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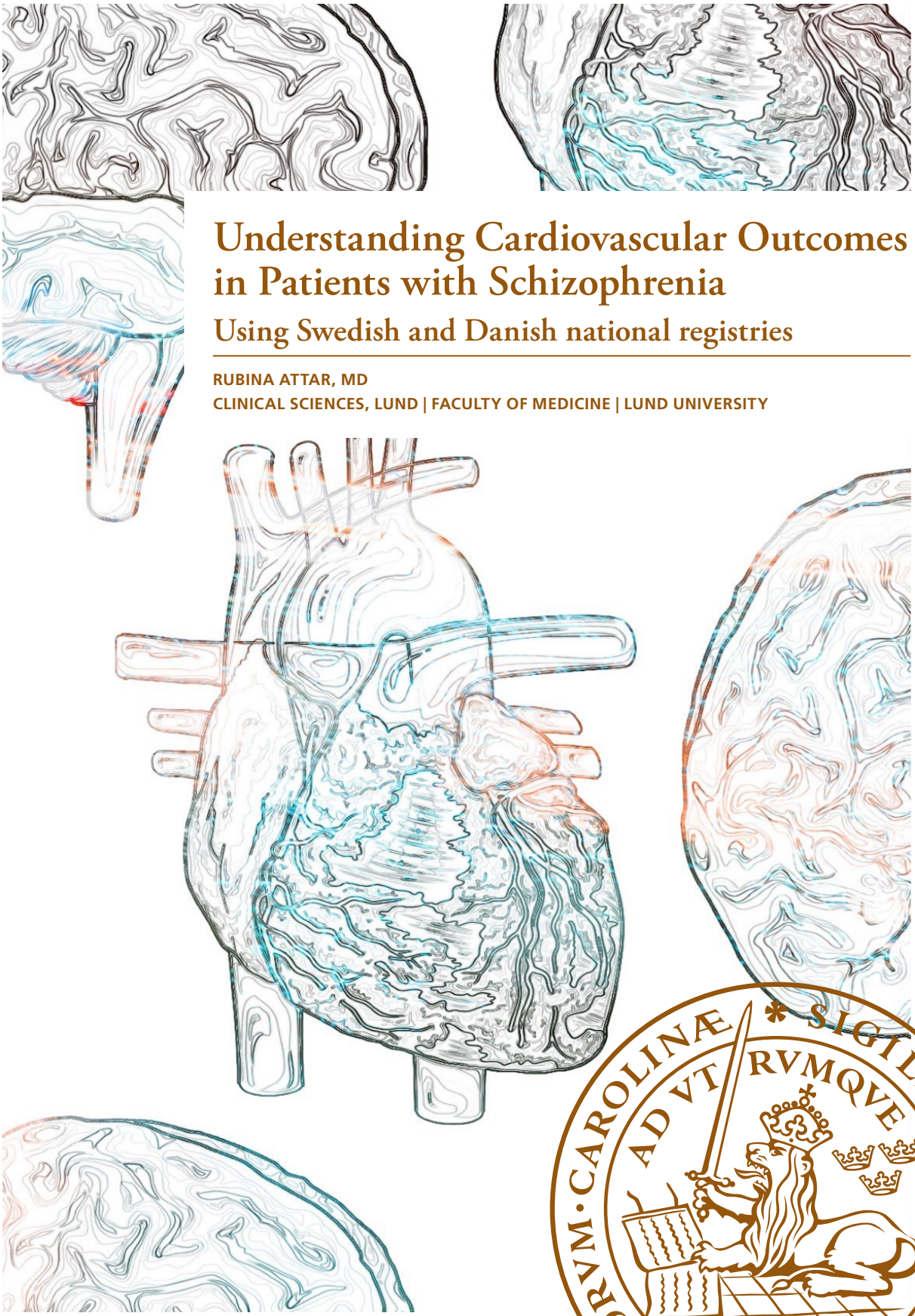
Attar, Rubina

2022

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



Understanding Cardiovascular Outcomes in Patients with Schizophrenia

Using Swedish and Danish national registries

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CLINICAL SCIENCES, LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

RUBINA ATTAR was born in Malmo, Sweden in 1994. She received her medical degree (MD) from Aalborg University, Denmark in 2020. In 2018, parallel to her medicine studies, she enrolled as a doctoral student at the Department of Cardiology at Lund University, Sweden. She is currently working as a physician at the Department of Cardiology at Rigshospitalet, Denmark. The focus of her doctoral thesis was to investigate cardiovascular outcome following myocardial infarction in patients with schizophrenia, a population with high mortality, primarily due to cardiovascular diseases.

Printed by Media-Tryck, Lund 2022 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Clinical Sciences, Lund, Cardiology

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2022:69
ISBN 978-91-8021-230-4
ISSN 1652-8220

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LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at BMC Segerfalksalen, Wallenberg Neurocentrum
11-05-2022 at 13:00

Faculty opponent
Rikke Sørensen, MD, PhD
Rigshospitalet, Copenhagen University

Organization LUND UNIVERSITY	**Document name** DOCTORAL DISSERTATION
Department of Cardiology, Clinical Sciences, Lund Faculty of Medicine, Lund University Lund, Sweden	**Date of issue** May 11th 2022
Author(s) Rubina Attar	Sponsoring organization

Title and subtitle
Understanding Cardiovascular Outcomes in Patients with Schizophrenia

Abstract

Introduction
Patients with schizophrenia have increased mortality compared to the general population, with a large proportion constituting cardiovascular mortality. This thesis aims to investigate cardiovascular outcomes in patients with schizophrenia and myocardial infarction (MI) in both Swedish and Danish quality-of-care registries.

Methods and results
Study I investigated major adverse cardiovascular events (MACE) following MI for 1,008 patients with schizophrenia using the nationwide SWEDEHEART registry in the period 2000-2018.

Study II investigated MACE following acute coronary syndrome (ACS) for 726 patients with schizophrenia using nationwide Danish registries in the period 1995-2013. Both study I and II showed increased risk of MACE; in study I patients with schizophrenia were less likely to be invasively investigated and discharged with recommended treatment compared to patients without schizophrenia.

Study III investigated temporal trends in treatment and outcomes following ACS in 734 patients with schizophrenia using nationwide Danish registries in the period 1996-2015. Study III showed lower rates of performed coronary procedures and increased mortality compared to patients without schizophrenia, with a relative difference that remained constant over the study period.

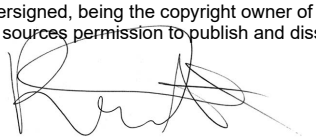
Study IV investigated coronary artery calcium score in 163 patients with schizophrenia at Aalborg University Hospital in the period 2015-2019 and found no difference in coronary artery calcium score compared to the general population.

Conclusion
This thesis highlights increased risk of adverse outcomes and suboptimal guideline-recommended cardiac treatment for patients with schizophrenia presenting with MI. Efforts to improve treatment and cardiovascular outcomes for this high-risk group are needed.

Key words: ACS, MI, CVD, schizophrenia, severe mental illness

Classification system and/or index terms (if any)

Supplementary bibliographical information		**Language** English
ISSN 1652-8220		**ISBN** 978-91-8021-230-4
Recipient's notes	**Number of pages** 84	Price
	Security classification	

Signature  Date 2022-04-04

Understanding Cardiovascular Mortality in Patients with Schizophrenia

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The mission of human beings is characterized by intelligence and thinking to understand the beauty of the world created by God

Cover photo by Fady Allan

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Lund, Sweden

ISSN 1652-8220
ISBN 978-91-8021-230-4
Lund University, Faculty of Medicine Doctoral Dissertation Series 2022:69

Printed in Sweden by Media-Tryck, Lund University
Lund 2022

To my parents,
for always believing in me

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I. Attar R, Wester A, Koul S*, et al*. Higher risk of major adverse cardiac events after acute myocardial infarction in patients with schizophrenia. *Open Heart* 2020;7:e001286. doi: 10.1136/openhrt-2020-001286

II. Attar R, Valentin JB, Freeman P, Andell P, Aagaard J, Jensen SE. The effect of schizophrenia on major adverse cardiac events, length of hospital stay, and prevalence of somatic comorbidities following acute coronary syndrome. *Eur Heart J Qual Care Clin Outcomes*. 2019;5(2):121-126. doi:10.1093/ehjqcco/qcy055

III. Attar R, Jensen SE, Nielsen RE, et al. Time Trends in the Use of Coronary Procedures, Guideline-Based Therapy, and All-Cause Mortality following the Acute Coronary Syndrome in Patients with Schizophrenia. *Cardiology*. 2020;145(7):401-409. doi:10.1159/000507044

IV. Trab, T., Attar, R., Jensen, S.E. *et al.* Coronary artery calcium in patients with schizophrenia. *BMC Psychiatry* **21,** 422 (2021). https://doi.org/10.1186/s12888-021-03412-x

Paper II was awarded Best Oral Presentation at European Society of Cardiology in 2018 (Barcelona).

In addition to the articles above, the author has published 9 other articles in international peer-reviewed journals.

Abbreviations

ACS	Acute Coronary Syndrome
CABG	Coronary Artery Bypass Graft
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CAG	Coronary Angiography
CNS	Central Nervous System
CT	Computed Tomography
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
ECG	Electrocardiogram
ECHO	Echocardiogram
EPS	Extrapyramidal Symptoms
HDL	High-Density Lipoprotein
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
STEMI	ST-Segment Elevation Myocardial Infarction

Abstract

Patients with schizophrenia have increased mortality compared to the general population, with a large proportion constituting cardiovascular mortality. This thesis aims to investigate cardiovascular outcomes in patients with schizophrenia and myocardial infarction (MI) in both Swedish and Danish quality-of-care registries.

Study I investigated major adverse cardiovascular events (MACE) following MI for 1,008 patients with schizophrenia using the nationwide SWEDEHEART registry in the period 2000-2018.

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This thesis highlights increased risk of adverse outcomes and suboptimal guideline-recommended cardiac treatment for patients with schizophrenia presenting with MI. Efforts to improve treatment and cardiovascular outcomes for this high-risk group are needed.

Sammanfattning (in Swedish)

Hjärtkärlsjukdom är den främsta orsaken till ökad dödlighet i världen, efterföljt av cancer och sjukdomar som drabbar lungor och luftvägar. Den ökade dödligheten är än mer framträdande hos patienter med psykiska sjukdomar, häribland patienter med schizofreni. Denna patientgrupp har 15 till 20 år kortare livslängd jämfört med befolkningen i övrigt. I denna doktorsavhandling undersöks patienter med schizofreni efter insjuknande i hjärtinfarkt avseende olika aspekter relaterade till behandling och prognos. Genom fyra delarbeten med svenska och danska kvalitetsregister undersökte avhandlingen skillnader mellan patienter med schizofreni och patienter utan schizofreni rörande behandling av hjärtinfarkt samt utfall efter utskrivning.

Studie I undersökte allvarliga kardiovaskulära händelser efter hjärtinfarkt för 1 008 patienter med schizofreni med hjälp av det rikstäckande SWEDEHEART-registret under perioden 2000–2018.

Studie II undersökte allvarliga kardiovaskulära händelser efter akut koronart syndrom för 726 patienter med schizofreni med hjälp av rikstäckande danska register under perioden 1995–2013. Både studie I och II visade ökad risk för allvarliga kardiovaskulära händelser; i studie I var det mindre sannolikt att patienter med schizofreni blev invasivt undersökta med kranskärlsröntgen, och lägre sannolikhet att de blev utskrivna med riktlinje-rekommenderad medicinsk behandling jämfört med patienter utan schizofreni.

Studie III undersökte tidsmässiga trender i behandling och dödlighet efter akut koronart syndrom hos 734 patienter med schizofreni med hjälp av rikstäckande danska register under perioden 1996–2015, och visade lägre frekvens av utförd kranskärlsröntgen, invasiva och noninvasiva behandlingar samt ökad dödlighet jämfört med patienter utan schizofreni. Denna skillnad förblev konstant över hela studieperioden.

Studie IV var en tvärsnittsstudie som undersökte kalk i kranskärlen hos 163 patienter med schizofreni vid Aalborg Universitetssjukhus under perioden 2015–

2019. Studien påvisade ingen skillnad i kalkmängd hos patienter med schizofreni jämfört med den allmänna befolkningen.

Denna doktorsavhandling belyser suboptimal riktlinje-rekommenderad hjärtbehandling och sämre utfall för patienter med schizofreni vid insjuknande i hjärtinfarkt. Det finns ett behov av insatser för att förbättra behandling och prognos efter hjärtinfarkt för denna högriskgrupp.

Introduction

The Heart

Historical background

The first written description of the heart dates back to Pharaonic Egypt around 15th century BC(1). The heart was described in the Ebers Papyrus chapter "Egyptian Book of Hearts", as *"the centre of the blood supply with vessels attached for every member of the body"* (Figure 1). Fascinatingly, in this chapter of the Ebers Papyrus, a cluster of symptoms with similarities to schizophrenia and affective disorders are described with association to the dysfunction of the heart(2). Many years later, in the 5th century BC, writings of Hippocrates described the heart as a muscle, but it was not until a century later that a detailed description of the heart was made by Aristotle. He described the heart in the centre of the human physiology, comprised of three chambers, one atrium and two ventricles connecting to the tissues by two major vessels(3).

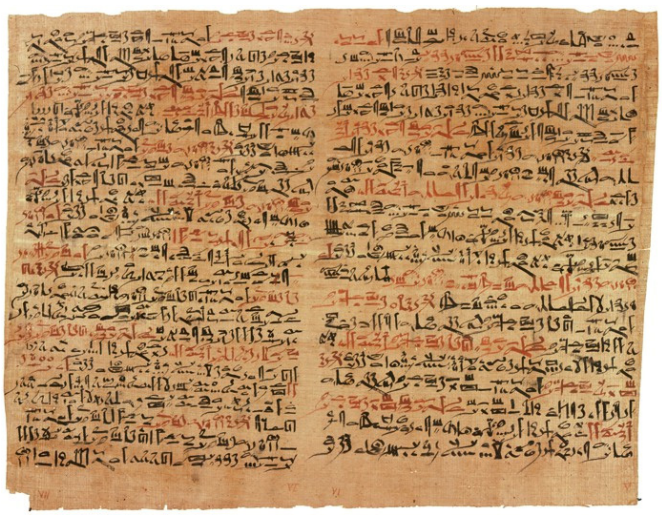

Figure 1: Excerpts taken from Magic and Medical Science in Ancient Egypt, by Paul Ghalioungui (1963)

Following this, in the 2nd century AD, Galen (129-200), a physician and philosopher during the Roman Empire revolutionized the antique understanding of the cardiovascular system following the teachings of Hippocrates and Aristotle. Though revolutionizing for that era, many of the teachings were gravely incorrect. Galen believed the liver to be the source of sanguification, that arteries were filled with air and blood and that blood could travel through the interventricular septum(4). Nevertheless, he more accurately described the pulsation of the heart and the difference in the structure of arteries and veins as well as describing the blood flowing in these vessels being of different colour. For the subsequent centuries following Galen, the Church viewed no interest in experimental science and held on to the scripts by Galen, since they theologically aligned with the teachings of the Church.

The first challenging of the Galenic schoolings was during the Islamic Golden Age by Ibn Al-Nafis (1213–1288). In the manuscript titled "*Sharah al Tashreeh al Qanoon"* or *"Commentary on the anatomy of Canon of Avicenna*" Al-Nafis stated that the blood did in fact not flow through the interventricular septum, described the veins, arteries, and bronchi of the lungs, and finally described the coronary arteries permeating the body of the heart to nourish the muscle. Seen as a pioneering father of the pulmonary circulation, his knowledge became a link in the long period between the Galenic teachings and the re-emerging of scientific curiosity in the Renaissance era(5).

One of the most famous persons during the Renaissance era was Leonardo da Vinci (1452-1519), an Italian artist, inventor, engineer and one of the earliest modern scientists with ideas ahead of his lifetime. With his passion for painting the human body grew his interest and fascination of the human anatomy and particularly, the heart; it is believed that he performed over thirty dissections of cadavers in his lifetime(6). He described the heart as "*instrumento mirabile invenzionato dal Sommo Maestro*" translating to *"a wonderful instrument invented by the Supreme Master*" (Figure 2). His scientific discoveries entailed a description of the four chambers of the heart, the hydrodynamics of the blood flow and function of the heart valves. He was also the first one to describe coronary artery calcification in a 100-year old man's cadaver and understood that reduction in blood flow led to cardiac dysfunction(7–9). Though revolutionizing in our understanding, many of the findings of da Vinci were never published and kept hidden for centuries since they contradicted the dogma of that era, an era strongly devoted to Galenic teachings.

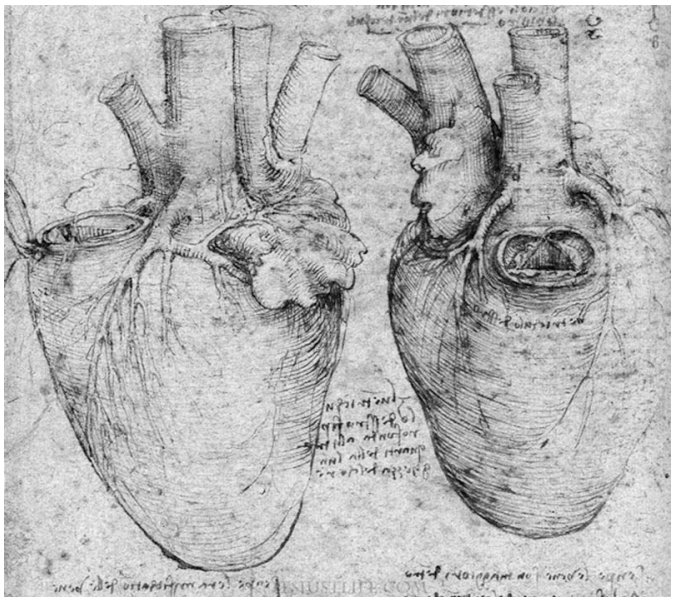

Figure 2: Drawings of the heart by Leonardo da Vinci circa 1510. Collection Windsor Castle, United Kingdom. Royal Collection Trust © Her Majesty Queen Elizabeth II

The subsequent advancement in cardiology was owed to the work of William Harvey (1578-1657). Harvey is considered the father of modern cardiovascular medicine with his discovery of the blood circulation following a study on 40 animals, described in his book "*De Motu Cordis"* translated to "*On the Motion of the Heart and Blood"*(10). Following his findings, the knowledge in the field accumulated exponentially to form cardiovascular medicine as we know it today.

While the fundamentals of the anatomy and physiology of the cardiovascular systems were being recognized, a new curiosity and understanding of symptomatology was born. In 1772, William Heberden (1710-1801) described a disorder of the breast with peculiar symptoms, similar to experiencing anxiety and the sensation of strangling. He further noted that these symptoms were attenuated by walking uphill, and relieved by standing still, but only during the first years of disease progression, later on the chest pain remained even upon lying down. Interestingly, he noted, that he mainly observed this odd symptom in middle aged men(11). It is safe to say that this description of myocardial ischaemia and angina has remained a textbook description until this day. It was a whole century later that the pathology behind angina, atherosclerosis and thrombosis was established(12).

The basics of the heart

The heart is a muscle responsible for providing all cells in the body with oxygenated blood through its pumping mechanism. There are four chambers in the heart, one atrium and one ventricle in each side of the heart. In each beat the oxygen rich blood travels in the systemic circulation from the left ventricle via the aorta and other arteries to all the organs in the body, where the red blood cell releases oxygen and the deoxygenated blood travels back to the right atrium via the venous system. The blood is continuously oxygenated by the lungs through travelling from the right ventricle to the lungs and then back to the left atrium, this is referred to as the pulmonary circulation. The pumping mechanism of the heart repeats itself between 60-100 times per minute, corresponding to the normal pulse(13). The heart has its own blood supply via the coronary arteries that leaves at the root of the aorta as the right coronary artery and left main artery. The left main artery further divides into the left ascending artery and circumflex artery. Arteries have three layers, the innermost layer is called the tunica intima and is made of squamous endothelial cells, the middle layer or tunica media consist of connective tissue and smooth muscle cells that can contract and relax, changing the diameter of the lumen and finally the outer layer or tunica externa which is made up of a strong adventitia layer.

Pathophysiology

Atherosclerosis is a complex process of plaque build-up in the arteries that can lead to rupture and the aggregation of thrombocytes causing an episode of acute coronary syndrome(14). The atherosclerotic process begins with the accumulation of lipids, especially low-density lipoprotein cholesterol (LDL-C) into the intimal layer of the artery and succeeding oxidation(15). Following this a release of cytokine and various inflammatory cells allows for the migration of monocytes into the subendothelial space where they undergo differentiation into macrophages. With the increase of LDL-C in the subendothelial space, the macrophages turn into foam cells subsequently creating a fatty streak(16). The fatty streak progresses into a plaque with the release of oxidative cytokines and multiplication of foam cells. Smooth muscle cells migrate into the intimal layer to duplicate and create a fibrous capsule around the atheromatous plaque (Figure 3). With time the plaque vascularizes with the formation of new blood vessels and usually progresses with calcification(17).

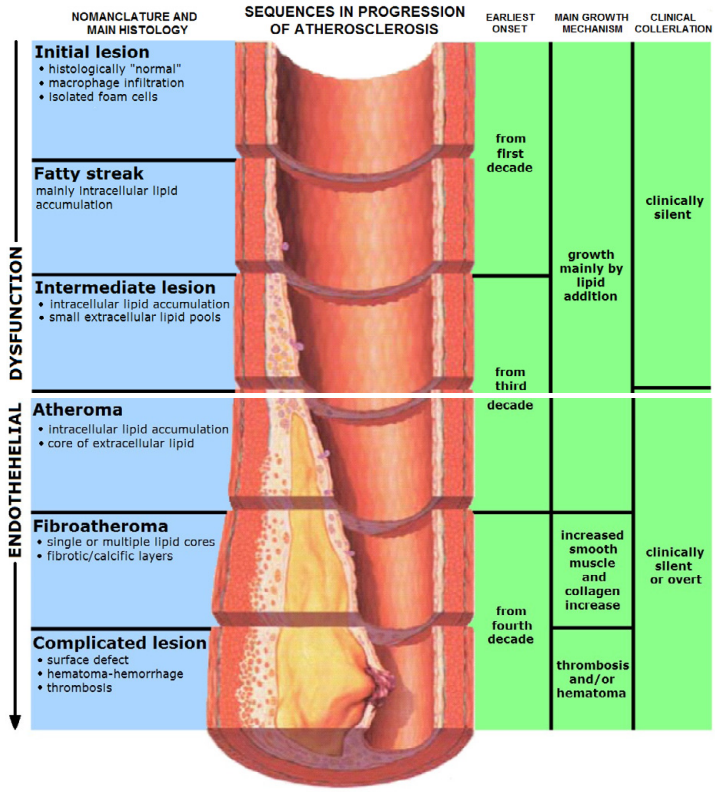

Figure 3: the progression of atherosclerosis with time

Coronary lesion

Multiple factors can transform the fibrous cap on the atherogenic plaque to become unstable. These include increased degradation of matrix metalloproteases, increased fibrinogen levels, higher blood viscosity and increased systemic inflammation(18). When the thin fibrous cap around the plaque becomes unstable, it can erode or rupture exposing the underlying thrombogenic products to the blood circulation, which causes platelet aggregation and ultimately the formation of a thrombus on the plaque. The thrombus formation can lead to sudden impairment of blood flow to the myocardium causing a myocardial infarction (MI), sudden cardiac death, or go unnoticed as silent ischaemia(19). The erosion or rupture of a thin cap fibroatheroma is the singular most common cause of an acute coronary syndrome (ACS)(20,21).

Cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death globally with an estimate of 18 million deaths annually(22). The term CVD is broad and covers multiple diseases of the heart and blood vessels, e.g., coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease, aortic atherosclerosis, and heart failure(23). Heart failure is a condition in which the function of the heart is reduced and involves the inability to meet the systemic requirement of arterial blood flow or the failure to accommodate the venous return, causing congestion. It can be caused by various differing mechanisms including CAD, hypertension, diabetes, electrical abnormalities, toxins, infections, and inflammation(24). CAD is the result of atherosclerosis in the coronary arteries. If the rupture of an atheromatous plaque leads to the sudden impairment of blood flow to the myocardium, also called myocardial ischaemia, it can lead to an episode of ACS. ACS is an umbrella term for three types of acute reduction or blockage of blood supply to the heart. These include unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI)(25). According to the Fourth Universal Definition of Myocardial Infarction, a MI is defined pathologically as cardiac myocyte necrosis due to prolonged ischaemia. The clinical criterion for a diagnosis of MI requires a dynamic rise and fall of cardiac troponins, as well as clinical evidence of ischaemia including characteristic symptoms (angina, dyspnoea, nausea, anxiety etc.), ECG changes (ST-segment deviations, pathological Q-waves, left bundle branch block, T-wave abnormalities) and angiographic or other imaging modalities with findings suggestive of intracoronary thrombus(26).

Risk factors

The conception we have of risk factors for the development of CAD is mostly derived from the Framingham study in 1961. Cardiologists, epidemiologists, and biostatisticians joined forces and investigated the lifestyle of residents in Framingham, Massachusetts to gain a better understanding of the factors that played a role in developing CAD(27). We know today that the risk factors for CAD can be both modifiable and non-modifiable. The modifiable risk factors are obesity, hyperlipidaemia, hypertension, diabetes, sedentary lifestyle, unhealthy dietary habits, smoking, drug abuse and excess alcohol consumption. The non-modifiable risk factors are older age, male sex, genetic factors, and family history of premature CAD. On a population level the modifiable risk factors contribute the most to the

high prevalence of CAD, underlining the importance of primary prevention to reduce the risk of developing these risk factors(28).

Non-invasive diagnostic modalities

An electrocardiogram (ECG) measures the electrical activity of the heart, and in the event of ischaemia, changes such as ST-segment deviation, pathological Q-waves, left bundle branch block, and T-wave abnormalities can be seen, however, the ECG can sometimes be normal despite ischaemia(29). An ECG can be supplemented with a stress test in non-acute situations, which measures the electrical activity of the heart during physical or pharmacological stress(30). Another imaging modality is an echocardiogram (ECHO), which uses ultrasound waves to portray the heart dimensions and functions(31). In the event of ischaemia there could be wall-motion abnormalities, reduced global left ventricular function, or mechanical complications such as ischaemic ventricular septum defects and mitral valve prolapse. During prolonged ischaemia as in the case of a MI, highly sensitive cardiac troponins are elevated in the blood and usually follows a dynamic pattern of rise and fall(32).

More recently an increase in the use of cardiac computed tomography (CT) has improved the diagnosis and prognosis in patients with stable CAD(33). It is an asset in evaluating the total plaque morphology as well as total plaque burden in patients with stable chest pain and can be a useful tool prior to invasive angiography. Atherosclerosis and plaque build-up can be quantified with a standardized coronary artery calcium (CAC) score and is a good predictor of cardiovascular morbidity(33).

Invasive diagnostic and treatment modalities

Until 60 years ago the gold standard for treating a MI was bed rest(34) and out of the patients who were privileged enough to reach a hospital in time, only 60% survived a MI(35). The alarmingly high rates of in-hospital mortality took a turn with the development of cardiac care units where patients could be closely monitored with continuous ECG and have proximity to nurses, who could aid in chest compressions and defibrillation in the event of ventricular arrhythmias. This initiative cut the in-hospital mortality by half(36).

One of the most remarkable events in the history of cardiovascular medicine was the first cardiac catherization by Werner Forssmann, which he performed on himself during local anaesthesia in 1929(37). This discovery would award him a shared

Nobel prize in 'Physiology or Medicine' in 1956(38) and would lead to the discovery of coronary angiography in 1958, an exceptionally valuable tool in visualization of the arteries prior to surgical revascularization(39). In 1977, Andreas Grüntzig introduced the first minimally invasive coronary revascularization technique called the percutaneous coronary intervention (PCI)(40). Grüntzig performed successful PCI with an inflatable balloon in 32 of the 50 patients included in the study. He also noted that PCI was suitable for simpler cases and estimated 10-15% of the candidates for coronary bypass surgery (CABG) would instead be suitable for PCI(40). Ever since, multiple randomized controlled trials have investigated CABG vs. PCI in patients with multivessel CAD, and thus far CABG remains superior to PCI, in patients with multivessel disease and diabetes(41). The PCI technique has advanced significantly from balloons and bare metal stents to the drug eluting stents and techniques we have today(42). The procedure can restore impaired blood flow in a coronary artery, and is the gold standard in the treatment of an MI(26).

Pharmacological treatment

Dual anti-platelet therapy

Dual anti-platelet therapy with aspirin and a $P2Y_{12}$ inhibitor creates the essential foundation in the treatment of an MI(26,43). Aspirin works by inhibiting platelet aggregation through suppression of thromboxane A2 and are recommended for lifelong treatment following a MI. The lifesaving effect of aspirin was established in 1974(44) and confirmed in a plethora of trials ever since(45). $P2Y_{12}$ inhibitors block adenosine diphosphate stimulated receptors and thus platelet activity. The three most common $P2Y_{12}$ inhibitors include clopidogrel, ticagrelor, and prasugrel. The current guidelines recommend ticagrelor or prasugrel for treatment of an ACS instead of the older clopidogrel due to a more rapid onset of action, higher platelet inhibition potency, low inter-drug variability, and greater reduction in subsequent ischaemic events(46,47).

Anticoagulation therapy

The clinical use of unfractionated heparin (UFH) in its therapeutic form started in the mid 1930's. Since the discovery of catheter-based angiography, UFH has remained the anticoagulant of choice during PCI(48). The anticoagulant effect of UFH derives from its ability to inactivate factor Xa and thrombin while activating antithrombin III. Alternatives to UFH include fondaparinux and enoxaparin which

have none to low anti-thrombin activity and thus not appropriate following PCI(48). The thrombin inhibitor Bivalirudin has success rates corresponding to that of UFH and therefore a suitable alternative during PCI(49).

Bleeding is the leading non-cardiac adverse effect following PCI that has increased with the use of anti-platelet and anticoagulation therapy(50). The challenge of benefit/risk ratio has birthed endless clinical trials to improve prognosis following PCI(51), which remains an ongoing challenge.

Treatment for CVD risk factors

Pharmacological treatments for the modifiable CVD risk factors are cornerstones in reducing cardiovascular morbidity and mortality. Pharmacological interventions for hyperlipidaemia include statins, with addition of ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in statin intolerant patients or in patients not reaching the target LDL goal(52). Cardiovascular risk can be reduced by 50% with a reduction of 20/20mmHg in blood pressure, making antihypertensive medications central in primary and secondary prevention(53). Recently focus on CVD risk in patients with diabetes has led to a reduction in mortality with the introduction of sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) analogues(54).

Another important aspect of slowing the progression of CAD is cardiac rehabilitation with exercise. It has shown beneficial in terms of cardiac pump function, symptom relief (angina and dyspnoea), fewer readmissions and lowering of cardiovascular risk factors(55,56). The health benefit of smoking cessation is well known. Smoking is responsible for 20% of CVD and cessation is associated with a CVD risk reduction of 40% compared to active smokers(57).

Schizophrenia

Historical Background

Schizophrenia is a severe mental illness which has existed throughout time and across cultures. In antiquity, it was described as a “madness” and has through historical metamorphism evolved into the definition we know it by today, a mental illness characterized by hallucinations and delusions. The first description of a cluster of symptoms like that of schizophrenia was in the Ebers Papyrus in the chapter “Egyptian Book of Hearts”, since it was presumed to be a disease of the heart, rather than the mind, although the distinction between the heart and mind had not yet been defined(1). Up until 135 years ago, most of the mental illnesses were clustered into the same category and treated similarly by unconventional means by today’s standards. Some believed that people with psychotic illnesses such as schizophrenia were possessed by demons and therefore underwent religious exorcistic rituals as a form of treatment(58,59).

It was not until 1887 that the German psychiatrist Emile Kraepelin categorized the various mental illnesses and popularized the term “dementia praecox” describing what we today know as schizophrenia. The term dementia was used to describe someone “being out of their mind” or simply “mad” and praecox referred to the premature onset of the illness(60). In 1908 the term dementia praecox was challenged by Swiss psychiatrist, Paul Eugen Bleuler, who argued that not all persons with schizophrenia would develop dementia, which by then had unravelled itself closely to the dementia we know of today(61), nor did the illness consistently debut prematurely(62). Dr Bleuler proposed the alternative term schizophrenia which comes from the old Greek s*chizein* (σχίζειν, "to split") and *phrēn*, (φρήν, "mind")(63), however, the term unintentionally led to the misconception that persons with schizophrenia have multiple or split personalities, which is a disorder on its own called Dissociative Identity Disorder(64).

Symptomatology

Dr Bleuler categorized the symptoms of schizophrenia into “positive” and “negative”, a description still utilized today. Positive symptoms are present during a psychotic episode and can include hallucinations, delusions and disorganized speech and thought. Negative symptoms are characterized by the inability to express

emotions, poverty of speech and the lack of motivation, pleasure, and desire to form relationships with other people(65). A third category of symptoms was described in 1992 that introduced cognitive impairment as a core feature in patients with schizophrenia. The impairments affects all cognitive domains resulting in difficulties with learning, memory and problem solving, and patients suffer rapid regression of cognitive function with increasing age(66).

Classification Systems

In modern time the two major classification systems, the International Classification of Disease (ICD) and The Diagnostic and Statistical Manual of Mental Disorders (DSM), have presented different versions of criteria for conceptualizing schizophrenia, with increasing similarities between the systems with each revision. The 11th, and latest version for classification of schizophrenia (ICD-11) was presented in June 2018, and the essential diagnostic features are as following(67):

Diagnostic Requirements for Schizophrenia from the ICD-11:

At least two of the following symptoms must be present (by the individual's report or through observation by the clinician or other informants) most of the time for a period of 1 month or more. At least one of the qualifying symptoms should be from item a) through d) below:

a. Persistent delusions (e.g., grandiose delusions, delusions of reference, persecutory delusions).

b. Persistent hallucinations (most commonly auditory, although they may be in any sensory modality).

c. Disorganized thinking (formal thought disorder) (e.g., tangentiality and loose associations, irrelevant speech, neologisms). When severe, the person's speech may be so incoherent as to be incomprehensible ('word salad').

d. Experiences of influence, passivity or control (i.e., the experience that one's feelings, impulses, actions or thoughts are not generated by oneself, are being placed in one's mind or withdrawn from one's mind by others, or that one's thoughts are being broadcast to others).

e. Negative symptoms such as affective flattening, alogia or paucity of speech, avolition, asociality and anhedonia.

f. Grossly disorganized behaviour that impedes goal-directed activity (e.g., behaviour that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interferes with the ability to organize behaviour.)

g. Psychomotor disturbances such as catatonic restlessness or agitation, posturing, waxy flexibility, negativism, mutism, or stupor. Note: If the full syndrome of Catatonia is present in the context of Schizophrenia, the diagnosis of Catatonia Associated with Another Mental Disorder should also be assigned.

The symptoms are not a manifestation of another medical condition (e.g., a brain tumour) and are not due to the effects of a substance or medication (e.g., corticosteroids) on the central nervous system, including withdrawal effects (e.g., from alcohol).

Pharmacological Treatment

The first pharmacological treatment for psychosis was unintentionally discovered while researchers were trying to find substitutes for the Malaria drug Quinin during the war shortage. The journey from malaria drugs to antihistamines and sedatives, serendipitously led to the discovery of Chlorpromazine, an agent of anaesthesia, in 1952(68). The depressing effects of the central nervous system were quickly described in papers and soon the drug was distributed to two psychiatric hospitals in Paris for testing in patients with psychotic symptoms(69). Following the success of this trial numerous antipsychotic agents were discovered, including Haloperidol in 1958(70). Researchers soon discovered side-effect associated with these first-generation antipsychotic drugs, involving tardive dyskinesia, dystonia, akathisia, and parkinsonism, jointly referred to as acute extrapyramidal symptoms (EPS)(70). First generation antipsychotics also entailed an increased risk of QT interval prolongation(71), arrythmias and sudden cardiac death(72). A decade later the first atypical antipsychotic drug without EPS, Clozapine, was introduced to the market and following this, several other drugs such as Risperidone and Olanzapine were discovered and added to the arsenal of atypical antipsychotics or second-generation antipsychotics(73). The second-generation antipsychotics, instead of EPS, carry an increased risk of metabolic side effects such as diabetes, hypertension, and increased cholesterol, which left untreated leads to the development of heart disease(74).

Epidemiology and aetiopathogenesis

The lifetime prevalence of schizophrenia is 1% worldwide, equally common in both sexes and usually debut in the early 20's(75). The aetiology of schizophrenia remains a conundrum, but researchers have proposed several contributing factors. Among these are the twin (76,77) and adoption studies (78) that demonstrate a clustering of the illness in siblings with genetic similarity, primarily in monozygotic twins. More recent, researchers have found multiple genetic mutations that play a role in the development of schizophrenia(79). Furthermore, obstetric complications such as preeclampsia, low birth weight and delivery difficulties have been suggested as contributing environmental factors(80). Moreover, CT and magnetic resonance imaging (MRI) studies (Figure 4) have shown abnormalities in various brain structures, including overall loss of brain volume in patients with schizophrenia(81). The dopamine hypothesis proposes increased dopamine activity in the brain of patients with schizophrenia, an observation made following the discovery of antipsychotic medications, which primarily had an antagonistic effect on dopaminergic receptors and reduced positive symptoms. The current version of the hypothesis suggests a dysregulation rather than a hyperactivity, since some parts of the brain have a depletion in dopamine, which may be responsible for the negative symptoms(82).

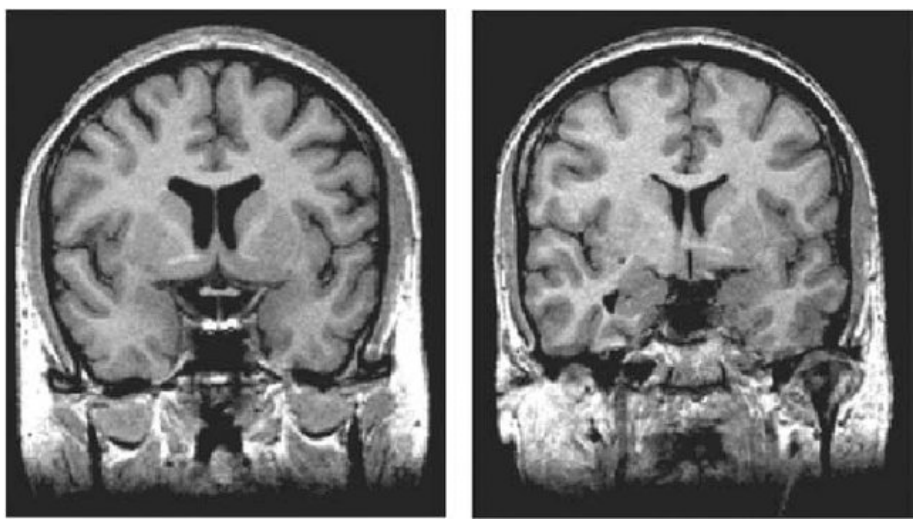

Figure 4: Magnetic reconance imaging (MRI) of a normal brain (left) and a brain of a person with schizophrenia (right) from the Maudsley Family Study. (Adapted from McDonald et al., 2002)

Cardiovascular disease in Schizophrenia

Patients with schizophrenia have on average 15-20 year shorter life expectancy(83). The leading cause of death is cardiovascular(84), followed by cancers and respiratory disease. The risk of developing CAD is almost doubled in patients with schizophrenia compared to the general population(85) largely due to an increased burden of cardiovascular risk factors in this population (85–87). Patients with schizophrenia have higher prevalences of diabetes mellitus (DM), hypertension and dyslipidaemia (88,89). They more often have unhealthy lifestyle habits including smoking(90), sedentary behaviour with low physical activity (91), poor diet(92) as well as substance and alcohol abuse(93). Furthermore, antipsychotic medications are associated with an increased risk of metabolic syndrome. Metabolic syndrome consists of a cluster of risk factors for CVD defined as an increased waist circumference, hypertension, impaired glucose tolerance, type 2 diabetes mellitus, and dyslipidaemia(94). Often adding to this myriad of risk factors is a lack of insight into their own wellbeing(95), which further complicates the prevention and treatment of CVD in patients with schizophrenia.

Aims

The overall aim of this thesis was to investigate treatment, management, and cardiovascular outcomes following acute coronary syndrome or myocardial infarction in patients with schizophrenia utilizing Swedish and Danish registries.

I. To investigate major adverse cardiovascular events (all-cause mortality, rehospitalization for myocardial infarction, stroke, or heart failure) five years after a first myocardial infarction as well as guideline-based management using the nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.

II. To investigate major adverse cardiovascular events (all-cause mortality, re-infarction, and stroke), length of hospital stays and development of comorbidities 1-, 5- and 10-years following a diagnosis of acute coronary syndrome using Danish national patient registries.

III. To investigate temporal trends in two decades regarding the use of invasive cardiac procedures (coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting), guideline-based therapy and all-cause mortality following acute coronary syndrome in patients with schizophrenia using Danish national patient registries.

IV. To investigate coronary artery calcium score with cardiac computed tomography in patients with schizophrenia using Danish national patient registries.

Methods

Descriptions of the registries

In study I, the data was obtained from SWEDEHEART registry, the Swedish National Patient Registry, as well as the Swedish National Population Registry. The data from study II-IV was derived from the Danish National Patient (DNPR) registries linked to other national registries described in detail below.

SWEDEHART

SWEDEHEART is a national registry including all patients hospitalized for symptoms suggestive of a MI at a coronary care unit as well as patients undergoing catheter-based diagnostic procedures and/or interventions for any indication. The SWEDEHEART registry was created after merging the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the National Registry of Secondary Prevention (SEPHIA) and the Swedish Cardiac Surgery Registry SWEDEHEART is extensive with an addition of 80.000 new cases each year and a high coverage percentage. There are over 175 variables available for those admitted for ACS or MI and over 150 variables for CAG. Upon entering the database, all personal identity numbers are replaced with a unique serial SWEDEHEART number to ensure anonymity. To guarantee high quality and calculate the validity of the database, a special designated committee does routine checks at randomly chosen hospitals in the country, where entered variable entries are compared to patient records(96).

Linking SWEDEHEART and other registries

All residents in Sweden have a unique personal identification number which allows for the linkage between SWEDEHEART and other national registries such as the Swedish National Patient Registry for personal data and other non-cardiac diagnoses, like schizophrenia. The diagnoses in the Swedish registries are based on

World Health Organizations (WHO) International Classification of Disease (ICD). The 9th version of ICD was used in the years 1987-1996, with the implementation of the 10th version on January 1st, 1997.

The Danish National Patient Registry

The DNPR is one of the oldest national registries in the world established in 1977. Initially it entailed somatic contacts but since 1995 the Danish Psychiatric Central Research Register was integrated in the DNPR along with emergency contacts. It contains administrative and clinical data on each patient including identification, municipality, information on hospital stay, admission and discharge diagnoses as well as types of investigation and treatment received(97). The validity of schizophrenia (98) and cardiovascular diagnosis(99) is high in the DNPR.

Linking the DNPR

All residents of Denmark are registered in the Danish Civil Registration System and assigned a personal number called the Civil Person Registration (CPR) number(100). The CPR number allows for the linkage between different national databases such as between the DNPR and the Danish National Prescription Registry and the Cause of Death Register. The Danish registries also follow the WHO ICD system; however, the 9th version of ICD was never introduced in Denmark, therefore prior to 1994 the diagnoses were based on ICD-8 and following January 1st, 1994, ICD-8 was replaced with the ICD-10.

Study populations

Study I

In the first Swedish nationwide cohort follow-up study, all patients ≥18 years diagnosed with a MI (STEMI or NSTEMI) in the period between January 1st, 2000, and May 29th, 2018, were included. Patient data was derived from the SWEDEHEART registry and from the Swedish National Patient Registry. MI was defined as having a discharge diagnosis of ICD-10 I21.0-I21.4. Patients with an additional diagnosis of schizophrenia ICD-9 295 (prior to 1997) or ICD-10 F20 and F25 (schizoaffective disorder) preceding the diagnosis of MI were compared to all patients without a diagnosis of schizophrenia.

Study II

In the second Danish nationwide cohort follow-up study patients with a discharge diagnosis of ACS entailing unstable angina pectoris I20.0, NSTEMI I21.4, STEMI I21.0-I21.3 and unspecified MI I21.9 as well as a diagnosis of schizophrenia 295 (ICD-9) or F20 and F25 (schizoaffective disorder) were compared to patients with ACS without any psychiatric diagnosis (ICD-10 F*, X60–X84, Y10–Y34 and ICD-8 290–315, E950–E959). Patients were matched 2:1 on age, sex (within one year), risk score and year of ACS diagnosis. Patients were included if the ACS diagnosis was given in the period from January 1st, 1995, until 31st of December 2013, and followed until 31st of December 2014, ensuring at least one-year follow up.

Study III

The third study was a cohort study including patients with a discharge diagnosis of ACS including unstable angina pectoris I20.0, NSTEMI I21.4, STEMI I21.0-I21.3 and schizophrenia 295 (ICD-9) or F20. Patients with both ACS and schizophrenia were compared to ACS patients without any psychiatric diagnosis. The comparison groups were matched 2:1 on age, sex (within one year), and year of ACS diagnosis. Patients where included January 1st, 1996, until December 31st, 2015, and followed an additional year until December 31st, 2016.

Study IV

The final study was a cross-sectional study performed in North Denmark Region including all patients ≥18 years with a diagnosis of schizophrenia 295 (ICD-9) or F20 and F25 (schizoaffective disorder). All patients included underwent a coronary CT scan in the years 2015-2019, and CAC score was assessed and compared to age and sex-matched norm percentiles.

Outcomes

Study I

The main outcome was MACE, a composite of all-cause mortality, rehospitalization for MI, stroke, or heart failure at five years following an MI. The remaining outcomes were the individual components of MACE, as well as hospitalisation/transfusion requiring bleeding, a comparison of proportions of patients receiving guideline-based treatment at discharge, patient- and system-delays, defined as time from symptom onset to ECG (patient delay) and time from ECG to CAG (system delay). We also studied symptom presentation, laboratory findings as well as invasive investigations, interventions, and medical treatment in all patients.

Study II

The primary outcomes resembled those in Study I, however with a different population and database. MACE in this study was a composite of all-cause mortality, re-infarction (proxy for rehospitalization for MI; (ICD-10 I21.0–I21.4, I21.9) or ischaemic/haemorrhagic stroke (ICD-10 I61, I63, I64, I69.3, and I69.4) following a diagnosis of ACS. The secondary outcomes were the individual components of MACE as well as length of hospital stays and the development of various comorbidities at 1-, 5- and 10-years following ACS.

Study III

The third study investigated temporal trends in the use of CAG, PCI and CABG following ACS over the course of 20 years comparing patients with schizophrenia to patients without schizophrenia. We also investigated 20-year trends in various guideline recommended medications following discharge, these included acetylsalicylic acid, P2Y12 inhibitors, lipid-lowering drugs, nitrates, β-blockers, calcium antagonists, and ACE-inhibitors/angiotensin receptor blockers. We also investigated the trend in 1-year all-cause mortality over the same period following ACS. Socioeconomic status was described using the International Standard Classification of Education and individual income levels divided into quartiles defined as ≤Q1, 195,151 DKK/year; >Q1–Q2, 195,151–251,185 DKK/year; >Q2–Q3, 251,185–377,046 DKK/year; >Q3–Q4, 377,046 DKK/year.

Study IV

The final study investigated CAC score in patients with schizophrenia and compared these to age and sex-matched norm percentiles. The CAC scores were categorized into four categories based on the risk of future CAD where a CAC score of 0 denoted a very low risk and a CAC score of above 300 denoted a moderate to severely increased risk. Assessment of CAC was done independently by two observers who marked the visible lesions and a CAC score was calculated according to the Agatston method (101) using an online software.

Statistical methods

Baseline characteristics were compared between groups using Student's t-test for normally distributed continuous variables and Mann-Whitney U-tests for non-normally distributed variables, and Pearson Chi-Square tests for comparisons in categorical variables. Continuous variables were presented as means with standard deviation (SD) or medians with 1^{st}-3^{rd} quartiles as appropriate; categorical variables were expressed as counts with percentages.

Survival analyses were performed for all outcomes where time to event was of interest, these included MACE and its individual components. The results for univariate analyses were presented graphically with the Kaplan-Meier estimator and the differences between the groups were tested using Log-rank tests. Cox proportional hazard models were used to investigate multivariable outcome analysis. The proportionality of hazard assumption was investigated by visual inspection and was satisfied. Results were presented as hazard ratio (HR) with 95% confidence intervals (95% CI).

A two-tailed p-value <0.05 was considered statistically significant. Analyses were performed using STATA version 14 (Study I and Study II), version 16 (Study IV), SPSS version 25 (Study I) or SAS version 9.4 (Study III).

Study I

Outcomes were analysed and presented in four different models of adjustment. Each model of adjustment entailed additional variables, with the first representing a crude HR. The following variables were adjusted for in model 2: age and sex, in model 3: model 2 and previous PCI, CABG, MI, heart failure, chronic kidney disease, chronic

obstructive pulmonary disease, peripheral artery disease, bleeding requiring hospitalisation, stroke, diabetes, hypertension, hyperlipidaemia and smoking, and finally in model 4: model 2, 3 and revascularisation method during hospitalisation (PCI, CABG or medical management) and guideline recommended discharge medications (ACEi, ARBs, beta-blockers, statins, aspirin and P2Y12 inhibitors). To investigate if schizophrenia was independently associated with the use of guideline-based medications after MI, a multiple logistic regression model, with the same variables as in model 3, was used.

Study II

Confounding risk assessment was performed using a risk score of 3 levels. Level 1 indicated zero comorbidities, level 2 indicated up to two comorbidities and level 3 indicated three or more comorbidities. For detailed description of the various comorbidities and codes se paper II. The risk score was included in the multivariate analyses to adjust for dissimilarities between the populations.

Study III

The data for the time trends in the two populations was presented as cumulative incidences in three different time periods (1996–2002, 2003–2009, and 2010–2015) to ensure sufficient data volume for each period. The relative difference between the populations was then quantified with a p-value using a time interaction term from a Cox proportional hazard model.

Study IV

The CAC score results were non-parametric and therefor log-transformed to normal distribution, confirmed by histograms, QQ-plot and Shapiro Wilk test for normality. The log-transformed CAC scores were analysed with univariate and multivariate linear regressions. Results from the logistic regression were presented as odds ratios (OR) and coefficients from the linear regressions were presented as percentage change in CAC score.

Ethical considerations

Study I was approved by the Swedish Ethical Review Authority at Lund University. Study II and III did not require ethical approval according to Danish legislation since all data was handled anonymously. Study IV was approved by the Regional Committee on Biomedical Research Ethics of North Jutland and conducted according to the declaration of Helsinki with all participants giving informed consent. The study was registered at clinicaltrials.gov with identifier NCT02885792.

Results

Study I

A total of 286 333 patients who had experienced a MI were included in the study, of these 1 008 patients had a diagnosis of schizophrenia prior to their MI. Patients with schizophrenia experienced a MI almost 10 years prior to the rest of the population and were more often smokers with higher prevalences of chronic obstructive pulmonary disease, diabetes, heart failure and bleeding. We also found lower prevalences of many important CVD risk factors such as hypertension and hyperlipidaemia in the population with schizophrenia. Laboratory findings for patients with schizophrenia showed higher creatinine and CRP levels, and slightly lower haemoglobin, triglyceride, cholesterol, and coronary marker levels. Patients with schizophrenia more often experienced dyspnoea and cardiac arrest as opposed to typical chest pain during MI. ECG readings were more often abnormal in patients with schizophrenia showing bundle branch blocks and pathological Q-waves. Similarly, ECHO showed worse left ventricular function in patients with schizophrenia.

Coronary intervention

Patients with schizophrenia had fewer coronary procedures performed including CAG, PCI, and CABG. Of the 59% of patients who received a CAG, no evident difference was seen in the angiographic findings between the populations.

Guideline recommended medications

Patients with schizophrenia were less likely to be discharged with guideline recommended medications, however, after multivariate adjusting only the rates of ACEi/ARBs and statins remained significantly lower.

Patient and system delays

Patients with schizophrenia averaged one day longer stay in the hospital. No differences were seen in the patient nor system delays.

Main outcome

Patients with schizophrenia had increased risk of MACE in all models ranging from a crude HR of 1.35 (1.23-1.47) to adjusted HR 2.05 (95% CI 1.63-2.58). This was also true for heart failure crude HR 1.25 (1.10-1.42) to adjusted HR 1.39 (1.04-1.86). Reinfarction, stroke and bleeding HR were not significantly increased in the population with schizophrenia (Table 6 from Study I).

Table 4 Recommended medications at discharge following acute myocardial infarction comparing patients with and without schizophrenia

	Schizophrenia (n=1008)	Without schizophrenia (n=285 325)	Total (n=286 333)	Missing n (%)	P value
Aspirin, n (%)	844 (83.7)	244 195 (85.6)	245 039 (85.6)	6514 (2.3)	0.001
P2Y12 inhibitor, n (%)	608 (60.3)	178 564 (62.6)	179 172 (62.6)	7848 (2.7)	0.005
ACEi/ARBs, n (%)	249 (24.7)	88 864 (31.1)	89 113 (31.1)	4495 (1.6)	<0.001
Beta blockers, n (%)	778 (77.2)	236 069 (82.7)	236 847 (82.7)	6633 (2.3)	<0.001
Statins, n (%)	703 (69.7)	210 379 (73.7)	211 082 (73.7)	7096 (2.5)	<0.001

ACEi, ACE-inhibitor; ARBs, angiotensin two receptor blocker.

Table 6 Clinical outcomes for patients with schizophrenia following an acute myocardial infarction compared with patients without schizophrenia at 5 years

		Adjusted HR (95% CI)		
	Unadjusted HR (95% CI)	Model 1	Model 2	Model 3
MACE	1.35 (1.23 to 1.47)*	2.44 (2.23 to 2.67)*	2.20 (1.79 to 2.72)*	2.05 (1.63 to 2.58)*
Mortality	1.44 (1.31 to 1.59)*	2.99 (2.72 to 3.29)*	2.53 (1.00 to 3.21)*	2.38 (1.84 to 3.09)*
Reinfarction	1.00 (0.82 to 1.24)	1.53 (1.25 to 1.89)*	1.41 (0.86 to 2.30)	1.29 (0.77 to 2.13)
Stroke	1.03 (0.80 to 1.34)	1.67 (1.29 to 2.17)*	1.72 (1.00 to 2.97)	1.72 (1.00 to 2.98)
Heart failure	1.25 (1.10 to 1.42)*	2.14 (1.88 to 2.42)*	1.49 (1.13 to 1.98)*	1.39 (1.04 to 1.86)*
Bleeding	1.09 (0.86 to 1.37)	1.55 (1.23 to 1.95)*	1.35 (0.85 to 2.14)	1.27 (0.79 to 2.05)

CAG, coronary angiography; MACE, major adverse cardiac outcome (all-cause mortality, rehospitalisation for AMI, hospitalisation for stroke or heart failure); PCI, percutaneous coronary intervention.

Study II

A total of 726 patients with ACS and schizophrenia were matched to 1452 ACS patients without schizophrenia. The mean age was 61 years and 62% were males. Like study I, several comorbidities had higher prevalences in patients with schizophrenia, these included diabetes, anaemia, heart failure, chronic obstructive pulmonary disease, and previous stroke, however, with lower prevalences of hypertension and hyperlipemia. This trend continued in the analysis on the development of comorbidities 1-, 5-, and 10-years following the diagnosis of ACS.

Length of hospital stay

No difference was seen in the number of days spent at the hospital following ACS between the populations, however, with a trend of shorter stay for patients with schizophrenia.

Main outcome

Patients with schizophrenia had increased HR of MACE, stroke, and all-cause mortality. No difference was seen for reinfarction (Table 3, Figure 1 in Study II).

Table 3 **Hazard ratios with 95% confidence intervals showing the difference in the primary endpoint major adverse cardiac events and individual endpoints in acute coronary syndrome patients with and without schizophrenia (psychiatric healthy control)**

	Population	Events, *n* (%)	HR (95% CI)	*P*-value
MACE	Schizophrenia	514 (70.8)	1.62 (1.45–1.81)	<0.0001
	PHC	749 (51.6)		
Re-infarction	Schizophrenia	143 (19.7)	0.88 (0.73–1.07)	0.2083
	PHC	369 (25.4)		
Stroke	Schizophrenia	82 (11.3)	1.51 (1.15–1.99)	0.0033
	PHC	136 (9.4)		
All-cause mortality	Schizophrenia	430 (59.2)	2.54 (2.22–2.90)	0.0000
	PHC	438 (30.2)		

MACE, major adverse cardiac events; PHC, psychiatric healthy control.

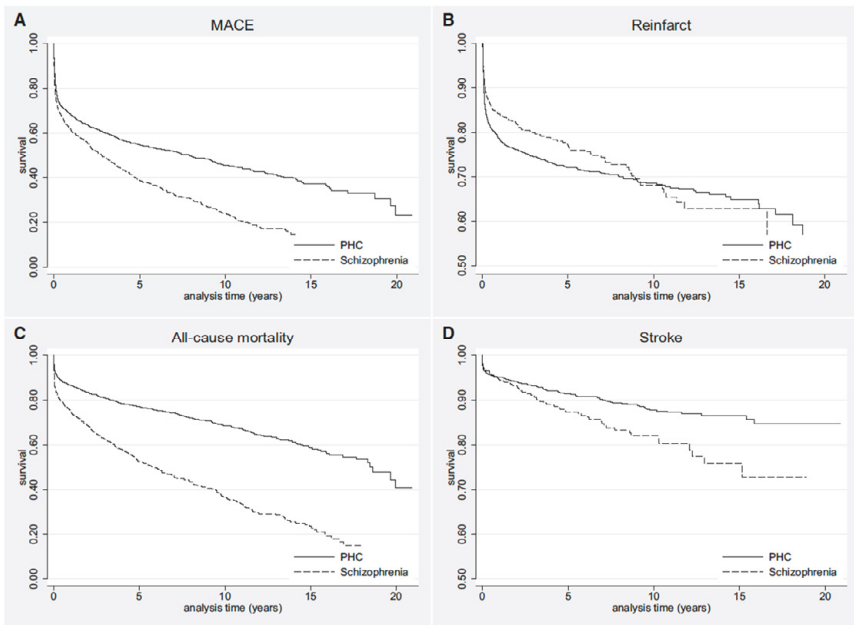

Figure 1 Kaplan–Meier curves showing estimates of (*A*) major adverse cardiac events, (*B*) re-infarction, (*C*) all-cause mortality, and (*D*) stroke comparing a population with schizophrenia to a psychiatric healthy control population.

Study III

The selection process is shown in the flowchart below (Figure 1 in Study III).

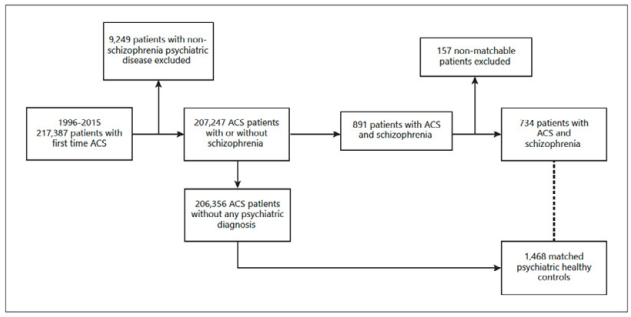

Figure 1. Flowchart illustrating the selection process. ACS, acute coronary syndrome.

At baseline the 734 patients with schizophrenia (mean age 58 years) had increased prevalences of diabetes, chronic obstructive pulmonary disease, and stroke, and a lower prevalence of hypertension was seen when compared to patients without schizophrenia (n = 1468).

Socioeconomic status

Having schizophrenia was associated with lower education and individual income levels, and patients with schizophrenia were more often living alone compared to patients without schizophrenia.

Trends in invasive procedures

Fewer CAGs were performed in the ACS population with schizophrenia (51% vs. 69% in patients without). The use of CAG increased over the two-decade study period for both populations, however the difference between the populations remained constant with a non-significant p trend for interaction (Figure 2 in Study III).

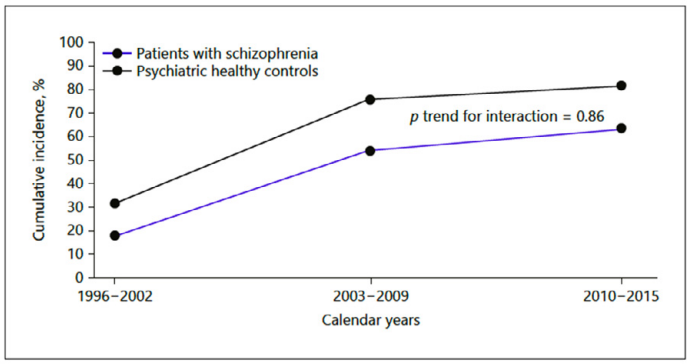

Figure 2. Trends in coronary angiography (CAG) between 1996 and 2015.

Of the patient receiving CAG the trend in PCI and CABG was not increasing nor did the relative difference between the populations change over time with non-significant p trends of interaction (Figure 3 in Study III).

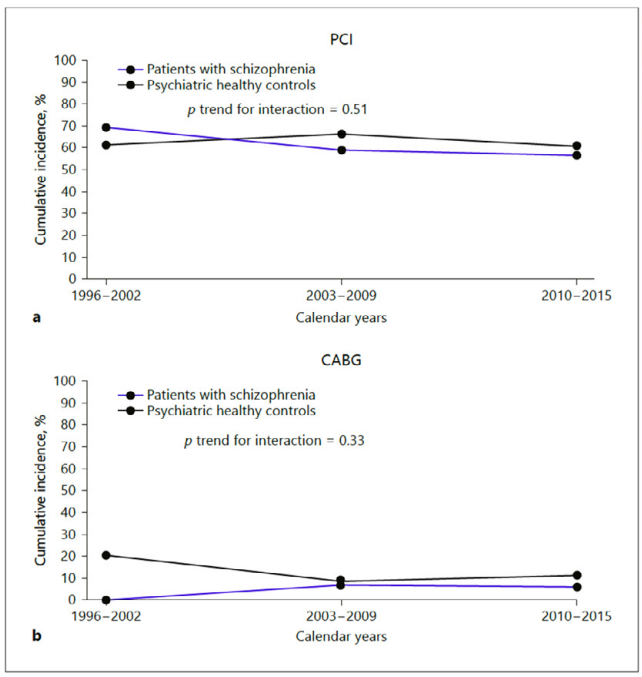

Figure 3. Trends in percutaneous coronary interventions (PCI; a) and coronary artery bypass grafts (CABG; b) in the population who underwent coronary angiography between 1996 and 2015.

Trend in mortality rates

The rate of mortality decreased slightly over the study period, however, the relative difference between the populations remained constant with an insignificant p trend for interaction (Figure 4 in Study III).

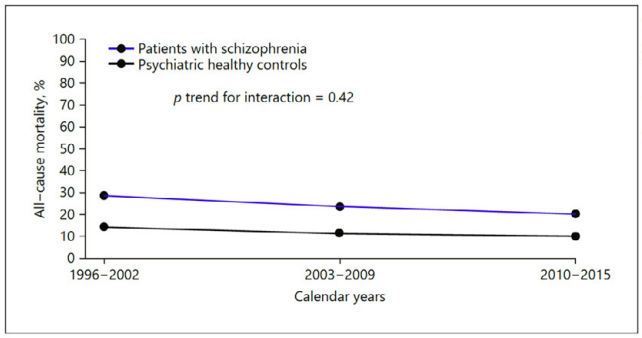

Figure 4. Trends in 1-year all-cause mortality between 1996 and 2015.

Trends in guideline-based treatment

Based on redeemed prescriptions, patients with schizophrenia continuously redeemed fewer for acetylsalicylic acid, P2Y12 inhibitors and statins throughout the study period (Figure 5 in Study III). The trend for prescriptions of nitrates, beta-blockers, calcium antagonists and ACEi/ARBs was not increasing over time, nor were there any significant changes (Figure 6 in Study III).

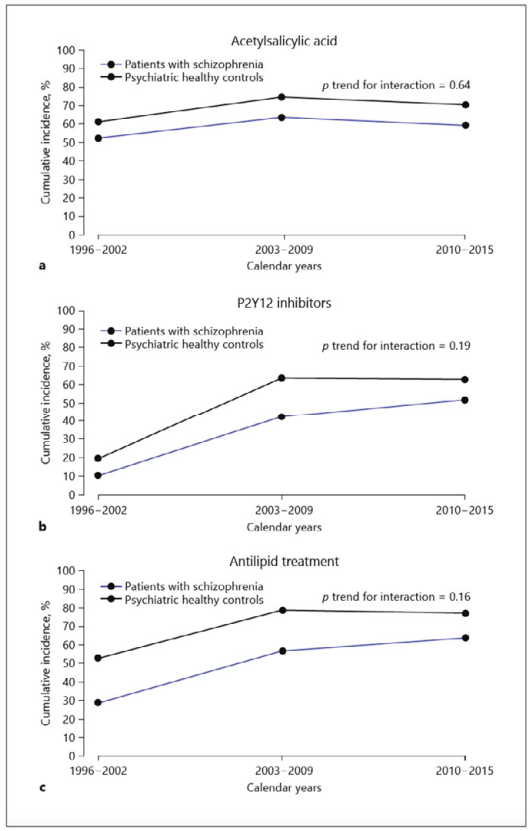

Figure 5. Trends in antiplatelet medication based on redeemed pharmacy prescriptions of acetylsalicylic acid, P2Y12 inhibitors and lipid-lowering drugs within 90 days following discharge between 1996 and 2015.

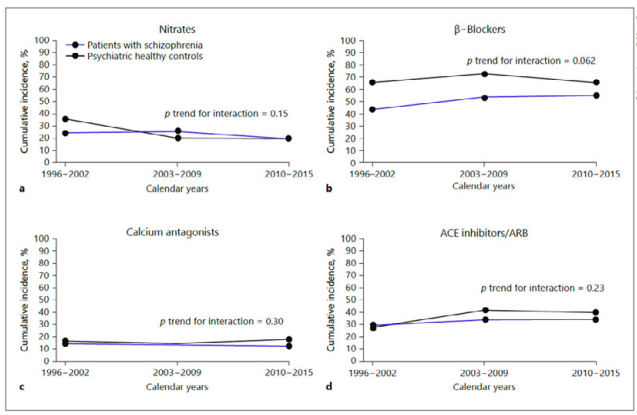

Figure 6. Trends in the prescription of nitrates (a), β-blockers (b), calcium antagonists (c), and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) (d) within 90 days following discharge between 1996 and 2015.

Study IV

The fourth and final study included 136 patients who all underwent cardiac CT-scans. The average age was 42 years (± 10 years) and roughly 60% were males. The average duration of schizophrenia was 20 years (SD ± 8 years). There were high prevalences of dyslipidaemia (67%), diabetes (20%), smoking (76%), hypertension (38%) and obesity (39%) in the population with schizophrenia.

Main outcome

The mean CAC score was 86.5 with a wide range (SD ± 376). Most patients (70%) had a CAC score equal to zero (Figure 1 in Study IV). Increased CAC score was associated with advanced age, duration of schizophrenia, dyslipidaemia, and smoking. Following univariate logistic regression, the association between increasing CAC score and age, dyslipidaemia and smoking was clear (Table 3 in Study IV). Dyslipidaemia was no longer significantly associated with increased CAC score following multivariate analysis. Log transformed CAC scores were associated with age and diabetes (Table 4 in Study IV).

Table 3. Logistic regression on the presence of CAC measured as CAC score

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.19 (1.12–1.26)	**< 0.001**	1.21 (1.13–1.29)	**< 0.001**
Male sex	1.33 (0.47–0.67)	0.415	3.15 (1.16–8.52)	**0.024**
Dyslipidemia	2.23 (1.01–4.94)	**0.048**	1.48 (0.52–4.23)	0.465
Diabetes	2.19 (0.98–4.90)	0.057	1.75 (0.60–5.16)	0.308
Smoking	3.94 (1.43–10.8)	**0.008**	3.95 (1.16–13.48)	**0.028**

Table 4. Linear regression on coronary artery calcium measured as log-transformed CAC scores above zero (n = 49)

Variables	Univariate			Multivariate		
	Coeff (95% CI)	Percent increase in CAC score (95% CI)[a]	*P*-value	Coeff (95% CI)	Percent increase in CAC score (95% CI)[a]	*P*-value
Age	0.06 (0l03–0.09)	15% (7–24%)	**< 0.001**	0.07 (0.04–0.10)	16% (9–25%)	**< 0.001**
Male sex	−0.35 (−0.91–0.22)	−55% (−88–164%)	0.222	−0.05 (−0.53–0.44)	−11% (68–173%)	0.839
Dyslipidemia	0.08 (−0.60–0.76)	19% (−75–472%)	0.822	0.17 (− 0.40–0.73)	47% (−60–436%)	0.556
Diabetes	0.76 (0.20–1.33)	577% (57–2020%)	**0.009**	0.71 (0.23–1.20)	419% (68–1500%)	**0.005**
Smoking	0.05 (−0.55–1.25)	126% (−72–1695%)	0.434	0.55 (− 0.19–1.28)	250% (−35–1792%)	0.140

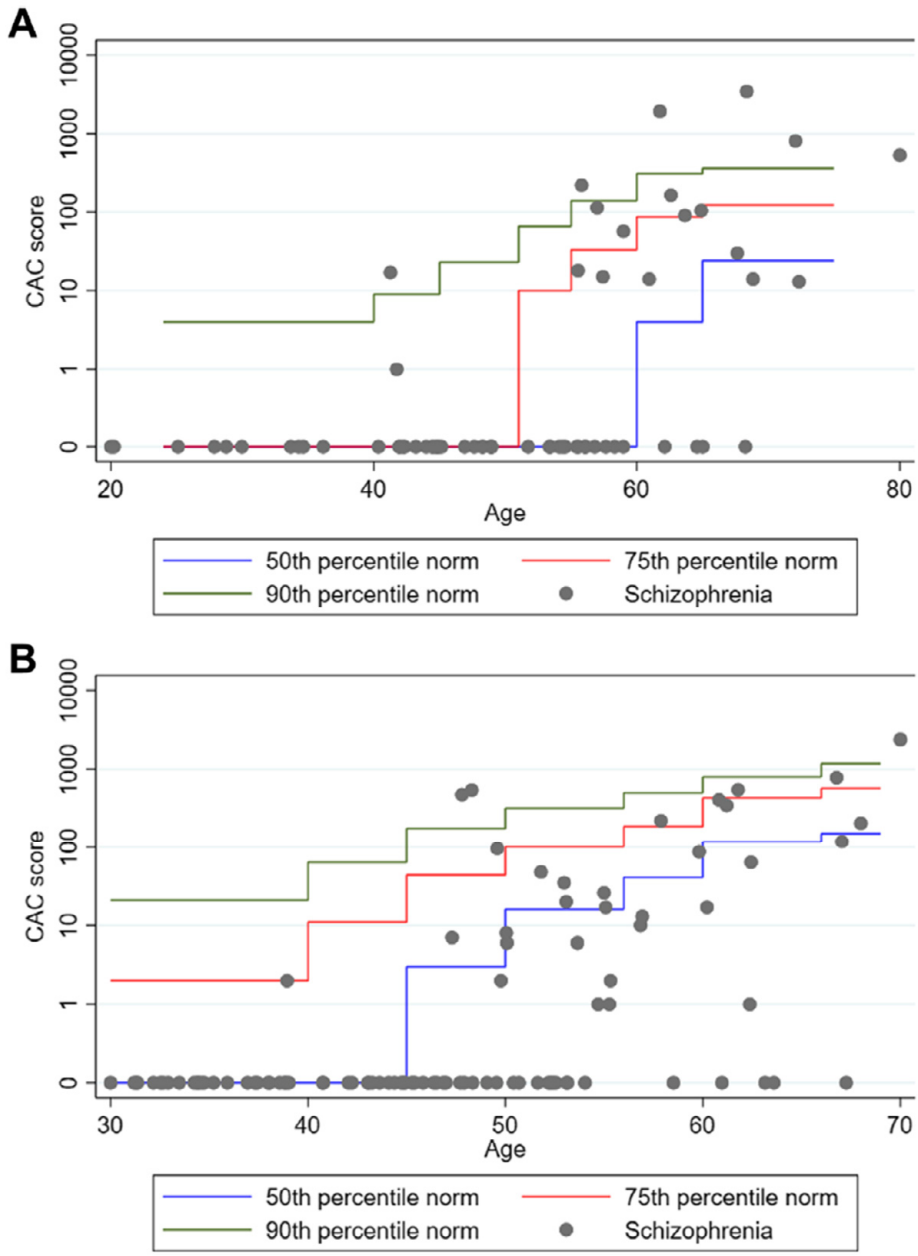

Figure 1. The CAC scores in patients with schizophrenia represented on a logarithmic scale in relation to age-specific norm 50th, 75th and 90th percentiles divided by sex. Zero was added on the otherwise logarithmic y-axis to show the large amount of patients having a CAC score of zero. A Females B Males.

Chapter 5. Discussion

Summary of findings

Patients with schizophrenia were on average ten years younger at the time of their first MI compared to patients without schizophrenia and had higher prevalences of comorbidities such as diabetes, chronic obstructive pulmonary disease, stroke, and heart failure. Following an MI, the risk of adverse outcome, e.g., all-cause mortality, heart failure and stroke was significantly higher in this population. Patients with schizophrenia underwent fewer coronary investigations and interventions (CAG, PCI, and CABG), and following discharge they received and redeemed fewer pharmacy prescriptions of guideline-based medications. The difference in performed interventions and discharge medications remained constant over two decades. Data from cardiac CT scans showed that the CAC score in these patients corresponded to that of the general population.

Cardiovascular disease

Excess cardiovascular morbidity and mortality in patients with schizophrenia has been ascribed to various factors, among these a sedentary lifestyle with poor lifestyle habits(92), antipsychotic medications(102),s and suboptimal healthcare due to healthcare bias and patient factors(103). Moreover, recent studies have shown the association between early psychosis and dysfunction of various organ systems, among these the immune and cardiometabolic systems, indicating a biological link between schizophrenia and CVD(104). One study found a genetic predisposition for cardiovascular abnormalities in patients with schizophrenia independent of antipsychotic use(104). However, using mendelian randomization R.R Veeneman et al. showed only a minimal genetic etiological association between schizophrenia and CVD(105). There are multiple mediators contributing to the development of CVD in patients with schizophrenia, however, it is yet to be determined to which

extent the various factors contribute, and in which order they arise. In this thesis the risk of adverse effects following ACS or MI were studied rather than the risk of developing CVD. A review of 14 studies established the CVD risk in this population to be nearly doubled(85).

Somatic comorbidity

For a long time, metabolic syndrome has been seen as a secondary result of schizophrenia, but an increasing amount of research has focused on the early years of schizophrenia to investigate if somatic comorbidities are already present in first time psychosis patients. One of these studies showed that antipsychotic naïve patients with schizophrenia have increased blood glucose levels during first episode of psychosis(106,107). Other early psychosis studies suggest increased levels of inflammatory markers(108,109), which are well-known mediators in the development of CVD(110), as an association between the development of the two. Newly diagnosed antipsychotic naïve schizophrenia is also significantly associated with increased risk of hypertension and chronic obstructive pulmonary disease(107,111). Contrary to this, we did not find an increased risk of hypertension in this group, a finding supported by a large meta-analysis(112). The patients in our cohort had lower prevalences of hypertension compared to the general population, possibly explained by underdiagnosis in this population, or as a result of a hypotensive side effect of antipsychotic medication(113).

While the risk of metabolic disease and consequently risk of CVD is increased in patients with early schizophrenia, it is markedly increased in chronic schizophrenia. Approximately one third of patients with schizophrenia has metabolic syndrome with an almost doubled relative risk compared to gender and age-matched controls(112,114).

This thesis investigated dyslipidaemia in three of the four studies. In study I no difference in the diagnosis of hyperlipidaemia was seen, however, at baseline clinically measured higher triglycerides and lower total cholesterol levels were found. Study II found lower diagnosis of hyperlipidaemia and in Study III no difference was found between the populations at baseline. This is partially in contradiction to the results found in a meta-analysis of 137 studies where higher levels of low high-density lipoprotein cholesterol and hypertriglyceridemia were seen(114). Possible explanations could be that current anti-lipid medication was not

accounted for in all studies, relatively small population samples and finally the possibility of underdiagnosis. Variance in age is not likely to explain the lower values of cholesterol in this thesis, since the individuals with schizophrenia in our study populations were around 20 years older compared to the above-mentioned meta-analysis populations, contradicting the fact that cholesterol levels increase with age.

Heart failure

Our results suggest an adjusted risk of over 40% of developing heart failure following MI in patients with schizophrenia. Some data suggests a causal link, independent of health behaviour, between schizophrenia and heart failure (105). This link was surprisingly not explained by an increased risk of CAD, suggesting atypical pathways responsible for the process of cardiac remodelling, perhaps by increased inflammation ultimately causing heart failure(108,109). The risk development of heart failure may also be increased a result of the pro-inflammatory response of the immune system due to antipsychotic medications(115,116).

Coronary artery disease

While no causal link was found between schizophrenia and CAD in the previously mentioned study, other data indicate an almost 60% increased risk of developing CAD later on(85), rendering results on this topic inconclusive. This thesis supports the first mentioned theory of no causal link between schizophrenia and CAD as seen in our finding presented in Study IV, where CAC scores in patients with schizophrenia were equivalent to population norms. Similar to this a third study found that patients with schizophrenia did have less severe coronary atherosclerosis(117).

Stroke

Among the adverse cardiac events studied in this thesis, stroke was increased both at baseline (Study II and III) and following a diagnosis of ACS (Study III). Stroke was also investigated in Study I, where a numerical increase in stroke was noted that was nonsignificant. The disparity in results can perhaps be explained by differing populations from Sweden (Study I) and Denmark (Study II and III). Diverse inclusion criteria resulted in dissimilar median ages of the populations; however,

patients were oldest (64 years in Study I) in the Swedish study compared to the Danish (61 years in Study II and 58 years in Study III). In Study I the population had lower prevalence of atrial fibrillation both as a baseline diagnosis and measured with ECG. However, this thesis does not differentiate between haemorrhagic and ischaemic stroke. At baseline bleeding requiring hospitalization was increased in Study I but following adjusted analysis there was no increased risk of bleeding after a MI. Current research suggests an increased risk of stroke in patients with schizophrenia(118,119), with the gap in risk of stroke closing as the populations get older, since many CVD risk factors are also present in the older general population(120). The increased risk of stroke remains following adjustment for various CVD risk factors, suggesting other contributors beyond the common risk factors(121). A possible explanation could be that the use of atypical antipsychotics induce histamine type 1 blockade that increases the risk of ischaemic stroke by 45% in the first two-weeks following exposure(122). Nevertheless, there remain many unsolved factors at play which warrants further research in the field.

Antipsychotic treatments

There exist no large-scale, long-term clinical trials with primary cardiovascular endpoints and therefore most of the knowledge in the area is derived from small, short-duration trials, efficacy trials or observational studies. A relatively recent meta-analysis of trials suggested an increased metabolic risk profile in patients with antipsychotic medications, but could not due to the low amount of trials included conclude an increased risk of CVD nor all-cause mortality(123). A simulation cohort model estimating the long-term risk of CAD found no difference between the antipsychotic vs. placebo group(124). In a larger study using patients from Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial the authors found that olanzapine was the antipsychotic associated with the largest elevation in CAD risk(102). Finally, a systematic review of observational studies did find an increase in CVD in patients taking antipsychotic medications, although this result was based on only a handful of studies(125).

The benefit versus side-effect of antipsychotics varies between the drugs available, most of them have a gradual efficacy on the symptoms. Clozapine, amisulpride, zotepine, olanzapine, and risperidone have proven to be most efficacious for positive symptoms. Zotepine, olanzapine and sertindole had the highest weight gain profile, with haloperidol causing the least significant weight gain, and ziprasidone,

chlorpromazine, zuclopenthixol, molindone, loxapine, sulpiride, levomepromazine and trifluoperazine not causing any significant weight gain(126). Adding to this, a recent study found low-dose olanzapine/quetiapine to be associated with cardiometabolic mortality(127).

The CATIE trial showed that within 18 months of the trial period, 74% of the patients discontinued their antipsychotic use. The rate of discontinuation due to metabolic effects was greatest for olanzapine, and for discontinuation due to extrapyramidal side effects was greatest for perphenazine(128). A meta-analysis found the major reason for discontinuation of antipsychotics due to inefficiency (40%) rather than side-effects (20%)(126). Adding to these discontinuation rates is the high noncompliance found in this population, where almost half of the patients having complete noncompliance and only one third with full compliance(129).

All-cause mortality

The all-cause mortality rates presented in this thesis were around 2.5 times higher compared to the population without schizophrenia, which corresponds well to the mortality reported in many other countries according to a review in 2014(83). The increased mortality rate translates roughly to a 10 to 20-year reduction in lifetime(84,130–132). The predominant cause of death in schizophrenia is from CVD, cancers and suicide(133–137), and the mortality rate from CVD is more than doubled(118,131) despite underdiagnosis(135). Recent studies have presented CVD as the leading cause of death as opposed to older studies where suicide was the predominant cause of death in this population. It should be noted that this thesis investigated all-cause mortality rather than CVD mortality due to the low validity of cause-specific death diagnoses in the Swedish and Danish death registries(138,139).

To demonstrate the difference in this mortality gap over time, we investigated temporal trends over two decades in Study III, where we concluded that the relative difference between the population with schizophrenia compared to the general population had not changed. In a systematic review from 2007 the authors established that the gap in mortality was in fact worsening over time(136), suggesting that individuals with schizophrenia has not benefitted from the advancements in health outcomes to the same extent as the general population.

Besides all-cause mortality, we also presented an increased prevalence of cardiac arrest (Study I) in patients with schizophrenia. This is in line with previous research that has reported three times increased likelihood of sudden cardiac death in this population(140). It can possibly be explained by the early repolarization patterns found in these patients(105,141), an association independent of QTc prolonging antipsychotic drug-use(102). Early-repolarization patterns, such as the one seen in Brugada Syndrome are associated with malignant ventricular arrythmias leading to sudden cardiac death in younger individuals(142).

The health-care system

There is a lack of integration between non-psychiatric and psychiatric hospitals leading to barriers in managing somatic health conditions in patients with mental illnesses(143,144). Additionally, patients with schizophrenia have inadequate access to medical care(145), which can be ascribed to both a limitation in the service provided for these patients as well as the patients willingness to participate(146). One study concluded a combination of lack of treatment offers from the doctors and lack of accepts from the patient to be the reason behind suboptimal treatment following MI(147). We presented results showing less cardiac interventions following MI for patients with schizophrenia. These results are in line with previous research that found hazard rates of cardiac interventions to be as low as 50% following ACS(148) and MI(149) in patients with schizophrenia. This could partly be explained by a remaining stigmatizing attitude and bias from healthcare professionals, delaying the time window for intervention or even failing to treat somatic conditions(103,150,151).

Mental health and lifestyle

Accumulating evidence show that patients with schizophrenia have a high co-occurrence of psychiatric comorbidities, with over 50% of patients having an additional diagnosis of either panic disorders, obsessive compulsory disorder, major depressive disorder, social phobia or substance abuse(152,153). This type of comorbidity is associated with functional impairment and may detrimentally interact with help-seeking behaviour(154). Other associated factors to limited help-seeking behaviour comes from fear of stigmatization and the lack of insight into

mental or somatic health(155). This is less of an issue for early schizophrenia patients who have an increased tendency to visit both psychiatric and non-psychiatric clinics(111), indicating an opportunity for early intervention.

Smoking remains a substantial risk of CVD by a 1.5-2 fold increase(156). The reporting on smoking prevalences in populations with schizophrenia are high and varies between 50-70%(157–161). In the CATIE trial 58% of the patient with schizophrenia were smokers(102), and in our studies we reported prevalence rates between 48% and 76% of active smoking, well corresponding to the literature. The relationship between smoking and schizophrenia is complex. The prevalence of smoking preceding the onset of schizophrenia is high, and research suggests tobacco smoking to be an independent risk factor for developing schizophrenia or psychosis(162,163) and is linked to altered gene-expressions in dopaminergic pathways following nicotine exposure in rat models(164). There also appears to be a shared genetic root between smoking and schizophrenia(165). According to the self-medication hypothesis(166) nicotine use is a form for self-medication due to the release of dopamine alleviating negative symptoms, however recent studies have questioned the benefits of smoking on these symptoms(167). Physicians can sometimes be hesitant on smoking cessation in patients with psychiatric diagnoses, but research shows that it does not lead to deterioration of mental health and rather improves the well-being of the patient(168,169).

Sedentary behaviour and inactivity rates are high in individuals with schizophrenia (170,171). A worldwide analysis established 9% of the burden from CAD to be due to physical inactivity(172). A limited number of clinical trials exist on the impact of physical activity on reducing the burden of disease in schizophrenia, and all trials concluded improvement in cardiorespiratory fitness(173–176). They were however limited by small population groups and difficulties with recruitment and participation. Reviews on the benefits of exercise in schizophrenia have shown significant improvements in cognitive, physical and mental health(177,178).

Deinstitutionalization started in the 1950s as an attempt to end the isolation of patients with mental illnesses and reintegrate them into the society. This transition has been successful with many previously institutionalized patients having become a part of the community(179). While the outcome is mostly positive, some patients with fewer resources have unfortunately not benefitted from the closing of mental facilities. Already in 1939, the Penrose hypothesis suggested an inverse relationship between the number of beds available in a psychiatric facility and the number of people in prison(180), which unfortunately become a reality for a substantial

minority of individuals with mental illness(181,182). This minority who could not adapt to the new circumstances nor received adequate care due to the limitation of inpatient beds, and would often end up homeless or incarcerated(183,184). Low resource individuals also tend to socially isolate, have low compliance and live a sedentary unhealthy lifestyle. When putting it in perspective to the structural living in facilities with social time, physical education, and timely medication, one could argue that this type of living condition is perhaps beneficial for a certain minority until more tailored individualized reintegration into society becomes available.

Limitations

There are certain limitations to drawing conclusion when analysing observational study data. The major limitations are the risks of selection bias, confounding by indication, or confounding by severity, e.g., where individuals with predominantly mild disease are included in studies, however, our patient populations were relatively old and therefore likely at an advanced disease stage. Another limitation when working with registries is from information bias due to misclassification or poor validity of registered data. Schizophrenia manifests in younger people while CVD in older, this could lead to temporal bias from date of schizophrenia diagnosis to date of CVD diagnosis. In the last study data on tobacco and medication use was self-reported and could contribute to recall bias.

There are both strengths and limitations to having a long inclusion period. It enables the inclusion of more participants in the study; however, it is limited to health care advancement and change in guideline recommendations over the time-period. We attempted to partially account for this by adding year of MI/ACS in the sensitivity analyses, which did not alter the results.

In some of the studies lifestyle risk factors or socioeconomic factors were not available for adjustment which may have influenced the outcomes. Furthermore, many diagnoses unfortunately lack validity in the Danish and Swedish registries.

Perspectives

This thesis highlights suboptimal care and outcomes following ACS or MI in patients with schizophrenia and suggests the following considerations for improvement:

It is important to change health behaviour in this population to reduce cardiovascular mortality. These include increased regular exercise, smoking secession and improvement in dietary habits. However, it is not sufficient with only secondary prevention since primary prevention in early schizophrenia can be more beneficial in stopping the development of CVD.

A more integrated somatic and psychiatric health care is of utmost importance. Screening of cardiovascular risk factors are not a priority in the psychiatric hospitals, but measuring blood pressure, fasting glucose, lipids and weight can help find patients with early signs of CVD and enable appropriate intervention.

Antipsychotic medications have a wide range of cardiovascular side effects, and many of them have different cardiometabolic risk profiles. The choice of antipsychotic should be carefully considered in patients with increased risk of cardiovascular disease.

Having schizophrenia is associated with cognitive and social difficulties, an effort to integrate these individuals in programs with educative material in social settings might provide better insights into symptoms and improve help-seeking behaviour.

Unfortunately, there exists a stigma around mental illness in the society, including in the hospital settings. Education and awareness around these matters are needed to improve the delayed diagnosis and suboptimal care given to patients with schizophrenia.

Compliance for medication continues to be an obstacle in treating these patients. Dedicated help from a caregiver or contact person could prove beneficial. There are also treatment alternatives for poor compliance of daily medications such as long-acting injectable cholesterol lowering medication. These should be considered in the case of hypercholesterolaemia, especially in patients already receiving long-acting injectable antipsychotic medications.

Conclusion

This thesis characterized patients with schizophrenia regarding management and outcomes following ACS or MI, as well as the change in outcomes over time and coronary calcium scores. We arrived at the following conclusions:

1. Having schizophrenia in Sweden was associated with an almost 10-year earlier diagnosis of first MI. These patients also less often underwent coronary procedures and were less treated with guideline-based medications. Following ACS, they had an almost doubled risk of major adverse cardiovascular events, heart failure, and all-cause mortality.

2. Patients with schizophrenia in Denmark similarly had an increased risk of adverse cardiovascular events following ACS, stroke, and all-cause mortality. There was also an underrepresentation of traditional cardiovascular risk factors such as hypertension and hyperlipidaemia.

3. The gap between patients with schizophrenia and the general population following MI in terms of invasive coronary procedures (CAG, PCI, and CABG), guideline-recommended therapy and all-cause mortality has remained constant over the past two decades.

4. The coronary artery calcium scores in patients with schizophrenia were corresponding to the norm percentiles in the general populations. A higher calcium score was associated with the conventional cardiovascular risk factors seen in the general population.

Acknowledgement

I would like to give my sincerest gratitude to my colleagues, family and friends who supported me throughout this thesis. A special thank you to:

Dr Pontus Andell, my dearest supervisor, your achievements have truly been an inspiration throughout. I am proud to be your first (of many) doctoral students. Thank you for the ton of splendid advice you have given me and for being supportive and reliable around the clock. I look forward to many more collaborations in the future.

Dr Svend Eggert Jensen, my co-supervisor, for taking me in as a research assistant at the age of 21 and teaching me the fundamentals of conducting research. You saw the potential in me before I even knew how to write a research proposal. Thanks to you I travelled the world and gained opportunities that paved the pathway of my not-nearly-finished academic career. A true honour to be your protégé.

Dr Sasha Koul, my co-supervisor, for the exchange of brilliant ideas over delicious dinners, for bringing me forward and giving me the confidence, you thought I deserved. Your humoristic and charismatic personality will forever be a highlight of my time as a doctoral student.

Professor David Erlinge, my co-supervisor, for giving me guidance during my time as a doctoral student and welcoming me with open arms to the Department of Cardiology in Lund.

Monica Magnusson, for always making sure that everything goes according to plan. Without you we would all be headless chickens. Thank you for helping me whole-heartedly throughout these four years.

My co-authors Dr Axel Wester, Dr Kristian Kragholm, Dr Christoffer Polcwiartek, Dr Phillip Freeman, Jan Brink Valentin, Professor Jørgen Aagard, Professor Rene Ernst Nielsen, and Dr Trine Trab for great research collaborations.

My parents Nasima and Asadullah Attar, for unconditionally loving me and always believing I should win the Nobel Prize, for no apparent reason. Thank you for shaping me into the independent woman that I have become.

My brothers Dr Bilal and Josef Attar, for being there for me whenever I needed it. A special thank you to the person I have the most unconditional love for in the world, my little sister Sabrina Attar, you have been my biggest supporter, adversary, and everything in between.

My partner Fady Allan, for being my emotional and intellectual support. I am truly grateful for everything you have done for me. I am looking forward to the rest of my life and academic career with you by my side.

My dearest friends, soon-to-be-Dr Nohad El-manzalawy, for being the best imaginable friend and sparring partner in the last 12 years. Dr Julia Kornblad, I cannot imagine what life would have been like if you were not there during medical school and doctorate (most likely tedious). Yasmin Aghajan, for being my rock through thick and thin. My precious friends Officer Rasha El-manzalawy, Ghuncha Wahab, Azra Karamehmedovic, nurse Elin Ahrent and Dr Maria Rahim, for supporting me in good and bad times. Bobica Willert, for being in my life since the 4th grade, first as a teacher and mentor, later as a colleague and now as a friend. Finally, I would like to thank the colleagues and friends not named, I am truly blessed to have had you all in my life.

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