



Aalborg Universitet

AALBORG UNIVERSITY  
DENMARK

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

Simoni, Amalie Helme

DOI (link to publication from Publisher):  
[10.54337/aau528206017](https://doi.org/10.54337/aau528206017)

Publication date:  
2023

Document Version  
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):  
Simoni, A. H. (2023). *Time trends in incidence, treatment, and clinical outcomes according to socioeconomic position in patients with acute coronary syndrome*. Aalborg Universitetsforlag.  
<https://doi.org/10.54337/aau528206017>

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

### Take down policy

If you believe that this document breaches copyright please contact us at [vbn@aub.aau.dk](mailto:vbn@aub.aau.dk) providing details, and we will remove access to the work immediately and investigate your claim.



**TIME TRENDS IN INCIDENCE, TREATMENT,  
AND CLINICAL OUTCOMES ACCORDING TO  
SOCIOECONOMIC POSITION IN PATIENTS  
WITH ACUTE CORONARY SYNDROME**

**BY  
AMALIE HELME SIMONI**

DISSERTATION SUBMITTED 2023



**AALBORG UNIVERSITY**  
DENMARK



# **TIME TRENDS IN INCIDENCE, TREATMENT, AND CLINICAL OUTCOMES ACCORDING TO SOCIOECONOMIC POSITION IN PATIENTS WITH ACUTE CORONARY SYNDROME**

by

Amalie Helme Simoni



**AALBORG UNIVERSITY**  
DENMARK

Dissertation submitted 2023

Dissertation submitted: February 2023

PhD supervisor: Prof. Søren Paaske Johnsen, MD, PhD,  
Aalborg University

Assistant PhD supervisors: Clinical Associate Prof. Svend Eggert Jensen, MD, PhD  
Aalborg University

Associate Prof. Henrik Bøggild, MD, PhD  
Aalborg University

Kristian Hay Kragholm, MD, PhD  
Aalborg University Hospital

PhD committee: Clinical Professor Peter Vestergaard (chair)  
Aalborg University, Denmark

Senior Professor Ulf de Faire  
Karolinska Institutet, Sweden

Professor Emeritus Allan Krasnik  
University of Copenhagen, Denmark

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

ISSN (online): 2246-1302  
ISBN (online): 978-87-7573-748-2

Published by:  
Aalborg University Press  
Kroghstræde 3  
DK – 9220 Aalborg Ø  
Phone: +45 99407140  
aauf@forlag.aau.dk  
forlag.aau.dk

© Copyright: Amalie Helme Simoni

Printed in Denmark by Stibo Complete, 2023

# ACKNOWLEDGEMENTS

First, I would like to express my gratitude to Karen Elise Jensens Fond for the financial support to this work. Furthermore, the work in this thesis could not have been done without support from several wonderful people around me. First, I would like to thank my main supervisor, Søren Paaske Johnsen for the introduction to the important area of health services research and the opportunity to conduct the work presented in this thesis. Thank you for your commitment and support, and always meeting me at the current state of work and mind, and for the sharp balance between the initial expectations and goals for this project, and the realism down the road in what was doable within the time and conditions after the unexpected delay in data delivery. Also, a great thanks to the rest of my supervisor team; Svend Eggert Jensen, Henrik Bøggild, and Kristian Hay Kragholm, for your always positive and inspiring feedback and ideas, and keeping me on track in regard of making the research relevant in the clinical and the public health scientific context.

I would like to thank my colleagues at the Danish Center for Clinical Health Service research for creating the inspiring and stimulating research environment and all the academic and non-academic discussions, and for keeping in contact during all the forced homework the last years. A special thanks to Juliane, for keeping both her and my head up during the process of the systematic literature screening and data extraction, and for screening and reading the great lot of papers with me, several times with short-term notice. Also, a special thanks to Jan Brink Valentin for patiently taking your time to provide qualified stepwise assistance with the statistics and identifying and suggesting doable and relevant methods throughout the project.

Thanks to Gregory Lip for the experience to visit the Liverpool Centre for Cardiovascular Science at the University of Liverpool. This experience has been of great importance to me, and I am grateful for being accepted as part the LCCS family.

Finally, a great thanks to my friends and family for your endless support. Thank you, Anders, for your enormous comfort, encouragement, and love. The everyday life is our common adventure and I look forward to the next one!

*Amalie Helme Simoni, Aalborg 2023*

TIME TRENDS IN INCIDENCE, TREATMENT, AND CLINICAL OUTCOMES ACCORDING TO SOCIOECONOMIC POSITION IN PATIENTS WITH ACUTE CORONARY SYNDROME



# 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

# TABLE OF CONTENTS

<b>Chapter 1. INTRODUCTION .....</b>	<b>13</b>
1.1. Socioeconomic disparity in health.....	13
1.1.1. Socioeconomic disparity in health behaviour.....	14
1.1.2. Socioeconomic position.....	15
1.1.3. Temporal trends in socioeconomic disparity.....	19
1.2. Acute coronary syndrome.....	21
1.2.1. Medical care in acute coronary syndrome.....	22
1.2.2. Temporal trends in acute coronary syndrome.....	23
1.2.3. Disparities in acute coronary syndrome.....	23
1.3. The Danish healthcare system.....	24
1.3.1. Strategies in the Danish healthcare system.....	25
<b>Chapter 2. AIMS OF THE THESIS.....</b>	<b>29</b>
2.1. Overall objective.....	29
2.1.1. Aim Study I.....	29
2.1.2. Aim Study II.....	29
2.1.3. Aim Study III.....	29
<b>Chapter 3. METHODS.....</b>	<b>31</b>
3.1. Systematic search strategy.....	32
3.2. Settings for the nationwide cohort studies.....	32
3.2.1. Data sources.....	33
3.3. Study populations.....	34
3.3.1. General population.....	34
3.3.2. ACS population.....	35
3.4. Socioeconomic position.....	35
3.5. Study outcomes.....	36
3.5.1. Incidence of ACS.....	36
3.5.2. Prevalence of ACS.....	36
3.5.3. Medical care.....	37
3.5.4. Mortality.....	37
3.5.5. Major adverse cardiac events.....	37
3.6. Covariates.....	38
3.7. Data handling.....	38
3.7.1. Data extraction and data synthesis.....	39
3.7.2. Statistical analyses.....	39
3.8. Ethics, registration, and reporting.....	40
<b>Chapter 4. RESULTS.....</b>	<b>41</b>
4.1. Study and population selection.....	41
4.2. Study and baseline characteristics.....	42
4.3. Disparity in incidence of ACS.....	43
4.3.1. Temporal trends in disparity in incidence of ACS.....	44
4.4. Disparity in prevalence of ACS.....	45

4.5. Disparity in medical care in ACS patients .....	46
4.6. Disparity in mortality in ACS patients.....	47
4.6.1. Temporal trends in disparity in mortality after ACS.....	49
4.7. Disparity in MACE in ACS patients .....	49
4.7.1. Temporal trends in disparity in MACE after ACS.....	51
<b>Chapter 5. DISCUSSION .....</b>	<b>53</b>
5.1. Key results .....	53
5.2. Comparison with existing literature.....	53
5.2.1. Disparity in incidence and prevalence of ACS .....	53
5.2.2. Disparity in medical care of the ACS patients.....	55
5.2.3. Disparity in clinical outcomes after ACS .....	57
5.3. Methodological considerations .....	58
5.3.1. Measuring socioeconomic position.....	58
5.3.2. Publication bias .....	59
5.3.3. Selection bias.....	60
5.3.4. Information bias.....	60
5.3.5. Confounding and mediation .....	61
5.3.6. External validity .....	62
<b>Chapter 6. CONCLUSIONS AND IMPLICATIONS .....</b>	<b>65</b>
<b>REFERENCES .....</b>	<b>67</b>
<b>SUPPLEMENTARY .....</b>	<b>91</b>
<b>APPENDICES.....</b>	<b>101</b>



# CHAPTER 1. INTRODUCTION

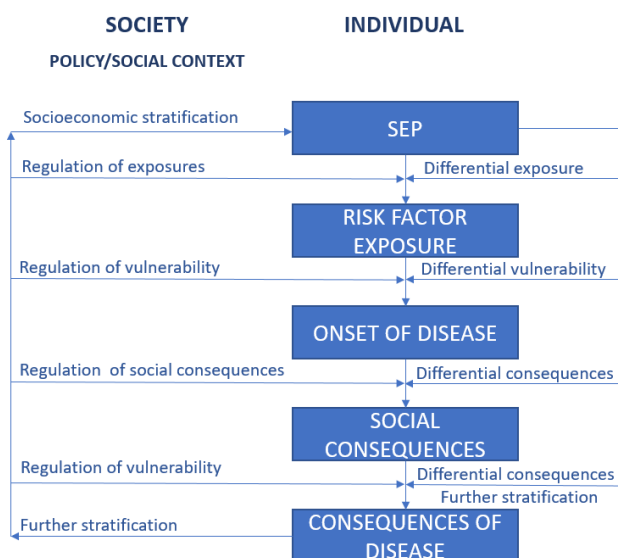
Acute coronary syndrome (ACS) is an acute presentation of coronary atherosclerosis, including myocardial infarction (MI) and unstable angina pectoris (UAP). ACS ranks as the leading cause of mortality globally, leading to about one-third of all deaths in the adult population.<sup>1-3</sup> Changes in the epidemiology of ACS across high-income countries during the last decades emphasize that ACS is widely preventable.<sup>4-6</sup> 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.<sup>4,7,8</sup> 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.<sup>4,7-10</sup> 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.<sup>11</sup> 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.<sup>7,12-14</sup> 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.<sup>11,15,16</sup> 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.<sup>11,17,18</sup> Hence, socioeconomic factors, including education, income level, occupation, sex, and ethnicity, have an important influence on how healthy a subject is.<sup>15</sup> Variations over time, within, or between countries, in any of these factors may give rise to variations in health disparities.<sup>17</sup> The World Health Organization reports that socioeconomic position (SEP) influence patients' treatment of illness as well as their health condition.<sup>13</sup> 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.<sup>15,16</sup> Generally, the age-adjusted mortality risk is two to three times higher for those with the lowest SEP than those with the highest.<sup>18</sup> 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.<sup>11,15,16</sup>

The mechanisms behind socioeconomic disparities in health are complex, and part of the disparities originate from relations sustaining through generations.<sup>16,19-21</sup> 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.<sup>16-20,22</sup> 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).<sup>16,18,23</sup>



**Figure 1-1 Central mechanisms in health disparity.**

A modified figure of Finn Diderichsen's model of health disparity.<sup>11,24</sup> 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

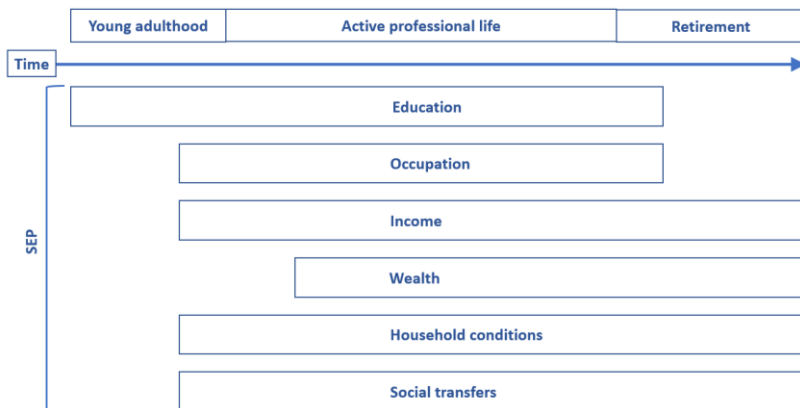
It is important to acknowledge, that material improvements do not automatically improve the health disparities. Over the last decades, health disparity in Western Europe seems to have persisted or widened, despite improvements in material well-being and welfare policies.<sup>17,21</sup> In high-income 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.<sup>16,17,19,20</sup> Overall, Western Europe welfare policies during the last decades have contributed making the more affluent lifestyles more affordable.<sup>17</sup> However, paradoxically this could have contributed to a widening of health disparities by distributing the immaterial factors for health more socially unequal.<sup>16,17,19,20</sup>

It may be discussed whether stratification of personal health according to social status is a free choice rather than a public health problem.<sup>11</sup> 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.<sup>11</sup> However, most individuals would probably not voluntarily select extensive obesity or addiction to alcohol consumption or smoking.<sup>11,23</sup> 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.<sup>11,23</sup> Generally, it is expected that health behavior itself accounts for around a quarter of the socioeconomic disparity in health.<sup>11,23</sup>

### 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.<sup>16,19</sup> 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*).<sup>16,19,20,23,25</sup> 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.<sup>16,19</sup> 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.<sup>16,19</sup> 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.<sup>16,19,20</sup> All SEP indicators used in this thesis were selected according to the principles from Galobardes et al. 2006.<sup>19</sup> These indicators, represent different influences on health and health behavior and are not interchangeable.<sup>19,23</sup> 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.<sup>16,19</sup> 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.<sup>16,22</sup> 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.<sup>16,19,20</sup> 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.<sup>16,19,20,26</sup> 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.<sup>16,19,20</sup> 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.<sup>16,19,20</sup> If income is collected using questionnaires, the willingness to disclose accurate data was lower than for educational and occupational data.<sup>16,19,20</sup> 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.<sup>11,25-27</sup> 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.<sup>16</sup> 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.<sup>28</sup>

### **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.<sup>16</sup> 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.<sup>11,23</sup> 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.<sup>16,19,20</sup> 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.<sup>29</sup> 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.<sup>29,30</sup> The ISCED was updated in 2011 and has been implemented in all data collections in the European Union since 2014.<sup>30</sup>

### **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.<sup>16,19,20</sup> 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.<sup>16,20</sup> 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.<sup>16,19,20</sup> 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.<sup>16,19,20,24</sup> 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*).<sup>16,19,20</sup>

#### **1.1.2.4 Health insurance**

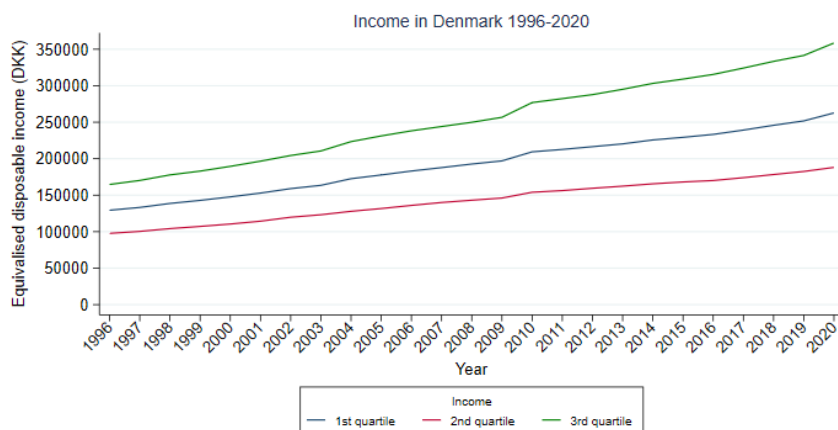
In epidemiological studies, health insurance coverage could be used as a measure of SEP.<sup>31,32</sup> Insurance status correlates with several other measures of SEP, including income, education, and occupation, and has been found to explain some of the disparity in health, especially in countries 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.<sup>31,32</sup> However, health insurance coverage also associates with general health behavior.<sup>31</sup> 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.<sup>31</sup> 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.<sup>31,32</sup>

#### **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.<sup>33,34</sup> 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.<sup>16,19,20</sup> 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.<sup>16,19,20</sup> 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.<sup>23</sup> 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.<sup>16,19,20</sup>

### 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.<sup>16</sup> 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.<sup>35-37</sup> 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.<sup>37-39</sup> 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.<sup>23</sup> 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.<sup>18,39,40</sup> Furthermore, the substantial disparity in health and mortality in the Nordic advanced welfare states also persists despite relatively low material disparities.<sup>17</sup> Some healthcare regulations, including stronger regulations of public smoking, may have led to a tendency towards an increasing disparity in smoking habits.<sup>17,41</sup>



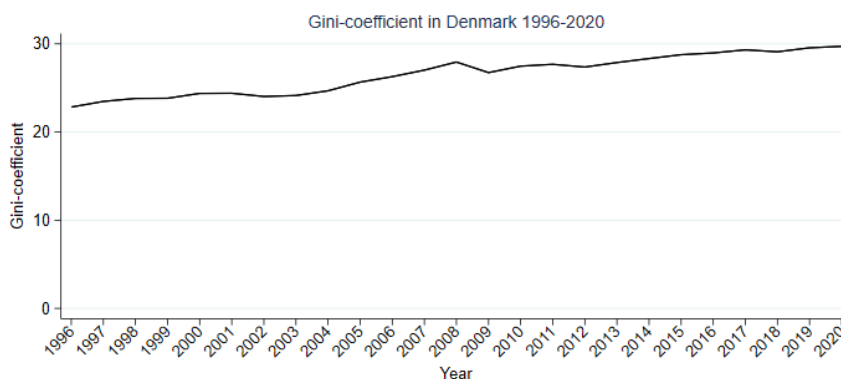
**Figure 1-3 Income over time in Denmark.**

Median and interquartile ranges for personal equivalent disposable income in Denmark 1996-2020.<sup>42,43</sup>

#### 1.1.3.1 Trends in socioeconomic disparity in Denmark

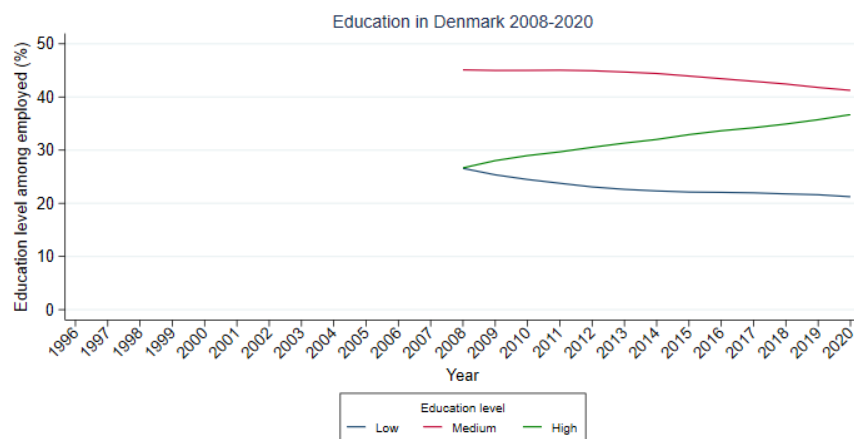
Denmark (Adult population N=4.8 million 2022)<sup>44</sup> is well-known for egalitarian policies and its welfare societal model characterized by universal access to income transfers including social pension, user-free education, and unemployment benefit.<sup>11,45</sup> From 2005 to 2015, life expectancy in Denmark increased from 77.9 years to 80.6 years.<sup>46</sup> 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.<sup>11,45,47–50</sup> 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.<sup>42,43</sup> 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*).<sup>42,51</sup>



**Figure 1-4 Income disparity over time in Denmark.**

The Gini-coefficient based on the personal equivalent disposable income in Denmark 1996-2020.<sup>42,43</sup>



**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 30<sup>th</sup> of September each year. Educational level is available from 2008.<sup>42,43</sup> 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.<sup>30,51</sup> 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.<sup>52,53</sup> The industrialization and following advances in public health have implied a major increase in life expectancy, especially in Europe and North America.<sup>18,52,53</sup> 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.<sup>52</sup> 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.<sup>2,18,52-54</sup>

ACS is the acute clinical presentation of coronary atherosclerosis causing cardiac ischemia, including MI and UAP.<sup>2,55,56</sup> The global incidence of ACS persists above 20 million cases yearly,<sup>2,57</sup> 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.<sup>1,2,58,59</sup> The most common pathophysiological mechanism of ACS is a rupture of an atherosclerotic plaque, resulting in partial or total occlusion of a coronary artery.<sup>52,60</sup> The plaque rupture exposes subendothelial collagen, activating the platelets and the coagulation cascade, generating a thrombus, which implies complete or partial coronary occlusion.<sup>60</sup> The coronary occlusion reduces the blood flow in the coronary artery resulting in cardiac ischemia and symptoms, typically chest pain.<sup>52,60</sup> The chest pain is often described as deep and prolonged, possibly radiating into one of the arms or ampits, jaw, tongue, teeth, or neck. Other symptoms may include dyspnea, nausea and vomiting, diaphoresis, and unexplained fatigue.<sup>60</sup> Adjustable patient risk factors, including lifestyle behavior are expected to play a large role regarding the risk of ACS.<sup>52,60</sup> 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.<sup>52,60</sup> 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).<sup>52,60</sup> If ACS is suspected, an electrocardiogram should be completed and evaluated immediately after hospital arrival.<sup>52,60</sup> 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.<sup>52,56,60-63</sup> 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.<sup>52,56,60-63</sup>

### 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.<sup>60,64-69</sup> 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.<sup>60,65,66</sup> 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.<sup>60,65,66</sup> 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.<sup>60</sup>

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.<sup>60,62</sup> 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.<sup>60,62,70</sup> 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.<sup>60,62,70</sup>

Recurrent ACS events and mortality after ACS are significantly reduced by the use of antiplatelets therapy (e.g., aspirin and/or thienopyridines/P2Y<sub>12</sub>-inhibitors) statins,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors (ACEi), or angiotensin II receptor blockers (ARBs).<sup>52,70,71</sup> 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.<sup>70,72</sup> 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 improve the physical and psychological functions in cardiac patients and has a major effect on the patients ability to return to a satisfying life.<sup>73-75</sup> 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.<sup>73-75</sup>

### 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 1980s.<sup>5,6,12,52,54,57,58,76</sup> 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.<sup>52,77</sup> This improvement also includes improved sensitivity and specificity of the biomarkers defining MI, which have affected the epidemiology of ACS.<sup>52,78</sup> 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.<sup>52,60,62</sup> However, this was not included in the universal definition of MI until 2007.<sup>52</sup> 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.<sup>52</sup> Additionally, the increasing use of preventative medications (aspirin, statins,  $\beta$ -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.<sup>52</sup> 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.<sup>62,71,79,80</sup> 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.<sup>52,81-84</sup>

### 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.<sup>85,86</sup> 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.<sup>87-89</sup> As for other disease outcomes, part of this association can be explained by lifestyle patterns and health behavior, since multiple risk factors are associated with ACS, including hypertension, hypercholesterolemia, diabetes, family history of coronary artery disease, and smoking habits.<sup>11,16-20</sup> 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.<sup>11,12,18,90,91</sup> Hence, persons with more resources according to SEP may both maintain a more healthy lifestyle and receive better medical care.<sup>11,18</sup> 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.<sup>92</sup> 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.<sup>93</sup> 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.<sup>7,94</sup> 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.<sup>7,92-94</sup> 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.<sup>7,12,13</sup> However, studies indicate that the improved treatment of hypertension and atherosclerosis could have led to a reduced disparity in heart disease.<sup>11,23</sup> 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.<sup>54</sup>

### 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.<sup>46,95-97</sup> 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.<sup>11,23,46</sup> 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%.<sup>46,97</sup> 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).<sup>98</sup> 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.<sup>22,99,100</sup> Still, health and diseases are unevenly distributed within society and the socioeconomic disparity in mortality is of a particular magnitude.<sup>45,47,48</sup> 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.<sup>101,102</sup> 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.<sup>48,99</sup> 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.<sup>14</sup> The socioeconomic disparity seems to present both in regard of prevention, early detection, treatment, and rehabilitation.<sup>99</sup> However, continuous monitoring and evaluation are lacking to identify whether the disparity in specific diseases and treatment changes for the better or the worse.<sup>47</sup>

### 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.<sup>100</sup> Since the 1940's, there has been a wide political agreement that healthcare should be available to everyone, independent of the place of residence and economic resources.<sup>22</sup> 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.<sup>22,97,100</sup> Since 2007, the full responsibility for all non-hospital based prevention, health promotion, and rehabilitation lies within the 98 municipalities. This was previously a shared responsibility.<sup>46,100,103</sup>

Denmark has had a national strategy on quality of care since 1993.<sup>97,104</sup> However, the focus and methods of the strategy have changed over the years.<sup>97,105</sup> 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.<sup>97,104,105</sup> 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.<sup>97</sup> At that time, all hospitals had completed two cycles of accreditation.<sup>46,97</sup> 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.<sup>46,105,106</sup> 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.<sup>46,97</sup> 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.<sup>97,106</sup> 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.<sup>14,46,48</sup> 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.**<sup>97,104</sup>

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.<sup>11,101,107-109</sup> This includes the Government's Public health program 1999-2008 representing a goal regarding reduced social disparity in health,<sup>107</sup> 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.<sup>11,109</sup> 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.<sup>11,99,101</sup> 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).<sup>47</sup> 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.<sup>47</sup>

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

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.<sup>111,112</sup> The Danish strategies regarding the treatment of ACS are based on the guidelines from the European Society of Cardiology.<sup>62,80</sup> 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.<sup>65-69</sup> 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.<sup>68,104,110,111</sup> 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”.<sup>46,104</sup> From 2000 to 2014, the number of CAG and PCI increased by 231% and 193%, respectively.<sup>111</sup> Denmark has presented the largest decline in cardiac-related mortality within the OECD countries, with a 69% decline from 2005 to 2012.<sup>46,113</sup> 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*.<sup>114-116</sup> 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.<sup>114</sup> 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.<sup>115,116</sup> 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
<b>Objectives</b>	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
<b>Setting</b>	Studies published 2009-2021	Denmark 1998-2017	Denmark 1998-2017
<b>Data sources</b>	PubMed and Embase	CRS, DNPR, DRCD, and IND	CRS, DNPR, IND, RMPS, PER, RAS, and DHR
<b>Study population</b>	General population (aim 1-2) and patients with ACS (aim 3-4)	The entire Danish population aged $\geq 20$ years	All patients with ACS aged $\geq 18$ years admitted to a hospital in Denmark
<b>Exposures</b>	SEP:		
	Income, education, insurance, occupation, and composite indicators of SEP	Equivalentized personal income quartile	Equivalentized personal income quartile and highest attained educational level
<b>Outcomes</b>	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
<b>Method of analyses</b>	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- <i>py</i> 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<sup>117</sup> and Embase<sup>118</sup>, using Medical subject heading (MeSH) terms, Emtree terms, and keywords.<sup>119</sup> 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 10<sup>th</sup> of July 2020 and rerun on the 5<sup>th</sup> of July 2021.<sup>114</sup> Furthermore, reference lists of the included studies were manually hand-searched and the studies were cross-referenced in the Web of Science.<sup>114</sup>

The identified literature was double-screened for eligibility with the four study aims, by two independent researchers, using the blinding function in Rayyan QCRI.<sup>120</sup> 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.<sup>114</sup> 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.<sup>114,121</sup>

*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 Population	ACS prevalence	Education, income, occupation, insurance, or composite SEP
I (aim 3)		Medical care	
I (aim 4)		Mortality	Personal income, educational level
III (trends)			Personal income, educational level
III (trends)		MACE	Personal income, educational level

*Abbreviations: 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.<sup>44</sup> 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.<sup>115,116</sup> The Danish Health Data Authority and Statistics Denmark are state institutions, containing

individual-level data from multiple administrative registers and governmental agencies<sup>42,122</sup> 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 <sup>117</sup>	2009-2021
Embase	I	Database of biomedical and pharmacological published literature, hosted by Elsevier <sup>118</sup>	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 <sup>44,95,123,124</sup>	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 <sup>96,124</sup>	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) <sup>125</sup>	1998-2017
IND	II & III	Data on tax-based annual equivalent income on personal level <sup>122,126</sup>	1997-2016
RMPS	III	ATC-code information on prescription pharmacotherapies within one year before the ACS diagnosis, used to define comorbidity <sup>127</sup>	1997-2017
PER	III	Data on personal highest attained educational level <sup>128</sup>	1998-2016
RAS	III	Data on personal employment status ultimo November <sup>51</sup>	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% <sup>111</sup>	2000-2017

*Abbreviations: 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.<sup>44,95,123,124</sup>

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.<sup>96,124</sup> 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.<sup>96,124</sup>

The Danish Register of Causes of Death (DRCD) holds information on the cause of death, reported using ICD-10 codes, since 1994.<sup>125</sup> 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.<sup>125</sup>

The Register of Medicinal Products Statistics holds information on all dispensed prescription pharmacotherapies according to the Anatomical Therapeutic Chemical classification system<sup>127,129</sup>. 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.<sup>127</sup>

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.<sup>111</sup>

Socioeconomic variables were retrieved from statistics Denmark on an individual level. Income data was collected from the personal income register, which holds information on tax-based annual income on personal level.<sup>122,126</sup> 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.<sup>42</sup> Education data was collected from the Danish Population's Education Register.<sup>128</sup> 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.<sup>128</sup> 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.<sup>51</sup>

### **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*).<sup>114,115</sup> 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.<sup>114</sup> In Study II, the population was defined as the general Danish population aged  $\geq 20$  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.<sup>42,115,122</sup>

### 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.<sup>114–116</sup> The study population for Study I (aim 3-4) and Study III was defined as a population with incident ACS (*Table 3-2*).<sup>114,116</sup> 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*).<sup>114</sup>

In Study III the incident ACS more specifically had to be based on an ICD-10 diagnosis, at a Danish hospital between January 1<sup>st</sup>, 1998, and December 31<sup>st</sup>, 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  $\geq 18$  years and living in Denmark, to be included.<sup>116</sup>

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

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

*Abbreviations: 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*).<sup>19</sup> 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.<sup>12,114,130–132</sup> 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.<sup>114</sup> However, SEP indicators according to childhood, parental, or partner factors were excluded.<sup>114,121</sup> 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.<sup>7,19,114–116</sup>

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.<sup>115,116</sup> 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.<sup>26,122</sup> 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.<sup>42,122,126</sup>

In study III, SEP was also retrieved as the personal level of highest educational attainment.<sup>116</sup> The highest completed level of education for each patient before the incident ACS was obtained from the PER in statistics Denmark.<sup>116,128</sup> 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.<sup>30,116,128</sup>

### 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.<sup>114</sup> 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.<sup>115,116</sup>

#### 3.5.1. INCIDENCE OF ACS

Incidence is ascertained by counting the number of new cases occurring during a period e.g., one year.<sup>54</sup> 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).<sup>114</sup>

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 1<sup>st</sup>, 1998, and December 31<sup>st</sup>, 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.<sup>115</sup>

#### 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).<sup>114</sup> 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.<sup>133</sup>

### 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.<sup>114</sup> 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.<sup>114</sup>

### 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- ( $\leq 30$  days after ACS) and long-term mortality ( $> 30$  days after ACS).<sup>114</sup>

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.<sup>116</sup>

*Table 3-5: Events and codes for major adverse cardiac events in Study III.*

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

*Abbreviations: ACS: acute coronary syndrome, CABG: coronary artery bypass grafting, CRS: the Civil Registration System, MACE: major adverse cardiac events, PCI: percutaneous coronary interventions, SKS: the healthcare classification 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.<sup>134–137</sup> 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  $\geq 7$  days after the hospital discharge from the incident ACS admission (*Table 3-5*).<sup>116,137</sup>

### 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.<sup>114,121</sup> However, adjusting for relevant prognostic covariates, was part of the quality assessment according to the Cochrane tools to assess the risk of bias for cohort-, case-control-, and cross-sectional studies, applied in Study I.<sup>138-141</sup> 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.<sup>114</sup>

In Study II, the available covariates were limited to those available on an aggregated level in the Statbank data.<sup>42</sup> 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  $\geq 80$  years).<sup>42,122</sup> A causal diagram was constructed, to identify whether the standardization using the available covariates was expected to imply confounding (*Supplemental Figure S4*).<sup>115</sup> 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.<sup>116</sup> 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.<sup>142</sup> 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*).<sup>116,143</sup>

### 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).<sup>114-116</sup> 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.<sup>114</sup> 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.<sup>114</sup> 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.<sup>114,138-140</sup>

### 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).<sup>115,116</sup> In Study II, direct standardized incidence rates (IR) were calculated using cell-specific equivalent income quartiles for the year before the incident ACS.<sup>115</sup> The income quartiles were standardized, according to year, sex and age-group.<sup>42</sup> Thus, yearly direct standardized IRs were presented as ACS cases pr. 100,000 person-years according to income quartile.<sup>115,144</sup> Standardized incidence rate ratios (IRR), were computed and graphically illustrated, using individuals in the highest-income quartile as the reference.<sup>115</sup> CIs at 95% were estimated using a method by Julious et al., 2001.<sup>145</sup> 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.<sup>115</sup>

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.<sup>146</sup> The cox-proportional hazards regressions were adjusted using the Doubly robust method, to compensate for the imbalance following IPTW.<sup>147</sup>

### **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.<sup>115</sup> 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.<sup>116</sup>

### **3.7.2.2 Stratified analyses**

Both in Study II and III, the analyses were stratified in multiple levels to identify possible effect modifications.<sup>115,116</sup>

## **3.8. ETHICS, REGISTRATION, AND REPORTING**

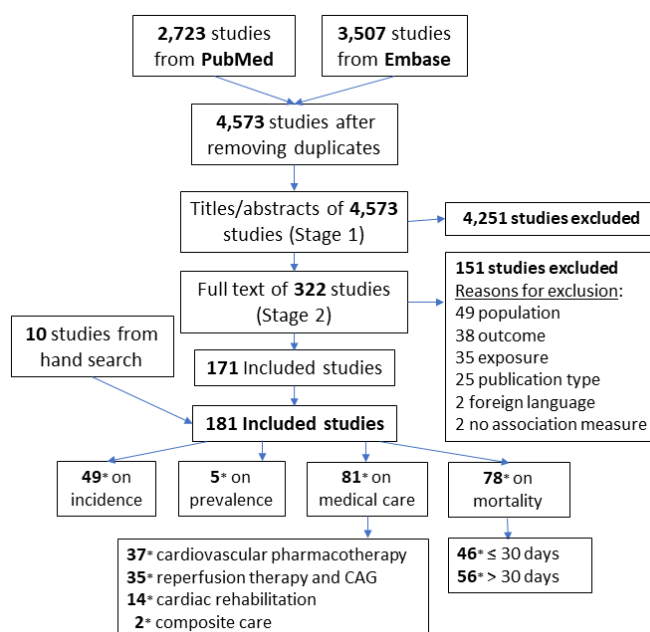
Pre-defined methods for the systematic literature review (Study I) were pre-registered in the International Prospective Register of Systematic Reviews (registration no.: CRD42020197654).<sup>114,121</sup> The cohort studies (Study II-III) were approved and registered at the local institutional review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

# 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.<sup>114</sup> 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).<sup>114</sup>

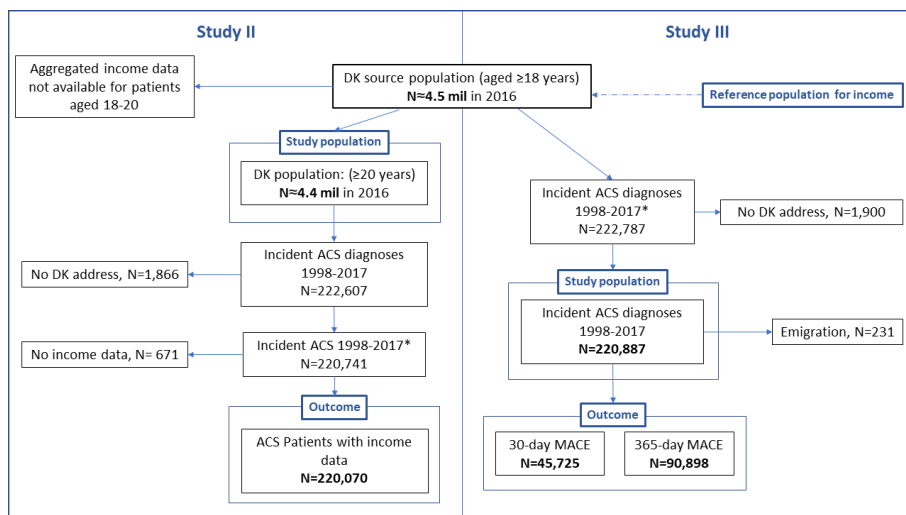


**Figure 4-1 Flowchart Study I.**

Systematic selection of the identified studies in Study I. Abbreviations: CAG: coronary angiography, \*: some studies presented results on multiple outcomes and/or sub-outcomes.<sup>114</sup>

In Study II, the general Danish population aged  $\geq 20$  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.<sup>115</sup> In Study III, 220,887 patients with an incident ACS diagnosis from 1998 to 2017, aged  $\geq 18$ , living in Denmark the year before diagnosis, were included in the study population (Figure 4-2, Study III).<sup>116</sup>



**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

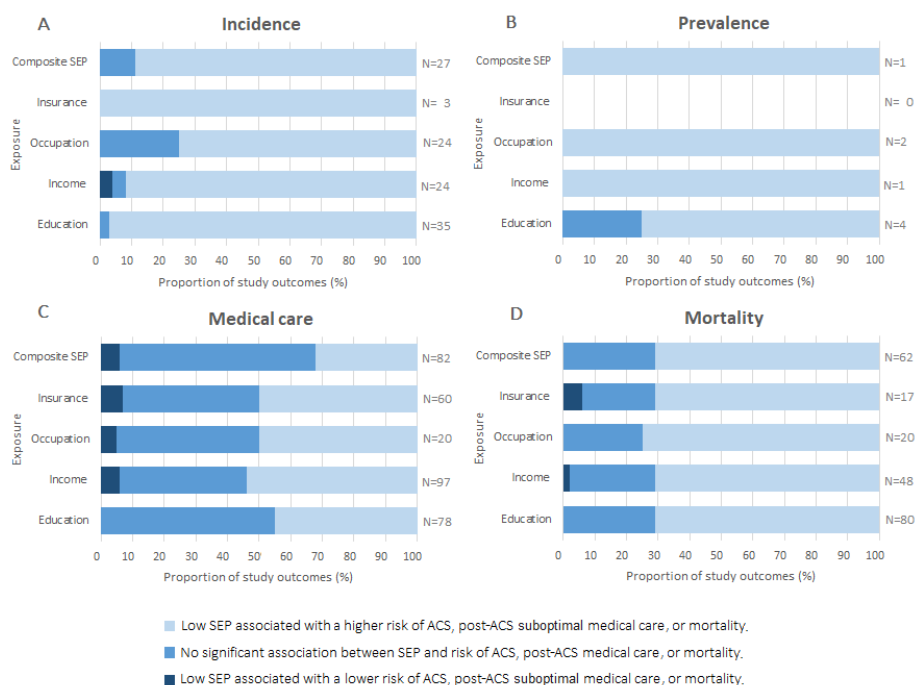
The included studies in Study I, were 155 cohort studies, 16 cross-sectional studies, and 10 case-control studies.<sup>114</sup> When categorized according to the World Bank assignment of income levels for world economies 2021,<sup>153</sup> 81% of the included studies were performed in high-income countries, 15% in upper-middle-income countries, 1% in lower-middle-income countries, 3% were multi-national, and none were performed in low-income countries.<sup>114</sup> 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.<sup>154-158</sup> 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.<sup>114</sup>

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.<sup>42,115,122</sup> However, 49% of the population in 2016 were males, and the

median yearly personal equivalent income in 2016 was 233,300 DKK.<sup>115</sup> 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.<sup>116</sup>

### 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*).<sup>114</sup> 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.<sup>6,33,162–171,34,172–181,131,182–191,154,192–200,157–161</sup> 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.<sup>114</sup>

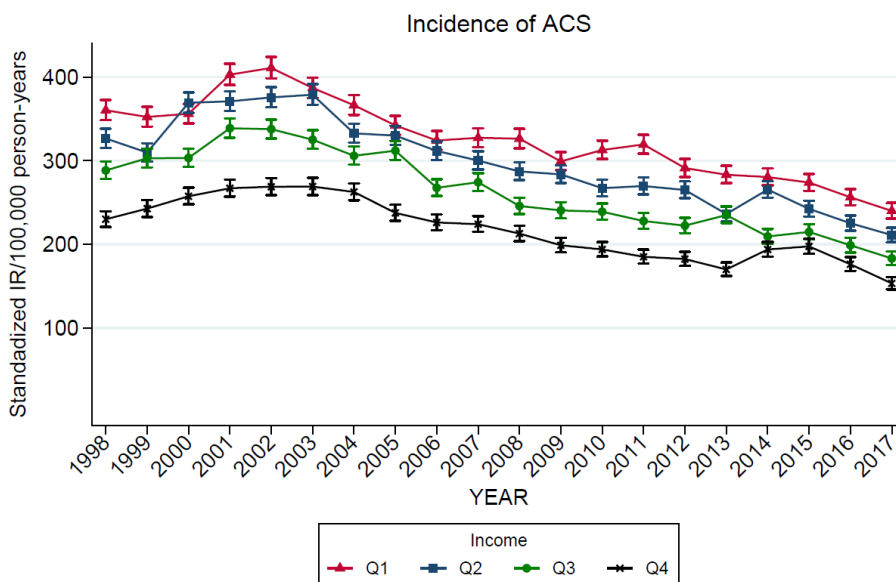


**Figure 4-3 Incidence and prevalence of ACS, and medical care and mortality after ACS, according to the SEP.** The associations identified across all the included studies according to the different exposures and A) incidence, B) prevalence, C) medical care, and D) mortality. Abbreviations: ACS: acute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

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].<sup>115</sup>

### 4.3.1. TEMPORAL TRENDS IN DISPARITY IN INCIDENCE OF ACS

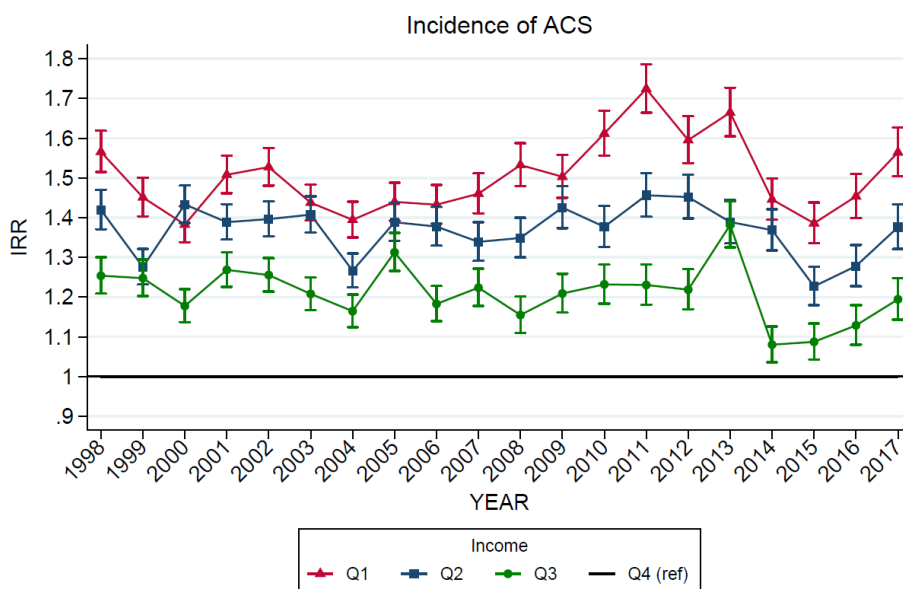
Among the studies on the socioeconomic disparity in the incidence of ACS identified in the systematic literature review (Study I), eight studies investigated time trends in socioeconomic disparity in the incidence of ACS in Norway, Sweden, the United Kingdom, the Netherlands, and Germany. More specifically, 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.<sup>6,131,168,171,175,181,191,193</sup> Also, no significant change was identified in socioeconomic disparity in the incidence of UAP.<sup>191</sup> 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.<sup>171</sup> 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.<sup>115</sup>



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.<sup>115</sup> 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.<sup>115</sup>

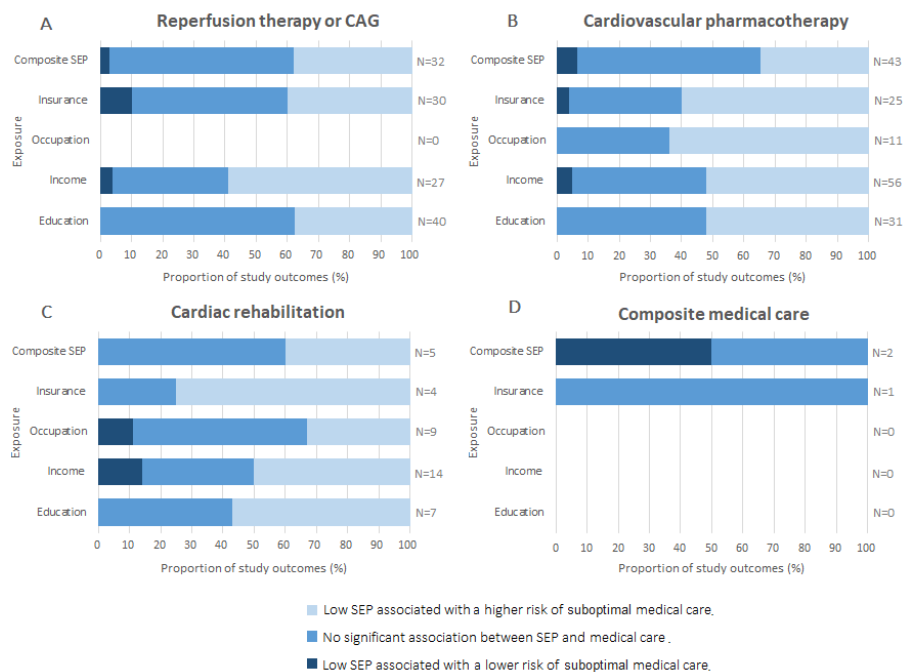


**Figure 4-5 Standardized Incidence rate ratios of ACS in Denmark according to personal income quartile.** Analyses were standardized according to year, sex, and age-group, and the results are presented with 95% confidence intervals. Abbreviations: ACS: acute coronary syndrome, IRR: incidence rate ratio, 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.<sup>115</sup>

#### 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*).<sup>114</sup> The odds ratios (ORs) were ranging from 1.8 to 3.9.<sup>201-205</sup> 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.<sup>114</sup> None of the identified studies investigated temporal trends in socioeconomic disparity in the prevalence of ACS.

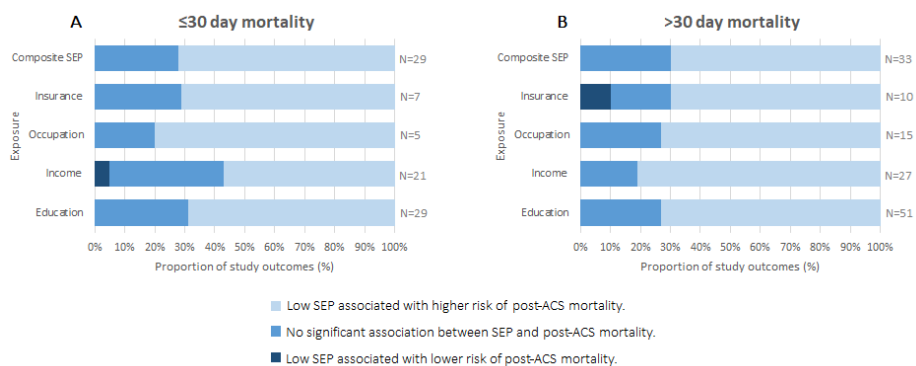


**Figure 4-6 Medical care categories after ACS according to the SEP indicator.** The figure illustrates the associations identified from the included studies according to exposure and A) reperfusion therapy or CAG, B) cardiovascular pharmacotherapy, C) cardiac rehabilitation, and D) composite medical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

## 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).<sup>114</sup> 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.<sup>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</sup> 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.<sup>114</sup> Four of the identified studies investigated temporal trends in medical care in the United Kingdom, Italy, Australia, and Denmark.<sup>220,243,256,260</sup> 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*).<sup>220,243,256,260</sup>

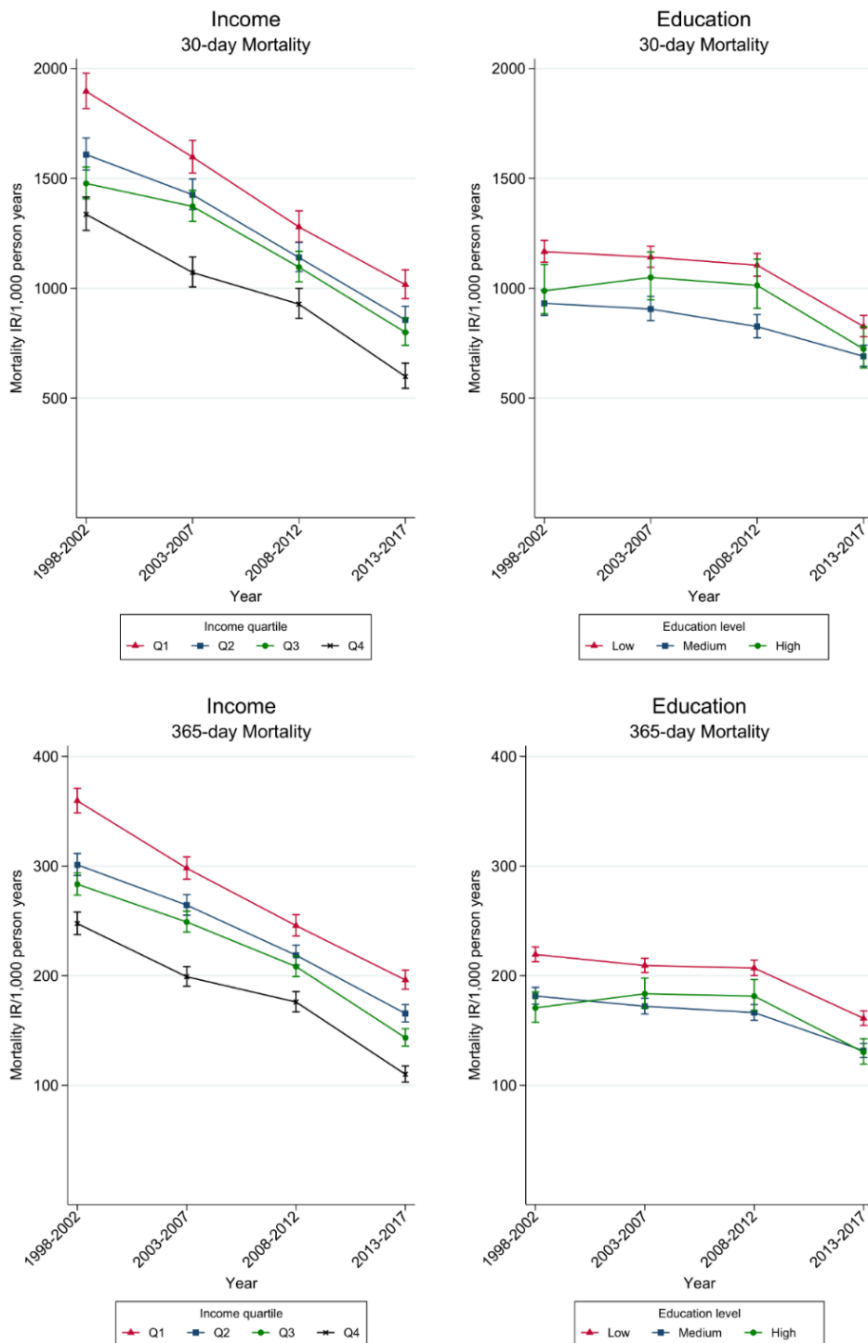


**Figure 4-7 Short- and long-term mortality in patients with ACS according to SEP indicator.** The figure illustrates the associations identified from the included studies according to exposure and A)  $\leq 30$ -day mortality, or B)  $> 30$ -day mortality. Abbreviations: ACS: acute coronary syndrome,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

## 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*).<sup>114</sup> 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*).<sup>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</sup> 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.<sup>114</sup>

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.<sup>116</sup> 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.<sup>116</sup> 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.<sup>116</sup>



**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).<sup>116</sup>

#### 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*).<sup>220,260,293,309</sup>

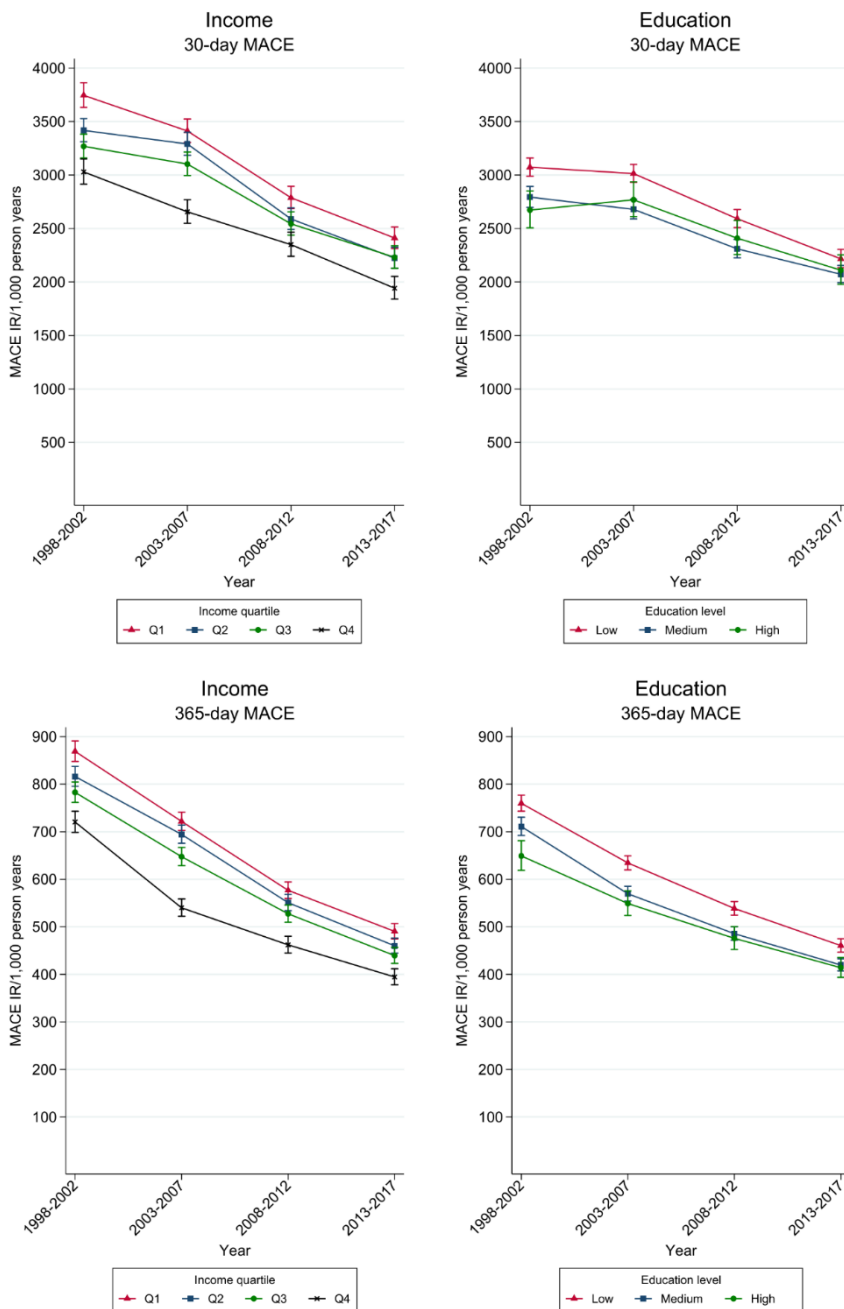
Study III also investigated temporal trends in income and educational disparity in all-cause mortality within 30- and 365-days after ACS. The socioeconomic disparity was present across the entire period when comparing patients from the lowest income quartile or educational level to those from the highest (*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)<sup>114</sup>. 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.<sup>134,300,303,314</sup> 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.<sup>116</sup> 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.<sup>116</sup> 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.<sup>116</sup>

TIME TRENDS IN INCIDENCE, TREATMENT, AND CLINICAL OUTCOMES ACCORDING TO SOCIOECONOMIC POSITION IN PATIENTS WITH ACUTE CORONARY SYNDROME



**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).<sup>116</sup>

#### **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.<sup>116</sup>





## 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.<sup>114</sup> 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.<sup>115</sup> 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.<sup>116</sup>

### 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.<sup>114,115</sup> 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.<sup>114</sup> 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,<sup>92</sup> with no studies recurring in Study I.<sup>114</sup> 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.<sup>93</sup> 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.<sup>12,57,76</sup> 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.<sup>115</sup>

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.<sup>67,69</sup> 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.<sup>96,131</sup> Hence, the DNPR captures disparity in hospital ACS admissions which may not necessarily be equal to the total population-based ACS incidence.<sup>96</sup> 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.<sup>115</sup> A few previous studies have also investigated socioeconomic disparity in fatal out-of-hospital MI.<sup>5,179,186</sup> However, the approach of including all deaths without a registered reason was not previously been applied in any identified studies.<sup>114,115</sup> 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.<sup>115,125</sup>

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.<sup>114,115</sup> Especially, considering the focus on minimizing health disparity, both on the global level,<sup>38,325</sup> and the national level in Denmark.<sup>11,101,107–109</sup> 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.<sup>38,115,325</sup> 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.<sup>171</sup> 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.<sup>131,168,175,181,191,193,326</sup> 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.<sup>168,191,326</sup> However, above that, no studies found changes in socioeconomic disparity in the incidence of ACS.<sup>6,131,168,175,181,191,193</sup> 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.<sup>92,114</sup> 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.<sup>53,327,328</sup> 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.<sup>79,329</sup> Furthermore, access to emergency care, invasive care, and guideline-recommended cardiovascular pharmacotherapy at hospital discharge, generally presents more barriers in low-income countries.<sup>79,329,330</sup> 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,<sup>195,200</sup> and both middle- and low-income countries were barely represented among previous studies within this field.<sup>92</sup> The two studies investigated and found disparity in the incidence of MI according to income, education, and occupation.<sup>195,200</sup> Furthermore, mechanisms in socioeconomic disparities in ACS could potentially also differ substantially across the high- and middle-high-income countries with different healthcare systems.<sup>92,331</sup> 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.<sup>329,330,332,333</sup>

According to a fundamental cause theory, disparity in health 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.<sup>11,18,24</sup> 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.<sup>11,18,24</sup> The disparity in disposable income have been increasing in Denmark during the last decades, resulting in an increase in the Gini-coefficient.<sup>42,43</sup> 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.<sup>114</sup> 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.<sup>114</sup> 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.<sup>7,94</sup> 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.<sup>7</sup> The definition of suboptimal medical care used in Study I, is based on indicators for receiving a certain care.<sup>114</sup> 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.<sup>114</sup>

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,  $\beta$ -blockers or clopidogrel) identifying various patterns with different directions of change in the disparity.<sup>220,243,256,260</sup> 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.<sup>7,62,80</sup> 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.<sup>260,334</sup> 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.<sup>260,334</sup> 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.<sup>66,69</sup> 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.<sup>260</sup> 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.<sup>335,336</sup> 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.<sup>114,239,268</sup> Except for one study, finding disparity in statins and  $\beta$ -blockers after MI according to income and education from 1995-2001,<sup>337</sup> 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.<sup>95,96,114</sup> This could of course 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.<sup>114,116</sup> 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.<sup>93</sup> 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.<sup>7,94,199,245,267</sup> 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.<sup>114-116</sup> 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.<sup>20-22,24</sup> 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.<sup>18,52,53</sup> 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.<sup>18,52,53,338</sup>

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.<sup>116</sup> Previous studies investigating temporal trends in socioeconomic disparity in mortality after ACS have identified small declines in the disparity until 2007 or persistence.<sup>14-16,25-29</sup> 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.<sup>116</sup>

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.<sup>114,239,260,261,268</sup> 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.<sup>339,340</sup> 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.<sup>17,37</sup>

## 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.<sup>16,19,20</sup> 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.<sup>16,19,20</sup> 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.<sup>17,114</sup> 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.<sup>114</sup> 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.<sup>114</sup> 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.<sup>115,116</sup> The income was based on the disposable taxable income data one year before the year of the incident ACS.<sup>115,116</sup> 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.<sup>17,19,122</sup> However, this permitted the use of nation-based income quartiles from the Danish background population according to age, sex, and specific year.<sup>122</sup>

In Study III, SEP was also included using the highest completed educational level before the incident ACS.<sup>116</sup> However, among the included patients with ACS, educational data was missing for 37% and missing were strongly correlated with year and patient age.<sup>116</sup> 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.<sup>30,42,115</sup> 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.<sup>17,19,116,122</sup> Although data was available in Study III, employment status was included as a covariate rather than an exposure.<sup>116</sup> 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.<sup>19,20,116</sup> 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.<sup>114</sup> 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.<sup>17,19,20</sup> However, national and international detailed standards for defining and investigating socioeconomic disparity are requested to enable proper accumulations of effects across studies and nations.<sup>16</sup>

### 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.<sup>114,341</sup> 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.<sup>92</sup> This sort of analysis was not applied in Study I, due to the acknowledgment of the heterogeneity of the studies included.<sup>114</sup> However, publication bias may be a bigger concern, when summarizing accumulated effects in a meta-analysis, than, when presenting results in the narrative synthesis.<sup>114</sup> However, Study I included multiple studies representing statistically insignificant and inconsistent results, both regarding incidence, medical care, and clinical outcomes of ACS.<sup>161,208,223,224,235,236</sup> 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.<sup>13,15,114</sup> Additionally, it is worth noticing that the included studies with a lower risk of bias, according to the classification from the Cochrane tools to assess 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.<sup>114</sup>

### 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.<sup>114,138-141</sup> 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.<sup>114</sup>

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.<sup>96</sup> 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.<sup>96,342</sup> However, if patients died from ACS without hospital admission or survived an unrecognized ACS, this would not be captured in the DNPR.<sup>96,343</sup> 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.<sup>114,138–141</sup>

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.<sup>115,144</sup> 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.<sup>115,144</sup> 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.<sup>96,131</sup> Hence, the DNPR may capture acute ACS admissions rather than the exact onset of population-based ACS incidence.<sup>96</sup> 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.<sup>125,344</sup> 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.<sup>125</sup> 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.<sup>343</sup> 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.<sup>96,345</sup> 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.<sup>345,346</sup> 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.<sup>44,123</sup>

### 5.3.5. CONFOUNDING AND MEDIATION

Confounding is a concern in all observational studies and attention towards measured and unmeasured confounding is important.<sup>143</sup> 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.<sup>114,138–141</sup> 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.<sup>114</sup> 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.<sup>114</sup>

Construction of causal diagrams was used, to identify whether the investigated associations were expected to be confounded in Study II-III.<sup>115,116,143</sup> 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.<sup>115</sup> 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.<sup>116,143</sup> 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.<sup>116</sup> 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 patient 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.<sup>116</sup> 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.<sup>116</sup>

### **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.<sup>115,116</sup> 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.<sup>45</sup> 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.<sup>114</sup> 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.

TIME TRENDS IN INCIDENCE, TREATMENT, AND CLINICAL OUTCOMES ACCORDING TO SOCIOECONOMIC POSITION IN PATIENTS WITH ACUTE CORONARY SYNDROME

## 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.

## REFERENCES

1. Al-Sharifi F, Frederiksen HW, Rossau HK, et al. Access to cardiac rehabilitation and the role of language barriers in the provision of cardiac rehabilitation to migrants. *BMC Health Serv Res* 2019; 19: 1–8.
2. Hodzic E, Perla S, Iglia A, et al. Seasonal Incidence of Acute Coronary Syndrome and Its Features. *Mater Socio Medica* 2018; 30: 10.
3. Sanchis-Gomar F, Perez-Quilis C, Leischik R, et al. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med* 2016; 4: 1–12.
4. Ignatiuk B. Socioeconomic status as a cardiovascular risk modulator: An emerging target for interventions. *Int J Cardiol* 2022; 361: 101–102.
5. Koopman C, Vaartjes I, Heintjes EM, et al. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment of coronary heart disease, 1998-2010. *Eur Heart J* 2013; 34: 3198–3205.
6. Yang D, Dzayee DA, Beiki O, et al. Incidence and case fatality after day 28 of first time myocardial infarction in Sweden 1987-2008. *Eur J Prev Cardiol* 2011; 19: 1304–1315.
7. Hyun KK, Brieger D, Woodward M, et al. The effect of socioeconomic disadvantage on prescription of guideline-recommended medications for patients with acute coronary syndrome: Systematic review and meta-analysis. *Int J Equity Health* 2017; 16: 1–10.
8. Akator AE, Blais C, Gamache P, et al. Exposure to guideline-recommended drugs after a first acute myocardial infarction in older adults: does deprivation matter? *Pharmacoepidemiol Drug Saf* 2020; 29: 141–149.
9. Winkleby MA, Jatulis DE, Frank E, et al. Socioeconomic status and health: How education, income, and occupation contribute to risk factors for cardiovascular disease. *Am J Public Health* 1992; 82: 816–820.
10. Blaxter M. Health and Social Class. *Lancet* 1987; July 4: 30–33.
11. Diderichsen F, Andersen I, Manuel C. Health Inequality - determinants and policies. *Scand J Public Health* 2012; 40: 12–105.
12. Hyun K, Redfern J, Woodward M, et al. Socioeconomic Equity in the Receipt of In-Hospital Care and Outcomes in Australian Acute Coronary Syndrome Patients: The CONCORDANCE Registry. *Hear Lung Circ* 2018; 27: 1398–1405.
13. World Health Organisation. Social Determinants of Health, [https://www.who.int/social\\_determinants/thecommission/finalreport/key\\_concepts/en/](https://www.who.int/social_determinants/thecommission/finalreport/key_concepts/en/) (2014, accessed 21 August 2020).
14. Thorup H, Frandsen K, Larsen HS, et al. *Forskelle i behandlingskvaliteten på sygehuse.* Rigsrevisionens beretning afgivet til Statsrevisorerne., [https://www.ft.dk/da/statsrevisorerne/nyheder/2019/01/behandlingskvalitete\\_n\\_paa\\_sygehuse](https://www.ft.dk/da/statsrevisorerne/nyheder/2019/01/behandlingskvalitete_n_paa_sygehuse) (2019, accessed 21 August 2021).
15. World Health Organization. Health inequities and their causes, <https://www.who.int/news-room/facts-in-pictures/detail/health-inequities->

- and-their-causes (2018, accessed 5 August 2022).
16. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007; 81–82: 21–37.
  17. Mackenbach JP. The persistence of health inequalities in modern welfare states: The explanation of a paradox. *Soc Sci Med* 2012; 75: 761–769.
  18. Phelan JC, Link BG, Tehranifar P. Social Conditions as Fundamental Causes of Health Inequalities: Theory, Evidence, and Policy Implications. *J Health Soc Behav* 2010; 51: S28–S40.
  19. Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health* 2006; 60: 7–12.
  20. Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 2). *J Epidemiol Community Health* 2006; 60: 95–101.
  21. Eikemo TA, Huijts T, Bambra C, et al. *Social Inequalities in Health and their Determinants - Topline Results from Round 7 of the European Social Survey*, [http://www.europeansocialsurvey.org/docs/findings/ESS7\\_toplines\\_issue\\_6\\_health.pdf](http://www.europeansocialsurvey.org/docs/findings/ESS7_toplines_issue_6_health.pdf) (2016).
  22. Immergut EM, Anderson KM, Devitt C, et al. *Health Politics in Europe: A Handbook*. Oxford University Press, 2021. Epub ahead of print 2021. DOI: <https://doi.org/10.1093/oso/9780198860525.003.0009>.
  23. Pampel FC, Krueger PM, Denney JT. Socioeconomic Disparities in Health Behaviors. *NIH Public Access* 2010; 36: 349–370.
  24. Diderichsen F, Evans T, Whitehead M. The Social Basis of Disparities. In: *Challenging inequities in health. From ethics to action*. 2001, pp. 12–23.
  25. Krieger N, Williams DR, Moss NE. Measuring social class in us public health research: Concepts, methodologies, and guidelines. *Annu Rev Public Health* 1997; 18: 341–378.
  26. Statistics Denmark. *Documentation of statistics for Income Statistics 2021*, <https://www.dst.dk/Site/Dst/SingleFiles/GetArchiveFile.aspx?fi=53186105886&fo=0&ext=kvaldel> (2021).
  27. Bleich SN, Jarlenski MP, Bell CN, et al. Health inequalities: Trends, progress, and policy. *Annu Rev Public Health* 2012; 33: 7–40.
  28. Allin S, Masseria C, Mossialos E. Measuring socioeconomic differences in use of health care services by wealth versus by income. *Am J Public Health* 2009; 99: 1849–1855.
  29. United Nations Educational Scientific and Cultural Organization. *International Standard Classification of Education ISCED*, [http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-1997-en\\_0.pdf](http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-1997-en_0.pdf) (1997).
  30. United Nations Educational Scientific and Cultural Organization. *International Standard Classification of Education (ISCED)*, [https://ec.europa.eu/eurostat/statistics-explained/index.php?title=International\\_Standard\\_Classification\\_of\\_Education\\_\(ISCED\)#Implementation\\_of\\_ISCED\\_2011\\_.28levels\\_of\\_education.29](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=International_Standard_Classification_of_Education_(ISCED)#Implementation_of_ISCED_2011_.28levels_of_education.29) (2011, accessed 10 January 2021).
  31. Lu N, Samuels ME, Wilson R. Socioeconomic differences in health: How much do health behaviors and health insurance coverage account for? *J*



- Health Care Poor Underserved* 2004; 15: 618–630.
32. Dickman SL, Himmelstein DU, Woolhandler S. Inequality and the health-care system in the USA. *Lancet* 2017; 389: 1431–1441.
  33. Kilpi F, Silventoinen K, Konttinen H, et al. Early-life and adult socioeconomic determinants of myocardial infarction incidence and fatality. *Soc Sci Med* 2017; 177: 100–109.
  34. Upadhyay R, Gohel BM, Chudasama RK. Determinants of Myocardial Infarction in Saurashtra Region, Gujarat: A Case–control Study. *Indian J Community Med* 2017; 42: 147–50.
  35. Whitehead M. The concepts and principles of equity and health. *Int J Heal Serv* 1992; 22: 429–445.
  36. OECD. *An overview of income inequalities in OECD countries: Main findings*, <https://www.ingentaconnect.com/content/oecd/16815378/2011/00002011/0000014/8111111ec003%0Awww.oecd.org/els/social/inequality%0Ahttps://www.oecd.org/els/soc/49499779.pdf> (2011).
  37. OECD. *Health for Everyone? Social inequalities in health and health systems*. 2019. Epub ahead of print 2019. DOI: 10.1097/00000446-194504000-00011.
  38. Mackenbach JP, Kulháňová I, Artnik B, et al. Changes in mortality inequalities over two decades: Register based study of European countries. *BMJ* 2016; 353: 1–8.
  39. Mackenbach JP, Valverde JR, Artnik B, et al. Trends in health inequalities in 27 European countries. *Proc Natl Acad Sci U S A* 2018; 115: 6440–6445.
  40. Zimmerman FJ, Anderson NW. Trends in Health Equity in the United States by Race/Ethnicity, Sex, and Income, 1993-2017. *JAMA Netw Open* 2019; 4–13.
  41. Tönnies T, Pohlabein H, Eichler M, et al. Relative and absolute socioeconomic inequality in smoking: time trends in Germany from 1995 to 2013. *Ann Epidemiol* 2021; 53: 89-94.e2.
  42. Statistics Denmark. [statbank.dk/FOLK1A, http://statbank.dk/statbank5a/default.asp?w=1920](http://statbank.dk/statbank5a/default.asp?w=1920) (2016, accessed 15 February 2022).
  43. Danmarks Statistik. *Ulighedsmål: Gini-koefficient*, [https://www.dst.dk/Site/Dst/SingleFiles/GetArchiveFile.aspx?fi=arbejde-loen-og-indkomst&fo=gini\\_2--pdf&ext=%7B2%7D](https://www.dst.dk/Site/Dst/SingleFiles/GetArchiveFile.aspx?fi=arbejde-loen-og-indkomst&fo=gini_2--pdf&ext=%7B2%7D) (2019, accessed 5 November 2022).
  44. Mainz J, Hess MH, Johnsen SP. The Danish unique personal identifier and the Danish Civil Registration System as a tool for research and quality improvement. *Int J Qual Heal Care* 2019; 31: 717–720.
  45. Mackenbach JP. Nordic paradox, Southern miracle, Eastern disaster: Persistence of inequalities in mortality in Europe. *Eur J Public Health* 2017; 27: 14–17.
  46. Ministry of Health, Healthcare Denmark. *Healthcare in Denmark*, <http://www.sum.dk> (2017).
  47. Gadeberg AK, Andersen I, Brønnum-Hansen H, et al. Indsatser mod ulighed i sundhed. 2020; 1, 8.

48. Udesen CH, Skaarup C, Petersen MNS, et al. *Social Inequality in Health and Disease 2010-2017: The Danish Health Authority [Social ulighed i sundhed og sygdom 2010 - 2017: Sundhedsstyrelsen]*. 2020.
49. Koch MB, Diderichsen F, Grønbæk M, et al. What is the association of smoking and alcohol use with the increase in social inequality in mortality in Denmark? A nationwide register-based study. *BMJ Open* 2015; 5: 1–9.
50. Nordahl H, Lange T, Osler M, et al. Education and cause-specific mortality: The mediating role of differential exposure and vulnerability to behavioral risk factors. *Epidemiology* 2014; 25: 389–396.
51. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011; 39: 95–98.
52. Ruff CT, Braunwald E. The evolving epidemiology of acute coronary syndromes. *Nat Rev Cardiol* 2011; 8: 140–147.
53. World Health Organization. The top 10 causes of death, <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death> (2020, accessed 15 December 2020).
54. Koch MB, Davidsen M, Andersen L V., et al. Increasing prevalence despite decreasing incidence of ischaemic heart disease and myocardial infarction. A national register based perspective in Denmark, 1980-2009. *Eur J Prev Cardiol* 2015; 22: 189–195.
55. Abbasi SH, De Leon AP, Kassaian SE, et al. Socioeconomic status and in-hospital mortality of acute coronary syndrome: Can education and occupation serve as preventive measures? *Int J Prev Med* 2015; 2015-May: 36.
56. Décano IR, Marrugat J, Grau M, et al. The association between education and cardiovascular disease incidence is mediated by hypertension, diabetes, and body mass index. *Sci Rep* 2017; 7: 1–8.
57. Neumann JT, Goßling A, Sörensen NA, et al. Temporal trends in incidence and outcome of acute coronary syndrome. *Clin Res Cardiol* 2020; 109: 1186–1192.
58. Hjerteforeningen. HjerTeTal.dk. 30. august, <https://hjerteforeningen.dk/alt-om-dit-hjerTe/hjertetal/hjertetal.dk/> (2019).
59. Kjærulff TM, Bihrmann K, Zhao J, et al. Acute myocardial infarction: Does survival depend on geographical location and social background? *Eur J Prev Cardiol* 2019; 26: 1828–1839.
60. Makki N, Brennan TM, Girotra S. Acute coronary syndrome. *J Intensive Care Med* 2015; 30: 186–200.
61. Roche JJW, Wenn RT, Sahota O, et al. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. *BMJ* 2005; 331: 1374.
62. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; 42: 1289–1367.
63. Fagring AJ, Lappas G, Kjellgren KI, et al. Twenty-year trends in incidence and 1-year mortality in Swedish patients hospitalised with non-AMI chest pain. Data from 1987-2006 from the Swedish hospital and death registries.

- Heart* 2010; 96: 1043–1049.
64. Thrane PG, Kristensen SD, Olesen KKW, et al. 16-year follow-up of the Danish Acute Myocardial Infarction 2 (DANAMI-2) trial: Primary percutaneous coronary intervention vs. fibrinolysis in ST-segment elevation myocardial infarction. *Eur Heart J* 2020; 41: 847–854.
  65. Moon JCC, Kalra PR, Coats AJS. DANAMI-2: Is primary angioplasty superior to thrombolysis in acute MI when the patient has to be transferred to an invasive centre? *Int J Cardiol* 2002; 85: 199–201.
  66. Andersen HR, Nielsen TT, Rasmussen K, et al. A Comparison of Coronary Angioplasty with Fibrinolytic Therapy in Acute Myocardial Infarction. *N Engl J Med* 2003; 349: 733–742.
  67. Thorsted Sørensen J, Steengaard C, Holmvang L, et al. [Primary percutaneous coronary intervention as a national Danish reperfusion strategy of ST-elevation myocardial infarction]. *Ugeskr læger* 2013; 175: 181–185.
  68. Sundhedsstyrelsen DK. Vedr. behandlingen af akut blodprop i hjertet: akut PCI (ballonudvidelse) i Danmark Danmark. 2013; 1–7.
  69. Terkelsen CJ, Jensen LO, Tilsted HH, et al. Primary percutaneous coronary intervention as a national reperfusion strategy in patients with ST-segment elevation myocardial infarction. *Circ Cardiovasc Interv* 2011; 4: 570–576.
  70. Bagnall AJ, Yan AT, Yan RT, et al. Optimal medical therapy for non-ST-segment-elevation Acute coronary syndromes exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. *Circ Cardiovasc Qual Outcomes* 2010; 3: 530–537.
  71. Smedegaard L, Charlot MG, Gislason GH, et al. Temporal trends in acute myocardial infarction presentation and association with use of cardioprotective drugs: A nationwide registry-based study. *Eur Hear J - Cardiovasc Pharmacother* 2018; 4: 93–101.
  72. Rashid M, Fischman DL, Gulati M, et al. Temporal trends and inequalities in coronary angiography utilization in the management of non-ST-Elevation acute coronary syndromes in the U.S. *Sci Rep* 2019; 9: 1–14.
  73. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: An American Heart Assoc. scientific statement from the Council on Clin. Cardiol. (Subcommittee on Exercise, Cardiac Rehabil., and Prevention) and the Council on Nutr., Phys. Activi. *Circulation* 2005; 111: 369–376.
  74. World Health Organization. *Rehabilitation of patients with cardiovascular diseases: report of a WHO Expert Committee [meeting held in Geneva from 23 to 29 July 1963]*, <https://apps.who.int/iris/handle/10665/40577> (1964).
  75. Graversen CB, Eichhorst R, Ravn L, et al. Social inequality and barriers to cardiac rehabilitation in the rehab-North register. *Scand Cardiovasc J* 2017; 51: 316–322.
  76. Schmidt M, Jacobsen JB, Lash TL, et al. 25 Year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: A Danish nationwide cohort study. *BMJ*; 344. Epub ahead of print 2012. DOI:

- 10.1136/bmj.e356.
77. Wang J li, Guo C yan, Chen H, et al. Improvement of long-term clinical outcomes by successful PCI in the very elderly women with ACS. *BMC Cardiovasc Disord* 2021; 21: 1–11.
  78. Jørgensen ME, Andersson C, Olsen AMS, et al. Danish trends in pharmacotherapy, comorbidities, and demographics in patients referred for coronary angiography: What changed during a decade? *Eur Hear J - Cardiovasc Pharmacother* 2015; 1: 157–165.
  79. Shimony A, Grandi SM, Pilote L, et al. Utilization of evidence-based therapy for acute coronary syndrome in high-income and low/middle-income countries. *Am J Cardiol* 2014; 113: 793–797.
  80. Ibanez B, James S. The 2017 ESC STEMI Guidelines. *Eur Heart J* 2018; 39: 79–82.
  81. McCartney D, Scarborough P, Webster P, et al. Trends in social inequalities for premature coronary heart disease mortality in Great Britain, 1994–2008: A time trend ecological study. *BMJ Open* 2012; 2: 1–7.
  82. Page A, Lane A, Taylor R, et al. Trends in socioeconomic inequalities in mortality from ischaemic heart disease and stroke in Australia, 1979–2006. *Eur J Prev Cardiol* 2012; 19: 1281–1289.
  83. Orvin K, Shechter A, Zahger D, et al. Temporal trends and outcome of patients with acute coronary syndrome and prior myocardial infarction. *J Clin Med*; 10. Epub ahead of print 2021. DOI: 10.3390/jcm10235580.
  84. Porter A, Paradkar A, Goldenberg I, et al. Temporal Trends Analysis of the Characteristics, Management, and Outcomes of Women With Acute Coronary Syndrome (ACS): ACS Israeli Survey Registry 2000–2016. *J Am Heart Assoc*; 9. Epub ahead of print 2020. DOI: 10.1161/JAHA.119.014721.
  85. Strand BH, Steingrímssdóttir ÓA, Grøholt E-K, et al. Trends in educational inequalities in cause specific mortality in Norway from 1960 to 2010: a turning point for educational inequalities in cause specific mortality of Norwegian men after the millennium? *BMC Public Health* 2014; 14: 1208.
  86. Ekholm O, Kjølner M, Davidsen M, et al. *Sundhed og sygelighed i Danmark & udviklingen siden 1987, Statens Institut for Folkesundhed. København. 2006.*
  87. Stringhini S, Berkman L, Dugravot A, et al. Socioeconomic status, structural and functional measures of social support, and mortality: The British Whitehall II Cohort Study, 1985–2009. *Am J Epidemiol* 2012; 175: 1275–1283.
  88. Kaplan GA, Salonen JT, Cohen RD, et al. Social connections and mortality from causes and from cardiovascular disease: Prospective evidence from eastern Finland. *American J Epidemiol* 1988; 128: 370–80.
  89. Di Girolamo C, Nusselder WJ, Bopp M, et al. Progress in reducing inequalities in cardiovascular disease mortality in Europe. *Heart* 2019; 40–49.
  90. Ohm J, Skoglund PH, Discacciati A, et al. Socioeconomic status predicts second cardiovascular event in 29,226 survivors of a first myocardial infarction. *Eur J Prev Cardiol* 2018; 25: 985–993.

91. Pilote L, Tu J V., Humphries K, et al. Socioeconomic Status, Access to Health Care, and Outcomes after Acute Myocardial Infarction in Canada's Universal Health Care System. *Med Care* 2007; 45: 638–646.
92. Manrique-Garcia E, Sidorchuk A, Hallqvist J, et al. Socioeconomic position and incidence of acute myocardial infarction: A meta-analysis. *J Epidemiol Community Health* 2011; 65: 301–309.
93. Coughlin SS, Young L. Social Determinants of Myocardial Infarction Risk and Survival: A Systematic Review. *Physiol Behav* 2020; 1: 139–148.
94. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *Int J Cardiol* 2016; 223: 436–443.
95. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014; 29: 541–549.
96. Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish National patient registry: A review of content, data quality, and research potential. *Clin Epidemiol* 2015; 17: 449–490.
97. Uggerby C, Kristensen S, MacKenhauer J, et al. From accreditation to quality improvement - The Danish National Quality Programme. *Int J Qual Heal Care* 2021; 33: 1–3.
98. Zinckernagel L, Schneekloth N, Zwisler ADO, et al. How to measure experiences of healthcare quality in Denmark among patients with heart disease? The development and psychometric evaluation of a patient-reported instrument. *BMJ Open* 2017; 7: 1–13.
99. Sundhedsstyrelsen. *Sundhedskompetence i det danske sundhedsvæsen - En vej til mere lighed*, <https://www.sst.dk/da/Udgivelser/2022/Sundhedskompetence-i-det-danske-sundhedsvaesen> (2022).
100. Pedersen KM, Christiansen T, Bech M. The Danish health care system: Evolution - Not revolution - In a decentralized system. *Health Econ*; 14. Epub ahead of print 2005. DOI: 10.1002/hec.1028.
101. Diderichsen F, Andersen I, Manuel C. *Ulighed i sundhed – årsager og indsatser*. København, 2011. Epub ahead of print 2011. DOI: 978-87-7601-340-0.
102. Mackenbach JP, Rubio Valverde J, Bopp M, et al. Progress against inequalities in mortality: register-based study of 15 European countries between 1990 and 2015. *Eur J Epidemiol*. Epub ahead of print 2019. DOI: 10.1007/s10654-019-00580-9.
103. Danish Ministry of Health. *The Super Hospital Programme*, <https://sum.dk/Media/0/2/TheDanishSuperHospitalProgramme2021.pdf> (2021).
104. Olejaz M, Juul Nielsen A, Rudkjøbing A, et al. *Denmark - health system review.*, <https://apps.who.int/iris/bitstream/handle/10665/330321/HiT-14-2-2012-eng.pdf?sequence=5&isAllowed=y> (2012).
105. Carstensen K, Kjeldsen AM, Lou S, et al. The Danish health care quality programme: Creating change through the use of quality improvement collaboratives. *Health Policy (New York)* 2022; 126: 749–754.

106. Mainz J, Kristensen S, Bartels P. Quality improvement and accountability in the Danish health care system. *Int J Qual Heal Care* 2015; 27: 523–527.
107. Government of Denmark. *Regeringens folkesundhedsprogram 1999–2008. Et handlingsorienteret program for sundere rammer i hverdagen*, <https://sum.dk/Media/E/C/Regeringens-folkesundhedsprogram-1999-2008.pdf> (1999).
108. The Ministry of Health. *Sund hele livet - de nationale mål og strategier for folkesundheden 2002-10*, <https://sum.dk/publikationer/2002/september/sund-hele-livet> (2002).
109. Regeringen. Sundhedspakke 2009. 2009; 1–36.
110. Andersen NS, Jensen JM, Sejr-Knudsen A, et al. Hjertepakken forkorter udredningsforløbet for patienter med iskæmisk hjertesygdom. *Ugeskr Laeger* 2011; 173: 798–801.
111. Özcan C, Juel K, Lassen JF, et al. The Danish Heart Registry. *Clin Epidemiol* 2016; 8: 503–508.
112. Abildstrøm SZ, Madsen M. The Danish heart register. *Scand J Public Health* 2011; 39: 46–49.
113. Flojstrup M, Bogh SBB, Bech M, et al. Mortality before and after reconfiguration of the Danish hospital-based emergency healthcare system: a nationwide interrupted time series analysis. *BMJ Qual Saf* 2022; 1–12.
114. Simoni AH, Frydenlund J, Kragholm KH, et al. Socioeconomic inequity in incidence, outcomes and care for acute coronary syndrome: A systematic review. *Int J Cardiol* 2022; 356: 19–29.
115. Simoni AH, Kragholm KH, Bøggild H, et al. Time Trends in Income-related Inequity in Incidence of Acute Coronary Syndrome. *[Manuscript Submitt.*
116. Simoni AH, Valentin JB, Kragholm KH, et al. Temporal trends in socioeconomic disparity in clinical outcomes for patients with acute coronary syndrome. *[Manuscript Submitt.*
117. United States National Institutes of Health’s National Library of Medicine. PubMed ®. *[internet]*, <https://pubmed.ncbi.nlm.nih.gov/>.
118. Elsevier. Embase. *[internet]*, <https://www.elsevier.com/solutions/embase-biomedical-research>.
119. Frandsen TF, Eriksen MB, Hammer DMG, et al. Using Embase as a supplement to PubMed in Cochrane reviews differed across fields. *J Clin Epidemiol* 2021; 133: 24–31.
120. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; 5: 1–10.
121. Simoni AH, Frydenlund JKS, Kragholm KH, et al. Associations between socioeconomic position, acute coronary syndrome, and outcomes: a Systematic review. *PROSPERO* 2020; 1–4.
122. Statistics Denmark. Documentation of statistics for Income Statistics, [http://www.dst.dk/Site/Dst/SingleFiles/kvaldekIbilag.aspx?filename=bf42084f-2efb-4091-a5e1-e196f1df4e98Income\\_Statistics\\_2016](http://www.dst.dk/Site/Dst/SingleFiles/kvaldekIbilag.aspx?filename=bf42084f-2efb-4091-a5e1-e196f1df4e98Income_Statistics_2016) (2016).
123. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; 39: 22–25.
124. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system

- and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019; 11: 563–591.
125. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health* 2011; 39: 26–29.
  126. Statistics Denmark. *Indkomster 2010 (DK)*, <http://www.dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=16210&sid=indk> (2010).
  127. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; 39: 38–41.
  128. Jensen VM, Rasmussen AW. *The Danish education registers*. 2011. Epub ahead of print 2011. DOI: 10.1177/1403494810394715.
  129. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, et al. Existing data sources for clinical epidemiology: The Danish National database of reimbursed prescriptions. *Clin Epidemiol* 2012; 4: 303–313.
  130. Rauch B. Socioeconomic status: A powerful but still neglected modulator of cardiovascular risk. *Eur J Prev Cardiol* 2018; 25: 981–984.
  131. Malki N, Koupil I, Eloranta S, et al. Temporal Trends in Incidence of Myocardial Infarction and Ischemic Stroke by Socioeconomic Position in Sweden 1987 – 2010. *PLoS One* 2014; 9: e105279.
  132. Kareem H, Shetty PN, Devasia T, et al. Impact of socioeconomic status on adverse cardiac events after coronary angioplasty: A cohort study. *Heart Asia* 2018; 10: 1–5.
  133. Setia MS. Methodology series module 3: Cross-sectional studies. *Indian J Dermatol* 2016; 61: 261–264.
  134. Jakobsen L, Niemann T, Thorsgaard N, et al. Dimensions of socioeconomic status and clinical outcome after primary percutaneous coronary intervention. *Circ Cardiovasc Interv* 2012; 5: 641–648.
  135. Poudel I, Tejpal C, Rashid H, et al. Major Adverse Cardiovascular Events: An Inevitable Outcome of ST-elevation myocardial infarction? A Literature Review. *Cureus*; 11. Epub ahead of print 2019. DOI: 10.7759/cureus.5280.
  136. Wang M, Vaez M, Dorner TE, et al. Sociodemographic, labour market marginalisation and medical characteristics as risk factors for reinfarction and mortality within 1 year after a first acute myocardial infarction: A register-based cohort study of a working age population in Sweden. *BMJ Open*; 9. Epub ahead of print 2019. DOI: 10.1136/bmjopen-2019-033616.
  137. Attar R, Valentin JB, Andell P, et al. Major adverse cardiovascular events following acute coronary syndrome in patients with bipolar disorder Rubina. *Int J Cardiol* 2022; Jun 15: S0167-5273(22)00937–8.
  138. Cochrane Bias Methods Group, CLARITY Working Group. Tools to Assess Risk of Bias in Cohort Studies. *The Cochrane Collaboration* 2013; 1–8.
  139. Cochrane Bias Methods Group. Tool to assess risk of bias in cohort studies., <http://methods.cochrane.org/sites/methods.cochrane.org/bias/files/uploads/Tool to Assess Risk of Bias in Cohort Studies.pdf> (2013, accessed 11 September 2020).
  140. Cochrane Bias Methods Group, CLARITY Working Group McMaster University. Tool to Assess Risk of Bias in Case Control Studies. *The*

- Cochrane Collaboration* 2013; 1–5.
141. Cochrane Bias Methods Group, CLARITY Group at McMaster University. Risk of bias instrument for cross-sectional surveys of attitudes and practices. *The Cochrane Collaboration* 2013; 1–5.
  142. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987; 40: 373–383.
  143. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008; 8: 1–15.
  144. Vandembroucke JP, Pearce N. Incidence rates in dynamic populations. *Int J Epidemiol* 2012; 41: 1472–1479.
  145. Julious SA, Nicholl J, George S. Why do we continue to use standardized mortality ratios for small area comparisons? *J Public Health Med* 2001; 23: 40–46.
  146. Zhang Z, Kim HJ, Lonjon G, et al. Balance diagnostics after propensity score matching. *Ann Transl Med* 2019; 7: 16–16.
  147. Kang JDY, Schafer JL. Demystifying double robustness: A comparison of alternative strategies for estimating a population mean from incomplete data. *Stat Sci* 2007; 22: 523–539.
  148. Simera I, Moher D, Hoey J, et al. A catalogue of reporting guidelines for health research. *Eur J Clin Invest* 2010; 40: 35–53.
  149. Welch V, Petticrew M, Tugwell P, et al. PRISMA-Equity 2012 Extension: Reporting Guidelines for Systematic Reviews with a Focus on Health Equity. *PLoS Med*; 9. Epub ahead of print 2012. DOI: 10.1371/journal.pmed.1001333.
  150. Welch V, Petticrew M, Petkovic J, et al. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): Explanation and elaboration. *J Clin Epidemiol* 2016; 70: 68–89.
  151. Benchimol EI, Smeeth L, Guttman A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med* 2015; 12: 1–22.
  152. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344–349.
  153. World Bank Group. World Bank Country and Lending Groups. *Country Classification*, <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups> (2021, accessed 31 August 2021).
  154. Hamad R, Öztürk B, Foverskov E, et al. Association of Neighborhood Disadvantage with Cardiovascular Risk Factors and Events among Refugees in Denmark. *JAMA Netw Open* 2020; 3: 1–14.
  155. Pearson-Stuttard J, Bajekal M, Scholes S, et al. Recent UK trends in the unequal burden of coronary heart disease. *Heart* 2012; 98: 1573–1582.
  156. Grey C, Jackson R, Wells S, et al. Twenty-eight day and one-year case fatality after hospitalisation with an acute coronary syndrome: a nationwide data linkage study. *Aust N Z J Public Heal* 2014; 38: 216–220.



157. Bhavsar NA, Gao A, Phelan M, et al. Value of Neighborhood Socioeconomic Status in Predicting Risk of Outcomes in Studies That Use Electronic Health Record Data. *JAMA Netw Open* 2018; 1: e182716.
158. Carlsson AC, Li X, Holzmann MJ, et al. Neighbourhood socioeconomic status and coronary heart disease in individuals between 40 and 50 years. *Heart* 2016; 102: 775–782.
159. Agyemang C, van Oeffelen AAM, Bots ML, et al. Socioeconomic inequalities in acute myocardial infarction incidence in migrant groups: has the epidemic arrived? analysis of nation-wide data. *Heart* 2014; 100: 239–246.
160. Andersson J, Wennberg P, Lundblad D, et al. Diabetes mellitus, high BMI and low education level predict sudden cardiac death within 24 hours of incident myocardial infarction. *Eur J Prev Cardiol* 2016; 23: 1814–1820.
161. Carls GS, Henke RM, Karaca Z, et al. The Relationship between Local Economic Conditions and Acute Myocardial Infarction Hospital Utilization by Adults and Seniors in the United States, 1995-2011. *Heal Serv Res* 2015; 50: 1688–1709.
162. Carter AR, Gill D, Davies NM, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. *Bmj* 2019; 365: 11855.
163. Chen L, Tan Y, Yu C, et al. Educational disparities in ischaemic heart disease among 0.5 million Chinese adults: A cohort study. *J Epidemiol Community Health* 2021; 1–11.
164. Cheraghian B, Nedjat S, Mansournia MA, et al. Different patterns of association between education and wealth with non-fatal myocardial infarction in Tehran, Iran: A population-based case-control study. *Med J Islam Repub Iran* 2015; 29: 160.
165. Chew DP, MacIsaac AI, Lefkovits J, et al. Variation in coronary angiography rates in Australia: correlations with socio-demographic, health service and disease burden indices. *Med J Aust* 2016; 205: 114–120.
166. Cho Y, Lim TH, Kang H, et al. Socioeconomic status and depression as combined risk factors for acute myocardial infarction and stroke: A population-based study of 2.7 million Korean adults. *J Psychosom Res* 2019; 121: 14–23.
167. Christensen A V, Koch MB, Davidsen M, et al. Educational inequality in cardiovascular disease depends on diagnosis: A nationwide register based study from Denmark. *Eur J Prev Cardiol* 2016; 23: 826–833.
168. Davies CA, Dundas R, Leyland AH. Increasing socioeconomic inequalities in first acute myocardial infarction in Scotland, 1990-92 and 2000-02. *BMC Public Health* 2009; 9: 134.
169. Deguen S, Lalloue B, Bard D, et al. A small-area ecologic study of myocardial infarction, neighborhood deprivation, and sex: a Bayesian modeling approach. *Epidemiology* 2010; 21: 459–466.
170. Dupre ME, George LK, Liu G, et al. The cumulative effect of unemployment on risks for acute myocardial infarction. *Arch Intern Med* 2012; 172: 1731–1737.
171. Geyer S, Tetzlaff J, Eberhard S, et al. Health inequalities in terms of

- myocardial infarction and all-cause mortality: a study with German claims data covering 2006 to 2015. *Int J Public Heal* 2019; 64: 387–397.
172. González-Zobl G, Grau M, Muñoz MA, et al. Socioeconomic status and risk of acute myocardial infarction. Population-based case-control study. *Rev Esp Cardiol* 2010; 63: 1045–1053.
  173. Guo J, Li W, Wang Y, et al. Influence of socioeconomic status on acute myocardial infarction in the Chinese population: The INTERHEART China study. *Chin Med J (Engl)* 2012; 125: 4214–4220.
  174. Hu B, Li W, Wang X, et al. Marital status, education, and risk of acute myocardial infarction in Mainland China: the INTER-HEART study. *J Epidemiol* 2012; 22: 123–129.
  175. Igland J, Vollset SE, Nygard OK, et al. Educational inequalities in acute myocardial infarction incidence in Norway: A nationwide cohort study. *PLoS ONE* 2014; 9.
  176. Kilpi F, Silventoinen K, Konttinen H, et al. Disentangling the relative importance of different socioeconomic resources for myocardial infarction incidence and survival: a longitudinal study of over 300,000 Finnish adults. *Eur J Public Heal* 2015; 26: 260–266.
  177. Kilpi F, Martikainen P, Konttinen H, et al. The Spillover Influence of Partner's Education on Myocardial Infarction Incidence and Survival. *Epidemiology* 2018; 29: 237–245.
  178. Kim D, Glazier RH, Zagorski B, et al. Neighbourhood socioeconomic position and risks of major chronic diseases and all-cause mortality: a quasi-experimental study. *BMJ Open* 2018; 8: e018793.
  179. Kjørulff TM, Bihmann K, Andersen I, et al. Geographical inequalities in acute myocardial infarction beyond neighbourhood-level and individual-level sociodemographic characteristics: a Danish 10-year nationwide population-based cohort study. *BMJ Open* 2019; 9: e024207.
  180. Koopman C, van Oeffelen AA, Bots ML, et al. Neighbourhood socioeconomic inequalities in incidence of acute myocardial infarction: a cohort study quantifying age- and gender-specific differences in relative and absolute terms. *BMC Public Health* 2012; 12: 617.
  181. Koopman C, Bots ML, van Oeffelen AA, et al. Population trends and inequalities in incidence and short-term outcome of acute myocardial infarction between 1998 and 2007. *Int J Cardiol* 2013; 168: 993–998.
  182. Korda RJ, Soga K, Joshy G, et al. Socioeconomic variation in incidence of primary and secondary major cardiovascular disease events: an Australian population-based prospective cohort study. *Int J Equity Heal* 2016; 15: 189.
  183. Kriegbaum M, Hougaard CØ, Andersen I, et al. Life course analysis on income and incident AMI: a Danish register-based cohort study. *J Epidemiol Community Heal* 2019; 73: 810–816.
  184. Kucharska-Newton AM, Harald K, Rosamond WD, et al. Socioeconomic indicators and the risk of acute coronary heart disease events: comparison of population-based data from the United States and Finland. *Ann Epidemiol* 2011; 21: 572–579.
  185. Lammintausta A, Immonen-Räihä P, Airaksinen JKE, et al. Socioeconomic

- Inequalities in the Morbidity and Mortality of Acute Coronary Events in Finland: 1988 to 2002. *Ann Epidemiol* 2012; 22: 87–93.
186. Mujahid MS, James SA, Kaplan GA, et al. Socioeconomic position, John Henryism, and incidence of acute myocardial infarction in Finnish men. *Soc Sci Med* 2016; 173: 54–62.
  187. Ngo-Metzger Q, Bierman AS, Borsky A, et al. Coronary Artery Disease, Acute Myocardial Infarction, and Ischemic Stroke Rates Among Inpatient Stays, 2001–2014: Statistical Brief #241. *Healthc Cost Util Proj Stat Briefs*.
  188. Odoi EW, Nagle N, Zaretzki R, et al. Sociodemographic determinants of acute myocardial infarction hospitalization risks in florida. *J Am Heart Assoc* 2020; 9: 1–21.
  189. Olesen K, Rugulies R, Rod NH, et al. Does retirement reduce the risk of myocardial infarction? A prospective registry linkage study of 617 511 Danish workers. *Int J Epidemiol* 2014; 43: 160–167.
  190. Oliveira A, Barros H, Azevedo A, et al. Impact of risk factors for non-fatal acute myocardial infarction. *Eur J Epidemiol* 2009; 24: 425–432.
  191. Pearson-Stuttard J, Bajekal M, Scholes S, et al. Recent UK trends in the unequal burden of coronary heart disease. *Heart* 2012; 98: 1573–1582.
  192. Pujades-Rodriguez M, Timmis A, Stogiannis D, et al. Socioeconomic deprivation and the incidence of 12 cardiovascular diseases in 1.9 million women and men: implications for risk prediction and prevention. *PLoS One* 2014; 9: e104671.
  193. Randall SM, Zilkens R, Duke JM, et al. Western Australia population trends in the incidence of acute myocardial infarction between 1993 and 2012. *Int J Cardiol* 2016; 222: 678–682.
  194. Rose KM, Suchindran CM, Foraker RE, et al. Neighborhood disparities in incident hospitalized myocardial infarction in four U.S. communities: the ARIC surveillance study. *Ann Epidemiol* 2009; 19: 867–874.
  195. Rosengren A, Subramanian S V, Islam S, et al. Education and risk for acute myocardial infarction in 52 high, middle and low-income countries: INTERHEART case-control study. *Heart* 2014; 95: 2014–2022.
  196. Safford MM, Reshetnyak E, Sterling MR, et al. Number of Social Determinants of Health and Fatal and Nonfatal Incident Coronary Heart Disease in the REGARDS Study. *Circulation* 2021; 244–253.
  197. Schmucker J, Seide S, Wienbergen H, et al. Socially disadvantaged city districts show a higher incidence of acute ST-elevation myocardial infarctions with elevated cardiovascular risk factors and worse prognosis. *BMC Cardiovasc Disord* 2017; 17: 254.
  198. Teo KK, Liu L, Chow CK, et al. Potentially modifiable risk factors associated with myocardial infarction in China: the INTERHEART China study. *Heart* 2009; 95: 1857–1864.
  199. Tetzlaff J, Geyer S, Westhoff-Bleck M, et al. Social inequalities in mild and severe myocardial infarction: how large is the gap in health expectancies? *BMC Public Health* 2021; 21: 1–10.
  200. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-

- income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020; 395: 795–808.
201. Min YI, Anugu P, Butler KR, et al. Cardiovascular Disease Burden and Socioeconomic Correlates: Findings From the Jackson Heart Study. *J Am Hear Assoc*; 6. Epub ahead of print 2017. DOI: 10.1161/JAHA.116.004416.
  202. Kelly MJ, Weitzen S. The Association of Lifetime Education with the Prevalence of Myocardial Infarction: An Analysis of the 2006 Behavioral Risk Factor Surveillance System. *J Community Health* 2009; 1–5.
  203. Giampaoli S, Palmieri L, Donfrancesco C, et al. Cardiovascular health in Italy. Ten-year surveillance of cardiovascular diseases and risk factors: Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey 1998-2012. *Eur J Prev Cardiol* 2015; 22: 9–37.
  204. Ayooobi F, Khalili P, Mohamadi M, et al. Activity status and cardiovascular diseases: a cross-sectional study based on the results of Rafsanjan Cohort Study (2020). *Iran Red Crescent Med J*; 23. Epub ahead of print 2021. DOI: 10.32592/ircmj.2021.23.4.322.
  205. Jeong NJ, Park E, Del Pobil AP. Effects of behavioral risk factors and social-environmental factors on non-communicable diseases in South Korea: A national survey approach. *Int J Environ Res Public Health* 2021; 18: 1–11.
  206. Abreu D, Salomé Cabral M, Ribeiro F. Factors associated with longer delays in reperfusion in ST-segment elevation myocardial infarction. *IJC Hear Vessel* 2014; 4: 97–101.
  207. Agarwal S, Garg A, Parashar A, et al. Outcomes and resource utilization in ST-elevation myocardial infarction in the United States: evidence for socioeconomic disparities. *J Am Hear Assoc* 2014; 3: e001057.
  208. Altenhöner T, Baczkiewicz C, Weishaar H, et al. Inequalities in therapeutic treatment during cardiac inpatient rehabilitation in Germany. *Int J Public Heal* 2012; 57: 175–184.
  209. Alter DA, Franklin B, Ko DT, et al. Socioeconomic Status, Functional Recovery, and Long-Term Mortality among Patients Surviving Acute Myocardial Infarction. *PLoS One* 2013; 8: e65130.
  210. Andrikopoulos G, Tzeis S, Terentes-Printzios D, et al. Impact of income status on prognosis of acute coronary syndrome patients during Greek financial crisis. *Clin Res Cardiol* 2016; 105: 518–526.
  211. Atkins ER, Du X, Wu Y, et al. Use of cardiovascular prevention treatments after acute coronary syndrome in China and associated factors. *Int J Cardiol* 2017; 241: 444–449.
  212. Bergström G, Redfors B, Angerås O, et al. Low socioeconomic status of a patient's residential area is associated with worse prognosis after acute myocardial infarction in Sweden. *Int J Cardiol* 2015; 182: 141–147.
  213. Bhasin V, Mehta A, Skopicki HA, et al. Predictors of Aspirin Nonadherence in Adults with Prior Myocardial Infarction. *Crit Pathw Cardiol* 2020; 19: 115–118.
  214. Biswas S, Andrianopoulos N, Duffy SJ, et al. Impact of Socioeconomic Status on Clinical Outcomes in Patients With ST-Segment-Elevation Myocardial Infarction. *Circ Cardiovasc Qual Outcomes* 2019; 12: e004979.

215. Bi Y, Gao R, Patel A, et al. Evidence-based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: Results from the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study. *Am Heart J* 2009; 157: 509-516.e1.
216. Blais C, Hamel D, Rinfret S. Impact of socioeconomic deprivation and area of residence on access to coronary revascularization and mortality after a first acute myocardial infarction in Québec. *Can J Cardiol* 2012; 28: 169–177.
217. Borg S, Öberg B, Leosdottir M, et al. Factors associated with non-attendance at exercise-based cardiac rehabilitation. *BMC Sport Sci Med Rehabil* 2019; 11: 1–10.
218. Bradshaw PJ, Trafalski S, Hung J, et al. Outcomes after first percutaneous coronary intervention for acute myocardial infarction according to patient funding source. *BMC Heal Serv Res* 2014; 14: 405.
219. Buja A, Canavese D, Furlan P, et al. Are hospital process quality indicators influenced by socio-demographic health determinants. *Eur J Public Heal* 2015; 25: 759–765.
220. Cacciani L, Agabiti N, Bargagli AM, et al. Access to percutaneous transluminal coronary angioplasty and 30-day mortality in patients with incident STEMI: Differentials by educational level and gender over 11 years. *PLoS One* 2017; 12: e0175038.
221. Carey IM, DeWilde S, Shah SM, et al. Statin use after first myocardial infarction in UK men and women from 1997 to 2006: Who started and who continued treatment? *Nutr Metab Cardiovasc Dis* 2012; 22: 400–408.
222. Cohen D, Manuel DG, Tugwell P, et al. Inequity in primary and secondary preventive care for acute myocardial infarction? Use by socioeconomic status across middle-aged and older patients. *Can J Cardiol* 2013; 29: 1579–1585.
223. Crowley MJ, Zullig LL, Shah BR, et al. Medication Non-Adherence After Myocardial Infarction: An Exploration of Modifying Factors. *J Gen Intern Med* 2015; 30: 83–90.
224. Cupples ME, Tully MA, Dempster M, et al. Cardiac rehabilitation uptake following myocardial infarction: Cross-sectional study in primary care. *Br J Gen Pract* 2010; 60: 431–435.
225. Danchin N, Neumann A, Tuppin P, et al. Impact of free universal medical coverage on medical care and outcomes in low-income patients hospitalized for acute myocardial infarction: An analysis from the french national health insurance system. *Circ Cardiovasc Qual Outcomes* 2011; 4: 619–625.
226. De Luca G, Petrelli A, L, et al. Geographic and socioeconomic differences in access to revascularization following acute myocardial infarction. *Eur J Public Heal* 2016; 26: 760–765.
227. Desai NR, Udell JA, Wang Y, et al. Trends in Performance and Opportunities for Improvement on a Composite Measure of Acute Myocardial Infarction Care: Findings from the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes*; 12. Epub ahead of print 2019. DOI: 10.1161/CIRCOUTCOMES.118.004983.
228. Deskur-Smielecka E, Borowicz-Bieńkowska S, Brychcy A, et al. Why

- patients after acute coronary syndromes do not participate in an early outpatient rehabilitation programme? *Kardiol Pol* 2009; 67: 632–638.
229. Doll JA, Hellkamp AS, Goyal A, et al. Treatment, outcomes, and adherence to medication regimens among dual Medicare-Medicaid-eligible adults with myocardial infarction. *JAMA Cardiol* 2016; 1: 787–794.
  230. Dunlay SM, Witt BJ, Allison TG, et al. Barriers to participation in cardiac rehabilitation. *Am Heart J* 2009; 158: 852–859.
  231. Evans LW, van Woerden H, Davies GR, et al. Impact of service redesign on the socioeconomic inequity in revascularisation rates for patients with acute myocardial infarction: a natural experiment and electronic record-linked cohort study. *BMJ Open* 2016; 6: e011656.
  232. Fabreau GE, Leung AA, Southern DA, et al. Sex, socioeconomic status, access to cardiac catheterization, and outcomes for acute coronary syndromes in the context of universal healthcare coverage. *Circ Cardiovasc Qual Outcomes* 2014; 7: 540–549.
  233. Foraker RE, Rose KM, Whitsel EA, et al. Neighborhood socioeconomic status, Medicaid coverage and medical management of myocardial infarction: atherosclerosis risk in communities (ARIC) community surveillance. *BMC Public Health* 2010; 10: 632.
  234. Forsberg PO, Li X, Sundquist K. Neighborhood socioeconomic characteristics and statin medication in patients with myocardial infarction: a Swedish nationwide follow-up study. *BMC Cardiovasc Disord* 2016; 16: 146.
  235. Fournier S, Muller O, Ludman AJ, et al. Influence of socioeconomic factors on delays, management and outcome amongst patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Swiss Med Wkly* 2013; 143: w13817.
  236. Gaedke MÂ, Costa JS, Manenti ER, et al. Use of medicines recommended for secondary prevention of acute coronary syndrome. *Rev Saude Publica*; 49.
  237. Gencer B, Rodondi N, Auer R, et al. Reasons for discontinuation of recommended therapies according to the patients after acute coronary syndromes. *Eur J Intern Med* 2015; 26: 56–62.
  238. Gnani R, Rusciani R, Dalmaso M, et al. Gender, socioeconomic position, revascularization procedures and mortality in patients presenting with STEMI and NSTEMI in the era of primary PCI. Differences or inequities? *Int J Cardiol* 2014; 176: 724–730.
  239. Graversen CB, Johansen MB, Eichhorst R, et al. Influence of socioeconomic status on the referral process to cardiac rehabilitation following acute coronary syndrome: a cross-sectional study. *BMJ Open* 2020; 10: e036088.
  240. Hagen TP, Häkkinen U, Iversen T, et al. Socio-economic Inequality in the Use of Procedures and Mortality Among AMI Patients: Quantifying the Effects Along Different Paths. *Heal Econ* 2015; 24: 102–115.
  241. Hanley GE, Morgan S, Reid RJ. Income-related inequity in initiation of evidence-based therapies among patients with acute myocardial infarction. *J Gen Intern Med* 2011; 26: 1329–1335.
  242. Hannan EL, Zhong Y, Walford G, et al. Underutilization of percutaneous coronary intervention for ST-elevation myocardial infarction in medicaid

- patients relative to private insurance patients. *J Interv Cardiol* 2013; 26: 470–481.
243. Hawkins NM, Scholes S, Bajekal M, et al. The UK National Health Service: delivering equitable treatment across the spectrum of coronary disease. *Circ Cardiovasc Qual Outcomes* 2013; 6: 208–216.
  244. Heo JY, Hong KJ, Shin SD, et al. Association of educational level with delay of prehospital care before reperfusion in STEMI. *Am J Emerg Med* 2015; 33: 1760–1769.
  245. Hughes V, Paige E, Welsh J, et al. Education-related variation in coronary procedure rates and the contribution of private health care in Australia: A prospective cohort study. *Int J Equity Health* 2020; 19: 1–12.
  246. Hussain S, Jamal SZ, Qadir F. Medication Adherence In Post Myocardial Infarction Patients. *J Ayub Med Coll Abbottabad* 2018; 30: 552–557.
  247. Jaquet E, Gencer B, Auer R, et al. Association between income and control of cardiovascular risk factors after acute coronary syndromes: an observational study. *Swiss Med Wkly* 2019; 149: w20049.
  248. Jin H, Tang C, Wei Q, et al. Age-related differences in factors associated with the underuse of recommended medications in acute coronary syndrome patients at least one year after hospital discharge. *BMC Cardiovasc Disord* 2014; 14: 1–9.
  249. Jin H, Wei Q, Chen L, et al. Obstacles and alternative options for cardiac rehabilitation in nanjing, china: An exploratory study. *BMC Cardiovasc Disord* 2014; 14: 1–9.
  250. Kassab YW, Hassan Y, Aziz NA, et al. Report: trends in adherence to secondary prevention medications in post-acute coronary syndrome patients. *Pak J Pharm Sci* 2015; 28: 641–646.
  251. King W, Lacey A, White J, et al. Equity in healthcare for coronary heart disease, Wales (UK) 2004-2010: A populationbased electronic cohort study. *PLoS One*; 12. Epub ahead of print 2017. DOI: 10.1371/journal.pone.0172618.
  252. King W, Lacey A, White J, et al. Socioeconomic inequality in medication persistence in primary and secondary prevention of coronary heart disease - A population-wide electronic cohort study. *PLoS One* 2018; 13: e0194081.
  253. Kirchmayer U, Agabiti N, Belleudi V, et al. Socio-demographic differences in adherence to evidence-based drug therapy after hospital discharge from acute myocardial infarction: a population-based cohort study in Rome, Italy. *J Clin Pharm Ther* 2012; 37: 37–44.
  254. Kitzmiller JP, Foraker RE, Rose KM. Lipid-lowering pharmacotherapy and socioeconomic status: Atherosclerosis Risk In Communities (ARIC) surveillance study. *BMC Public Health* 2013; 13: 488.
  255. Korda RJ, Clements MS, Kelman CW. Universal health care no guarantee of equity: comparison of socioeconomic inequalities in the receipt of coronary procedures in patients with acute myocardial infarction and angina. *BMC Public Health* 2009; 9: 460.
  256. Korda RJ, Clements MS, Dixon J. Socioeconomic inequalities in the diffusion of health technology: Uptake of coronary procedures as an example. *Soc Sci*

- Med* 2011; 72: 224–229.
257. Matetic A, Bharadwaj A, Mohamed MO, et al. Socioeconomic Status and Differences in the Management and Outcomes of 6.6 Million US Patients With Acute Myocardial Infarction. *Am J Cardiol*. Epub ahead of print 2020. DOI: 10.1016/j.amjcard.2020.05.025.
  258. Mathews R, Wang TY, Honeycutt E, et al. Persistence with secondary prevention medications after acute myocardial infarction: Insights from the TRANSLATE-ACS study. *Am Hear J* 2015; 170: 62–69.
  259. Melloni C, Alexander KP, Ou FS, et al. Predictors of Early Discontinuation of Evidence-Based Medicine After Acute Coronary Syndrome. *Am J Cardiol* 2009; 104: 175–181.
  260. Mårtensson S, Gyrd-Hansen D, Prescott E, et al. Socio-economic position and time trends in invasive management and case fatality after acute myocardial infarction in Denmark. *Eur J Public Heal* 2015; 26: 146–152.
  261. Mårtensson S, Gyrd-Hansen D, Prescott E, et al. Does access to invasive examination and treatment influence socioeconomic differences in case fatality for patients admitted for the first time with non-ST-elevation myocardial infarction or unstable angina? *EuroIntervention* 2016; 11: 1495–1502.
  262. Niedzwiecki MJ, Hsia RY, Shen YC. Not All Insurance Is Equal: Differential Treatment and Health Outcomes by Insurance Coverage Among Nonelderly Adult Patients With Heart Attack. *J Am Hear Assoc*; 7. Epub ahead of print 2018. DOI: 10.1161/JAHA.117.008152.
  263. Niu S, Zhao D, Zhu J, et al. The association between socioeconomic status of high-risk patients with coronary heart disease and the treatment rates of evidence-based medicine for coronary heart disease secondary prevention in China: Results from the Bridging the Gap on CHD Secondary . *Am Heart J*; 157. Epub ahead of print 2009. DOI: 10.1016/j.ahj.2008.12.009.
  264. Ohlsson H, Rosvall M, Hansen O, et al. Socioeconomic position and secondary preventive therapy after an AMI. *Pharmacoepidemiol Drug Saf* 2010; 19: 358–366.
  265. Ohm J, Skoglund PH, Häbel H, et al. Association of Socioeconomic Status with Risk Factor Target Achievements and Use of Secondary Prevention after Myocardial Infarction. *JAMA Netw Open* 2021; 4: 1–14.
  266. Parashar S, Spertus JA, Tang F, et al. Predictors of early and late enrollment in cardiac rehabilitation, among those referred, after acute myocardial infarction. *Circulation* 2012; 126: 1587–1595.
  267. Patel N, Gupta A, Doshi R, et al. In-Hospital Management and Outcomes After ST-Segment-Elevation Myocardial Infarction in Medicaid Beneficiaries Compared With Privately Insured Individuals. *Circ Cardiovasc Qual Outcomes* 2019; 12: e004971.
  268. Pedersen M, Egerod I, Overgaard D, et al. Social inequality in phase II cardiac rehabilitation attendance: The impact of potential mediators. *Eur J Cardiovasc Nurs* 2018; 17: 345–355.
  269. Peng Y, Du X, Li X, et al. Associations Between Education Level and In-hospital Treatment and Outcomes Among Acute Coronary Syndrome in



- China. *Am J Med Sci* 2021; 361: 253–260.
270. Perelman J, Shmueli A, McDonald KM, et al. Inequality in treatment use among elderly patients with acute myocardial infarction: USA, Belgium and Quebec. *BMC Heal Serv Res* 2009; 9: 130.
271. Peters AE, Keeley EC. Trends and Predictors of Participation in Cardiac Rehabilitation Following Acute Myocardial Infarction: Data From the Behavioral Risk Factor Surveillance System. *J Am Heart Assoc*; 7. Epub ahead of print 2018. DOI: 10.1161/JAHA.117.007664.
272. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Medication adherence and its determinants in patients after myocardial infarction. *Sci Rep* 2020; 10: 1–11.
273. Pietrzykowski Ł, Kasprzak M, Michalski P, et al. Therapy Discontinuation after Myocardial Infarction. *J Clin Med* 2020; 9: 4109.
274. Rose KM, Foraker RE, Heiss G, et al. Neighborhood Socioeconomic and Racial Disparities in Angiography and Coronary Revascularization: The ARIC Surveillance Study. 2012; 22: 623–629.
275. Santos VB, Silva LL, Guizilini S, et al. Adherence to antiplatelet and statin therapy by patients with Acute Coronary Syndrome following discharge. *Enferm Clin*. Epub ahead of print 2020. DOI: 10.1016/j.enfcli.2020.02.020.
276. Sulo E, Nygård O, Vollset SE, et al. Coronary angiography and myocardial revascularization following the first acute myocardial infarction in Norway during 2001–2009: Analyzing time trends and educational inequalities using data from the CVDNOR project. *Int J Cardiol* 2016; 212: 122–128.
277. Sunamura M, ter Hoeve N, Geleijnse ML, et al. Cardiac rehabilitation in patients who underwent primary percutaneous coronary intervention for acute myocardial infarction: Determinants of programme participation and completion. *Netherlands Heart J* 2017; 25: 618–628.
278. Tang X, Liu L, Yang J, et al. Evidence-based oral antiplatelet therapy among hospitalized Chinese patients with acute myocardial infarction: results from the Chinese acute myocardial infarction registry. *BMC Cardiovasc Disord* 2021; 21: 1–12.
279. Udell JA, Desai NR, Li S, et al. Neighborhood Socioeconomic Disadvantage and Care After Myocardial Infarction in the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes* 2018; 11: e004054.
280. Wasser J, Goldberg RJ, Spencer FA, et al. Multidecade-long trends (1986–2005) in the utilization of coronary reperfusion and revascularization treatment strategies in patients hospitalized with acute myocardial infarction: A community-wide perspective. *Coron Artery Dis* 2009; 20: 71–80.
281. Yong CM, Abnoui F, Asch SM, et al. Socioeconomic inequalities in quality of care and outcomes among patients with acute coronary syndrome in the modern era of drug eluting stents. *J Am Heart Assoc* 2014; 3: e001029.
282. Zhang LM, Geater AF, McNeil EB, et al. Health Inequalities of STEMI Care Before Implementation of a New Regional Network: A Prefecture-Level Analysis of Social Determinants of Healthcare in Yunnan, China. *Int J Heal Policy Manag* 2021; 1–12.
283. Zhou S, Chen J, Xu RY, et al. Factors associated with the use of percutaneous

- coronary intervention in elderly Chinese patients with a first ST elevated acute myocardial infarction. *Patient Prefer Adherence* 2014; 8: 257–262.
284. Ahmadi A, Khaledifar A, Sajjadi H, et al. Relationship between risk factors and in-hospital mortality due to myocardial infarction by educational level: a national prospective study in Iran. *Int J Equity Heal* 2014; 13: 116.
285. Ahmadi A, Soori H, Mehrabi Y, et al. Epidemiological pattern of myocardial infarction and modelling risk factors relevant to in-hospital mortality: the first results from the Iranian Myocardial Infarction Registry. *Kardiol Pol* 2015; 73: 451–457.
286. Al-Zakwani I, Mabry RM, Zubaid M, et al. Association between education and major adverse cardiac events among patients with acute coronary syndrome in the Arabian Gulf. *BMJ Glob Heal* 2019; 4: e001278.
287. Bang DW, Manemann SM, Gerber Y, et al. A novel socioeconomic measure using individual housing data in cardiovascular outcome research. *Int J Env Res Public Heal* 2014; 11: 11597–11615.
288. Berman AN, Biery DW, Ginder C, et al. Association of Socioeconomic Disadvantage with Long-term Mortality after Myocardial Infarction: The Mass General Brigham YOUNG-MI Registry. *JAMA Cardiol* 2021; 6: 880–888.
289. Bucholz EM, Ma S, Normand S, et al. Race, Socioeconomic Status, and Life Expectancy After Acute Myocardial Infarction. *Circulation* 2015; 132: 1338–1346.
290. Cafagna G, Seghieri C. Educational level and 30-day outcomes after hospitalization for acute myocardial infarction in Italy. *BMC Heal Serv Res* 2017; 17: 1–11.
291. Coady SA, Johnson NJ, Hakes JK, et al. Individual education, area income, and mortality and recurrence of myocardial infarction in a Medicare cohort: the National Longitudinal Mortality Study. *BMC Public Health* 2014; 14: 705.
292. Consuegra-Sánchez L, Melgarejo-Moreno A, Galcerá-Tomás J, et al. Educational Level and Long-term Mortality in Patients With Acute Myocardial Infarction. *Rev Esp Cardiol (Engl Ed)* 2015; 68: 935–942.
293. Davies CA, Leyland AH. Trends and inequalities in short-term acute myocardial infarction case fatality in Scotland, 1988-2004. *Popul Heal Metr* 2010; 8: 33.
294. Donyavi T, Naieni KH, Nedjat S, et al. Socioeconomic status and mortality after acute myocardial infarction: a study from Iran. *Int J Equity Heal* 2011; 10: 9.
295. Foraker RE, Patel MD, Whitsel EA, et al. Neighborhood socioeconomic disparities and 1-year case fatality after incident myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) Community Surveillance (1992-2002). *Am Hear J* 2013; 165: 102–107.
296. Gabet A, Danchin N, Puymirat E, et al. Early and late case fatality after hospitalization for acute coronary syndrome in France, 2010-2015. *Arch Cardiovasc Dis* 2019; 112: 754–764.
297. Gerber Y, Benyamini Y, Goldbourt U, et al. Neighborhood socioeconomic

- context and long-term survival after myocardial infarction. *Circulation* 2010; 121: 375–383.
298. Guhl EN, Zhu J, Johnson A, et al. Area deprivation index and cardiovascular events can cardiac rehabilitation mitigate the effects? *J Cardiopulm Rehabil Prev* 2021; 1–7.
  299. Hasan O, Orav EJ, Hicks LS. Insurance status and hospital care for myocardial infarction, stroke, and pneumonia. *J Hosp Med* 2010; 5: 452–459.
  300. Huo X, Khera R, Zhang L, et al. Education level and outcomes after acute myocardial infarction in China. *Heart* 2019; 105: 946–952.
  301. Igland J, Vollset SE, Nygård OK, et al. Educational inequalities in 28 day and 1-year mortality after hospitalisation for incident acute myocardial infarction—a nationwide cohort study. *Int J Cardiol* 2014; 177: 874–880.
  302. Kim Y, Oh J, Jha A. Contribution of hospital mortality variations to socioeconomic disparities in in-hospital mortality. *BMJ Qual Saf* 2014; 23: 741–748.
  303. Kim JH, Jeong MH, Park IH, et al. The association of socioeconomic status with three-year clinical outcomes in patients with acute myocardial infarction who underwent percutaneous coronary intervention. *J Korean Med Sci* 2014; 29: 536–543.
  304. Kirchberger I, Meisinger C, Golüke H, et al. Long-term survival among older patients with myocardial infarction differs by educational level: results from the MONICA/KORA myocardial infarction registry. *Int J Equity Heal* 2014; 13: 19.
  305. Klitkou ST, Wangen KR. Educational attainment and differences in relative survival after acute myocardial infarction in Norway: a registry-based population study. *BMJ Open* 2017; 7: e014787.
  306. Lin X, Cai M, Tao H, et al. Insurance status, inhospital mortality and length of stay in hospitalised patients in Shanxi, China: a cross-sectional study. *BMJ Open* 2017; 7: e015884.
  307. Liu B, Yan H, Guo R, et al. The basic social medical insurance is associated with clinical outcomes in the patients with ST-elevation myocardial infarction: a retrospective study from Shanghai, China. *Int J Med Sci* 2014; 11: 905–917.
  308. Machón M, Aldasoro E, Martínez-Cambor P, et al. Socioeconomic differences in incidence and relative survival after a first acute myocardial infarction in the Basque Country, Spain. *Gac Sanit* 2011; 26: 16–23.
  309. Malki N, Hägg S, Tiikkaja S, et al. Short-term and long-term case-fatality rates for myocardial infarction and ischaemic stroke by socioeconomic position and sex: a population-based cohort study in Sweden, 1990-1994 and 2005-2009. *BMJ Open* 2019; 9: e026192.
  310. Mehta RH, O’Shea JC, Stebbins AL, et al. Association of mortality with years of education in patients with st-segment elevation myocardial infarction treated with fibrinolysis. *J Am Coll Cardiol* 2011; 57: 138–146.
  311. Molshatzki N, Drory Y, Myers V, et al. Role of socioeconomic status measures in long-term mortality risk prediction after myocardial infarction. *Med Care* 2011; 49: 673–678.

312. Ng DK, Brotman DJ, Lau B, et al. Insurance status, not race, is associated with mortality after an acute cardiovascular event in Maryland. *J Gen Intern Med* 2012; 27: 1368–1376.
313. Notara V, Panagiotakos DB, Pitsavos C, et al. Lower Financial Status and Adherence to Medication Determines 10-Year (2004-2014) All-Cause Mortality and Risk for Acute Coronary Syndrome Incidence Among Cardiac Patients: the GREECS Study. *Curr Vasc Pharmacol* 2015; 13: 771–777.
314. Notara V, Panagiotakos DB, Kogias Y, et al. The Impact of Educational Status on 10-Year (2004-2014) Cardiovascular Disease Prognosis and All-cause Mortality Among Acute Coronary Syndrome Patients in the Greek Acute Coronary Syndrome (GREECS) Longitudinal Study. *J Prev Med Public Heal* 2016; 49: 220–229.
315. Pancholy S, Patel G, Pancholy M, et al. Association Between Health Insurance Status and In-Hospital Outcomes After ST-Segment Elevation Myocardial Infarction. *Am J Cardiol* 2017; 120: 1049–1054.
316. Pocock SJ, Huo Y, de Werf F, et al. Predicting two-year mortality from discharge after acute coronary syndrome: An internationally-based risk score. *Eur Hear J Acute Cardiovasc Care* 2019; 8: 727–737.
317. Roth C, Berger R, Kuhn M. The role of the socio-economic environment on medical outcomes after ST-segment elevation myocardial infarction. *BMC Public Health* 2019; 19: 630.
318. Smolina K, Wright FL, Rayner M, et al. Incidence and 30-day case fatality for acute myocardial infarction in England in 2010: National-linked database study. *Eur J Public Health* 2012; 22: 848–853.
319. Steele L, Palmer J, Lloyd A, et al. Impact of socioeconomic status on survival following ST-elevation myocardial infarction in a universal healthcare system. *Int J Cardiol* 2019; 276: 26–30.
320. Stirbu I, Looman C, Nijhof GJ, et al. Income inequalities in case death of ischaemic heart disease in the Netherlands: a national record-linked study. *J Epidemiol Community Heal* 2012; 66: 1159–1166.
321. van Oeffelen AA, Agyemang C, Bots ML, et al. The relation between socioeconomic status and short-term mortality after acute myocardial infarction persists in the elderly: results from a nationwide study. *Eur J Epidemiol* 2012; 27: 605–613.
322. Vujcic I, Vlajinac H, Dubljanin E, et al. Long-term prognostic significance of living alone and other risk factors in patients with acute myocardial infarction. *Ir J Med Sci* 2014; 1–6.
323. Wadhwa RK, Bhatt DL, Kind AJH, et al. Association of Outpatient Practice-Level Socioeconomic Disadvantage with Quality of Care and Outcomes among Older Adults with Coronary Artery Disease: Implications for Value-Based Payment. *Circ Cardiovasc Qual Outcomes*. Epub ahead of print 2020. DOI: 10.1161/CIRCOUTCOMES.119.005977.
324. Wang JY, Wang CY, Juang SY, et al. Low socioeconomic status increases short-term mortality of acute myocardial infarction despite universal health coverage. *Int J Cardiol* 2014; 172: 82–87.
325. World Health Organization. *Global Action Plan For The Prevention And*

- Control Of Noncommunicable Diseases 2013-2020*. 2020.
326. Hallqvist J, Lundberg M, Diderichsen F, et al. Socioeconomic differences in risk of myocardial infarction 1971-1994 in Sweden: Time trends, relative risks and population attributable risks. *Int J Epidemiol* 1998; 27: 410–415.
  327. Gupta R, Yusuf S. Challenges in management and prevention of ischemic heart disease in low socioeconomic status people in LLMICs. *BMC Med* 2019; 17: 209.
  328. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations. *Int J Cardiol* 2013; 168: 934–945.
  329. Huber K, Gersh BJ, Goldstein P, et al. The organization, function, and outcomes of ST-elevation myocardial infarction networks worldwide: Current state, unmet needs and future directions. *Eur Heart J* 2014; 35: 1526–1532.
  330. Murphy A, Palafox B, O'Donnell O, et al. Inequalities in the use of secondary prevention of cardiovascular disease by socioeconomic status: evidence from the PURE observational study. *Lancet Glob Heal* 2018; 6: e292–e301.
  331. Rosselló X, Huo Y, Pocock S, et al. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. *Int J Cardiol* 2017; 245: 27–34.
  332. Kunst AE, Bos V, Andersen O, et al. Monitoring of trends in socioeconomic inequalities in mortality: Experiences from a European project. *Demogr Res* 2004; 10: 229–254.
  333. Crombie I, Irvine L, Elliott L, et al. Closing the health inequalities gap: an international perspective. *World Heal Organ* 2005; 1–80.
  334. Rasmussen JN, Rasmussen S, Gislason GH, et al. Persistent socio-economic differences in revascularization after acute myocardial infarction despite a universal health care system - A Danish study. *Cardiovasc Drugs Ther* 2007; 21: 449–457.
  335. Fleurbaey M, Schokkaert E. Unfair inequalities in health and health care. *J Health Econ* 2009; 28: 73–90.
  336. Svendsen MT, Bak CK, Sørensen K, et al. Associations of health literacy with socioeconomic position, health risk behavior, and health status: A large national population-based survey among Danish adults. *BMC Public Health* 2020; 20: 1–12.
  337. Rasmussen JN, Gislason GH, Rasmussen S, et al. Use of statins and beta-blockers after acute myocardial infarction according to income and education. *J Epidemiol Community Health* 2007; 61: 1091–1097.
  338. Myers V, Drory Y, Goldbourt U, et al. Multilevel socioeconomic status and incidence of frailty post myocardial infarction. *Int J Cardiol* 2014; 170: 338–343.
  339. Pichora E, Polsky JY, Catley C, et al. Comparing individual and area-based income measures: impact on analysis of inequality in smoking, obesity, and diabetes rates in Canadians 2003–2013. *Can J Public Heal* 2018; 109: 410–418.
  340. Niederdeppe J, Kuang X, Crock B, et al. Media campaigns to promote smoking cessation among socioeconomically disadvantaged populations:

- What do we know, what do we need to learn, and what should we do now? *Soc Sci Med* 2008; 67: 1343–1355.
341. Rasmussen LN, Montgomery P. The prevalence of and factors associated with inclusion of non-English language studies in Campbell systematic reviews: A survey and meta-epidemiological study. *Syst Rev* 2018; 7: 1–12.
  342. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: A validation study. *BMJ Open*; 6. Epub ahead of print 2016. DOI: 10.1136/bmjopen-2016-012832.
  343. Soliman EZ. Silent myocardial infarction and risk of heart failure: Current evidence and gaps in knowledge. *Trends Cardiovasc Med* 2019; 29: 239–244.
  344. Ylijoki-Sørensen S, Sajantila A, Lalu K, et al. Coding ill-defined and unknown cause of death is 13 times more frequent in Denmark than in Finland. *Forensic Sci Int* 2014; 244: 289–294.
  345. Jensen TW, Blomberg SN, Folke F, et al. The National Danish Cardiac Arrest Registry for Out-of-Hospital Cardiac Arrest – A Registry in Transformation. *Clin Epidemiol* 2022; 14: 949–957.
  346. Møller S, Wissenberg M, Starkopf L, et al. Socioeconomic disparities in prehospital factors and survival after out-of-hospital cardiac arrest. *Heart* 2021; 107: 627–634.

# SUPPLEMENTARY

## INDEX:

Supplemental Figure S1. Graphical abstract Study I

Supplemental Figure S2. Graphical abstract Study II

Supplemental Figure S3. Graphical abstract Study III

Supplemental Figure S4. Causal diagram Study II

Supplemental Figure S5. Causal diagram 1 Study III

Supplemental Figure S6. Causal diagram 2 Study III

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

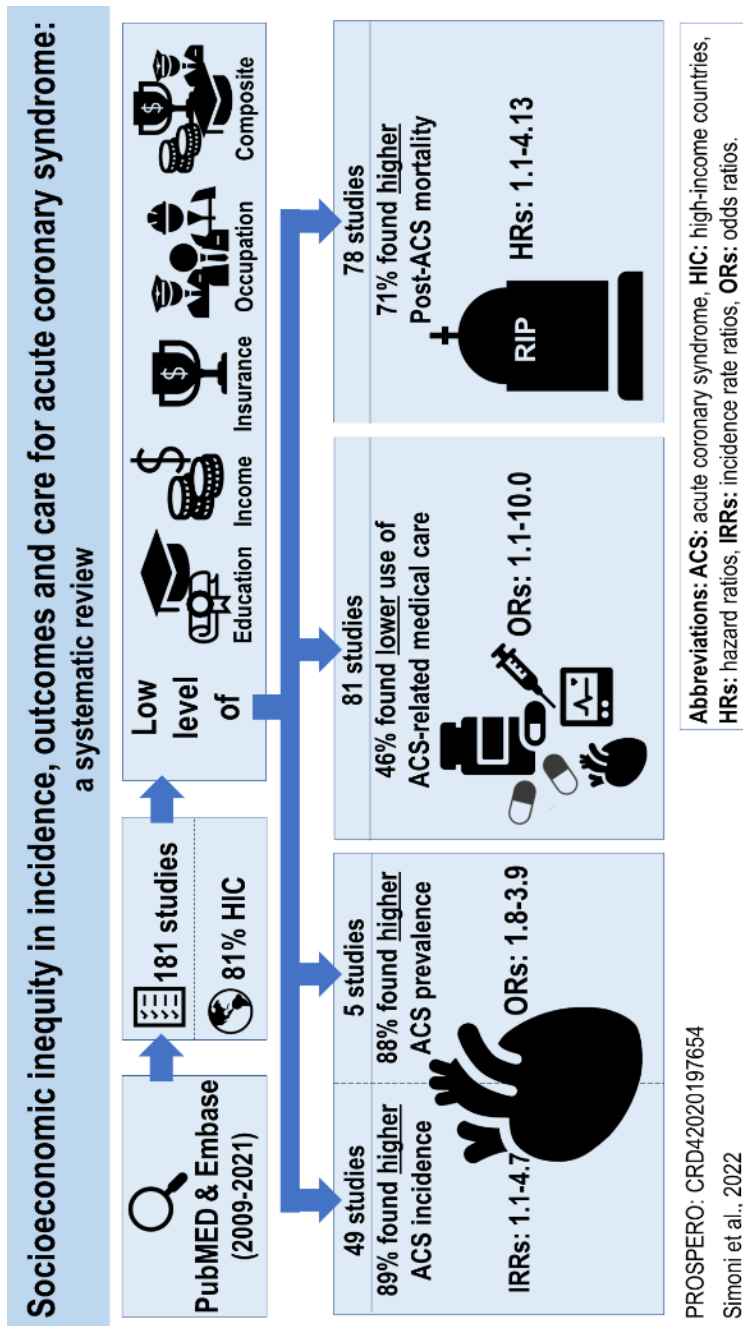
Supplemental Table S2. Characteristics of the identified in Study I regarding the association between SEP and temporal trends in medical care after ACS.

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

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

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

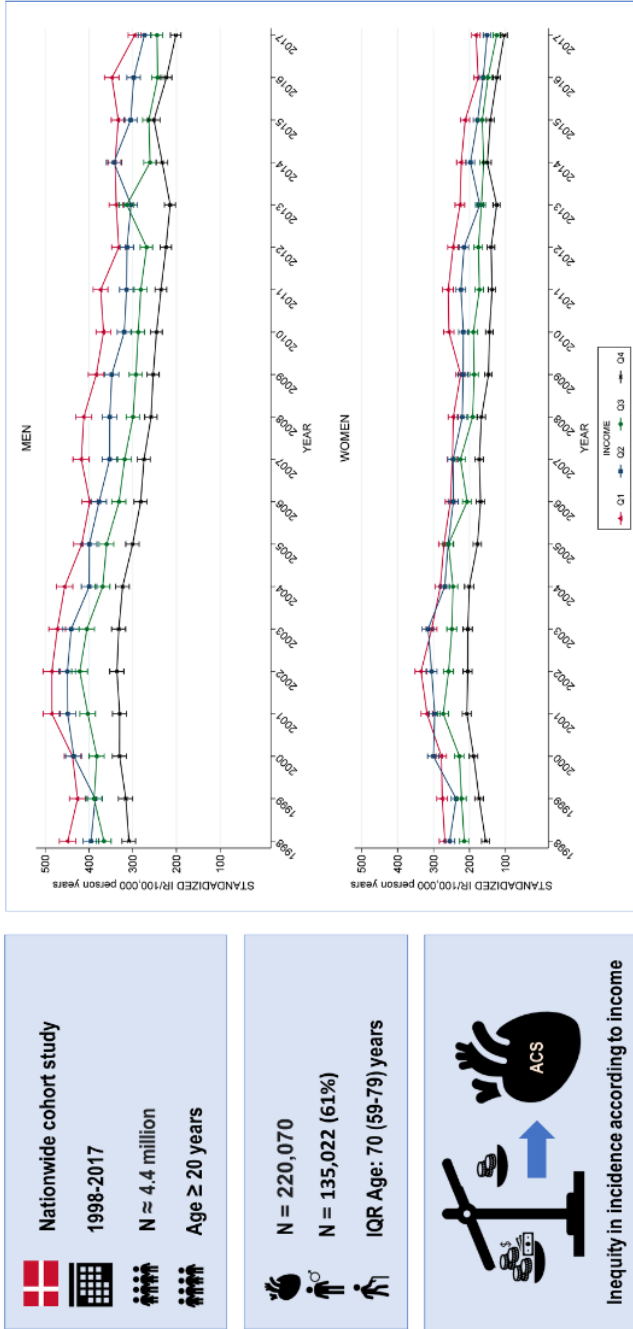
Supplemental Figure S1. Graphical abstract Study I<sup>14</sup>





Supplemental Figure S2. Graphical abstract Study II

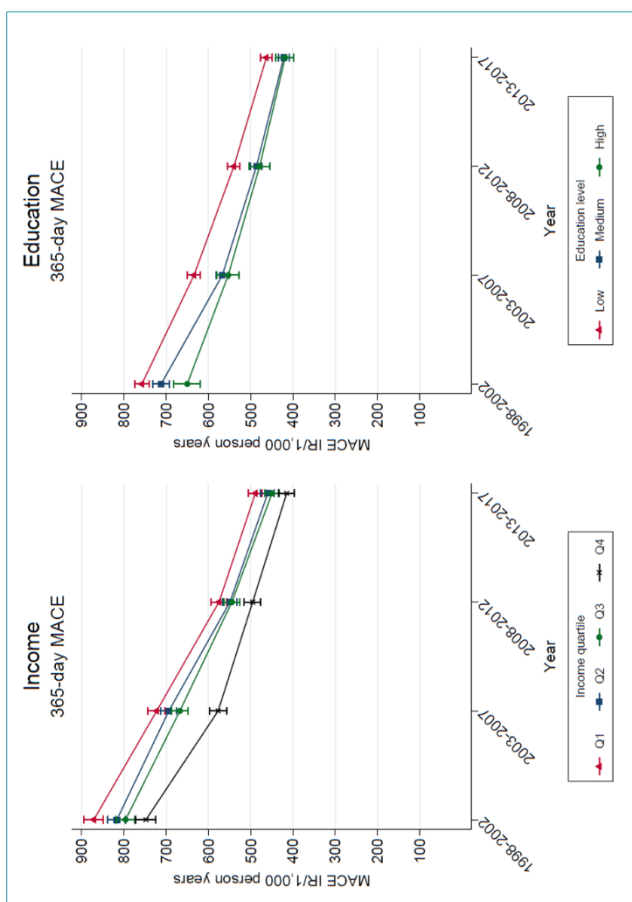
Time Trends in Income-related Inequity in Incidence of Acute Coronary Syndrome



Simoni et al., 2022

Supplemental Figure S3. Graphical abstract Study III<sup>116</sup>

Temporal trends in socioeconomic disparity in clinical outcomes for patients with acute coronary syndrome



**Nationwide cohort study**

1998-2017

N = 220,887 ACS patients

N = 135,551 (61%)

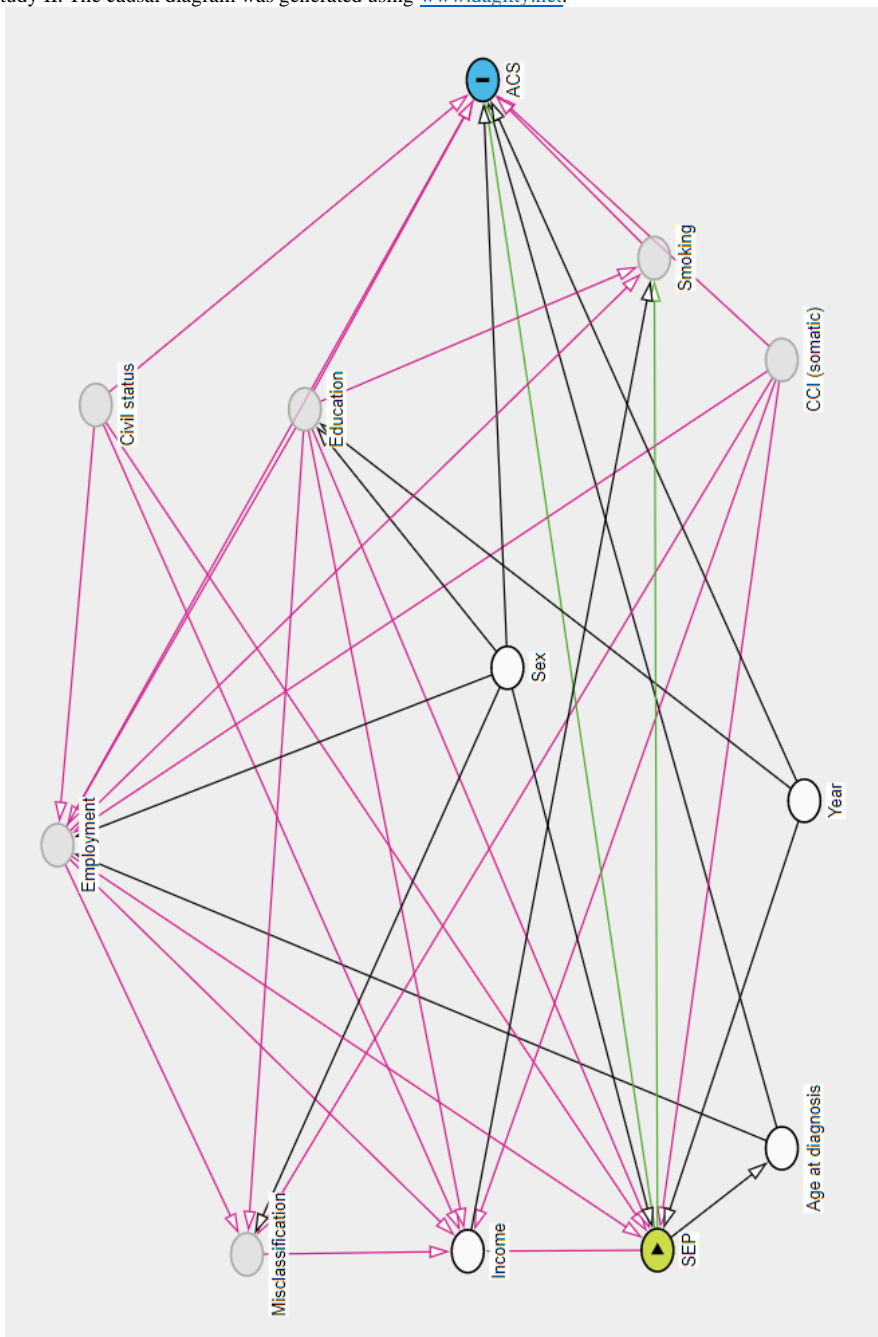
IQR Age: 70 (59-79) years

**Socioeconomic disparity in MACE after ACS**

Simoni et al., Abbreviations: ACS: acute coronary syndrome, MACE: major adverse cardiac events, N: number of individuals/patients, IR: incidence rate, Q: income quartile (1: low, 4: high) IQR: interquartile ranges

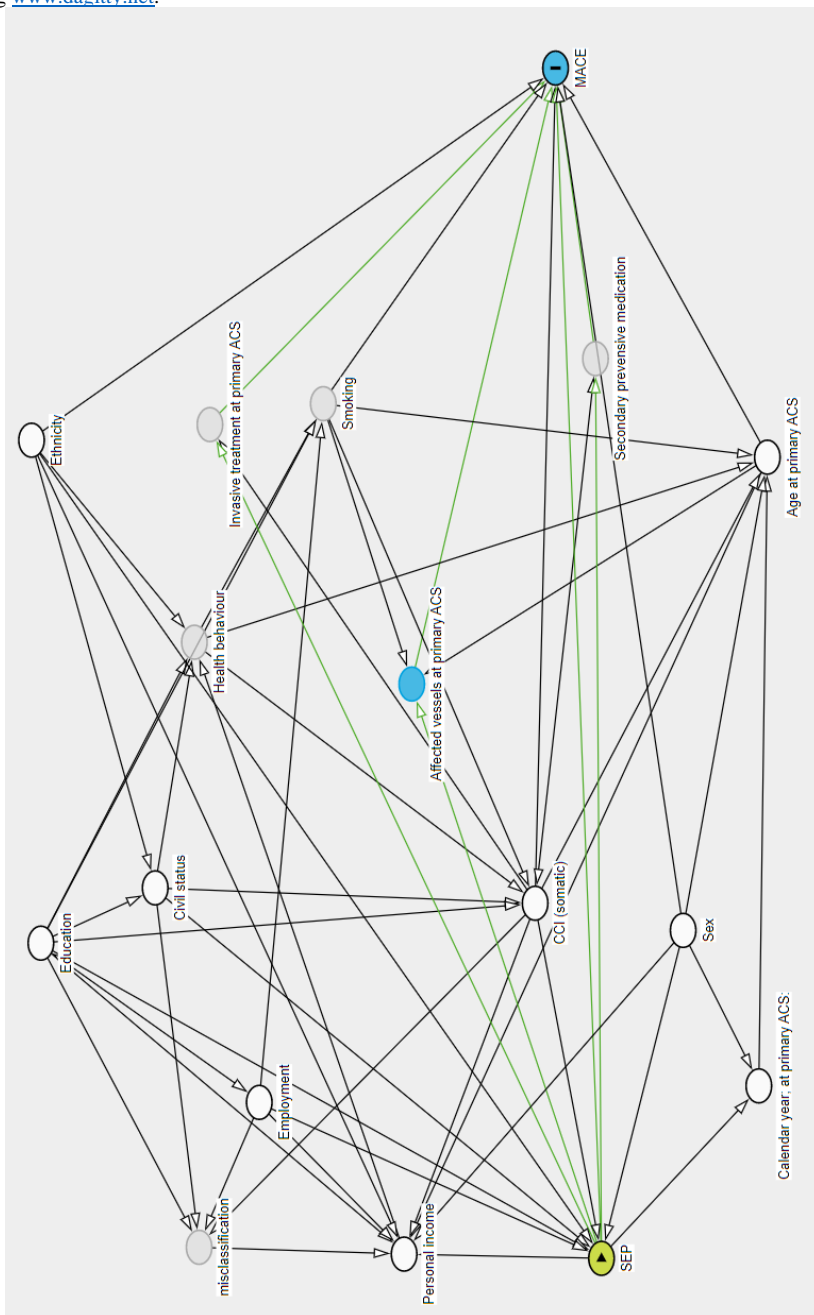
**Supplemental Figure S4. Causal diagram Study II<sup>115</sup>**

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](http://www.dagitty.net).



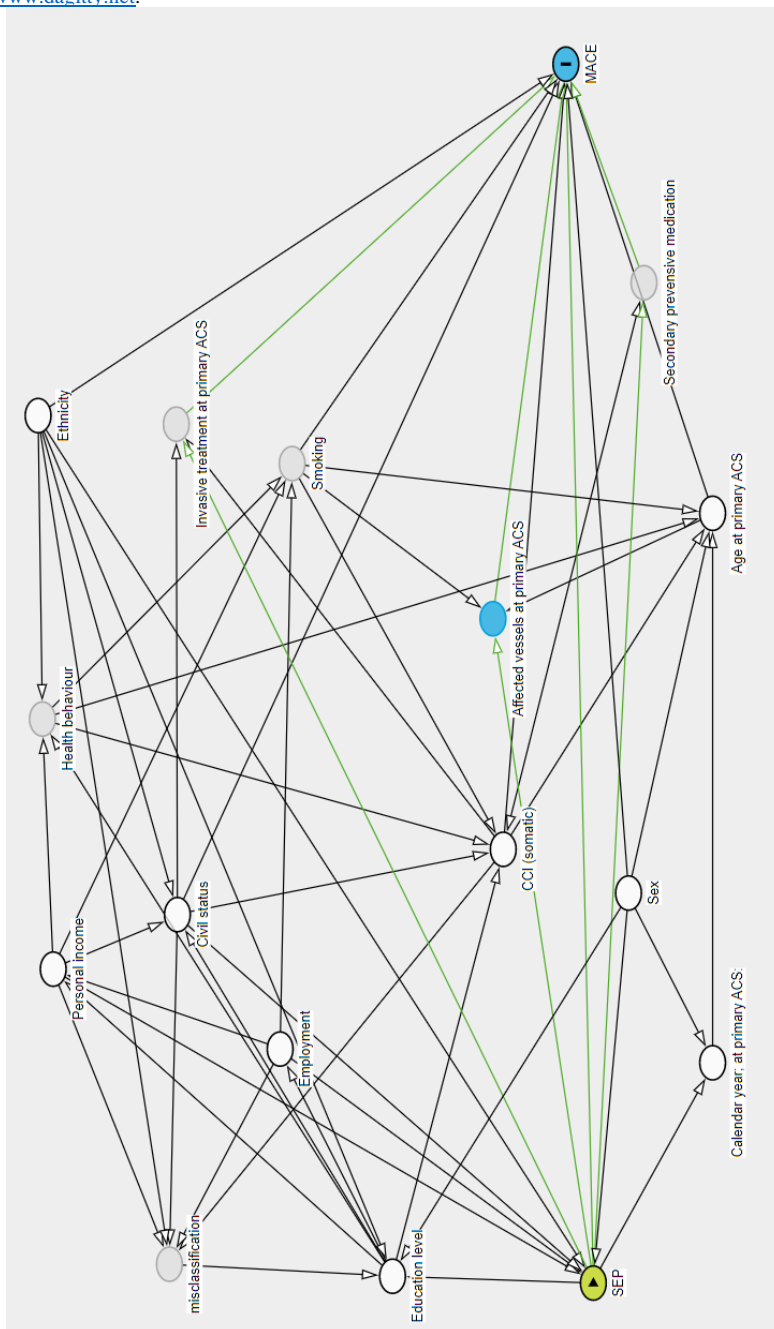
### Supplemental Figure S5. Causal diagram 1 Study III<sup>116</sup>

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](http://www.dagitty.net).



**Supplemental Figure S6. Causal diagram 2 Study III<sup>116</sup>**

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](http://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).<sup>6,131,168,171,175,181,191,193</sup>*

**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).<sup>220,243,256,260</sup>*

**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).<sup>220,260,293,309</sup>*

**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.<sup>134,303,314,316</sup>*

**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. Short education was associated with a higher risk of MACE than long education. Unemployment was associated with a higher risk of MACE than employment	HR: 1.68 [1.47-1.92] HR: 1.19 [0.99-1.40] HR: 1.75 [1.46-2.10]	1+ 0 1+
Kim et al., 2014b	Follow-up to 3 years	High area-based SEP was not associated with higher MACE than low deprivation. Tax-payer insurance was not associated with higher MACE than individual insurance. Low education was associated with a higher 3-year MACE compared to higher education	HR: 1.13 [0.95-1.33] HR: 1.25 [0.98-1.60] HR: 2.02 [1.54-2.64]	0 0 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.* <sup>134,303,314,316</sup>



# 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

ISSN (online): 2246-1302  
ISBN (online): 978-87-7573-748-2

**AALBORG UNIVERSITY PRESS**