTS

The results in this thesis illustrate that lower SEP was associated with a higher incidence and prevalence of ACS and associated with suboptimal medical care, and higher mortality among patients with ACS in most peer-reviewed studies published within the last decade. Those findings were robust across different indicators of SEP, including education, income, occupation, insurance status, or composite indicators, and were especially obvious in high-income countries and in studies representing a lower risk of bias.[114] Despite the large decrease in the yearly incidence of ACS in Denmark from 1998 to 2017, the income-related disparity between the lowest and the highest-income quartiles only decreased with up to maximum five cases pr. 100.000-person pr. year.[115] Furthermore, the socioeconomic disparity in MACE and all-cause mortality the year after ACS persisted, with a higher incidence among patients with a lower income or educational level compared to a high level.[116]

5.2. COMPARISON WITH EXISTING LITERATURE

5.2.1. DISPARITY IN INCIDENCE AND PREVALENCE OF ACS

The results in this thesis (Study I-II) indicate that socioeconomic disparity in the incidence and prevalence of ACS remains an unsettled and common global issue, independent of which SEP indicator is used to investigate this.[114,115] Low SEP was associated with a higher incidence or prevalence of ACS, compared to high SEP, in respectively 89% and 88% of the studies investigating this matter, published from 2009 until July 2021, both according to income, education, occupation, insurance status, and composite indicators of SEP.[114] A meta-analysis by Manrique-Garcia et al., 2011, based on studies published from 1966 to April 2009, also outlined systematic socioeconomic disparity in the incidence of MI according to an individual or household level SEP indicators based on income, education, or occupation,[92] with no studies recurring in Study I.[114] Additionally, a systematic review by Coughlin et al., 2019, demonstrated a higher risk of MI among individuals from a disadvantaged neighborhood across studies published from 1970 to May 2019.[93] Together with the findings from Study I, this presents a broader picture of the socioeconomic disparity as well the dimension of this unsolved issue, despite intensified preventive efforts and the declining general incidence of ACS the recent decades.[12,57,76] Furthermore, Study II adds to this, that income-related disparity in the incidence of hospitalized ACS and out-of-hospital fatal ACS was presented in the welfare state of Denmark across the last two decades, despite the substantial decline in the overall incidence.[115]

Since incidence is often represented as hospitalized patients with a specific diagnosis, changes over time in diagnostic practice and hospital admission for ACS patients, as those represented in the Danish healthcare system in the last decades, are potential sources of bias in incidence studies.[67,69] Although access to the Danish tax-funded healthcare system is theoretically equal and formally independent of socioeconomic factors, the disparity in diagnoses, due to approaches to healthcare-seeking behavior and abilities to express symptoms and need for care may exist.[96,131] Hence, the DNPR captures disparity in hospital ACS admissions which may not necessarily be equal to the total population-based ACS incidence.[96] To overcome this challenge, fatal out-of-hospital ACS diagnoses and individuals with a registered sudden unknown reason of death or no received attest in the DRCD were included in the sensitivity analyses in Study II.[115] A few previous studies have also investigated socioeconomic disparity in fatal out-of-hospital MI.[5,179,186] However, the approach of including all deaths without a registered reason was not previously been applied in any identified studies.[114,115] The results in Study II were robust across the analyses, although the last analysis clearly included an uncertain number of individuals with other causes of death.[115,125]

Acknowledging, that socioeconomic disparity in the incidence of ACS is still presented across the majority of studies and countries recently investigating this, the importance of investigating possible widening or narrowing of the socioeconomic disparity is obvious.[114,115] Especially, considering the focus on minimizing health disparity, both on the global level,[38,325] and the national level in Denmark.[11,101,107–109] Hence, the identified narrowing in the income-related disparity in Study II, of maximum five ACS cases yearly pr. 100.000 persons between the highest and lower income quartiles from 1998 to 2017, represents a minimal clinically relevant effect, regarding the intention to eliminate the disparity.[38,115,325] However, these findings are in correspondence with findings from other studies investigating temporal trends in socioeconomic disparity in the incidence of ACS. Geyer et al., 2019, found income-related disparity in the incidence of MI between the individuals with income below 40% and above 80% of the national average, decreased by 4% pr. year from 2006 to 2015 among men in Germany.[171] Other studies applied other indicators of SEP, investigating the socioeconomic disparity in the incidence of ACS, according to education, occupation, and area-based composite indicators of SEP.[131,168,175,181,191,193,326] From 1971 to 1994 in Sweden, 1990 to 2002 in Scotland, and 1999 to 2007 in the UK, the socioeconomic disparity in the incidence of MI widened according to occupation or composite SEP indicators.[168,191,326] However, above that, no studies found changes in socioeconomic disparity in the incidence of ACS.[6,131,168,175,181,191,193] Thus, it seems that the clinical implication of socioeconomic disparity in the incidence of ACS is an international unsolved issue, which will persist for many decades if changes in strategies for prevention are not made.

Lacking data from middle and low-income countries, regarding the socioeconomic disparity in incidence or prevalence of ACS, were elucidated both in Study I and in the previous meta-analyses by Manrique-Garcia 2011.[92,114] This is concerning, since ACS represents a global leading cause of mortality and, with a rising burden in the low-income countries, due to changes in the demographics.[53,327,328] Studies have suggested, that incident ACS patients from low- and lower-middle-income countries in general are younger and have fewer of the traditional risk factors for cardiovascular disease, than patients from high-income countries.[79,329] Furthermore, access to emergency care, invasive care, and guideline-recommended cardiovascular pharmacotherapy at hospital discharge, generally presents more barriers in low-income countries.[79,329,330] It is challenging, that socioeconomic disparity in incidence and prevalence of ACS or medical care and mortality after ACS is only elucidated in low-income countries within the last decade, by two studies across multiple countries,[195,200] and both middle- and low-income countries were barely represented among previous studies within this field.[92] The two studies investigated and found disparity in the incidence of MI according to income, education, and occupation.[195,200] Furthermore, mechanisms in socioeconomic disparities in ACS could potentially also differ substantially across the high- and middle-high-income countries with different healthcare systems.[92,331] Hence, it could be problematic to compare socioeconomic disparity across changing or different living standards and treatment opportunities, but this sort of monitoring is essential to enable an actual reduction or elimination of the socioeconomic disparity in health.[329,330,332,333]

According to a fundamental cause theory, disparity in heath origin from the unequal distribution of resources in society, including knowledge, money, power, prestige, and networks, since these resources could be used to gain health advantage.[11,18,24] If this theory was directly factual, disparity in health would be affected by the degree of resource disparity including increases and decreases in the income disparities, as measured by the Gini-coefficient.[11,18,24] The disparity in disposable income have been increasing in Denmark during the last decades, resulting in an increase in the Gini-coeficient.[42,43] In this perspective, it is important to acknowledge, that the widening in income disparity have not lead to a widening in the socioeconomic disparity in the incidence of ACS or subsequent incidence of MACE in Denmark during the last decades according to the results from Study II-III. Hence, it is clear, that this theory does not reflect a direct connection between the SEP and ACS epidemiology.

5.2.2. DISPARITY IN MEDICAL CARE OF THE ACS PATIENTS

The socioeconomic disparity also associates with the treatment in patients with ACS.[114] The results from Study I in the present thesis illustrate that socioeconomic disparity in the medical care of ACS patients exists both when looking at reperfusion therapy or CAG, use of cardiovascular pharmacotherapy, and participation in CR, across all investigated indicators of SEP.[114] This adds to the similar findings from previous reviews, describing the socioeconomic disparity in use of guideline-recommended pharmacotherapies and participation in cardiac rehabilitation according to occupation, income, and educational level.[7,94] Since the risk of having ACS was also higher in the population with lower SEP, this lower probability of receiving optimal medical care was possibly not related to lower requirements among the patients with a low SEP. Considering that all these categories of medical care after ACS are crucial for morbidity and mortality among the patients on the short- or longer-term, the identified socioeconomic disparities are critical.[7] The definition of suboptimal medical care used in Study I, is based on indicators for receiving a certain care.[114] However, it is important to acknowledge, that whether the clinical indication and possible contraindications for a certain procedure or pharmacotherapy was present was not accessible in most of the studies, since they were of observational design.[114]

Few studies investigated the temporal trends in socioeconomic disparity in medical care among ACS patients, investigating receipt of reperfusion therapy or CAG and use of cardiovascular pharmacotherapy (aspirin, ACEi, ARBs, β-blockers or clopidogrel) identifying various patterns with different directions of change in the disparity.[220,243,256,260] Hence, on the international level, the socioeconomic disparity in medical care continues to exist, despite the massive effort on improving clinical guidelines and patient pathways for the ACS patients to provide proper care to all patients.[7,62,80] However, in the Danish context, the study by Mårtensson et al., 2015 found that a lower level of education was associated with a lower chance of having CAG within one or three days after MI during 2001-2003 than a higher level of education and another study found a disparity in CABG and PCI more than two days after MI in Denmark from 1996 to 2004.[260,334] The disparity in CAG was not present in 2007-2009 and the disparity in CABG and PCI more than two days after MI was not evaluated within this timeframe.[260,334] The absence of finding disparity in CAG could be related to the implementation of guidelines regarding primary PCI in 2003 in Denmark, among other initiatives that have had a substantial impact on the healthcare of patients with ACS in Denmark, resulting in a high increase in the use of CAG with a less selective patient selection, eliminating the disparity.[66,69] Ideally, this elimination of the socioeconomic disparity in revascularization, would imply a similar effect within the disparity in clinical outcomes on shorter and longer terms after ACS. However, this was not the case in the study by Mårtensson et al., 2015, as the disparity in mortality persisted.[260] However, when looking at the use of cardiac rehabilitation and cardiovascular pharmacotherapy, structural health communicative barriers and personal recourses could play a larger role regarding the access and use of medical care.[335,336] Other studies investigating medical care after ACS in Denmark, identified in Study I, found a socioeconomic disparity in being invited to and attending cardiac rehabilitation programs after ACS.[114,239,268] Except for one study, finding disparity in statins and β-blockers after MI according to income and education from 1995-2001,[337] no studies were available, investigating the use of cardiovascular pharmacotherapy after an incident ACS in the concurrent Danish setting with partial reimbursement of prescription pharmacotherapies.[95,96,114] This could of cause also sustain a disparity in clinical outcomes especially on longer terms after ACS.

5.2.3. DISPARITY IN CLINICAL OUTCOMES AFTER ACS

The results in this thesis (Study I and III) further indicate that socioeconomic disparity in mortality and MACE after the ACS exists and persists across all the used indicators of SEP, both on the short- and long-term.[114,116] Coughlin et al., 2019, more specifically demonstrated a lower survival after MI among patients from more disadvantaged neighborhoods (including deprived resources, poverty, and low education) in the systematic review of studies published from 1970 to May 2019.[93] The socioeconomic disparity in clinical outcomes after ACS could arise from multiple pathways, including the severity of the diagnosis at hospitalization, access to medical care including reperfusion or CAG, compliance to the cardiovascular pharmacotherapy, or cardiac rehabilitation, and personal resources to actively change lifestyle behavior after the ACS event.[7,94,199,245,267] Hence, the overall pattern presented in the results in this thesis is that individuals with a low SEP are both experiencing a higher risk of an incident ACS, receiving less medical care after the ACS, and have a worse prognosis.[114–116] The disparity in prognosis presented in Study III did not only illustrate socioeconomic disparity mortality, but also in recurrent ACS, revascularization, and stroke after discharge within the first year after ACS, in favor of those with a higher income or education. Socioeconomic disparities in these clinical outcomes have previously been illustrated, up to 10 years after the ACS diagnosis.[20–22,24] In general ACS have been reported to play a significant role in the socioeconomic disparity in mortality and life expectancy, which still presents an unsolved problem.[18,52,53] This illustrates the magnitude of this socioeconomic disparity of clinical outcomes among patients with ACS, and the consequences regarding public health, possibly including both morbidity and mortality resulting in a significant disparity in healthy life years and frailty.[18,52,53,338]

The results in Study III represent a considerable socioeconomic disparity in mortality and MACE, both according to income and educational level even in a tax-financed universal healthcare system with free access for all citizens, without changes in the temporal trends over the 20 years.[116] Previous studies investigating temporal trends in socioeconomic disparity in mortality after ACS have identified small declines in the disparity until 2007 or persistence.[14–16,25–29] However, although the disparity did not decline, the MACE incidence in Study III declined substantially among patients within all levels of SEP during the 20 years investigated, indicating that outcomes after ACS have also improved among ACS patients with a low SEP.[116]

According to the studies recently investigating medical care provided after ACS in Denmark, it seems that the socioeconomic disparity in mortality and clinical outcomes are least related to access to acute revascularization.[114,239,260,261,268] Rather, the persistent disparity in MACE identified in Study III, could arise from a widespread socioeconomic disparity in risk factors both before and after the incident ACS. This includes multiple pathways, such as the participation and compliance in cardiac rehabilitation, promoting the importance of a healthy lifestyle (e.g., smoking, diet, and physical activity) after the incident ACS as well as access and compliance to cardiovascular pharmacotherapy.[339,340] Hence, as long as there is insufficient political support for interventions aiming at reducing the socioeconomic disparity in risk factors and healthy lifestyles among the disadvantaged populations, clinically effective narrowing of the socioeconomic disparity in the incidence of ACS and following clinical outcomes could not be expected.[17,37]

5.3. METHODOLOGICAL CONSIDERATIONS

The studies in this thesis are based on a systematic literature search and two cohort studies of observational design, to investigate the incidence, treatment, and clinical outcomes according to SEP in patients with ACS, including temporal trends in Denmark. Both study designs require thorough methodological considerations to evaluate the effect of systematic or random errors on the results. The methodological considerations which are necessary for proper implementation of the results and conclusions in the present thesis will be discussed in the following sections.

5.3.1. MEASURING SOCIOECONOMIC POSITION

In this thesis, SEP was used to refer to the socioeconomic factors positioning an individual or group within the structure of the society, to evaluate the disparities in ACS.[16,19,20] Across Study I-III, a wide range of indicators for SEP were included, acknowledging that each indicator provides additional information describing the social distribution of the population and pointing to specific explaining mechanisms of the progress and persistence of disparity in ACS.[16,19,20] Hence, the heterogeneity of the studies included from the systematic literature search in Study I is a methodological strength, emphasizing the structure of the socioeconomic disparity in incidence, treatment, and outcomes after ACS is robust across the structural socioeconomic factors.[17,114] Thus, differences in the indicators for SEP were considered in the interpretation of the results. The indicators included income, education, occupation, insurance status, and composite indicators, and were based on many different classifications and categorizations, and collected on the individual-, household-, or area-level in Study I.[114] However, this heterogeneous use of the concept of SEP also meant that meta-analysis, estimating the total effect of SEP or each indicator of SEP was not found to be appropriate.[114] In Study II-III SEP was collected as equivalent personal income quartile and in Study III also as educational level, to reflect two possible pathways of the socioeconomic disparities.[115,116] The income was based on the disposable taxable income data one year before the year of the incident ACS.[115,116] Although this is a strong indicator of available economic resources, this could be sensible to life changes, such as acute or chronic illnesses possibly implying reverse causality.[17,19,122] However, this permitted the use of nation-based income quartiles from the Danish background population according to age, sex, and specific year.[122]

In Study III, SEP was also included using the highest completed educational level before the incident ACS.[116] However, among the included patients with ACS, educational data was missing for 37% and missing were strongly correlated with year and patient age.[116] The information on educational attainment on an aggregated level for Study II was not available for standardization in the Statbank data for patients aged more than 45 years, and thus, this indicator could not be applied.[30,42,115] However, despite the expected differences in pathways for socioeconomic disparity according to income and educational level, overall, the educational level represented the same pattern of disparity and temporal trends regarding clinical outcomes the year after ACS as the income level in Study III.[17,19,116,122] Although data was available in Study III, employment status was included as a covariate rather than an exposure.[116] This decision was made, based on the distribution and age of the ACS patients according to employment, unemployment, and retirement, with the large majority of the patients being at the retirement age, meaning that age and frailty were possibly highly associated with employment status, implying a large risk of reverse causality affecting the results.[19,20,116] This decision differs from Study I, where employment was included in the occupation indicator, to comprehend the overall structural association between connection to the labor market and incidence, treatment, and clinical outcomes in ACS.[114] Overall, the combination of the higher degree of specificity of SEP indicators in Study II-III, and the wide definitions of SEP accepted in Study I, is a strength of the present thesis, acknowledging multiple pathways for disparity according to SEP.[17,19,20] However, national and international detailed standards for defining and investigating socioeconomic disparity are requested to enable proper accumulations of effects across studies and nations.[16]

5.3.2. PUBLICATION BIAS

Overestimation of the associations identified in Study I, regarding socioeconomic disparity in incidence, treatment, and outcomes in ACS, could be implied from publication bias and the restriction to specific publication-language. Submission and acceptance of peer-reviewed publications are generally more frequent for statistically significant results, especially in English-language journals.[114,341] The meta-analysis regarding the association between SEP and the incidence of MI by Manrique-Garcia et. al., 2011 investigated publication bias using funnel plots, asymmetry- and correlation tests, identifying some possible publication bias for the studies on income and occupation but none for the studies on education.[92] This sort of analysis was not applied in Study I, due to the acknowledgment of the heterogeneity of the studies included.[114] However, publication bias may be a bigger concern, when summarizing accumulated effects in a meta-analysis, than, when presenting results in the narrative synthesis.[114] However, Study I included multiple studies representing statistically insignificant and inconsistent results, both regarding incidence, medical care, and clinical outcomes of ACS.[161,208,223,224,235,236] Considering the increasing focus on socioeconomic disparity in health, studies presenting statistically insignificant results on socioeconomic disparity also have a fairly high probability of publication.[13,15,114] Additionally, it is worth noticing that the included studies with a lower risk of bias, according to the classification from the Cochrane tools to access the risk of bias, seemed more likely to identify socioeconomic disparity in incidence, outcomes, and care for ACS patients than studies with a higher risk of bias. This opposes, that publication bias has had a major effect on the results in Study I if acknowledging that study design and bias also affect the probability of publishing.[114]

5.3.3. SELECTION BIAS

Bias occurs if selection is different among the exposed non exposed individuals in a study. This may occur already at the inclusion of individuals, or it may occur during the study, due to loss to follow-up. The Cochrane tools used to evaluate the risk of bias in Study I, included evaluation of possible selection bias in the studies. Most of the studies had a low, or medium-low risk of selection bias, however, some studies had problems accounting for the selection of the exposed and unexposed populations, due to presentation at different points of care or accounting for reasonable follow-up of the included patients using apps, phone calls or letters, with unsuccessful follow-up for a large part of the population. This resulted in a high or medium-high risk of selection bias.[114,138–141] However, the overall risk of bias, including the risk of selection bias, was comprised in the interpretations of the results of each of the included studies in Study I.[114]

The two cohort studies were conducted using a population-based design. Hence, inclusion of individuals in Study II was based on being counted in the Statbank data each year, and inclusion of patients in Study III was based on diagnoses from the DNPR. The population included from the Statbank data, was defined as exposed (lowest income quartile) or unexposed (highest income quartile), based on their yearly equivalized disposable income according to the median and IQR for individuals with the same age and sex the same year. Hence, all citizens were accounted, and collection of other variables were not affected by economic barriers in access to healthcare or willingness to participate. The income was accessed and standardized according to the population income the year before the incidence of ACS. Furthermore, the follow-up in Study II was accomplished, using the DNPR. The Danish national healthcare is tax-supported, and hospital admissions are free, thus, selection of the ACS patients was based on hospital admissions and diagnosis registration in the DNPR. The DNPR is used as an administrative tool for healthcare planning, and therefore, DNPR is considered complete regarding all hospital-based diagnoses in Denmark.[96] Selection of ACS patients in Study III, based on DNPR, were therefore also expected to be independent of the SEP exposures. During 1996-2012, the positive predictive value for MI and UAP in the DNPR was almost 100% and up to 88%, respectively.[96,342] However, if patients died from ACS without hospital admission or survived an unrecognized ACS, this would not be captured in the DNPR.[96,343] Hence, it is important to acknowledge, that patients were included in Study III based on ACS diagnoses at hospital admission. If hospital admission at ACS is associated with SEP level, this could have introduced some selection bias. However, the follow-up was accomplished using the CRS, and the DNPR, ensuring a very low number of losses to follow-up. The known number of patients lost to follow-up in Study III was only 231(0.1%), who emigrated during the study period.

5.3.4. INFORMATION BIAS

Lack of accurate measurements of important variables may lead to the occurrence of information bias, implying bias in the estimates of the association between the exposure and outcome. In the systematic review (Study I) the risk of information bias was evaluated as how definite the assessment of exposure and outcome was, according to the Cochrane risk of bias.[114,138–141]

All data for Study II-III originated from routinely collected data in a tax-financed universal healthcare system and other administrative registers. These registries are considered reliable; however, some misclassification may occur, potentially resulting in information bias. In Study II the study population may be classified as a dynamic population, rather than a defined closed cohort with a specific entry date.[115,144] All Danish citizens aged 20 years or more contribute with one year at risk each year, independent of previous ACS diagnoses. Hence the calculated standardized IRs are consciously approximations to cases pr. person-years.[115,144] Although access to healthcare is in principle equal across citizens in the Danish public-funded system, there might still be differences in diagnoses, due to approaches to healthcare-seeking behavior and abilities to express symptoms and medical needs.[96,131] Hence, the DNPR may capture acute ACS admissions rather than the exact onset of population-based ACS incidence.[96] To evaluate the effect of this, the fatal out-of-hospital ACS diagnoses were included from the DRCD, which contains all registered deaths in Denmark. However, the DRCD data is based on some uncertainty, mainly because forensic autopsies are executed on very few death investigations related to unknown cause of death (<3%) in Denmark.[125,344] Hence, individuals with a registered sudden unknown reason of death or no received attest in the DRCD were also included as possible ACS cases in Study II, to investigate whether this could affect the results.[125] However, unrecognized MI without a fatal outcome may overall account for up to half of all MIs and are not captured in the DRCD or DNPR.[343] Similarly, the diagnosis codes used to define the MACE outcomes from the DNPR are hospital-based, meaning that the outcomes of recurrent ACS, stroke, and cardiac arrest, are possibly affected by information bias related to whether the patients were hospitalized with the correct diagnosis. This is mainly a problem for the cardiac arrest diagnosis since a relatively low proportion of individuals with out-of-hospital cardiac arrest still reach the hospital alive.[96,345] This has however been prominently increasing in the Danish population hospitalization from 2001 to 2017, which means that possible actual changes in the incidence of out-of-hospital cardiac arrest after ACS would not be visible in the available results.[345,346] However, the most dominantly represented of the MACE was the all-cause mortality. The variable for this outcome was collected from the CRS and therefore considered as completely correct follow-up.[44,123]

5.3.5. CONFOUNDING AND MEDIATION

Confounding is a concern in all observational studies and attention towards measured and unmeasured confounding is important.[143] Furthermore, it is important to avoid overadjustment when accounting for confounding, i.e., adjusting for factors that do not affect the relationship between the exposure and the outcome. This may as well introduce confounding and imply biased estimates of the association. In the systematic review (Study I) the risk of confounding across all studies was assessed through the evaluation of adjustment or matching according to relevant covariates.[114,138–141] However, the least adjusted estimates were considered in the summary tables and narrative analysis, to achieve the most comparable results. However, these estimates may be affected by differences in age, sex, and other covariates, which could both affect the outcome and be unequally distributed within the exposed and unexposed population.[114] The lowest level of adjustment of the results varied considerably across the included studies. However, all of the studies included in Study I contribute with systematically collected evidence regarding the socioeconomic disparity in the risk, care, and mortality for ACS.[114]

Construction of causal diagrams was used, to identify whether the investigated associations were expected to be confounded in Study II-III.[115,116,143] Since the available data on covariates in Study II was rather limited, other unmeasured socioeconomic factors, such as education and occupation, were expected to partially explain the disparity identified in this study, and could introduce confounding according to the causal diagram. These covariates would have been informative in Study I; however, the socioeconomic disparity is nonetheless distinctive, although the association cannot necessarily be classified as neither causal nor mediated.[115] In Study III, available covariates included age, sex, employment, migrant status, civil status, and comorbidity level, and the covariates included in the multivariable analyses were selected based on the causal diagrams.[116,143] The analyses were adjusted in three levels: 1) unadjusted, 2) a simple model adjusted for age, sex, and migrant status, and 3) a complex model adjusted for age, sex, migrant status, the patient’s civil status, occupation status, and comorbidity level measured by the CCI, as well as income or educational level (depending on the exposure). The simple model in Study III aimed to evaluate the general association between SEP and MACE after ACS using income and educational level as proxies. The complex model aimed to estimate the causal effect of income and education on MACE after ACS, respectively, without the association mediated through e.g., the patient comorbidity level.[116] Thus, it is noticeable that the socioeconomic disparity in MACE after ACS appeared to diminish in the complex model, especially according to educational level. This indicates that a relevant part of the socioeconomic disparity in MACE after ACS could derive from the general patent health or comorbidity status before the incident ACS. Possible mediating factors included the comorbidity level, affected coronary arteries, and invasive treatment of the ACS. Furthermore, information on patient smoking status, data on general health behavior, as well as the number of vessels affected by severe atherosclerosis for all the patients would have been interesting for the investigation of the pathways in the socioeconomic disparity in ACS and clinical outcomes.[116] When adjusting the analyses, some variables could not be balanced from the propensity score matching, especially according to educational level and across the measures of SEP, which was highly correlated. This was managed using doubly robust adjusting in the HR model. [116]

5.3.6. EXTERNAL VALIDITY

Considering the external validity of the two Danish nationwide cohort studies (Study II-III), it is important to acknowledge the structure of the Danish tax-supported healthcare system, the primary PCI setting for all STEMI patients, and a long-term political intention to limit the disparity in healthcare, despite the pending success.[115,116] Thus, the findings regarding socioeconomic disparities and temporal trends in ACS incidence and clinical outcomes in these studies, may not be generalized to other countries, maybe except the other Scandinavian countries, with similar tax-supported healthcare settings.[45] However, if socioeconomic disparities are presented in ACS incidence and clinical outcomes in a country with free access to the healthcare system, and partial reimbursement of cardiovascular pharmacotherapy, the disparity may be of even bigger concern in countries where healthcare is e.g., insurance based. The findings from the systematic literature review (Study I), illustrated, that the socioeconomic disparity was presented across most studies investigated this during the last decade, especially across high- and middle-high-income countries.[114] This indicates that socioeconomic disparity in ACS is a problem that can be generalized to a lot of countries in the world. However, studies in low-income countries are still underrepresented, making the external validity low for the results in such a setting.

CHAPTER 6. CONCLUSIONS AND IMPLICATIONS

The aim of this thesis was to review the scientific literature regarding socioeconomic disparity in the incidence and prevalence of ACS, as well as medical care and all-cause-patient-mortality and to examine 20-year temporal trends in socioeconomic disparities in the incidence of ACS and clinical outcomes in patients with an incident ACS admitted to a hospital in Denmark. The findings from Study I reveal an overall higher incidence and prevalence of ACS among individuals with a lower SEP, as well as an increased risk of suboptimal medical care (reperfusion or CAG, cardiovascular pharmacotherapy, and cardiac rehabilitation) and a higher risk of short- and long-term mortality among ACS patients with a lower SEP, compared to those with the highest level of SEP. These findings were robust across all indicators of SEP, including education, income, occupation, insurance status, and composite indicators of SEP, despite the major differences in hypotheses and methodology in the literature. These findings were most obvious across the studies from high-income countries and the studies representing a lower risk of bias.

Furthermore, Study II-III revealed a socioeconomic disparity in the incidence of ACS and severe clinical outcomes within the first year after ACS in Denmark every year from 1998 to 2017. Thus, the patients with a lower income had a higher incidence of ACS than those with a higher income, and ACS patients with lower income or educational level had a higher incidence of MACE including death within the first year after ACS compared to the patients with higher income or education. Despite a large decrease in the yearly incidence of ACS and major improvements in the prognosis in general, the socioeconomic disparities in the incidence of ACS and the following clinical outcomes within the first year after ACS have remained virtually unchanged during the last 20 years. Thus, it seems that reducing socioeconomic disparity in the incidence and prognosis of ACS is an unsolved issue in the Danish welfare state.

The findings presented in this thesis contribute to the existing evidence on socioeconomic disparities in ACS, and the lack of narrowing in disparity despite an increasing global and national focus. A most striking finding from this thesis is that SEP decides both the risk of the individual being affected by acute disease and subsequently recovering. Between two groups of individuals, the most deprived and the most affluent in society, those with low SEP had a higher risk of ACS, less care, and the worst clinical outcomes, without any prospect of improving this disparity within the nearest future. Hence, continuous monitoring of socioeconomic disparity in ACS is still of major importance, to diminish the risk and improve the medical care and prognosis of ACS in the most vulnerable populations since a reduction of socioeconomic disparity in ACS incidence and following clinical outcomes may be key to reducing the general disparity in mortality. Furthermore, these findings illustrate, that efforts and strategies to reduce socioeconomic disparities applied until now have not had a major effect, regarding the risk of ACS onset and subsequent clinical outcomes.

Proposals for future initiatives include a better focus on risk stratification according to SEP in a larger perspective, identifying the most vulnerable individuals who require the more interventions and resources. The traditional interventions to reduce the incidence and mortality of ACS, have mainly focused on improving the pathways and quality of in-hospital care, and individual responsibility for a behavior reducing the exposure to several risk factors and increasing adherence to prescribed medication. However, interventions targeting the socioeconomic disparity in incidence, treatment, and clinical outcomes should probably increase the focus on how to implement structural behavioral changes in the more vulnerable populations when designing interventions. Such interventions could include more health education and improved health literacy, better access to preventive healthcare, screening of the most disadvantaged individuals, or increased tax or decreased availability of sugar, fat, and cigarettes. This sort of initiatives might be more challenging to implement and are expected to represent a slower but more effective change, which could accomplish some improvement and reduction of disparity requested for decades in the Danish healthcare system, both within ACS and mortality.

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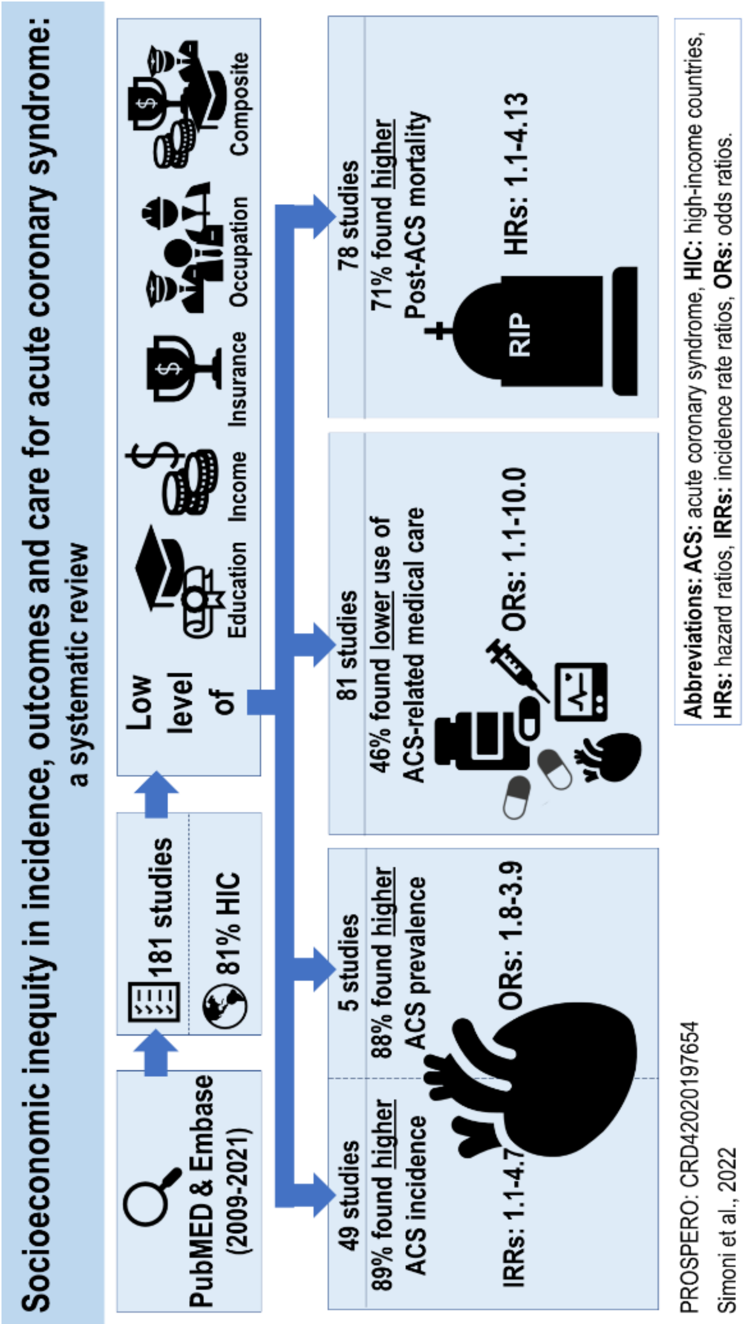
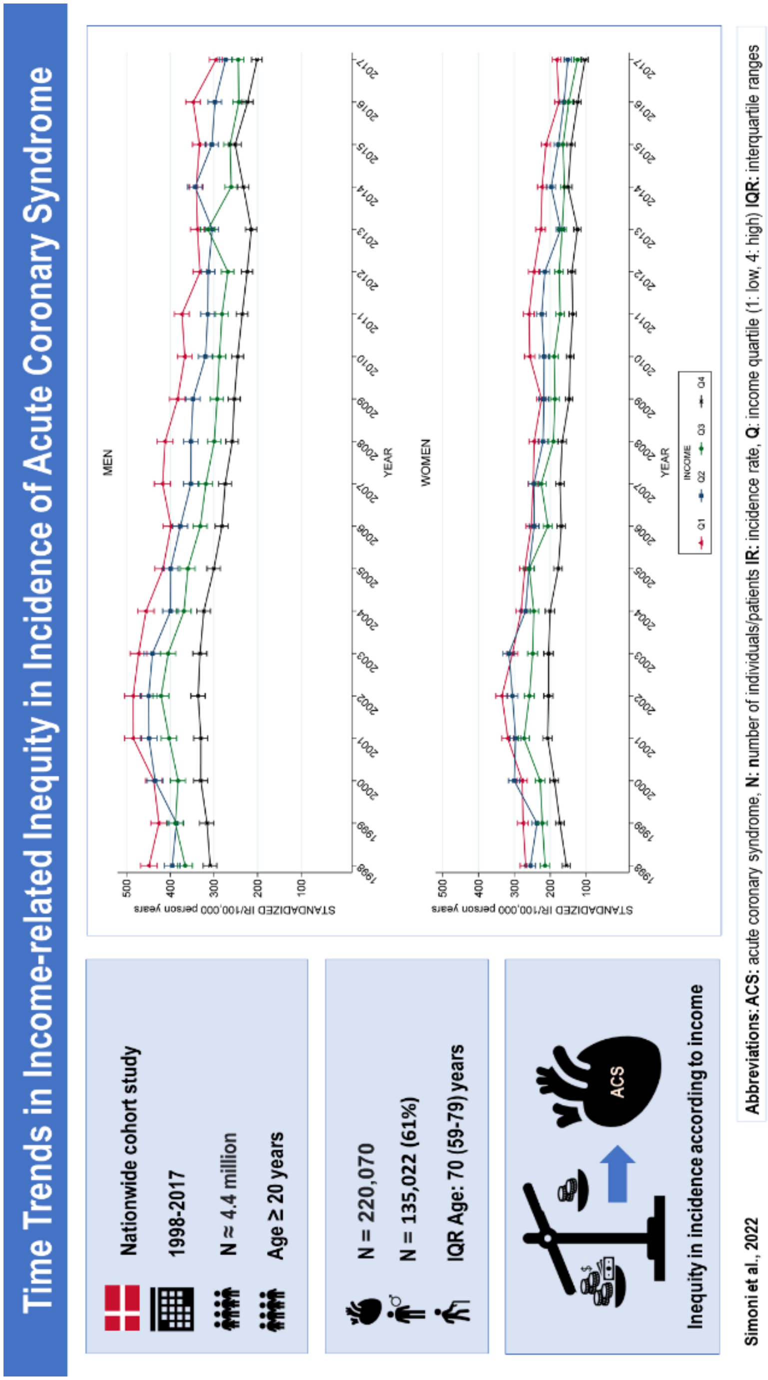
SUPLEMENTARY

INDEX:

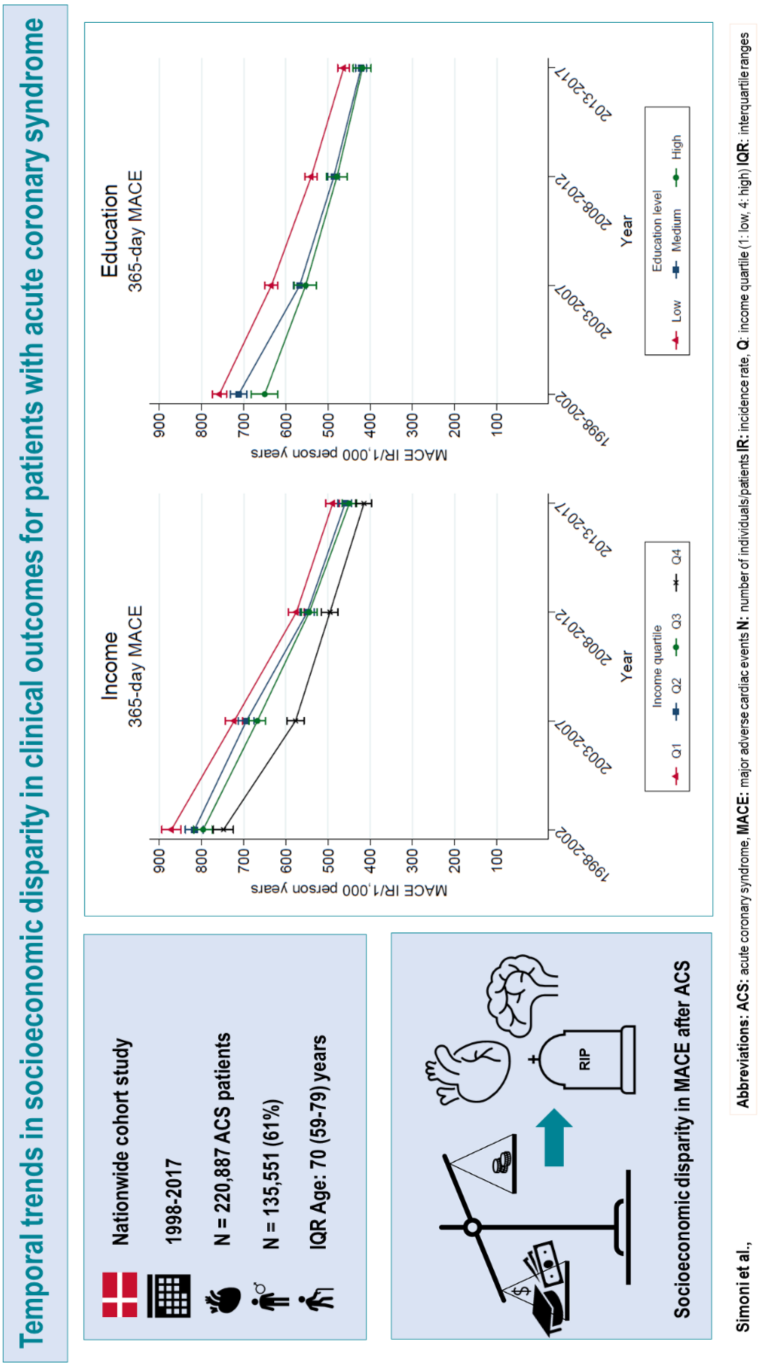
Supplemental Figure S1. Graphical abstract Study I[114]



Supplemental Figure S2. Graphical abstract Study II

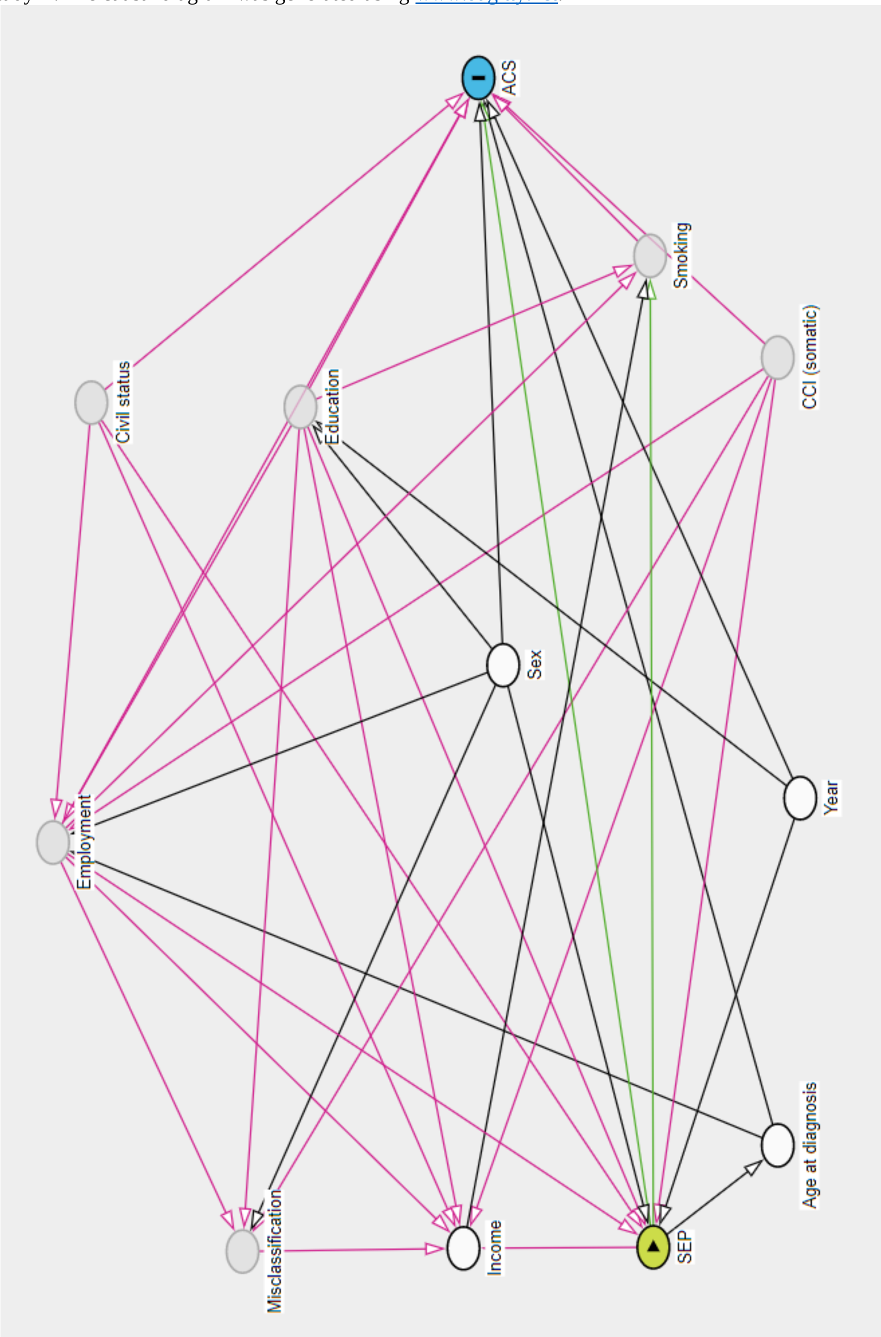


Supplemental Figure S3. Graphical abstract Study III[116]



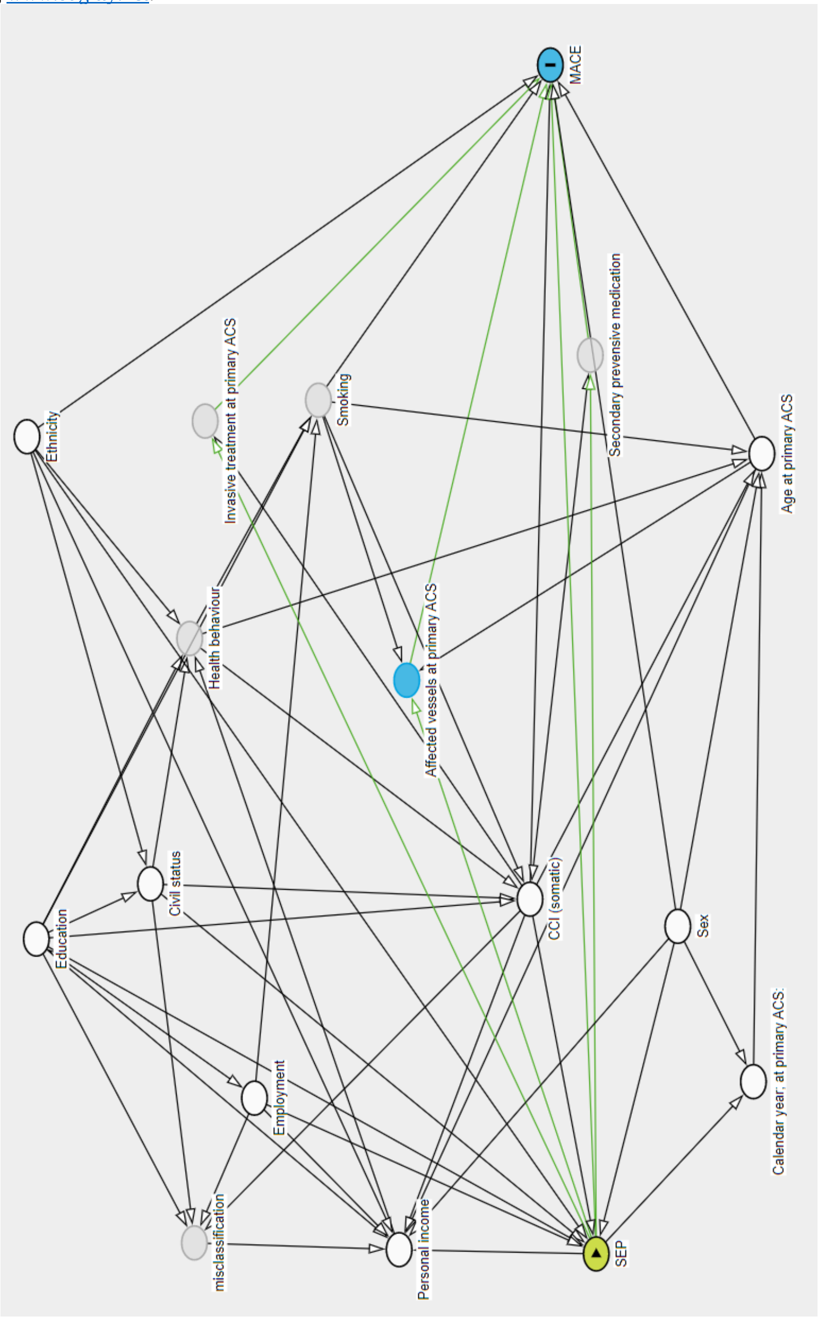
Supplemental Figure S4. Causal diagram Study II[115]

Directed Acyclic Graph used to evaluate possible confounding according to the available covariates in study II. The causal diagram was generated using www.dagitty.net.



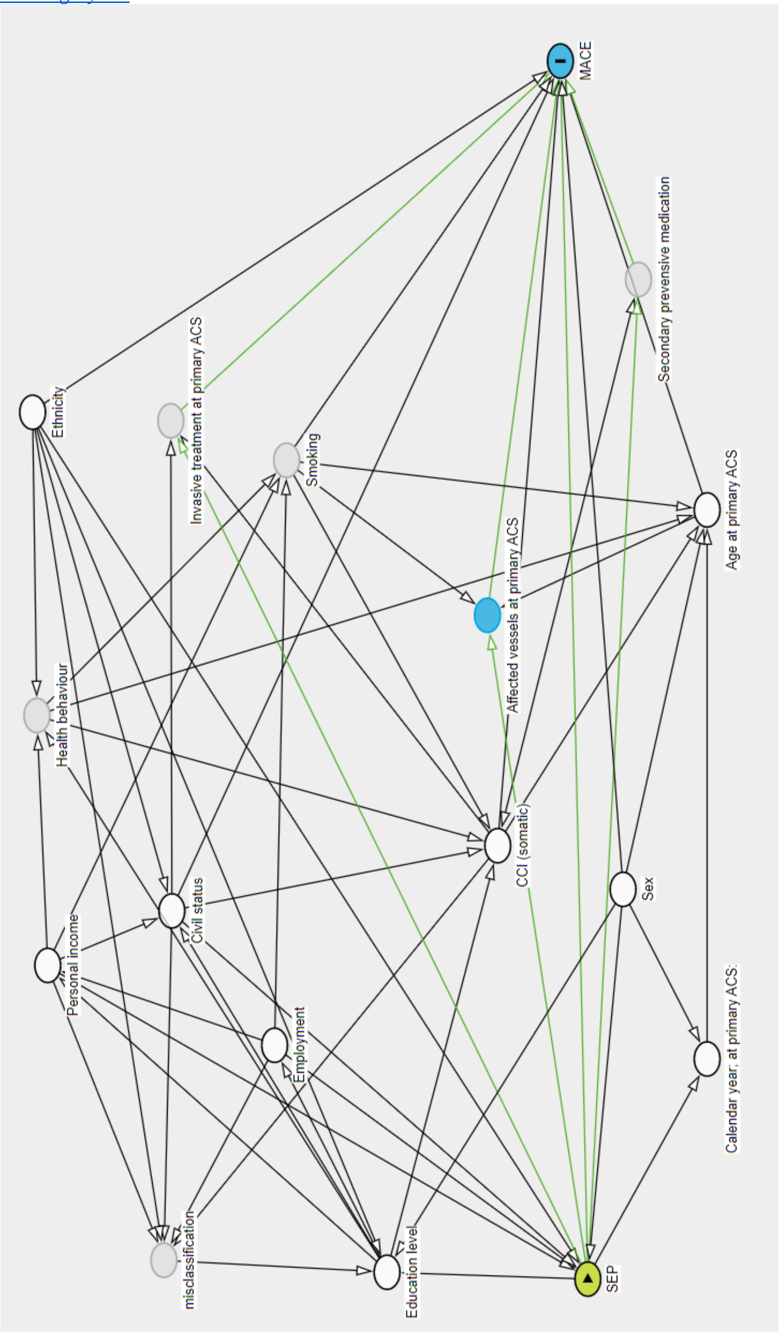
Supplemental Figure S5. Causal diagram 1 Study III[116]

Directed Acyclic Graph with income as the indicator for socioeconomic position used to select covariates included in the simple and the complex model of adjustment in study III. The causal diagram was generated using www.dagitty.net.



Supplemental Figure S6. Causal diagram 2 Study III[116]

Directed Acyclic Graph with education as the indicator for socioeconomic position used to select covariates included in the simple and the complex model of adjustment in study III. The causal diagram was generated using www.dagitty.net.



Supplemental Table S1. Results for studies identified in Study I regarding the association between SEP and temporal trends in incidence of ACS.

Study	Outcome	SEP indicator	Results	*
Davies et al., 2009, UK	MI incidence, and trends	Composite SEP (DEPCAT)	Disparity increased from 1990–92 to 2000–02	↑
Geyer et al., 2019, Germany	MI incidence, and trends	Income according to national averages	Income disparity in men were slowly narrowing from 2006-2015, not in women	↓ 0
Igland et al., 2014b, Norway	MI incidence, and trends	Educational level the year before MI,	The relative differences did not change during 2001–2009	0
Koopman et al., 2013, the Netherlands	Incidence of hospitalized-out-of-hospital fatal MI, and trends	Area-based composite SEP	The decline in MI incidence was smallest among the least affluent individuals 1998-2007	↑
Malki et al., 2014, Sweden	MI incidence, and trends	Manual- or non-manual occupation.	The disparity in MI incidence was stable over time for both men and women from 1987 to 2010	0
Pearson-Stuttard et al., 2012, UK	MI and UAP incidence, and trends	Composite SEP (IMD)	The disparity persisted or worsened from 1999 to 2007	0 ↑
Randall 2016;	MI incidence and trends	Area-based composite SEP	There was no change in disparity from 1993-2012	0
Yang et al., 2011, Sweden	MI incidence (non-fatal), and trends	Educational level	There was no change in disparity from 1987-2008	0

*More specific characteristics and results of the identified studies regarding the association between SEP and temporal trends in incidence of ACS are available in the supplementals for Study I, including study design, sample size, age. The results in this table are only based on the investigated temporal trends. Abbreviations: DEPCAT: Deprivation Category, IMD: Index of Multiple Deprivation, MI: myocardial infarction, SEP: socioeconomic position, UK: United Kingdom, *: indicates the direction of change in disparity (↑indicates an increase in disparity, 0 indicates no change, and ↓ indicates a decrease in the disparity).* [6,131,168,171,175,181,191,193]

Supplemental Table S2. Characteristics of the identified in Study I regarding the association between SEP and temporal trends in medical care after ACS.

Study	Outcome	SEP indicator	Results	*
Cacciani et al., 2017, Italy	Trends in PCI 2 days after hospitalization	Educational level	Disparity in PCI persisted from 2001-2007, to 2007-2012. (Disparity declined in the adjusted analyses)	0
Hawkins et al., 2013, UK	Aspirin, ACEi/ARBs, BB and Clopidogrel.	Composite SEP (IMD)	No disparities identified in medical care in 2003 nor 2007	0
Korda et al., 2011, Australia	Trends in receipt of CAG, PCI and/or CABG	Area-based composite SEP	No disparity in CAG 1989-1994, or 2001-2003, but from 1995-2000. No disparity in PCI 1989-1994 in men, but in 1995-2003. Opposite for women. Disparity in CABG 1992-1994 in men and 1989-1994 in women, no disparity 1995-2003	↑ ↓ ↑ ↓ ↓
Mårtensson et al., 2015, Denmark	CAG within day 1, day 3 and day 30	Educational level	1 day disparity in 2001-3 but not 2004-9. 3 days disparity in 2001-6 but not 2007-9. 30 days disparity within in 2001-9	↓ ↓ 0

*More specific characteristics and results of the identified studies regarding the association between SEP and temporal trends in medical care after ACS are available in the supplementals for Study I, including study design, sample size, and age. The results in this table are only based on the investigated temporal trends. Abbreviations: ACEi: angiotensin-converting enzyme inhibitor, ARBs: angiotensin II receptor blocker drugs, BB: β-blockers, coronary artery bypass grafting, CAG: coronary angiography, IMD: Index of Multiple Deprivation, PCI: percutaneous coronary intervention, SEP: socioeconomic position. *: indicates the direction of change in disparity (↑indicates an increase in disparity, 0 indicates no change and ↓ indicates a decrease in the disparity).* [220,243,256,260]

Supplemental Table S3. Characteristics of the identified in Study I regarding the association between SEP and temporal trends in mortality after ACS.

Study	Outcome	SEP indicator	Results	*
Cacciani et al., 2017, Italy	30-day mortality	Educational level	Disparity in mortality remained or increased from 2001-20012	0 ↑
Davies and Leyland 2010, UK	28-day mortality	Composite SEP (DEPCAT)	The disparity in mortality remained from 1988-2004	0
Malki et al., 2019, Sweden	1-day and 1-year mortality	Manual- or non-manual occupation.	Disparity in short- and long-term mortality were generally stable from 1990-1994 to 2005-2009	0 0
Mårtensson et al., 2015, Denmark	30- and 365-day mortality	Educational level	Disparity in short- and long-term mortality were generally stable from 2001-2009	0

*More specific characteristics of the identified studies regarding the association between SEP and temporal trends in mortality after ACS are available in the supplementals for Study I, including study design, sample size, and age. The results in this table are only based on the investigated temporal trends. Abbreviations: DEPCAT: Deprivation Category, SEP: socioeconomic position, UK: United Kingdom. *: indicates the direction of change in disparity (↑indicates an increase in disparity, 0 indicates no change and ↓ indicates a decrease in the disparity).*[220,260,293,309]

Supplemental Table S4. Characteristics of the identified studies regarding the association between SEP and MACE after ACS.

Study	Design	Sample size	Outcome	SEP indicator
Huo et al., 2019, China	Cohort	N=3,369 consecutive MI patients	MACE; all-cause mortality, recurrent MI, stroke, or heart failure	Self-reported education: high/medium/low
Jakobsen et al, 2012, Denmark	Cohort	N=7,385 STEMI patients who underwent PCI	MACE: cardiac death, recurrent MI, or revascularization.	Employment, education, and household income
Kim et al., 2014B, South Korea	Cohort	N=2,358 MI patients who underwent PCI	MACE: all-cause mortality, recurrent MI, or revascularization	Self-reported education, area-based composite SEP, and insurance
Notara et al., 2016, Greece	Cohort	N=2,172 ACS patients	Recurrent ACS	Self-reported educational level

Abbreviations: ACS: acute coronary syndrome, MACE: major adverse cardiac events MI: myocardial infarction, N: number of participants, PCI: percutaneous coronary intervention SEP: socioeconomic position, STEMI: ST-segment elevation myocardial infarction.[134,303,314,316]

Supplemental Table S5. Results from the identified studies regarding the association between SEP and MACE after ACS.

Study	Follow-up	Results	Measure [CI]	A
Huo et al., 2019,	Within 1 year of discharge.	Low education was associated with a higher 1-year MACE than high education	HR: 2.41 [1.72-3.37]	1+
Jakobsen et al, 2012,	Up to 8.8 years to 2010.	Lower income associated with a higher risk of MACE than higher income.	HR: 1.68 [1.47-1.92]	1+
		Short education was associated with a higher risk of MACE than long education.	HR: 1.19 [0.99-1.40]	0
		Unemployment was associated with a higher risk of MACE than employment	HR: 1.75 [1.46-2.10]	1+
Kim et al., 2014b	Follow-up to 3 years	High area-based SEP was not associated with higher MACE than low deprivation.	HR: 1.13 [0.95-1.33]	0
		Tax-payer insurance was not associated with higher MACE than individual insurance.	HR: 1.25 [0.98-1.60]	0
		Low education was associated with a higher 3-year MACE compared to higher education	HR: 2.02 [1.54-2.64]	1+
Notara et al., 2016,	10-year follow-up	Low education did not associate with higher risk of recurrent ACS than high education	aHR:1.28[0.93-1.78]	0

The results for the included studies are presented as the unadjusted or the least adjusted results available in the paper. A: Association: 1+: the study reports an association between low SEP and higher risk of less favorable outcome (or high SEP and lower risk of less favorable outcome). 0: the study reports no statistically significant association between SEP and the risk of outcome, 1-: the study finds an association between high SEP and greater risk of less favorable outcome1 (or low SES and lower risk of less favorable outcome). Abbreviations: CI: confidence interval, HR: hazard rate ratio, MACE: major adverse cardiac events, SEP: socioeconomic position, [] represents 95% CI: confident intervals. [134,303,314,316]

APPENDICES

Appendix A: Article of study I – see separate file

Appendix B: Article of study II – see separate file

Appendix C: Article of study III – see separate file

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