Coronary heart disease in women by history of preterm delivery - Register-based studies on clinical presentation and treatment outcome

Handmark, Moa

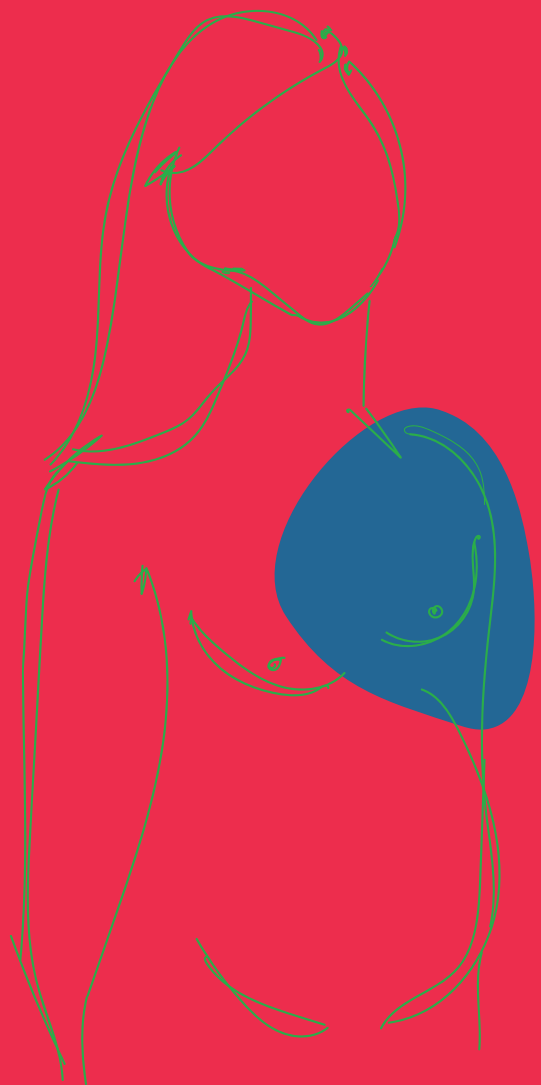
2024

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

Coronary heart disease in women by history of preterm delivery

Register-based studies on clinical presentation and treatment outcome

MOA HANDMARK
CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY



Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

MOA HANDMARK grew up near Eksjö, Sweden. She received her medical degree from Lund University in 2021 and is currently working in the Department of Obstetrics and Gynaecology at Skåne University Hospital in Malmö.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences, Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:78
ISBN 978-91-8021-573-2
ISSN 1652-8220

Coronary heart disease in women by history of preterm delivery

Register-based studies on clinical presentation and treatment outcome

Coronary heart disease in women by history of preterm delivery

Register-based studies on clinical presentation and treatment outcome

Moa Handmark

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 7th of June at 09.00 in the Auditorium of the Department of Obstetrics and Gynaecology, Skåne University Hospital, Jan Waldenströms gata 47, Malmö

Faculty opponent
Michael C. Honigberg, Assistant Professor of Medicine
Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA

Organization: LUND UNIVERSITY

Document name: Doctoral thesis **Date of issue:** 2024-06-07

Author(s): Moa Handmark **Sponsoring organization:**

Title and subtitle: Coronary heart disease in women by history of preterm delivery – Register-based studies on clinical presentation and treatment outcome

Abstract

Background: A history of preterm delivery is an established risk factor for future maternal coronary heart disease and associated with 1.5–2 times higher risk of incident events. It is yet to be thoroughly studied how a history of preterm delivery is associated with the specific treatment and clinical presentation of coronary heart disease in women with at least one delivery.

Objectives: I aimed to meet the overall objective of gaining a better understanding of how a history of preterm delivery is associated with treatment and presentation of coronary heart disease by studying the association between a history of preterm delivery, long-term outcome after coronary stenting, coronary artery restenosis, and myocardial injury at myocardial infarction, respectively.

Methods: Nationwide samples of women aged ≤65 years included between 5766 and 8320 individuals. The data originated mainly from two registers: the Swedish Medical Birth Register and the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. Regression models were used to evaluate the association between preterm delivery and outcomes.

Results: A history of preterm delivery was associated with worse prognosis following coronary artery stenting through an increased risk of major adverse cardiovascular events (adjusted hazard ratio (HR): 1.19, 95% confidence interval (CI): 1.03–1.38) and a higher mortality rate (HR: 1.38, 95% CI: 1.02–1.85). No association between a history of preterm delivery and coronary artery restenosis, nor an association with indicators of a more severe myocardial injury at time of first myocardial infarction, was found

Conclusions: The results indicate that a history of preterm delivery might be relevant in a secondary prevention setting of coronary heart disease and not only in a primary prevention setting. In all, this project highlights that a woman's pregnancy history is not only relevant to obstetrician-gynaecologists but might warrant wider attention among clinicians.

Key words: pregnancy history, coronary heart disease, percutaneous coronary intervention

Classification system and/or index terms (if any) Supplementary bibliographical information

Language: English **ISSN and key title**: 1652-8220

ISBN: 978-91-8021-573-2

Recipient's notes **Number of pages**: 94

Price Security classification

Signature Date 2024-04-23

Coronary heart disease in women by history of preterm delivery

Register-based studies on clinical presentation and treatment outcome

Moa Handmark

LUND
UNIVERSITY

Cover and photo by Anna Jonsson (2023)

Faculty of Medicine
Department of Clinical Sciences, Malmö

ISBN 978-91-8021-573-2
ISSN 1652-8220
Lund University, Faculty of Medicine Doctoral Dissertation Series 2024:78

Printed in Sweden by Media-Tryck, Lund University
Lund 2024

Till Mamman

Table of Contents

Preface

It is August or September of 2015. A couple of days ago I got a call telling me that I was accepted to medical school, and now I am standing in a room with a handful of my new classmates. A teacher has just explained how medicine stands on two pillars – humanism and science – and now they want us to choose. Right side of the room if you consider yourself a humanist, left side for science. There is a nervous, first-day energy in the room. What if there is a wrong answer? Is this some kind of test? The teacher looks up, one, two, three – go. I am the only one who goes right.

As a child being a doctor was a job to me, just as any other. When I was four or five years old, I asked my mum what a university was. She answered me: "That's where you go to school as an adult, it's where you become something". I contemplated this for a moment and then said "Oh, so like a taxi driver or a doctor?" It is a cute story, but it is also very telling. I, together with my brothers, have grown up knowing that we are allowed the freedom to choose our future, and for me, this choice was easy. For as long as I can remember, my best friends have lived in other worlds. They have been able to ride dragons, have long philosophical monologues out of the blue, and fall in love overnight. Books, words, languages, stories – that was my future. So I chose the social disciplines, opting out of chemistry, physics, and biology in favour of history, philosophy, and psychology. I was a humanist, not a scientist.

It is safe to say that medicine, becoming a doctor, did not fall into my lap. I was not born into a family of doctors. Medicine was a very active choice for me, something I worked, and still am working, hard for. The logic and robust rules of science have not always agreed with my daydreaming mind, and I have many times questioned my place in medicine. During medical school I found a safe space working at the women's health clinic. I found a sense of purpose and genuine interest. I found that, for me, identifying as a humanist was beneficial in my understanding of the patient, and I found a new future, a new goal to work towards, and I did my best. I worked every other weekend for over a year, evenings after school and during the summer. I chose women's medicine as the subject of both my bachelor and master thesis, and when I got the chance to become a PhD-student in gynaecology and reproductive medicine the choice was, once again, easy.

My PhD-studies have continuously challenged and pushed me. Time and time again I have stepped out of my comfort zone. These last four years have, without a doubt, been the hardest and most insightful years of my education, and slowly but surely I have started to gain a new understanding of who I am. I still highly value the arts, and I am fascinated by the complexity of human nature. A lot of my best friends still live, and always will live, in books. I am still a humanist.

But today, I also choose science.

Abstract

Background

A history of preterm delivery is an established risk factor for future maternal coronary heart disease and associated with 1.5–2 times higher risk of incident events. It is yet to be thoroughly studied how a history of preterm delivery is associated with the specific treatment and clinical presentation of coronary heart disease in women with at least one delivery.

Objectives

I aimed to meet the overall objective of gaining a better understanding of how a history of preterm delivery is linked with treatment and presentation of coronary heart disease by studying the association between a history of preterm delivery, long-term outcome after coronary stenting, coronary artery restenosis, and myocardial injury at myocardial infarction, respectively.

Methods

Nationwide samples of women aged ≤65 years included between 5766 and 8320 individuals. The data mainly originated from three registers: the Swedish Medical Birth Register and the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. Regression models were used to evaluate the association between preterm delivery and outcomes.

Results

A history of preterm delivery was associated with worse prognosis following coronary artery stenting through an increased risk of major adverse cardiovascular events (adjusted hazard ratio (HR): 1.19, 95% confidence interval (CI): 1.03–1.38) and a higher mortality rate (HR: 1.38, 95% CI: 1.02–1.85). No association between a history of preterm delivery and coronary artery restenosis, nor an association with indicators of a more severe myocardial injury at time of first myocardial infarction, was found.

Conclusions

The results indicate that a history of preterm delivery might be relevant in a secondary prevention setting of coronary heart disease, and not only in a primary prevention setting. In all, this project highlights that a woman's pregnancy history is not only relevant to obstetrician-gynaecologists but might warrant wider attention among clinicians.

Populärvetenskaplig sammanfattning

Hjärt- och kärlsjukdom är den vanligaste dödsorsaken både globalt och i Sverige, och idag lider över två miljoner svenskar av tillstånd som klassas under begreppet. Kranskärlssjukdom, hjärtsjukdom som utgår från de kärl som försörjer hjärtat med blod, är en av de vanligaste typerna av hjärt- och kärlsjukdom. Kranskärlssjukdom uppkommer oftast av en förträngning till följd av fettinlagringar i kranskärlen och kan antingen vara vilande eller symptomgivande. Inom begreppet ryms bland annat diagnoserna hjärtinfarkt och kärlkramp. Perkutan koronarintervention (PCI), även kallat ballongvidgning, är standardbehandling vid större, symptomgivande kranskärlsförträngningar. PCI är en behandling som oftast sker i lokalbedövning där läkaren för in en kateter i en artär via ljumsken eller handleden, som sedan guidas med hjälp av röntgen till kranskärlen. En ballong kan sedan öppna upp kranskärlet igen genom att vidgas vid platsen för förträngningen, och för att kärlet ska fortsätta hålla sig öppet så sätts idag nästan alltid en stent, ett cylinderformat metallnät, där ballongvidgningen skett.

Historiskt sett har kvinnor försummats inom hjärt- och kärlforskning. År 1977 gick United States Food and Drug Aministration (FDA), USA:s livsmedels- och läkemedelsmyndighet, ut med riktlinjer som uteslöt alla kvinnor i barnafödande ålder ur läkemedelsprövningar. Detta som ett svar på den omskakande Neurosedynskandalen under 1960-talet där förskrivning av läkemedlet Neurosedyn till gravida kvinnor, för bland annat illamående, resulterade i allvarliga fosterskador. De här riktlinjerna var sedermera aktiva i över 15 år och kan antas ha satt sina spår i hur forskare utser studiedeltagare. Mellan år 2010 och 2017 var under 40% av alla deltagare i hjärt- och kärlrelaterade prövningar världen över kvinnor. Tidigare forskning har visat att kvinnligt kön är associerat med sämre utfall efter behandling av kranskärlssjukdom och att kvinnor, jämfört med män, i lägre utsträckning får behandling för kranskärlssjukdom enligt standardiserade riktlinjer. Kvinnors kranskärlssjukdom visar sig dock senare i livet jämfört med mäns och kvinnor har vid tidpunkten för insjuknande fler andra diagnoser.

De senaste tjugo åren har forskning avseende könsspecifika riskfaktorer för hjärt- och kärlsjukdom ökat och i och med detta har graviditetskomplikationer framkommit som riskfaktorer för framtida hjärt- och kärlsjukdom hos kvinnor som fött barn. Prematur, eller för tidig, förlossning är en av graviditetskomplikationerna som är associerad med framtida hjärt- och kärlsjukdom hos kvinnor som fött barn. Prematur förlossning innebär förlossning innan graviditetsvecka 37 och är bland annat associerat med andra graviditetskomplikationer, exempelvis havandeskapsförgiftning, kroniska sjukdomar hos mamman, såsom diabetes, och infektion. Studier har visat att en historik av prematur förlossning är associerat med en upp till två gånger ökad risk för framtida hjärt- och kärlsjukdom och att den här ökade risken kan hålla i sig upp till 40 år efter förlossning för vissa typer av hjärt- och kärlsjukdom. Idag finns det ett kunskapsglapp i hur kvinnor med en historik av

prematur förlossning presenterar med, och svarar på behandling för, kranskärlssjukdom. Studier kring detta skulle kunna bidra till en ökad förståelse kring hur prematur förlossning och framtida kranskärlssjukdom är förknippade med varandra.

Den här avhandlingen ämnar bidra till en bättre förståelse för hur en historik av prematur förlossning är sammankopplad med presentation och behandling av kranskärlssjukdom hos kvinnor som har fött barn. Med hjälp av information från huvudsakligen två svenska dataregister har fyra studier utförts:

Artikel I har undersökt om en historik av prematur förlossning är associerat med ett nytt kardiovaskulärt insjuknande eller död efter kranskärlsstent hos 5766 kvinnor.

Artikel II och III har undersökt en potentiell association mellan flera olika aspekter av en kvinnas graviditetshistorik, inkluderat både prematur förlossning och havandeskapsförgiftning, och förekomst av restenos, en ny förträngning i kranskärlen på samma plats som den gamla PCI-behandlade förträngningen, efter PCI hos 6027, respektive 6065 kvinnor.

Artikel IV har undersökt huruvida en historik av prematur förlossning, havandeskapsförgiftning och/eller att föda ett för graviditetslängden för litet barn är associerat med en allvarligare typ av hjärtinfarkt hos 8320 kvinnor som fött barn.

Resultaten från dessa studier indikerar att en historik av prematur förlossning inte enbart är en riskfaktor för att insjukna i hjärt- och kärlsjukdom en första gång, utan också en riskfaktor för sekundära hjärt- och kärlhändelser efter behandling av kranskärlssjukdom. Detta, tillsammans med fynd av ett möjligt samband mellan graviditetskomplikationer och allvarlighetsgrad av hjärtinfarkt, belyser än en gång att en kvinnas graviditetshistorik inte enbart är av intresse för gynekologer/ förlossningsläkare, utan bör till högre grad uppmärksammas även av andra läkare.

För att ytterligare fördjupa förståelsen kring kopplingen mellan graviditets-komplikationer och framtida hjärt- och kärlsjukdom hos kvinnor som fött barn krävs vidare forskning. Nya studier gällande förebyggande behandling för hjärt- och kärlsjukdom kan, i teorin, hjälpa oss att förstå om vi kan minska risken för sämre utfall efter behandling av kranskärlssjukdom hos kvinnor med en historik av prematur förlossning, och om förebyggande behandling kan minska risken för en värre typ av hjärtinfarkt hos kvinnor med vissa graviditetskomplikationer. Vidare behövs studier kring uppkomst av kranskärlsjukdom hos kvinnor med en historik av graviditetskomplikationer för att fullständigt förstå sambandet. Ur ett bredare perspektiv ska också vikten av informationsspridning kring sambandet mellan graviditetskomplikationer och framtida hjärt- och kärlsjukdom belysas, då detta hade kunnat leda till mer forskning på kvinnors hjärt- och kärlhälsa, och i slutändan sannolikt resultera i bättre, mer evidensbaserad, hjärtsjukvård gällande kvinnor.

List of papers included in thesis

Paper I

Pehrson M, Edsfeldt A, Sarno G, Fraser A, Rich-Edwards JW, Pihlsgård M et al. Long-Term Outcome Following Coronary Artery Stenting by History of Preterm Delivery. JACC: Advances. 2022 Dec. 1;1(5):100142.

Paper II

Pehrson M, Edsfeldt A, Sarno G, Fraser A, Rich-Edwards JW, Goncalves I et al. Coronary artery restenosis and target lesion revascularisation in women by pregnancy history. Open Heart. 2023;10(1):e002130.

Paper III

Lin A, **Pehrson M**, Sarno G, Fraser A, Rich-Edwards JW, Goncalves I et al. Coronary Artery Restenosis in Women by History of Preeclampsia. J Am Heart Assoc. 2022 Sep. 20;11(18):e026287.

Paper IV

Handmark M, Lin A, Edsfeldt A, Sarno G, Fraser A, Rich-Edwards JW et al. STEMI, revascularization, and peak troponin by adverse pregnancy outcomes in women with myocardial infarction. 2023. In manuscript.

Author's contribution to the papers

Paper I

Design of the work, statistical analyses, interpretation of data, drafting the work, revising and final approval of version to be published.

Paper II

Design of the work, input on conducting the statistical analyses, interpretation of data, drafting the work, revising and final approval of version to be published.

Paper III

Design of the work, interpretation of data, revising and final approval of version to be published.

Paper IV

Design of the work, statistical analyses, interpretation of data, drafting the work, revising and final approval of version to be published.

List of papers not included in thesis

Sederholm Lawesson S, Swahn E, Pihlsgård M, Andersson T, Angerås O, Bacsovics Brolin E, Bergdahl E, Blomberg M, Christersson C, Goncalves I, Gunnarsson OS, Jernberg T, Johnston N, Leander K, Lilliecreutz C, **Pehrson M**, Rosengren A, Sandström A, Sandström A, Sarno G, Själander S, Svanvik T, Thunström E, Wikström AK and Timpka S. Association Between History of Adverse Pregnancy Outcomes and Coronary Artery Disease Assessed by Coronary Computed Tomography Angiography. JAMA. 2023 Feb. 7;329(5):393-404. doi: 10.1001/jama.2022.24093

Abbreviations

ACS	Acute coronary syndrome
APO	Adverse pregnancy outcome
BMI	Body mass index
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
DES	Drug-eluting stent
ECG	Electrocardiogram
ESC	European Society of Cardiology
GH	Gestational hypertension
HDP	Hypertensive disorders of pregnancy
HR	Hazards ratio
ICD	International Classification of Diseases
IHD	Ischaemic heart disease
IQR	Inter quartile range
LAD	Left anterior descending artery
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MBR	The Swedish Medical Birth Register
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MMP	Matrix metalloproteinase
NSTEMI	Non-ST-elevation myocardial infarction

OR	Odds ratio
PCI	Percutaneous coronary intervention
PE	Preeclampsia
PPROM	Preterm premature rupture of membranes
PTD	Preterm delivery
RIKS-HIA	Register of Information and Knowledge About Swedish Heart Intensive Care Admissions
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCAD	Spontaneous coronary artery dissection
SCD	Sudden cardiac death
SD	Standard deviation
sFlt-1	Soluble fms-like tyrosine kinase-1
SGA	Small for gestational age
STEMI	ST-elevation myocardial infarction
SWEDEHEART	The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TLR	Target lesion revascularization
WHO	World Health Organization

Introduction

Cardiovascular disease (CVD) is the leading cause of death in women, with coronary heart disease (CHD) being one of the largest contributors.(1, 2) During the last two decades the age-standardized mortality for CHD has declined in general.(1) However, this decline has not been as apparent in young women.(3) Studies on modifiable CVD risk factors, such as diabetes and hypertension, in young individuals with myocardial infarction (MI) over the same time period show a prevalence increase.(4, 5) It has been suggested that the before-mentioned mortality trend is partly due to the risk factor burden in young women, and that more focus on primary prevention of both traditional and sex-specific risk factors in women is needed.(6) In a primary prevention setting, adverse pregnancy outcomes (APOs) are known risk factors of future CHD in women.(7) Preterm delivery (PTD), i.e. delivery before 37 weeks of gestation, is one of these APOs today known as a risk factor of future incident CHD in women who have given birth.(8) A history of PTD has been shown to be associated with an up to two times increased risk of CVD in women, with an increased risk of ischaemic heart disease (IHD) up to 40 years after delivery.(8, 9)

Female sex is a known predictor of worse outcome following invasive treatment for CHD with percutaneous coronary intervention (PCI).(10) This begs the question if there could be sex-specific risk factors at play. Previous studies have shown a possible association between preeclampsia (PE), another APO associated with future maternal CHD, and worse outcome following PCI.(11, 12) Studies on CHD presentation in women by APO history have indicated an earlier presentation of MI after delivery in women with a history of APOs compared to women with no such history,(13) and that a history of PE is associated with a higher proportion of ST-elevation MI (STEMI).(14, 15) Today, other CHD risk factors influence the course of treatment for CHD, such as diabetes mellitus,(16) and choice of secondary prevention, e.g. diabetes mellitus and chronic kidney disease,(17) but there is insufficient evidence to consider pregnancy history in this setting.

As PTD is a common pregnancy complication with a global prevalence of 9.9%, with rates varying between approximately 4–16% in different countries,(18) understanding more about the link between PTD and future CHD could be beneficial for many women. But to assess a potential need for a different prevention strategy in this group of patients, more data on CHD presentation and treatment in women with a history of APOs is needed.

Background

> I read it [history] a little as a duty, but it tells me nothing that does not either vex or weary me. The quarrels of popes and kings, with wars or pestilences, in every page; the men all so good for nothing, and hardly any women at all – it is very tiresome[…].
>
> Jane Austen, Northanger Abbey

In ancient Greece, Aristotle proclaimed the female offspring a deviation.(19) In contrast to the male ideal, women were seen as faulty versions of men with one sole purpose – reproduction, and as women were all but equal to their reproductive organs, the womb was thought to be the source of all their illnesses.(20) This organ, the uterus, defined women's place in Western medicine, and society, for centuries, and diagnoses like wandering womb and womb suffocation can be found in Western medical history. The Hippocratic Corpus indirectly described how the womb would cause problems if the need of carrying a child was not met. During the European Middle Ages, and through the upswing of Christianity, an empty uterus was thought to attract evil and as a result, women without children were at risk of being accused of, and executed for, witchcraft. In the 17th century the term 'hysteric symptoms' was frequently mentioned in relation to an unwell uterus. This directly translates to symptoms from the uterus and is later developed throughout the late 17th and 18th centuries to the diagnosis of hysteria. When medics treated women, hysteria was likely a very convenient diagnosis as it included every symptom or illness in a woman which could not be explained. In other words, hysteria could be whatever you wanted it to be as long as one diagnosis criterion was fulfilled – the patient being a woman. Through the 19th century women were often "treated" for hysteria by being sent away from society. During the 20th century, diagnoses such as wondering womb were discarded, but as women's medicine instead shifted to a focus on hormones, the idea of a woman's illness stemming first and foremost from her reproductive organs still lingered.

As a result of women being considered as smaller, lesser versions of men, with the main purpose of reproduction, we lack data on the health and diseases of women throughout history.(19) The idea that women's illnesses stem entirely from their reproductive organs has thankfully been questioned and dismissed over the years,(20) and today we know that men and women differ on several medical aspects, such as symptom presentation and response to treatment.(21, 22) Nevertheless, the idea of men and women being physiologically different, has not

been questioned on a broader scale until recently.(19) As such, men and women have been thought of as more or less physiologically the same during a time of great medical progress, and if men and women are the same, why go through the trouble of collecting any data on women when you could just use, the often more easily accessible, data on men? Sweden is a prime example of data on men being more readily available as it has been routinely collected on men entering military service.(23) To my knowledge, the same effort has not to any great extent been made to collect data on women, which consequently has led to many Swedish epidemiological studies being based on young, healthy men. The US Food and Drug Administration (FDA) did not have a requirement of reporting clinical data by sex until 1998, thus the data on sex before the 2000s is limited.(6) In regard to clinical trials, women have been, and still are, underrepresented. From 2010 to 2017, less than 40% of participants in cardiovascular clinical trials on a global level were women, with women being better represented in America compared to Europe.(24) Partly in response to the Thalidomide scandal in the 1960s, the FDA published guidelines in 1977 which excluded all women of "childbearing potential", i.e. most women of reproductive age, from phase 1 and early phase 2 clinical drug trials.(25) These guidelines were active for over 15 years and were not retired until 1993. It should also be noted that, to this day, pregnancy typically results in exclusion from participation in drug trials, with the result of very little data on pregnant women.(26) The same pattern of excluding women as research subjects can be seen in pre-clinical trials, where male animals are still used more often than female animals.(27)

Over time, efforts have been made to include more women in medical research. In 1999, the Swedish Medical Research Council established a policy document requiring researchers to argue for their choice of study population.(28) Similar requirements have also been applicable to applications submitted to the American National Institutes of Health (NIH) since the 1990s.(29) A study published in 2020 which assessed articles published in the BMJ concluded that women, from 1948 to 2018, had become more prominent in BMJ articles.(30) However, the rate of increase was higher in relation to the mention of the word 'woman' or 'women' in articles than that for articles on women-specific topics.

It is undeniably so that women, as a whole, have not historically been treated well by medicine, and a review of women as patients and research subjects through the years, even a compressed one such as this, could very well leave a bitter aftertaste. But I would like to invite you to look at history and learn from it, as I believe, that with history as fuel we can do better. In order to make up for historical oversights of women in medical research, and to obtain a more comprehensive picture of women's illnesses, not only research on women-specific topics is needed but research on women overall. CVD is the leading cause of death in women worldwide,(2) and studies on women-specific risk factors for CVD, like the ones studied in this work, could somewhat help reduce the current knowledge gap, and have the potential of being beneficial for many women.

Coronary heart disease

In clinical practice, CHD is often referred to as synonymous with coronary artery disease (CAD), acute coronary syndrome (ACS), or even IHD, though it should be noted that this is not strictly true. CHD is a subgroup of CVD and should be seen as a consequence of CAD, with ACS being a subgroup of CAD.(31, 32) Whilst ACS is most often symptomatic, CAD can be subclinical and is sometimes used interchangeably to describe a pathological process in the coronary arteries called atherosclerosis.(32) IHD, on the other hand, is a collective name of conditions resulting in ischemia of the myocardium where atherosclerosis is the most common underlying pathology.(33) In this thesis, CHD will in summary henceforth be regarded as a concept including both CAD and ACS.

According to the Swedish Heart Lung Foundation, over two million patients suffer from CVD in Sweden.(34) It is the leading cause of death both in Sweden and worldwide, with IHD, and thus CHD, being one of the largest contributors.(1, 35) According to the World Health Organization (WHO), an estimated 17.9 million individuals die from CVD globally each year.(36) A worldwide decline in age-standardized CVD mortality can be seen over the last three decades.(1) This is reflected in the Swedish population where the National Board of Health and Welfare presented statistics in 2021 showing a >50% decline in CVD age-standardized mortality during the last two decades.(37) However, during the same time period there was an increase, with an almost doubled total number of CVD cases globally.(1) The Global Burden of Disease Study estimated the total cases of IHD in 2019 to be 197 million, with an increase in total IHD numbers in almost all countries. A growing, ageing, and changing population, together with more sensitive diagnostic methods and better treatments, could explain this somewhat contradictory pattern in CVD epidemiology.

Pathophysiology

CHD very much depends on CAD and therefore, in turn, on atherosclerosis.(32) Atherosclerosis is a disease of arteries which is likely driven by accumulation of lipids in the innermost part of the arterial wall, causing an inflammatory response.(38, 39) The relatively slow progressing nature of the disease results in older patients making up a major part of affected individuals.(38) In short, atherosclerosis can be seen as a fatty lesion in the intima part of the vessel wall under a layer of endothelial cells. However, to better understand the pathophysiology of CHD, a slightly more detailed view is needed. Today, there is strong evidence for a key role of a ‘dysfunctional’ endothelium in atherosclerotic disease, and atherosclerotic plaques are commonly found in arterial regions with turbulent flow.(40) The turbulent flow is thought to affect the composition of the endothelium, effectively making it easier for larger molecules, such as lipids, to

reach the intima.(38) The activation of the endothelial cells will also contribute to the attraction of immune cells which further contributes to plaque formation and progression.(40)

If the atherosclerotic plaque continues to grow it will reach to a point where it hinders sufficient blood flow in the affected artery,(38) but the more well-known clinical presentation of atherosclerosis is due to an acute rupture of an unstable plaque. The stability of a plaque is mainly dependent on its composition, where a fibrous plaque is generally more stable than a plaque rich in lipids and inflammatory cells. When a plaque ruptures, a blood clot will be formed which will limit or cut off the blood flow. This will cause ischaemia in the downstream tissues and subsequent cell death. If this happens in the coronary arteries it will result in a MI – a major clinical presentation of CHD (Figure 1).

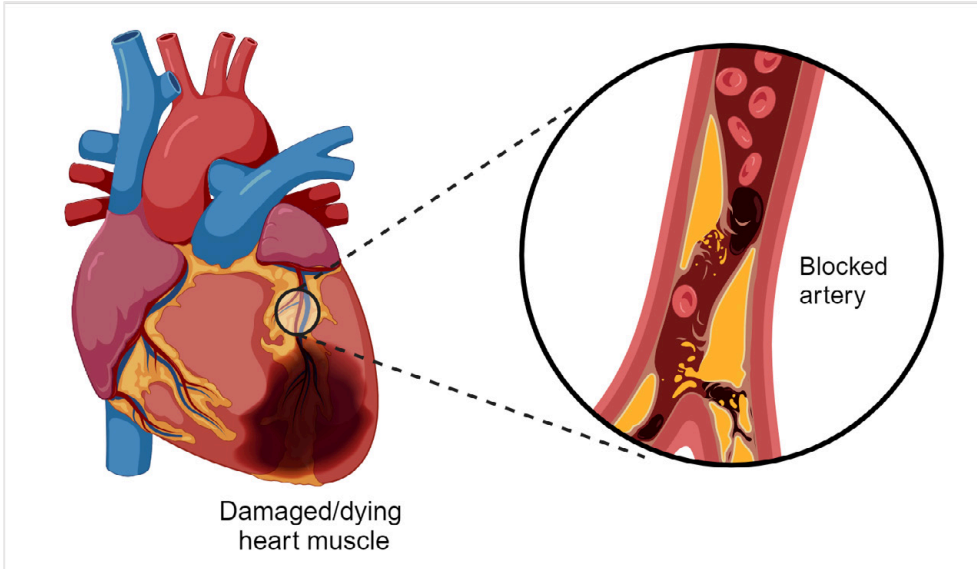


Figure 1. Myocardial infarction.
A ruptured coronary atherosclerotic plaque with a thrombus which occludes the arterial lumen resulting in myocardial ischaemia. Adapted from "Myocardial Infarction (Heart Attack)", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates.

Clinical presentation

The clinical presentations of CHD include stable angina, unstable angina, MI, and cardiac death.(31) Stable angina is part of a collective group of clinical presentations of CAD called chronic coronary syndromes (CCS).(41) It is a result of progressing CAD where a narrowing of the coronary artery vessel lumen results in temporary reduction of blood flow to the myocardium,(38) resulting in what is referred to as angina pectoris. According to the European Society of Cardiology (ESC) guidelines

on CCS the typical anginal symptoms are as follows: constricting discomfort in the front of the chest or in the neck, jaw, shoulder or arm; precipitated by physical exertion; relieved by rest or nitrates within 5 minutes.(41) What distinguishes stable and unstable angina from each other is the timing and progress of these symptoms.(41, 42) Unstable angina is defined as anginal symptoms presenting in a resting state, in a state of minimal physical activity, as a rapid aggravation of stable angina, or as new, sudden onset of symptoms in the absence of vigorous physical activity.(42)

Unstable angina and MI are collectively known as ACS.(43) Though it should be noted that this is slightly simplified as MI, using this definition includes mainly MIs resulting from a thrombotic event – type 1 MIs.(42) There are other causes of myocardial ischaemia and MI (type 2–5), but these will not be further discussed here. Going forward, MI will be referring to type 1 MI. According to the Fourth Universal Definition of MI, MI is defined as a rise and/or fall of cardiac biomarkers (preferably troponin) together with clinical manifestations of ischaemia, where electrocardiogram (ECG) alterations, ischaemic symptoms, and imaging findings are all known clinical manifestations of cardiac ischaemia.(44) Unstable angina, on the other hand, presents with similar symptoms as an MI but without a clear dynamic change in cardiac biomarker levels.(43) Eighty percent of patients with ACS present with chest pain.(42) Based on the ECG, MIs are classified as STEMI or non-ST-elevation MI (NSTEMI).(45) STEMI is associated with a more severe myocardial injury compared to NSTEMI,(46) and in an acute setting, this classification of MI helps clinicians to decide how to proceed with diagnostics and treatment.(42) The peak levels of circulating cardiac markers can be used to predict both infarct size and patient outcome.(47, 48)

Even though a thrombotic event is still the underlying cause of an MI in a large proportion of cases, it has become clear in recent years that this is not always the case.(43) MI with non-obstructive coronary arteries (MINOCA) is a condition where a patient presents with elevated cardiac biomarkers and symptoms related to ACS but with no obstruction of the coronary arteries.(42) MINOCA is only seen in a minority of ACS cases, with prevalence varying between 1 to 14% across studies. Another cause of ACS not necessarily associated with a thrombotic event is spontaneous coronary artery dissection (SCAD).(43) SCAD is a condition where a spontaneous tear (thus not associated with e.g. trauma) in the intima part of the artery leads to the formation of a false lumen in the arterial wall. This can in turn reduce the lumen of the coronary artery and subsequently result in oxygen deprivation and MI. Under 5% of ACS cases are associated with SCAD.

Sudden cardiac death (SCD) is undoubtedly the most severe clinical presentation of CHD. Even though not all who suffer SCD have CHD, CHD is the underlying condition in approximately 80% of the SCD cases.(49) SCD can be the initial presentation of CHD, and it is associated with the severity and anatomic distribution of atherosclerosis.(50)

Risk factors and prevention

Risk factors for CVD, and in turn CHD, are traditionally grouped into modifiable, meaning that measures can be taken to change them, or non-modifiable, meaning risk factors that cannot be changed. The ESC uses the terminology risk factors, meaning causal risk factors, and risk modifiers, meaning additional factors also modifying CVD risk.(17) The global CVD burden due to modifiable risk factors has increased over the last two decades,(51) and preventive strategies for CVD risk factors are constantly relevant. In light of a growing and ageing population, this is not very surprising. However, studies show that an increased prevalence of CVD risk factors has been noted in young individuals presenting with CHD over approximately the same time period.(4, 5)

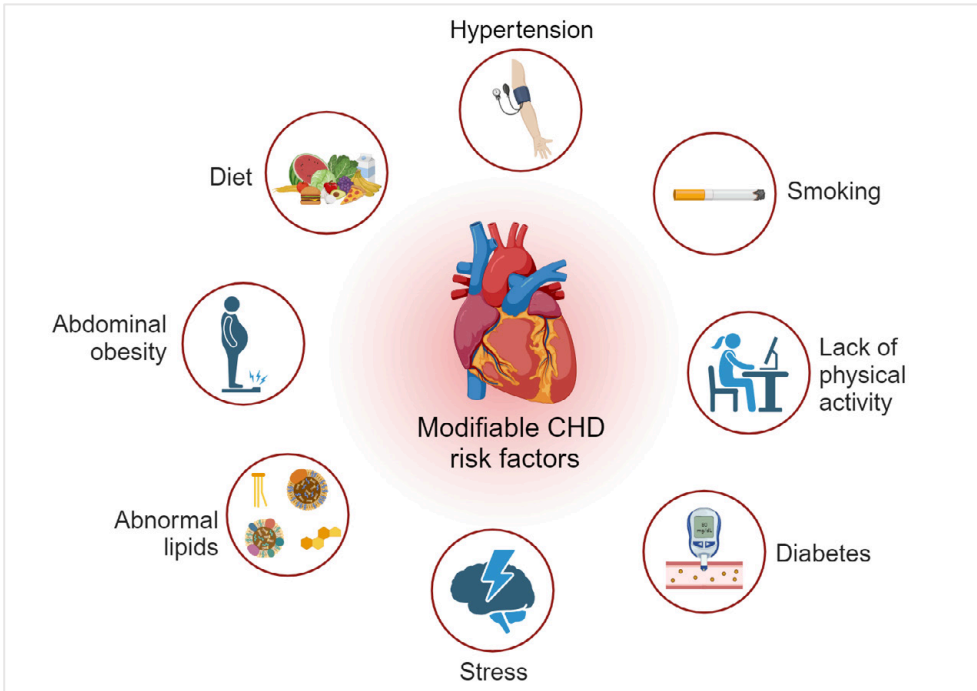


Figure 2. Main modifiable risk factors for coronary heart disease.
Modifiable risk factors for CHD. CHD: coronary heart disease. Adapted from "Stroke Circle Diagram (Layout)", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates.

Abnormal lipids, high blood pressure, cigarette smoking, and diabetes mellitus are the major causal, modifiable risk factors for CVD,(17) of which high blood pressure has the largest impact on the global CVD burden.(52) These risk factors, together with the other modifiable risk factors for CVD (abdominal obesity, stress, low consumption of fruit and vegetables, alcohol consumption, and lack of regular physical activity), have been shown to account for over 90% of the risk of an initial

MI (Figure 2).(53) Traditionally, body mass index (BMI) has been used to determine excess body weight, and in turn, CVD risk. A high BMI, particularly obesity (BMI 30,0–39,9), is associated with an increased CVD risk.(54) However, study results are conflicting on whether BMI or other body measures, such as hip-to-waist ratio, is the best way to determine excess body weight, with some studies showing a higher association with CVD risk when determined by hip-to-waist ratio, and some showing no difference between BMI and other measurements.(55) Non-modifiable risk factors for CVD include age, ethnicity, and genetics.(17) In recent years medicine has started to differentiate between sex, referring to biological sex, and gender, referring to socially and culturally constructed identities of men, women, and non-binary individuals.(56) Sex-related factors influencing CVD risk include genetics and sex hormones.(57) Gender-related CVD risk factors are not as well studied as sex-related factors but include mental wellbeing and communication with health care, and are primarily prominent in women. In addition to these risk factors, there are also other conditions associated with CVD, e.g. autoimmune conditions and chronic kidney disease.(58, 59)

CVD prevention is based on CVD risk assessment, which means to identify patients who would benefit from preventive actions, i.e. patients with higher risk.(17) In general, a patient with high CVD risk will respond more effectively to preventive actions compared to a patient with low CVD risk. In apparently healthy individuals, i.e. in a primary prevention setting, the ESC guidelines first recommend smoking cessation, blood pressure control, and lifestyle changes. After this, the decision to initiate other primary preventive measures, such as statin treatment, and ultimately the prevention goal, is based on the estimated 10-year CVD risk using the Systematic Coronary Risk Estimation 2 (SCORE-2) risk charts.(60) The SCORE-2 risk estimation is based on age, sex, blood pressure, smoking status, and lipid levels, hence including all major causal risk factors for CVD apart from diabetes. This is because a diagnosis of type 2 diabetes in itself, in absence of other CVD risk factors, is considered as a patient being at moderate risk for CVD, and a patient with diabetes and severe organ damage is considered to be at similar risk for CVD as patients with established CVD.(17) Therefore, there are separate recommendations for CVD prevention in patients with diabetes mellitus.(61) Patients with established CVD, i.e. in a secondary prevention setting, are considered to be at very high risk for another CVD event, and smoking cessation, lifestyle changes, antithrombotic treatment in the absence of high bleeding risk, and risk factor treatment (for hyperlipidaemia and hypertension) are recommended for all patients.(17) As for primary prevention, there are specific recommendations for secondary prevention in patient groups with high risk of another CVD event. For example, in patients with high ischaemic risk (e.g. patients with diabetes or chronic kidney disease), prescription of a second antithrombotic drug in addition to Aspirin may be considered in the absence of high risk of bleeding, and patients with diabetes and established CVD are also recommended to use an SGLT2 inhibitor to improve CVD outcomes.

Treatment with percutaneous coronary intervention

PCI is a collective name for procedures that aim to reopen coronary artery obstructions and restore myocardial blood flow with a percutaneous approach, and is the preferred invasive treatment for symptomatic patients with CHD.(62) By X-ray guidance, a wire is advanced towards the affected coronary artery, through peripheral access (usually the right radial or femoral artery). When in place, a balloon is threaded over the wire and inflated at the place of the occlusion, which opens up the artery. In most cases, a stent is inserted and dilated on the site of the occlusive lesion, which will help the artery to maintain the blood flow (Figure 3). Stents were first introduced in the 1990s, and before that PCIs were only performed using balloon-dilation. The first generation of stents were bare metal stents (BMS) and over time drug-eluting stents (DES) were developed. The effect that stent development has had on adverse outcomes of PCI will be further discussed in a later section.

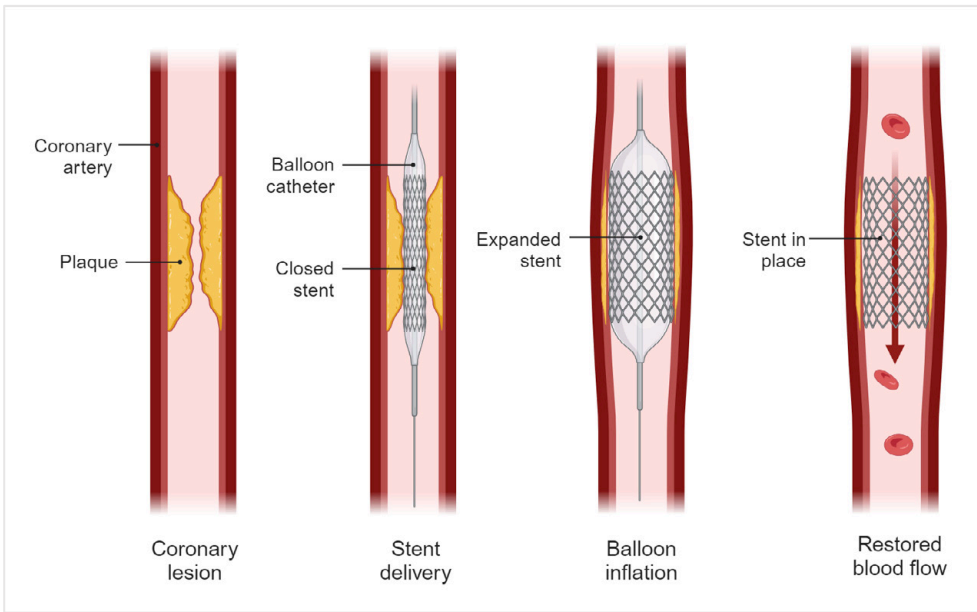


Figure 3. Percutaneous coronary intervention
The main steps of a stent placement during a percutaneous coronary intervention. Adapted from "Percutaneous Coronary Intervention", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates.

In patients with stable angina, any invasive treatment should be seen as a complement to medical therapy and should only be considered in relation to symptom relief or improvement of prognosis.(41) In ACS patients, invasive revascularization is the preferred treatment.(42) All patients with a working

diagnosis of STEMI should, if available, undergo PCI within 120 minutes of diagnosis. This is often referred to as a primary PCI strategy. In contrast to the previous guidelines on NSTEMI and unstable angina, the new ESC guidelines on ACS (2023) recommend an in-patient invasive strategy in all ACS patients. Previous guidelines recommended an invasive strategy in high-risk patients with NSTEMI or unstable angina, and a more selective approach otherwise.(63) Today, NSTEMI and unstable angina patients are recommended an immediate invasive strategy, with angiography and PCI if needed, in the presence of any very high-risk criteria, such as acute heart failure or haemodynamic instability, and an early (within 24 hours) approach in the presence of any high-risk criteria, such as a confirmed diagnosis of NSTEMI or dynamic ST-segment changes.(42) In diabetic patients presenting with multiple vessel disease, evidence supports the use of a coronary artery bypass graft (CABG) over PCI to minimize adverse outcomes.(16)

Adverse outcomes following percutaneous coronary intervention

In this section the focus will be on adverse outcomes following PCI included in this thesis, mainly major adverse cardiovascular events (MACE) and restenosis. As such, this excludes other complications such as bleeding,(62) and is in no way a complete review of adverse outcomes following PCI.

Major adverse cardiovascular events

MACE is often defined as stroke, MI, or CVD death.(64) However, this definition differs between studies and can, for example, also include repeated PCI or only include cardiac death.(65, 66) This makes it hard to review specific predictors of MACE. This introduction will therefore focus on predictors of adverse outcomes following PCI, both new cardiovascular events and/or mortality, which include both procedure and patient-related factors. There are many risk-scores for outcomes after PCI,(67) some just including clinical variables and others also including procedure-related variables, but as none of them are really comprehensive enough to say something about adverse outcomes after PCI in general, a broader perspective than one single risk-score is needed. Procedure-related predictors of adverse outcomes following PCI include markers of worse baseline disease, such as multiple vessel disease and lesion localization, where proximal lesions are associated with worse outcomes.(68, 69) Type of stent(s) used and number of stents placed are also associated with PCI outcome.(70) Patient-related predictors of both short- and long-term adverse outcomes following PCI include female sex, older age, and comorbidities such as renal insufficiency, traditional CVD risk factors, and heart failure, where low baseline left ventricular ejection fraction (LVEF) is a strong predictor.(66, 69, 71, 72) Indication for PCI is also associated with the outcome after PCI, where a clinical presentation with STEMI is associated with more adverse short-term outcomes.(72, 73)

Restenosis

What a PCI ultimately does is that it causes a vessel injury by dilating an artery.(62) This, together with stent implantation, triggers an inflammatory response in order to heal the injury.(74) In some cases this healing process can result in restenosis of the coronary artery through a pathological process called neo-intimal hyperplasia. This process, which is primarily associated with early restenosis (<1 year), is caused by smooth muscle cells migrating towards the damaged arterial wall and may lead to narrowing of the arterial lumen, restenosis, and blood flow obstruction.(62, 75) The dilation of the arterial wall will also damage the endothelial barrier which can result in an impaired healing process.(76) A functioning endothelium is vital in the control of other vessel structures, and a dysfunctional endothelium can cause a pro-inflammatory and pro-coagulant vessel environment associated with CVD development.(76, 77) Persistent endothelial dysfunction is associated with the development of stent thrombosis, but it is also associated with neoatherosclerosis.(76) Neoatherosclerosis develops within the neointima in much the same way as atherosclerosis develops in a previously healthy artery, though much faster, and is associated with late restenosis (>1 year).(74-76)

Factors associated with restenosis can be divided into patient-related, anatomical as well as procedure and stent-related.(74) Older age, female sex, and comorbidities like diabetes and chronic kidney disease are all known clinical predictors of restenosis. Other traditional CHD risk factors such as hypertension and dyslipidaemia have also been shown to be associated with the development of restenosis.(78) Anatomical factors associated with restenosis are related mainly to vessel size and lesion composition.(74) Small vessels are at higher risk of developing restenosis, which might depend on a higher degree of vessel damage compared to larger vessels. More complex lesions are associated with restenosis, e.g. lesions with a high degree of calcification or lesions with high thrombus burden. Procedure-related factors include inadequate stent expansion and stent gap. In the case of a stent gap, the lack of stent coverage over the whole lesion results in a zone not influenced by the drugs eluted by DES, that does not have the mechanical support introduced by stents. The number of stents placed also influences the risk of restenosis, as does the total stent length.(70) The introduction of BMS in the 1990s primarily reduced the risk of acute vessel occlusion by stent thrombosis or vessel recoil.(62) It also decreased the rate of restenosis from 20–50% to 10–30%. DES were later developed and further reduced the risk of restenosis. DES are drug-coated stents that release drugs that reduce the neo-intimal proliferation after revascularization. The first-generation DES lowered the rate of restenosis to approximately 5% but had a higher risk of late stent thrombosis compared to BMS. Today, with the use of third-generation DES, late stent thrombosis rates are lower than those in BMS, and rates of treatment for restenosis are at approximately 1–2%.(62, 74) The time frame of restenosis development differs between BMS and DES.(74) Neo-intimal accumulation peaks at 6-8 months for BMS and develops up

to 5 years after DES implantation, and neoatherosclerosis develops earlier after DES implantation compared to BMS.

The treatment for restenosis is primarily repeat revascularization by PCI, referred to as target lesion revascularization (TLR).(74) Even though rates of TLR are down to 1–2%, restenosis is still a current problem due to the sheer number of stents placed globally every year. Restenosis often presents as unstable symptoms with many patients presenting with ACS,(74) and during the last decade PCI for restenosis made up approximately 10% of all PCI procedures in the US.(79) It should also be mentioned that 10–20% of patients with restenosis will develop another restenosis.(74)

Coronary heart disease in women

CVD is the leading cause of death in women both in Sweden and worldwide.(2, 35) As mentioned before, women have historically been neglected in cardiovascular research.(19, 24) Since the 1990s there has been an ongoing campaign to raise awareness of CHD in women,(6, 80) and during the first decade of the 2000s the rate of awareness of CHD as the leading cause of death in women nearly doubled.(80) Women's lack of awareness of their CHD risk probably largely stems from the fact that cardiovascular research in women has not been prioritized to any great extent, but could also be a result of media and cultural representations of women with CHD. A Canadian study from 2017 on how CVD was portrayed in North American popular media showed that the typical patient was portrayed as a man, where the CVD diagnosis was a result of hard work.(81) Women's CVD, however, was presented as a result of ageing and ignorance, among other things.

Clinical presentation and treatment

Women presenting with CHD are generally older and have a higher comorbidity burden compared to men.(53, 82) Subgroups of CHD more prevalent in women than men include MINOCA and SCAD, where a large part of MIs associated with pregnancy is due to SCAD.(43) However, the most common clinical presentation of ACS in women is NSTEMI or angina.(83) A constant topic among clinicians is the debate on 'typical' vs 'atypical' symptoms in patients presenting with ACS. The traditional chest pain associated with MI is generally assigned to male patients, even though it is the most common symptom in both men and women.(22, 42) This phenomenon probably stems from the fact that other ACS symptoms, such as nausea and fatigue, are more common in women than in men. Studies regarding ACS symptoms in men and women have suggested that the labelling of symptoms as 'atypical', or similar, could possibly result in a delayed diagnosis and a subsequently

worse outcome.(84) In a recent update of ACS guidelines, the ESC specifically states that the term 'atypical' in reference to ACS symptoms should be avoided.(42) In ACS patients, female sex is a known predictor of worse outcome following PCI.(10, 85) It has also been shown that women receive guideline recommended diagnostics and therapies to a lesser extent than men.(86) A possible explanation for this could be that women have been shown to seek medical care for ACS at a later stage than men.(87) This has been attributed to socioeconomic factors, lack of knowledge, and barriers to self-care, among other things.(88)

Cardiovascular risk and prevention

During the last two decades research on female-specific cardiovascular risk factors has greatly increased, highlighting both sex-specific and female-dominating factors associated with CVD. Examples of sex-specific factors for women associated with CVD are menopause and pregnancy history.(6) Women's cardiovascular risk increases post menopause, and theories regarding changes in oestrogen concentrations have been presented as possible explanations.(89) The effect of hormone replacement therapy (HRT) to reduce risk of CVD has been shown to be dependent on the timing of HRT in relation to onset of menopause.(90) For CHD, HRT has been shown to reduce the risk if initiated in women <60 years or <10 years since menopause. Aspects of pregnancy history as sex-specific non-modifiable risk factors for CHD in women will be discussed in detail in a later section. Female-dominating factors associated with CVD include autoimmune disease,(59) where up to 80% of all autoimmune cases present in women,(91) and mental health conditions,(6) such as depression and anxiety.(92) As mentioned before, primary CVD risk prevention is based on CVD risk calculated using causal CVD risk factors such as high blood pressure and abnormal lipids.(60) Even though the risk factors in these kinds of risk assessment scores are the major CVD risk factors in women,(6) they do not include sex-specific or female-dominating factors as the ones discussed in this section.

Preterm delivery

According to the WHO, PTD is defined as delivery before 37+0 weeks of gestation (Figure 4).(93) The lower limit, which differentiates PTD from spontaneous abortion, varies between different countries. PTD can further be divided into late PTD (34+0–36+6 weeks of gestation), moderate PTD (32+0–33+6 weeks of gestation), very PTD (28+0–31+6 weeks of gestation), and extremely PTD (<28 weeks of gestation).(94, 95)

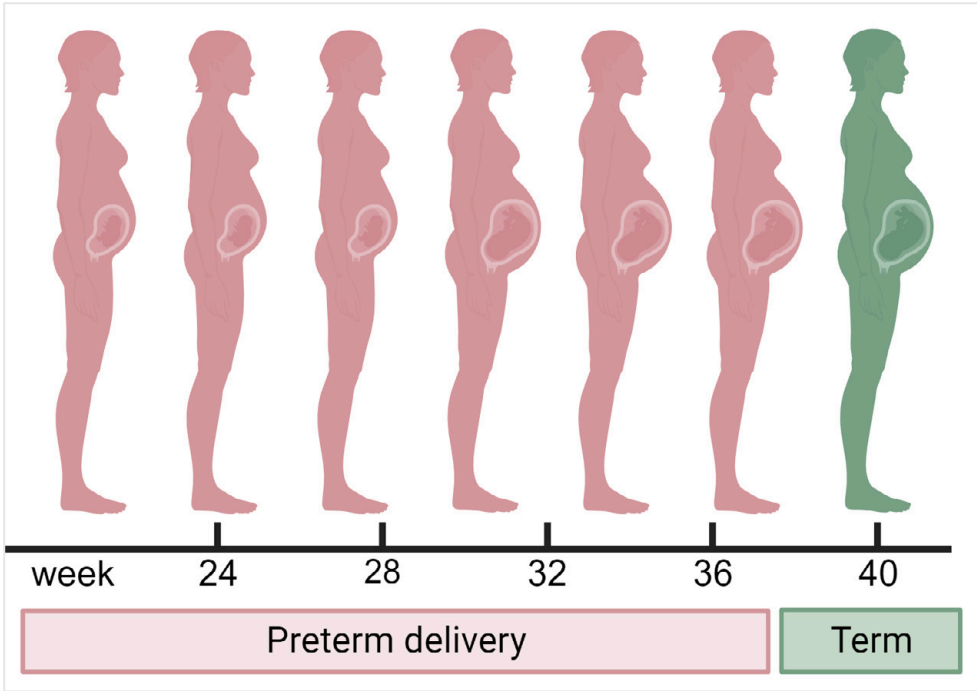


Figure 4. Classification of delivery.
Preterm delivery defined as delivery before 37 weeks of gestation, and term delivery defined as delivery ≥37 weeks of gestation. Created with BioRender.com.

In 2020, approximately 13.4 million babies were born preterm, with an estimated global PTD prevalence of 9.9%.(18) The rates between countries varied between 4 and 16%, and these rates have been reasonably stable during the last decade. Between 1990 and 2010 an increase in PTD rate was noted in high-income countries, even though a decrease in the total number of deliveries was observed overall.(94) Part of this trend is possibly explained by improved pregnancy dating during this time.

According to the Swedish National Board of Health and Welfare, between 110 000 and 120 000 infants are born in Sweden each year, with approximately 5% of the deliveries being classified as preterm.(96) In 2020, the Swedish PTD rate was estimated to be 5.4%.(18)

Aetiology and risk factors

The aetiology of PTD is heterogeneous, with multiple risk factors and associated conditions.(95) On the base of aetiology, it is categorized into spontaneous PTD,

preterm premature rupture of membranes (PPROM), and medically indicated PTD, though PPROM is often considered as part of spontaneous PTD.(95, 97)

Spontaneous preterm delivery

Spontaneous preterm labour is thought of as a syndrome dependent on multiple underlying mechanisms, and in a large part of cases, the exact underlying mechanism is not known.(95) This is not surprising, as the underlying mechanism for the timing of human labour is not yet fully understood.(98) As the name suggests, it is defined as a spontaneous start of labour before 37 weeks of gestation and it represents approximately 50% of all PTDs.(97) PPROM, usually considered as part of spontaneous PTD when discussing aetiology, is defined as a rupture of the amniotic membranes more than one hour before the start of contractions before 37 weeks of gestation, and stands for another 25% of all PTDs.(95, 97, 99) Factors associated with spontaneous PTD are infection and inflammation, socioeconomic factors, race, and genetics.(98)

Infection is the underlying cause of a large part of spontaneous PTDs,(95) and it is closely associated with PPROM.(99) The infection can be symptomatic, but is more often subclinical up until labour. It is thought to trigger PTD through a maternal, and possibly foetal, inflammatory response where an increased concentration of prostaglandins triggers contractions and indirectly a rupture of the membranes.(100) Socioeconomic status is associated with spontaneous PTD,(101) with studies, for example, showing an association between low occupational level and PTD.(102) Maternal race is also associated with spontaneous PTD, with black women more likely to have a PTD compared to white women.(95) As socioeconomic status has not been shown to fully account for this racial difference in PTD rate, genetics and social stress have instead been proposed as potential contributors to the association.(98) A history of spontaneous PTD is a strong risk factor for a future PTD,(103) indicating a consistent underlying factor such as genetics. A Swedish sibling study from the early 2000s showed that correlations for gestational length were higher in monozygotic compared to dizygotic twins.(104) Today, genetics is well established as a factor associated with spontaneous PTD.(98)

Medically indicated preterm delivery

A medically indicated, iatrogenic PTD is associated with maternal and/or foetal conditions and stands for approximately 25% of all PTDs.(97) However, a recent study from the United Kingdom showed that over half of singleton PTDs in England during the period 2015–2017 were medically indicated.(105) Because of limited data on subtypes of PTD in many countries, it is hard to compare these kind of trends on a global level.(106) The labour foregoing a medically indicated PTD is induced, or the infant is delivered by caesarean section, for medical reasons. Causes of medically indicated PTD can be grouped into obstetric complications, foetal conditions, and maternal conditions.(107)

Obstetric complications resulting in PTD include vaginal bleeding and hypertensive disorders of pregnancy (HDP).(95) Medially indicated PTDs are associated with placental disorders such as PE, one of the conditions grouped under HDP.(108, 109) Foetal conditions associated with medically indicated PTDs are, for example, growth restrictions and foetal distress,(108) and maternal conditions associated with medically indicated PTDs can be both chronic, such as diabetes mellitus, and acute.(95) Acute maternal indications of PTD include sepsis, making infection not only associated with spontaneous PTD but also medically indicated PTD.(107) It should also be noted that medically indicated PTD is a risk factor for a future PTD, just as is spontaneous PTD.(103)

Multiple gestations

Multiple gestation pregnancies are associated with an increased risk of both spontaneous and medically indicated PTD.(95) The link between multiple gestation pregnancies and spontaneous PTD is thought to be mechanical, where an increase in intrauterine pressure results in PPROM and/or contractions and subsequently PTD.(109) Multiple gestation pregnancies are mainly associated with medically indicated PTD through foetal conditions, as multiple gestation is associated with both foetal distress and growth restrictions.(107, 110)

Pregnancy history and future coronary heart disease

Pregnancy complications, sometimes referred to as APOs, and other aspects of pregnancy history have emerged as sex-specific risk factors for future CHD in women during the last two decades.(7) A history of APOs has been shown to be associated with more progressed coronary artery atherosclerosis and a difference in overall distribution of coronary atherosclerosis in middle-aged women,(111) and women with a history of APOs have been shown to present with MI sooner after delivery compared to women with no APO history.(13) In this section the main focus will be on the aspects of pregnancy history included in this thesis, though it should be noted that other aspects of pregnancy history, such as gestational diabetes and placental abruption, are also associated with future maternal CHD.(112)

Preterm delivery

A history of PTD is associated with an up to two-fold increased risk of future maternal CHD, and the earlier the delivery, the higher the risk.(8) Women with a history of PTD are more likely to experience a future cardiovascular event or a CVD-related death compared to women who only delivered at term.(112) The risk increases with the recurrence of PTD,(8, 113) and is present in both women with a history of spontaneous and medically indicated PTDs.(114) A history of PTD has

been shown to be associated with IHD up to 40 years after delivery, with each additional week of pregnancy resulting in a 6% lower risk of IHD.(9) A history of PTD has also been shown to be associated with a higher coronary artery calcium score in middle-aged women,(111) indicating a higher risk of future coronary events.(115) Other APOs, such as HDP, are strongly associated with PTD,(108) but HDP, in particular PE, has only been shown to explain up to 25% of the association between PTD and future maternal CVD.(116) Another factor strongly associated with PTD, and other APOs, is multi-foetal pregnancies.(95) The association between multi-foetal pregnancies and future CVD will be discussed in more detail in a later section, but multi-foetal pregnancies in themselves are not thought to be associated with an increased risk of CVD.(117) In summary, a history of PTD is thought of as an independent risk factor for future CHD in women who have given birth.

Studies on presentation of CHD by history of PTD are scarce, with prior studies primarily examining the association between a history of HDP and CHD presentation.(14, 15) However, a recent study looked at the presentation of MI by APO history, including PTD, showing an overall association between APO history and MI presentation at a younger age, but no association between MI presentation and PTD specifically.(13)

Even though a history of PTD has also been shown to be associated with post-partum development of hypertension, dyslipidaemia, and diabetes mellitus type 2, independent of other APOs,(118-121) the association between PTD and future CVD is thought to depend very little, or not at all, on post-partum development of traditional CVD risk factors.(122, 123) It has also been shown that the risk factor trajectories in women with a history of PTD are similar to those of women who have only delivered at term.(124) In other words, the underlying association between a history of PTD and future maternal CHD is not very clear cut and is not yet fully understood. Inflammation has been suggested as a possible pathway, as inflammation has been shown to be associated with both CVD in women and spontaneous PTD,(125, 126) but studies on long-term persistent inflammation post-delivery have been inconclusive.(127) Vascular, and specifically endothelial, dysfunction has also been suggested to explain the association seen between PTD and future CVD. In general, studies on this topic have not shown any significant associations between a history of PTD and future endothelial dysfunction.(127, 128) Another way of approaching this problem is by suggesting that women who deliver preterm do so due to an underlying increased risk of CVD. As many APOs have been shown to be associated with pre-pregnancy subclinical vascular and/or metabolic dysfunction, pregnancy has been suggested to unmask patients at risk of future CVD.(129)

Other aspects of pregnancy history

Hypertensive disorders of pregnancy

HDP is an umbrella term for conditions with high blood pressure during pregnancy.(130) It is mainly used to refer to PE and gestational hypertension (GH), but sometimes also includes essential hypertension during pregnancy. PE is the most severe form of HDP defined as GH (hypertension onset after 19+6 weeks gestation) with proteinuria, signs of organ damage, and/or uteroplacental dysfunction and can develop into a seizure disorder called eclampsia.(131) It is estimated to effect 2–4% of all pregnancies globally,(131) and in 2022, 3.8% of pregnancies in Sweden were affected by PE.(132)

Women with a history of PE have more than double the odds of future CVD, with a two-fold increased risk of CHD and an increased risk of developing hypertension compared to women without a history of PE.(133, 134) GH is also associated with an increased risk of CVD.(7) PE and GH are both associated with more progressed subclinical coronary artery atherosclerosis in middle-aged women,(111) and PE has also been shown to be associated with greater risk of obstructive coronary artery stenosis.(135) In women with ACS, a history of PE has been shown to be associated with STEMI,(14, 15) and a history of PE might also be associated with adverse outcomes after PCI, such as restenosis.(11, 12)

There are two main theories regarding the pathogenesis of future maternal CVD in women with a history of HDP: (I) women who develop HDP do so because of an already existing subclinical risk of CVD or (II) HDP, mainly PE, permanently causes cardiovascular damage resulting in future CVD development. In pregnancy, the placental implantation leads to oxygen delivery to the placenta and reduced systemic vascular resistance, and an abnormal placentation consequently leads to reduced oxygen supply to the placenta and risk of placental ischaemia.(130) Abnormal placentation leads to placental expression of antiangiogenetic factors, mainly soluble fms-like tyrosine kinase (sFlt-1). sFlt-1 inhibits endothelial and placental growth factors and causes systemic endothelial dysfunction. Endothelial dysfunction has been shown to persist up to three years post-partum in women who were diagnosed with PE,(136) and, as endothelial dysfunction is known to be associated with the development of CVD,(77) this is thought to be one of the possible theories of how PE and future maternal CVD are connected. However, studies on twin pregnancies indicate that women who experienced PE during a multiple gestation pregnancy do not have an increased risk of future CVD, despite having elevated sFlt-1 levels.(117, 137) These results suggest that the elevated CVD risk seen in women with a history of PE might not fully depend on elevated sFlt-1 levels, but rather on something else. Previous study results have implied that women who develop HDP might have an impaired vascular function pre-pregnancy.(129) This suggests that pregnancy could act like a stress-test, possibly unmasking subclinical risk of future CVD.(138)

Small for gestational age

Small for gestational age (SGA) is defined by the Swedish Medical Birth Register (MBR) as >2 standard deviations (SD) below the normal weight by infant sex and length of pregnancy, or below the 2.3rd percentile.(139) The definition of an SGA infant varies globally, and is often defined as birth weight for gestational age and sex below the 10th percentile.(140) This variation in definition mostly influences studies on perinatal outcomes of the newborn, as the proportion of infants classified as SGA differs between studies and should in theory not influence the study results on the future maternal CVD risk very much. However, difference in SGA definitions can make it harder to pinpoint the association between a history of SGA and future maternal CHD throughout studies.

Women with a history of delivering an SGA infant have an increased risk of future CVD, independent of other APOs.(7, 123) As SGA is associated with intrauterine growth restriction it is also, in turn, associated with placental dysfunction.(141) This means that SGA and PE share etiological pathways, and as for PE it has been suggested that a persistent endothelial dysfunction is also the pathway for development of future CVD in women with a history of SGA.(142) However, delivering an SGA infant and CVD development share common risk factors such as hypertension and smoking,(140) and smoking has been shown to explain nearly 50% of the increased risk of future CVD seen in women with a history of delivering an SGA infant.(123)

Parity

The association between parity and future maternal CVD is not as straightforward as the association between other APOs and CVD and takes on slightly different expressions when looking at risk of CVD mortality or general risk of CVD. The association between parity and future CVD mortality has been shown to take on the form of a J-shaped curve, with the lowest risk of CVD mortality at parity equal to four.(143) But for non-fatal events, the risk of CVD increases for every live birth, and a potential non-linear J-shaped dose-response relationship has been suggested.(144) This relationship could potentially be explained by an association with subclinical atherosclerosis in women with 0–1 live births and in women with ≥4 live births, and it has been suggested that a prolonged exposure to the cardiovascular changes associated with pregnancy is what drives the association between parity and future maternal CVD.(145) Alternatively, raising a larger family may increase CVD risk via adverse effects on modifiable CVD risk factors such as diet and physical activity.

Age at first delivery

Studies have shown a potential inverse association between age at first delivery and future CVD, and socioeconomic factors have been suggested as the most probable explanation for this.(146) However, it has also been suggested that the

cardiovascular changes associated with pregnancy might affect an adolescent body in a different way compared to an adult body. The association may also stem from the fact that other APOs, such as PTD and SGA, have been shown to be associated with low maternal age.(147, 148)

Multiple gestations

It has been previously shown that a twin pregnancy in itself is not associated with an increased risk of future CVD.(117) To my knowledge there are no studies principally studying the future risk of CVD in singleton vs multi-foetal pregnancies complicated by PTD. However, there are studies like this on women with a history of HDP. A recent Swedish study showed that women with a history of multi-foetal pregnancies did not have an increased risk of future CVD, even in the presence of PE.(117) In contrast, a recent Dutch study showed that the future risk of CVD mortality is similarly increased both after twin and singleton pregnancies complicated by HDP.(149) Looking at these studies, a history of a multi-foetal pregnancy in itself does not seem to be associated with an increased risk of future CHD. It has been suggested that because the causes of APOs differ between singleton and multi-foetal pregnancies, possibly depending more largely on a larger pregnancy burden in multi-foetal pregnancies,(109, 150) the association with future CVD may very well differ as well.(117)

Pregnancy history and coronary heart disease in clinical practice

The ESC guidelines on CVD prevention in clinical practice (2021) highlight the elevated risk of CVD in women with a history of PE and state that it is not wrong to screen these women for diabetes and hypertension,(17) and the American College of Cardiology (ACC) and American Heart Association (AHA) updated recommendations for primary prevention of CVD in women (2020) recommend that women with APOs undergo cardiovascular risk screening within three months post-partum.(151) Some studies have aimed to investigate the extent to which information on APO history adds to the CVD prediction in women, showing only minor or no improvement.(152-154)

To what extent the ESC and ACC/AHA guidelines are actually followed in regard to APO history is hard to say, as there is a very limited number of studies on this topic. Studies on the awareness of APOs and future maternal CVD/CHD among physicians have shown a possible knowledge gap that varies between specialities.(155, 156) A treating physician's lack of knowledge will presumably result in women not being asked about APO history and lead to it not being documented, making it even harder to take APOs into account. A recent study on patients undergoing PCI showed that medical providers, in general, did not ask female patients about their obstetric history.(157)

Aim of thesis

General aim

To gain a better understanding of the link between a history of PTD and the presentation and outcome of CHD in women with at least one delivery.

Specific aims

I: To evaluate a history of PTD as a possible predictor of MACE and mortality following coronary artery stenting in women with at least one delivery.

II: To evaluate pregnancy history variables (PTD, SGA, age at first delivery, and parity) as possible predictors of restenosis and TLR following PCI in women with at least one delivery.

III: To evaluate a history of PE as a possible predictor of restenosis and TLR following PCI in women with at least one delivery.

IV: To study the association between a history of APOs (PTD, HDP, and SGA) and clinical indicators of a more severe myocardial injury at the time of MI in women with at least one delivery.

Methods

Data sources

In this section the registers used in this work will be presented. The information from the different registers has been linked using the Swedish personal identity number.(158) The personal identity number has been in use since 1947 and is assigned to all Swedish citizens at birth or to residents intending to stay in Sweden for more than one year. For residents intending to stay in Sweden less than one year, a coordination number will be issued instead. In health care, the personal identity number is used mainly for tracking patients and medical records, but also has an important role in linking registers for medical research.

SWEDEHEART

Data on PCIs and MIs from 2009 and onwards originated from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). The SWEDEHEART registry is a Swedish national quality registry of all in-hospital patients with ACS and patients undergoing some sort of coronary intervention.(159) It was launched in 2009 by merging four already existing quality registries, and of these four registries two have been used for this work – the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) and the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). RIKS-HIA has collected data on patients admitted to Swedish cardiac care units since 1995 and SCAAR is a procedure-related registry which has collected information on angiographies and PCI procedures in Sweden since 1998. The data in SCAAR is presented both on a patient level and a coronary segment level. A segment is defined as a specific vessel or part of a specific vessel, and a patient can have multiple registrations from the same procedure if interventions were done to more than one segment. The SWEDEHEART registries have 100% coverage of all patients undergoing angiography, angioplasty, or heart surgery.(159) In regard to MIs, it only captures around 60% of all MIs, as all MI patients are not admitted to cardiac care units. However, younger patients with MIs are captured to a greater extent than older patients, and of patients admitted to cardiac care units, the SWEDEHEART registry captures almost 100% of all ACS patients.

The Swedish Medical Birth Register

Data on pregnancy history originated from the Swedish MBR. The MBR is a Swedish national register that has collected data on most pregnancies and subsequent deliveries since 1973.(160) The goal of the register is to capture all live births and all stillbirths from 22 weeks of gestation, with the result of abortions and miscarriages before 22 weeks of gestation not being included. From 1973 until mid-2008, stillbirths were only included from 28 weeks of gestation and onwards. From the year 2000, the register captures 97–99% of all deliveries in Sweden, and since 2015 it includes information on over 99% of all deliveries.

Additional registers

In addition to SWEDEHEART and the MBR, additional data used in this work has been collected from three registries: Statistics Sweden, the Swedish Cause of Death Register, and the National Patient Register. Data on emigration originated from Statistics Sweden.(161) Established in 1858, Statistics Sweden is the governmental agency responsible for official statistics in Sweden.(162, 163) Data on cause of death originated from the Swedish Cause of Death register, a national, government-funded register collecting data on all causes of death since 1911, with almost complete data since 1952.(164) It collects data on cause of death based on International Classification of Diseases (ICD) codes and is mandatory for all Swedish care givers. Part of the data on events during follow-up and data on MIs before 2007, not included in RIKS-HIA, originated from the National Patient Register.(165) It is a national, government-funded register including information on all in-patient care since 1987.

Definitions

In the following section, definitions of variables included as exposures or outcomes in papers I–IV will be presented. For definitions of patient and procedure-related variables not included as an exposure or outcome in any paper, please see the respective methods section of papers I–IV.

Exposures

Preterm delivery

PTD was defined as delivery before 37+0 weeks of gestation, and further subcategorized into late PTD (34+0–36+6 weeks of gestation) and early PTD (22+0–33+6 weeks of gestation).(166) The decision to keep late PTD as its own

group and combining moderate, very, and extreme PTD into an early PTD group was partly based on few observations in the early PTD groups but also on the fact that the association between PTD and future CHD is stronger in women who have delivered in earlier weeks of gestation.(9, 122) PTD was further defined as a woman's most PTD prior to the index event. Gestational age was determined using ultrasound for most deliveries. However, as ultrasound was not used nationally in Sweden until the 1980s, gestational age may be calculated from last menses or by clinical estimation for deliveries in the 1970s and early 1980s.

Hypertensive disorders of pregnancy

HDP was defined in accordance with the ICD 8, 9, and 10 (Table 1), and diagnoses were set according to clinical practice at the time of diagnosis. In Paper III, HDP was divided into three categories: normotensive, non-PE hypertension (GH or essential hypertension), and PE. PE was further subcategorized into preterm PE (delivery gestational week <37+0) and term PE (delivery gestational week 37+0 or later). In Paper IV, HDP was coded as a binary variable, but also further categorized as preterm PE, term PE, and non-PE hypertension (either GH or essential hypertension). GH and essential hypertension were combined into the category non-PE hypertension because of the exposures being rare. In both papers, HDP was defined based on a woman's most severe diagnosis prior to the index event in the following ascending order: normotensive, non-PE hypertension, term PE, and preterm PE.

Table 1. Definition of hypertensive disorders of pregnancy
List of diagnoses according to ICD 8–10 used to define hypertensive disorders of pregnancy in Paper III and Paper IV. ICD: International Classification of Diseases; PE: preeclampsia.

ICD (years used)	Preeclampsia	Non-PE hypertension
ICD 8 (1973–1986)	637.03, 637.04, 637.09, 637.10	637.01
ICD 9 (1987–1996)	642E, 642F, 642G	642D, 642X
ICD 10 (1997 and onwards)	O14, O15	O13.9

Small for gestational age

Ever SGA was defined as ever delivering an SGA infant prior to the index event. SGA is defined as >2 SD below the normal weight by infant sex and length of pregnancy.(139)

Parity

Parity was defined as the total number of deliveries registered in the MBR prior to the index event and categorized as 1, 2–3, and ≥4. Parity = 1 was set as the reference category. The categorization was based on prior studies showing an association between high (>4) parity and future maternal CVD mortality,(143) and an

association between 0–1 live births or ≥4 live births and future subclinical atherosclerosis.(145)

Age at first delivery

By assessing deliveries prior to the index event, age at first delivery was categorized into the categories <20 years, 20–34 years, and ≥35 years. Age at first delivery <20 years was set as the reference category. The categorization was based on prior studies on age at first delivery and future maternal CHD and CVD.(146)

Outcomes

Paper I: Major adverse cardiovascular events

MACE was defined as a cardiovascular event or a cardiovascular related death >30 days from the index procedure. Only outcomes >30 days from the index procedure were included to minimize the risk of capturing the patient's primary event. Patients with ≥1 diagnoses presented in Table 2 as one of their first three diagnoses during a hospital stay >30 days from coronary stent were considered to have an event.

Table 2. Definition of major adverse cardiovascular events
List of diagnoses according to ICD 10 used to define MACE in Paper I. ICD: International Classification of Diseases; MACE: major adverse cardiovascular events.

Cardiovascular events	**ICD 10**
Acute myocardial infarction	I21
Subsequent myocardial infarction	I22
Unstable or unspecified angina	I20.0, I20.9
Cerebral infarction	I63
Stroke, not specified as haemorrhage or infarction	I64
Cardiovascular deaths	**ICD 10**
Acute myocardial infarction	I21
Subsequent myocardial infarction	I22
Unstable or unspecified angina	I20.0, I20.9
Chronic ischaemic heart disease	I25.0, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9
Cardiac arrest	I46
Sudden death, cause unknown	R96, R98, R99
Atrial fibrillation and flutter	I48
Ventricular fibrillation and flutter	I49.0
Heart failure	I50
Cerebral infarction	I63

Paper II and Paper III: Clinical restenosis and target lesion revascularization

Restenosis is defined by SCAAR as a stenosis assessed via visual inspection on coronary angiography as >50%, or alternatively assessed via fractional flow reserve as ≤0.80, in a previously stented segment. Patients were only examined if experiencing symptoms, i.e. not all patients were re-examined.

TLR was defined as a repeated PCI targeting any segment included in the index procedure or CABG after the index procedure, whichever came first.

Paper IV: Indicators of myocardial injury

STEMI (vs. NSTEMI), invasive revascularization, and peak troponin levels were used as indicators of a more severe myocardial injury at time of the MI diagnosis. Type of MI was defined by the treating physician in each individual case and then recorded as STEMI or NSTEMI in RIKS-HIA. Invasive revascularization was defined as a patient undergoing PCI or CABG during the hospital stay corresponding with the first MI diagnosis, and peak troponin value was defined as recorded by the treating physician in each individual case in RIKS-HIA.

As previously described, STEMI is the most severe form of ACS presentation traditionally associated with transmural infarction and is associated with a more severe myocardial injury compared to NSTEMI.(45, 46) Invasive revascularization at time of MI is primarily preformed on patients with more severe CAD, i.e. patients at risk of a larger myocardial injury,(42, 167) and high a peak troponin value is a marker of infarct size and a predictor of worse outcome following MI.(47, 48) Previous studies on clinical characteristics of MI have used similar markers to identify more severe cases of MI.(13, 168)

Data management and statistical analyses

Two statistical programmes were used in this work. In Paper I and Paper IV statistical analyses were conducted using Stata 16.0 (StataCorp LLC). In Paper II and Paper III SAS version 9.4 was used. A significance level of p <0.05 was used for hypothesis testing in all papers.

Prior to analysis, potential covariables were identified from previous studies, and processed in a standardized manner, e.g. checking for outliers, and checking for empty cells in cross tabulation, before potentially being included in the analysis (Table 3). The choice of covariables will be discussed for each paper in later sections, but in general, known predictors of the outcome in the respective papers were included as covariables.

Table 3. Data processing prior to analysis
Covariable and sample check prior to analysis: used for papers I–IV.

Standardized data check	Description
Visual inspection 1	• Browse data • Descriptive charts • Look at data distribution
Visual inspection 2	Check for outliers and/or unreasonable values • Histograms for continuous variables • Frequency tables for categorical variables
Cross tabulation	Cross tabulation of potential covariables with exposure • Check for empty cells and number of observations • >4 observations/cells are enough observations • Check frequency in all exposure groups
Missing values	Covariables with >10% missing are not to be included • Note missingness of each variable for Table 1
Missingness in sample	Complete case analysis may be used as the primary analysis if the proportion of missing data in sample is below 5% • Exclude any individual with missing data for complete case analysis • Note proportion of missing data in sample
Multiple imputation	If needed: imputation of covariables with missing data
Regression analysis	If multiple imputation was needed, this should be used as the main analysis

Multiple imputation as a way of handling missing data

In epidemiological studies, some proportion of missing data is more or less inevitable.(169) However, missing data can cause bias and information loss, and the use of complete case samples can result in loss of both information and statistical power. Multiple imputation is one way to deal with missing data. Simply put, multiple imputation means that missing values in a statistical analysis are replaced by new values so that an analysis can be conducted on the complete data set.(169, 170) It creates multiple versions of a complete data set, with predictive values, stemming from a (modelled) predictive distribution based on existing data, taking the place of the missing observations. The analysis is then conducted on all datasets and a combination of all analyses gives the final estimate.

Multiple imputation requires that data is missing at random.(169, 170) If not, there is a risk of introducing bias, and in retrospective observational studies the mechanism that gives rise to missing values is usually not known. So even though we assume missing at random, there is a risk of introducing bias with multiple imputation. This can, however, be avoided to some extent if variables predictive of the missing values are included in the imputation.(169) For example, patients with hyperlipidaemia are at greater risk of a coronary event compared to patients with normal lipid status, and if we do not include the outcome when imputing missing

values for hyperlipidaemia, the associations between hyperlipidaemia and coronary events are at risk of being underestimated. When data is missing not at random, the bias introduced by multiple imputation analyses can be bigger than that of the complete case analyses. Notably different results from complete case and imputed analyses should always lead to some suspicion and further investigations. As the impact of potential pitfalls increases with the proportion of missing data, multiple imputation should be carefully considered. However, to my understanding, universal consensus on the maximum proportion of missing data allowed for multiple imputation does not yet exist.

In this work, multiple imputation was used to address missing covariable (i.e. not variables included as exposures or outcomes) data on a patient level. As mentioned before, variables with >10% missing have not been included in any of the analyses (Table 3). In papers I–IV twenty imputed datasets were created using multiple imputation by chained equations. All covariables, outcomes, and exposures in each respective paper were included in the imputation model. In Paper I and Paper IV data was analysed using mi estimate in Stata, and in Paper II and Paper III using PROC MIANALYZE in SAS. All analyses were also repeated on complete case samples for comparison. See Table 4 for information on proportion of missing data in papers I–IV.

Table 4. Proportion of missing data

Proportion of missing data in papers I–IV, i.e. proportion of data imputed for main analyses and proportion of data excluded for complete case analyses.

Paper I (N = 5766)	n = 293 (5.1%)
Paper II (N = 6027)	n = 329 (5.5%)
Paper III (N = 6065)	n = 333 (5.5%)
Paper IV (N = 8320)	n = 512 (6.2%)

Introducing an age restriction

For all papers an age restriction of ≤65 years was used. This restriction was primarily based on data limitation. As the MBR started registering data in 1973 and the outcome data is from 2006 (papers I–III) or 2007 (Paper IV), one can assume that there are missing data on a substantial proportion of older women: women with delivery before 1973, women who do not have their first delivery registered in the MBR (an inclusion criterion to ascertain pregnancy history), and/or women with an outcome before 2006 or 2007. So, to avoid differential inclusion of older women, an age restriction of ≤65 was set. Old age is also a known prognostic marker of worse outcome following PCI,(67, 74) and by including women ≤65 years a more homogenous study sample was obtained. This upper age limit also has the advantage of harmonizing with other studies on the topic, enabling comparability.(13, 111) It

should also be noted that the association between APOs and future CVD in women has been shown to attenuate with age.(171)

Paper I

Study sample

First, I started by including women aged ≤65 years without prior revascularization procedures, who had their first coronary artery stent after their first delivery registered in the MBR. To ensure complete pregnancy history, all included women had to have their very first delivery registered in the MBR. I then excluded women with PCI before the year 2006, as SCAAR does not have complete coverage for all variables used before this. Lastly, women with missing data on PTD were excluded. This resulted in a study sample of 5766 women (Figure 5).

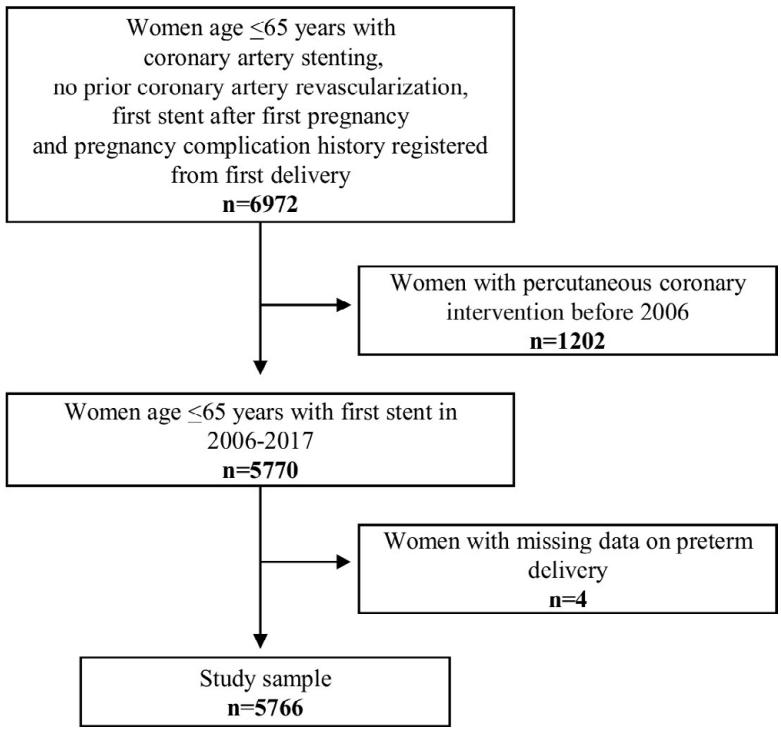


Figure 5. Flowchart of study sample in Paper I
The inclusion and exclusion criteria for the study sample in Paper I.

Exposures and outcomes

The exposure in Paper I was PTD, and the primary outcome was MACE >30 days from first coronary artery stent. Please see prior section for full definitions. As a secondary outcome, mortality >30 days from coronary stent was studied. As for MACE, only deaths >30 days from coronary stent were included to minimize the risk of capturing a patient's primary event as the outcome.

Statistical analysis

Characteristics of the study sample were summarized as means or percentages. Event rates were assessed using the Kaplan-Meier method and comparisons made using the log-rank test. Proportional hazards regression was used to evaluate a history of PTD as a prognostic marker of MACE following a first coronary artery stenting. Right censoring during follow-up occurred at the end of follow-up in 2017, migration out of Sweden, or death not related to MACE, whichever came first. Adjustment for possible prognostic markers of adverse outcomes following coronary artery stenting occurred in three steps (Table 5). Model I included PTD history and age. Model II was additionally adjusted for procedure-related predictors of adverse outcomes following PCI. To account for general improvement of care during the study period, I also included year of procedure in model II. Model III was additionally adjusted for patient-related predictors of worse outcome following PCI.

Table 5. Variables included in Paper I

Variables included in Paper I. MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; PTD: preterm delivery; STEMI: ST-segment elevation myocardial infarction.

Model	Variables included
Model I	PTD history; age at coronary artery stenting (continous).
Model II	Procedure type (PCI, PCI ad hoc); indication for coronary artery stenting (STEMI, NSTEMI, unstable coronary artery disease, stable coronary artery disease, other); year of procedure (2006–2009, 2010–2013, 2014–2017); number of vessels treated (1, ≥2); number of stents (1, 2, ≥3); multiple vessel disease (yes/no); drug-eluting stent (yes/no); left main stem or left anterior descending artery treated (yes/no); right coronary artery treated (yes/no); left circumflex coronary artery treated (yes/no); any other vessel treated (yes/no).
Model III	Diabetes (yes/no); smoking (never smoker, ex-smoker, current smoker); hypertension (yes/no); dyslipidemiea (yes/no); prior MI (yes/no).

Cardiac function (LVEF), renal function (creatinine), and BMI were not included as covariables as they all had >10% missing values. To evaluate a history of PTD as a prognostic marker of mortality, I also used proportional hazards regression. Right censoring during follow-up occurred at the end of follow-up in 2017, or migration out of Sweden, whichever came first. The analysis was adjusted as described for the analysis on MACE. All analyses were repeated with subgroups of PTD (late PTD

and early PTD) as the exposure. The proportional hazards assumption was assessed graphically. To evaluate whether any association between a history of PTD and any of the outcomes might be driven by a history of HDP or diabetes mellitus at the time of PCI, secondary analyses restricted to women with no history of HDP and women with no diagnosis of diabetes were performed. I also repeated the main analysis, additionally adjusting for antithrombotic treatment before and during the procedure in model II.

Paper II and Paper III

Study sample

In papers II and III we started by including women aged ≤65 years with first PCI in SCAAR during 2006–2017. Women with PCI before 2006 were not included as SCAAR does not have complete coverage for all variables used before 2006. To ensure pregnancy history, women also had to have their very first delivery registered in the MBR. After this, women with missing segment data were excluded. Women with planned CABG procedures at the time of index PCI were also excluded, to ensure that these procedures were not included as TLR, as were women with missing data on pregnancy history. Lastly, women with stenosis classified in SCAAR as "other" were excluded. This resulted in a study sample of 6027 patients with interventions on 9397 segments in Paper II (Figure 6) and 6065 patients with interventions on 9452 segments in Paper III (See Figure 1 in Paper III).

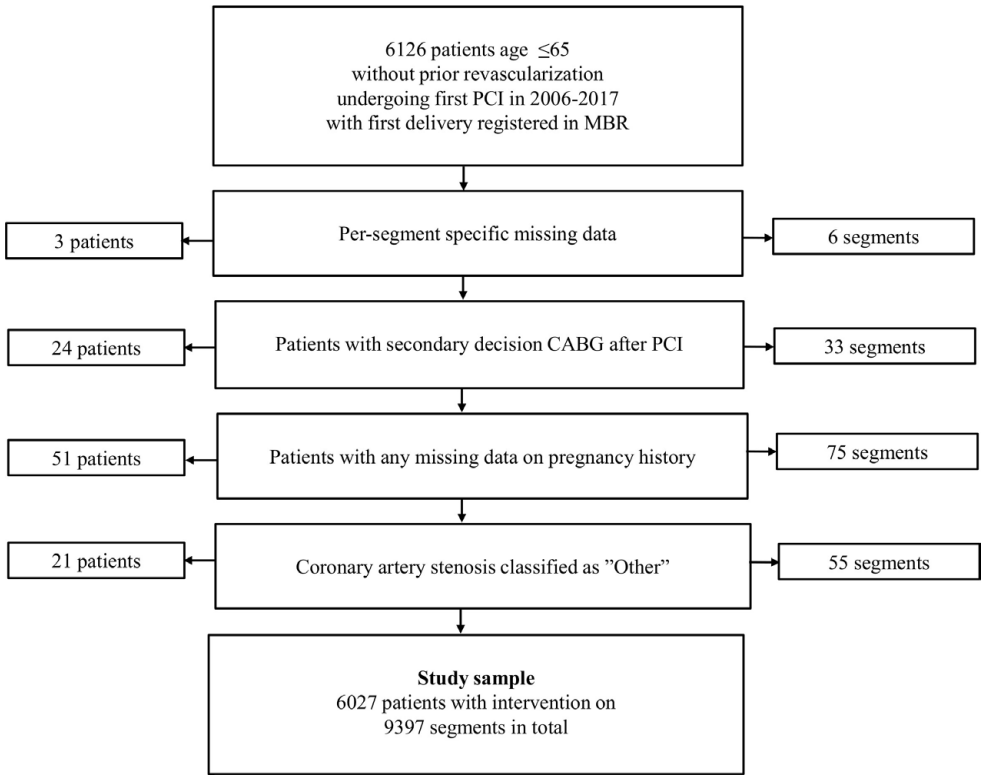


Figure 6. Flowchart of study sample in Paper II
Inclusion and exclusion criteria for the study sample in Paper I. CABG: coronary artery bypass graft; MBR: Medical Birth Register; PCI: percutaneous coronary intervention.

Exposures and outcomes

The exposures were PTD, SGA, parity, and age at first delivery in Paper II, and HDP in Paper III. Please see prior section for definitions. Restenosis and TLR, as previously defined, were included as outcomes in both papers.

Statistical analysis

Characteristics of the study sample at time of PCI were summarized as means or percentages, and percentages of missing data were calculated for each variable. Event rates were assessed using the Kaplan-Meier method, and the log-rank test was used for comparison. To allow for a more comprehensive picture of the results, two complementary sets of analyses were conducted, both per-segment analyses to study clinical restenosis and per-patient analyses to study TLR.

Proportional hazards regression was used to assess pregnancy history as a prognostic marker of clinical restenosis in the per-segment analyses. Right

censoring during follow-up occurred at two years of follow-up, end of follow-up in 2017, or migration out of Sweden or death, whichever came first. As the proportional hazards regression assumes independence of observations included in the analysis, a Jackknife estimator of variance, on a patient level, was used to account for possible dependence between coronary artery segments in the same patient. The per-segment analyses were adjusted for prognostic markers of restenosis in three steps (Table 6). Model I included pregnancy history and age. Model II additionally adjusted for procedure-related variables, and model III additionally adjusted for patient-related variables.

Table 6. Variables included in Paper II and Paper III

Variables included in Paper II and III, and how adjustment for possible prognostic markers of restenosis following percutaneous coronary intervention occurred in three steps. MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

Model	Variables included
Model I	Pregnancy history; age at index PCI (continous).
Model II	Indication for PCI (STEMI, NSTEMI, unstable coronary artery disease, stable coronary artery disease, other); year of procedure (2006–2009, 2010–2013, 2014–2017); treated vessel (right coronary artery, left main, left anterior descending artery, left circumflex coronary artery, other); class of stenosis (A, B1, B2, C); type of device(s) (bare metal stent only [bare metal stent, predilation with balloon], drug-eluting stent only [drug-eluting stent, predilation with balloon], [balloon only, drug coated], [balloon only, not drug coated]); length of stent (mm); stent diameter >3 mm (yes/no).
Model III	Diabetes (yes/no); smoking (never smoker, ex-smoker, current smoker); hypertension (yes/no); dyslipidemiea (yes/no); prior MI (yes/no).

Proportional hazards regression was also used to assess pregnancy history as a prognostic marker of TLR in the per-patient analyses. As for the per-segment analyses, right censoring occurred at two years of follow-up, end of follow-up in 2017, migration out of Sweden, or death, whichever came first. The per-patient analyses were adjusted for prognostic markers of TLR in three steps, as with the per-segment analyses, with some exceptions: segment-specific variables, such as class of stenosis and type of device used, were not included in model II, treated vessels were included as not mutually exclusive binary variables, and total number of treated vessels was also included. Lastly, in Paper III, proportional hazards regression was also used to assess PE as a prognostic marker of mortality following PCI. The analysis was adjusted for age and right censoring occurred at two years, end of follow-up in 2017, or migration out of Sweden, whichever came first. The proportional hazards assumption was assessed graphically in both papers.

Paper IV

Study sample

First, I started by including women aged ≤65 years with a first MI in RIKS-HIA in 2007 and onwards after first delivery in MBR in 1973 and onwards, and to assure complete pregnancy history, a woman's very first delivery had to be recorded in the MBR. After this, to only include first MIs, I excluded women with MI before 2007 using the National Patient Registry, and as MIs during pregnancy are often aetiologically different to other MIs,(6, 43) women with MI during any pregnancy were also excluded. Next, to ensure a study sample of primarily coronary healthy women prior to MI, women with a history of revascularization (PCI or CABG) were excluded. Lastly, women with missing data on exposures or outcomes were excluded. This resulted in a study sample of 8320 women (Figure 7).

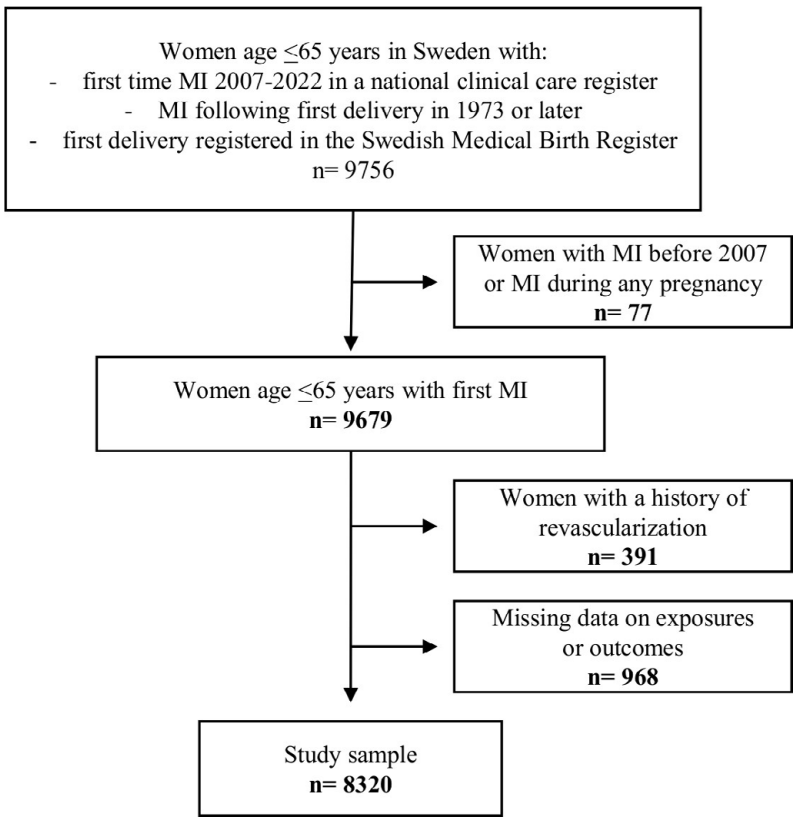


Figure 7. Flowchart of study sample in Paper IV

The inclusion and exclusion criteria for the study sample in Paper IV. MI: myocardial infarction.

Exposures and outcomes

Exposures used in Paper IV were PTD, HDP, and SGA. STEMI (vs NSTEMI), invasive revascularization, and high peak troponin value were identified as outcomes to assess a possible association between a more severe myocardial injury at first MI and the chosen exposures. Please see earlier sections for definitions.

Statistical analysis

Characteristics of the study sample were summarized as means or percentages, and percentages of missing data were calculated for each variable. Logistic (Bernoulli) regression was used to assess the association between APOs and STEMI, adjusting for covariables in two steps. Model I included APO history (HDP, PTD, or SGA) and age. Model II was additionally adjusted for known predictors of CHD at time of MI: BMI, diabetes, hypertension, smoking status, and treatment for dyslipidaemia. Logistic regression was also used to study the association between APOs and invasive revascularization at MI, and the analysis was adjusted as described for the STEMI analysis. To study the mean difference in peak troponin levels by APO history, a standard linear regression model was used, and to assess a possible association between particularly high peak troponin and APOs, logistic regression was used. Peak troponin ≥ the top quartile was used to indicate a particularly high peak troponin value. To analyse peak troponin, regardless of troponin type, each type of peak troponin (Troponin T, highly sensitive Troponin T, Troponin I and highly sensitive Troponin I) was first log transformed, as the data is highly skewed. After this, z-scores for each type of peak troponin were calculated, which harmonized troponin types and allowed for a pooled analysis. Troponin analyses were adjusted for covariables as described for the STEMI analysis, and also stratified by STEMI or NSTEMI in additional analyses, as infarct type is associated with severity of myocardial injury.(45, 46)

Model assumption checks for the logistic regression showed that the residual deviance per degree of freedom was below 1, indicating a reasonable overall fit and no over-dispersion. Linear regression assumptions were checked by visual inspection of the QQ-plot of residuals and residuals vs predicted mean levels.

As PTD is strongly associated with HDP,(95) additional analyses subgrouping PTD into normotensive PTD and hypertensive PTD were also performed, and as parity is associated with the probability of having an APO and risk of future maternal CVD,(144) an additional analysis was performed additionally adjusting for parity in model I. Lastly, to assess the impact of covariables on the model, analyses were conducted with adjustments made for each covariable individually, in addition to age at MI.

Ethical considerations

The General Data Protection Regulation (GDPR) controls the protection of personal data.(172) The handling of previously collected sensitive personal data is generally not legally allowed without information being provided to the individual in question, but exceptions to this apply to historical or medical research.(173) Article 14 of the GDPR states that the requirement for informed consent is disregarded in the event that "…the provision of such information proves impossible or would involve a disproportionate effort…". Instead, so-called presumed consent comes into effect where the researchers inform the public about a planned study, often by publishing information in the daily media.

The studies presented in this thesis all fall under the principle of presumed consent, as none of the research subjects have given their consent for these specific studies. However, all individuals included in SWEDEHEART have been informed that data regarding them is stored, and they have been given the chance to decline participation in the registry.(159) In regard to the MBR, any disclosure from the register must be preceded by a written request to the Swedish National Board of Health and Welfare, which then decides on the disclosure of data based on a confidentially test.(174, 175)

The Declaration of Helsinki states that, "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."(176) Thus, medical research can be viewed as navigating between the advantages of the research and the privacy concerns of the individual. It is arguably easier for a medical researcher to argue that the public interest in improving healthcare, with the help of medical research, outweighs the individual's personal integrity, than for an uninitiated individual to argue the opposite. Because of this imbalance, it is of the utmost importance to maintain a high level of data security and respect for the individual's privacy.

In order to achieve the necessary level of data security, all data was anonymized before analysis, and the results are exclusively presented at a group level. All data was processed in a secure server environment at Lund University (LUSEC). Ethical permission for the separate works presented in this thesis were obtained from the Ethical Review Board in Lund (2015/792, 2018/23) and the Swedish Ethical Review Authority (2021-04863).

Results

Paper I

In a national study sample of 5766 women with first time coronary artery stent, 963 women (16.7%) had a history of a PTD. At the time of the index procedure, women with a history of PTD were younger and more often presented with the traditional CVD risk factors diabetes, dyslipidaemia, and hypertension, compared to women who had only a history of delivering at term (Table 7). STEMI was the most common indication for coronary artery stenting in both groups. Procedure-related characteristics were similar between groups, though women with a history of late PTD more often presented with multiple vessel disease. For more information on procedure-related variables by history of PTD, please see Table 2 in Paper I.

Table 7. Characteristics of study sample in Paper I by history of PTD (N = 5766)
Clinical characteristics of study sample at time of coronary artery stent. Values are presented as mean ± SD or n (%). CAD: coronary artery disease; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PTD: preterm delivery; STEMI: ST-segment elevation myocardial infarction.

	Ever preterm delivery (n = 963)	Never preterm delivery (n = 4803)
Age, years	53.9 ± 6.9	55.3 ± 6.4
Diabetes mellitus	225 (23.5)	673 (14.1)
Hypertension	451 (47.4)	2094 (44.2)
Dyslipidemiea	340 (35.8)	1412 (29.9)
Current smoker	458 (49.3)	2145 (46.1)
Prior MI	54 (5.7)	168 (3.5)
Indication for coronary artery stenting		
STEMI	341 (35.4)	1743 (36.3)
NSTEMI	126 (13.1)	657 (13.7)
Unstable CAD	311 (32.3)	1571 (32.7)
Stable CAD	148 (15.4)	697 (14.5)
Other	37 (3.8)	135 (2.8)
Year of procedure		
2006–2009	230 (23.9)	1288 (26.8)
2010–2013	336 (34.9)	1617 (33.7)
2014–2017	397 (41.2)	1898 (39.5)

Major adverse cardiovascular events following coronary artery stenting

During follow-up, 236 women (24.5%) with a history of PTD experienced a MACE compared to 964 women (20.0%) who only delivered at term. The median follow-up time from the index procedure was 3.69 years (inter quartile range (IQR): 1.43–6.74 years), 3.35 years (IQR: 1.31–6.23 years) in women with a history of PTD and 3.77 years (IQR: 1.46–6.86 years) in women with no history of delivering preterm. Women with a history of PTD had an increased unadjusted rate of MACE compared to women with no history of delivering preterm (Figure 8).

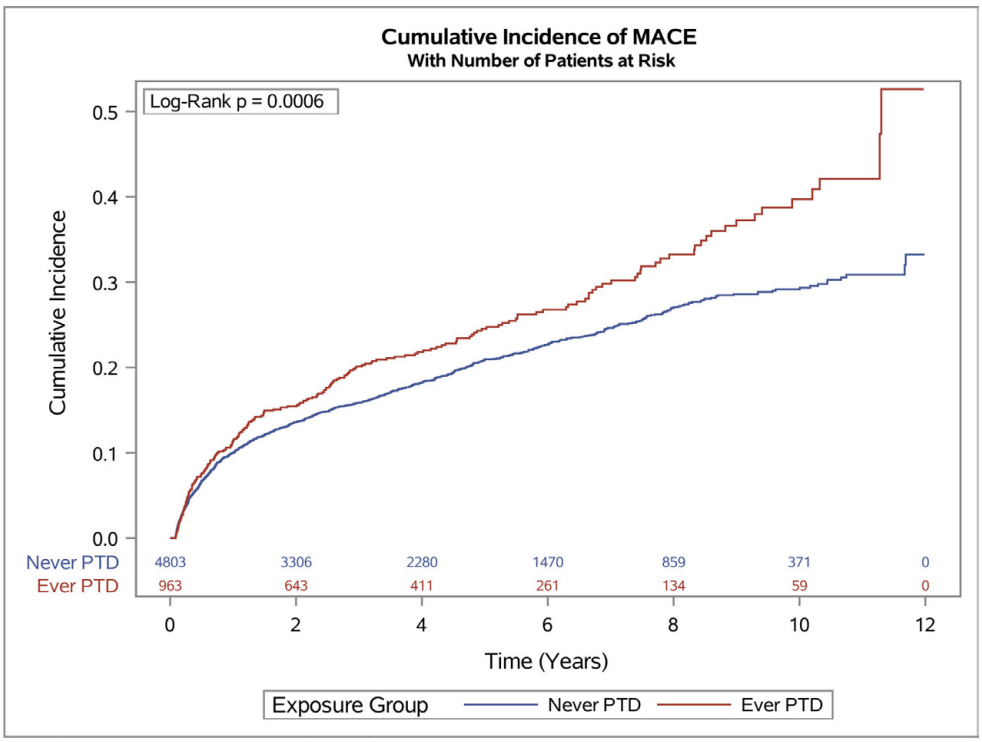


Figure 8. Cumulative incidence of MACE by PTD history

The unadjusted rate of MACE by history of preterm delivery. Event rates were estimated using the Kaplan-Meier method and comparisons made using the log-rank test. MACE: major adverse cardiovascular event; PTD: preterm delivery. Adapted from figure by Pehrson, et al. © 2022 Pehrson, et al. Reprinted under the CC BY license (https://creativecommons.org/licenses/by/4.0/).

See Table 8 for the proportional hazards regression analysis on MACE by PTD history, where a history of PTD was associated with a higher risk of MACE following first coronary artery stenting (adjusted hazard ratio (HR): 1.19, 95% confidence interval (CI): 1.03–1.38). When analysing subgroups of PTD, this association was only present in the late PTD group (adjusted HR: 1.31, 95% CI: 1.11–1.55), and not in the early PTD group (adjusted HR: 0.97, 95% CI: 0.75–1.24).

For more information on subgroup analyses, please see Table 3 in Paper I. Results were similar in the complete case analysis (Supplemental Table 2 in online appendix of Paper I).

Table 8. MACE by history of PTD (N = 5766)
MACE following coronary artery stenting by history of PTD. Subgroups of PTD not shown. CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular event; PTD: preterm delivery.

PTD history (Events/ Person years)	**Model I** HR (95% CI)	*p*	**Model II** HR (95% CI)	*p*	**Model III** HR (95% CI)	*p*
Never PTD (964/21089)	1 (reference)		1 (reference)		1 (reference)	
Ever PTD (236/3902)	1.27 (1.10-1.46)	0.001	1.25 (1.08-1.45)	0.002	1.19 (1.03-1.38)	0.02

Long-term mortality following coronary artery stenting

During follow-up, 59 women (6.1%) with a history of PTD died compared to 204 women (4.2%) who only delivered at term. The median follow-up time was 4.90 years (IQR: 2.42–7.93 years), 4.70 years (IQR: 2.34–7.62 years) in women with a history of PTD and 4.95 years (IQR: 2.44–7.99 years) in women with no history of delivering preterm. Women with a history of PTD had an increased unadjusted mortality rate compared to women with no such history (Figure 9).

See Table 9 for the proportional hazards regression analysis on mortality by PTD history, where a history of PTD was associated with a higher risk of mortality following first coronary artery stenting (adjusted HR: 1.38, 95% CI: 1.02–1.85). For subgroup analyses, please see Table 4 in Paper I, where both subgroups of PTD were associated with mortality in model I, but not in the fully adjusted model (model III). Results were similar in the complete case analysis (Supplemental Table 5 in online appendix of Paper I).

Table 9. Mortality by history of PTD (N = 5766)
Mortality following coronary artery stenting by history of PTD. Subgroups of PTD not shown. CI: confidence interval; HR: hazard ratio; PTD: preterm delivery.

PTD history (Events/ Person years)	**Model I** HR (95% CI)	*p*	**Model II** HR (95% CI)	*p*	**Model III** HR (95% CI)	*p*
Never PTD (204/25443)	1 (reference)		1 (reference)		1 (reference)	
Ever PTD (59/4916)	1.63 (1.22-2.18)	0.001	1.59 (1.19-2.14)	0.002	1.38 (1.02-1.85)	0.04

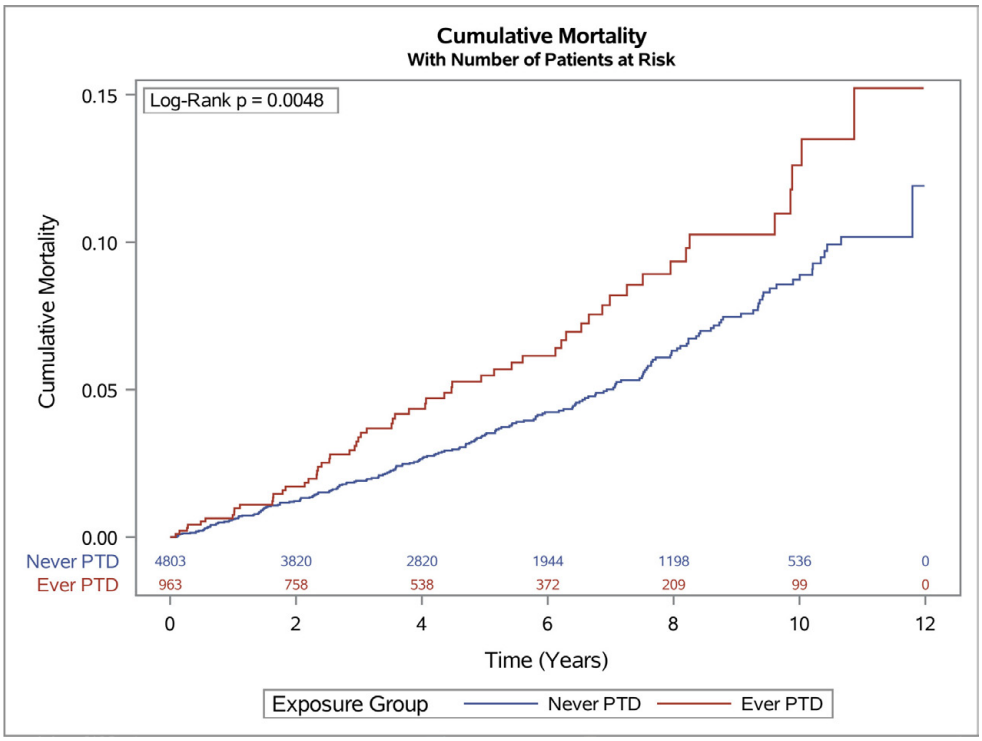


Figure 9. Cumulative mortality by PTD history
The unadjusted mortality rate by history of PTD. Event rates were estimated using the Kaplan-Meier method and comparisons made using the log-rank test. PTD: preterm delivery. Adapted from figure by Pehrson, et al.

Secondary analyses

In secondary analyses restricted to women with no history of HDP, a history of PTD remained a prognostic marker of both MACE (adjusted HR: 1.21, 95% CI: 1.02–1.43; see Supplemental Table 3 in online appendix of Paper I) and long-term mortality (adjusted HR: 1.58, 95% CI: 1.15–2.18; see Supplemental Table 6 in online appendix of Paper I). Similarly, secondary analyses on women without diabetes mellitus at time of coronary artery stenting also showed that a history of PTD remained a prognostic marker of both MACE (adjusted HR: 1.24, 95% CI: 1.05–1.48; see Supplemental Table 4 in online appendix of Paper I) and long-term mortality (adjusted HR: 1.49, 95% CI: 1.04–2.16; see Supplemental Table 7 in online appendix of Paper I).

Table 10 shows an additional analysis on subgroups of PTD where women with a history of early PTD had a lower risk of MACE after first coronary artery stenting compared to women with a history of late PTD, as did women with no history of

PTD. However, women with a history of early PTD had the same risk of mortality following coronary artery stenting as women with a history of late PTD, as did women with no history of PTD (data not shown).

Additional analyses on MACE after first coronary artery stenting by history of PTD, adjusting for antithrombotic treatment before and during coronary artery stent, showed similar results as presented in the main analysis (data not shown).

Table 10. MACE by subgroups of PTD history, late PTD as reference (N = 5766)
MACE following coronary artery stenting by history of PTD. Late PTD as reference group. CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular event; PTD: preterm delivery.

PTD history (Events/ Person years)	**Late PTD** (169/2552)	**Early PTD** (67/1350)		**Never PTD** (964/21089)	
	HR (95% CI)	HR (95% CI)	*p*	HR (95% CI)	*p*
Model I	1 (reference)	0.76 (0.57-1.01)	0.06	0.73 (0.62-0.85)	<0.001
Model II	1 (reference)	0.77 (0.58-1.02)	0.07	0.74 (0.62-0.87)	<0.001
Model III	1 (reference)	0.74 (0.55-0.98)	0.04	0.76 (0.65-0.90)	0.001

Paper II

In 6027 women with first time PCI, with a corresponding 9397 segments, 1005 women (16.7%) had a history of PTD. Median time from first delivery to index procedure was 31.0 years (IQR: 25.0–35.4 years). At time of first PCI, women with a history of PTD more often presented with traditional CHD risk factors (diabetes, hypertension, dyslipidaemia, and active smoking status) compared to women with no history of PTD (Table 11). Women with a history of PTD also more often had a history of a previous MI compared to women who only ever delivered at term. For complete patient characteristics at first PCI by SGA, parity, and age at first delivery, please see Table 1 in Paper II. In short, women with a history of SGA were more often active smokers compared to women with no such history. Unipara women at time of PCI more often presented with traditional CHD risk factors compared to multiparous women, except for smoking status, where women with parity ≥4 were more likely to be active smokers compared to women with a lower parity. Women who experienced their first delivery at age <20 years were more often active smokers at time of first PCI compared to women who experienced their first delivery at an older age. STEMI was the most common indication for PCI in all groups, closely followed by unstable CAD. Segment characteristics were similar for all exposures (Supplemental Table 1 in online appendix of Paper II).

Table 11. Characteristics of study sample in Paper II by history of PTD (N = 6027)
Clinical patient characteristics of study sample in Paper II at time of index PCI. Information presented per patient as mean ± SD or n (%). CAD: coronary artery disease; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; PTD: preterm delivery; STEMI: ST-segment elevation myocardial infarction.

	Ever preterm delivery (n = 1005)	Never preterm delivery (n = 5022)
Age, years	54.0 ± 6.8	55.3 ± 6.4
Diabetes mellitus	237 (23.6)	707 (14.1)
Hypertension	479 (47.7)	2179 (43.4)
Dyslipidemiea	356 (35.4)	1457 (29.0)
Current smoker	469 (46.7)	2218 (44.2)
Prior MI	55 (5.5)	177 (3.5)
Indication for PCI		
STEMI	359 (35.7)	1843 (36.7)
NSTEMI	131 (13.0)	696 (13.9)
Unstable CAD	326 (32.4)	1614 (32.1)
Stable CAD	150 (14.9)	715 (14.2)
Other	39 (3.9)	154 (3.1)
Year of index PCI		
2006–2009	239 (23.8)	1315 (26.2)
2010–2013	351 (34.9)	1685 (33.6)
2014–2017	415 (41.3)	2022 (40.3)

Clinical restenosis following percutaneous coronary intervention

In total, 343 (3.7%) cases of clinical restenosis occurred following first PCI during a follow-up time of 15 981 segment-years. A history of PTD was not associated with an increased unadjusted rate of clinical restenosis (Figure 10), nor were any of the other studied aspects of pregnancy history (see Figure 2 in Paper II). In the proportional hazards regression, no associations were seen between any of the studied aspects of pregnancy history and clinical restenosis, though it should be noted that HRs for late PTD, SGA, and higher parity were all greater than one (see Table 2 in Paper II). Results were similar in the complete case analysis (data not shown).

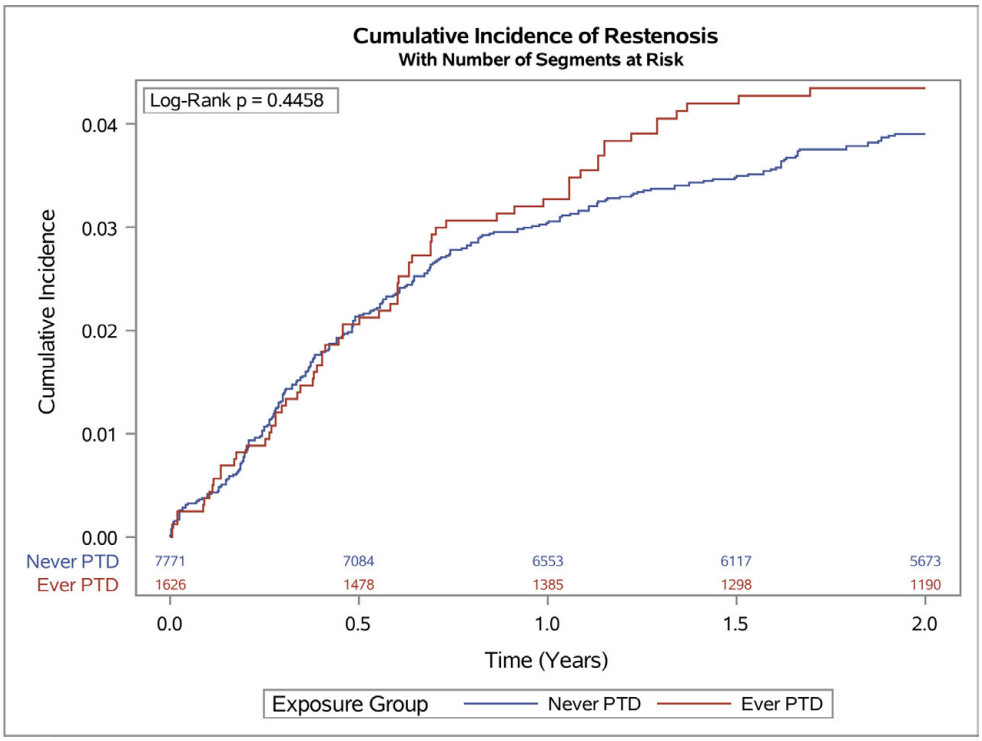


Figure 10. Cumulative incidence of restenosis by PTD history
The unadjusted rate of restenosis by history of preterm delivery. Event rates were estimated using the Kaplan-Meier method and comparisons made using the log-rank test. PTD: preterm delivery. Adapted from figure by Pehrson, et al.

Target lesion revascularization following percutaneous coronary intervention

In total, 383 women (6.4%) underwent TLR during a follow-up time of 10 103 person-years. Figure 11 shows the cumulative incidence of TLR following first PCI by PTD history. A history of PTD was not associated with an increased unadjusted rate of TLR, nor were any of the other studied aspects of pregnancy history (see Figure 3 in Paper II). As in the clinical restenosis analysis, no association was seen between any of the studied aspects of pregnancy history and TLR in the proportional hazards regression (Supplemental Table 2 in online appendix of Paper II). Results were similar in the complete case analysis (data not shown).

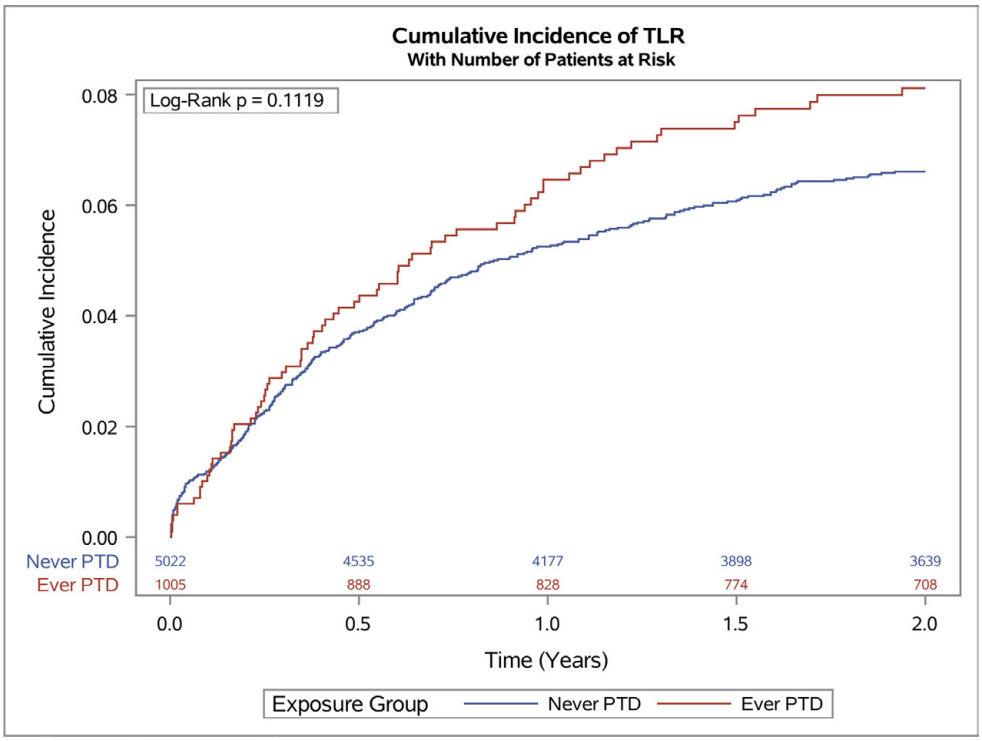


Figure 11. Cumulative incidence of TLR by PTD history
The unadjusted rate of TLR by history of preterm delivery. Event rates were estimated using the Kaplan-Meier method and comparisons made using the log-rank test. PTD: preterm delivery; TLR: target lesion revascularization. Adapted from figure by Pehrson, et al.

Paper III

In a sample of 6065 women with first PCI, corresponding to 9452 segments, 841 women (13.9%) had a history of HDP. Median time from first delivery to index PCI was 30.9 years (IQR: 25.0–35.4 years). Table 12 shows the patient characteristics at time of first PCI by HDP history. Compared to women with normotensive pregnancies, women with a history of PE or non-PE hypertension were more likely to present with diabetes and hypertension at time of first PCI and were less likely to be active smokers. For patient characteristics of PE subgroups please see Supplemental Table 1 in online appendix of Paper III. Table 1 in Paper III shows the patient and procedural characteristics per segment. There were no major differences in procedural characteristics between exposure groups.

Table 12. Characteristics of study sample in Paper III by history of HDP (N = 6065)
Clinical patient characteristics of the study sample in Paper III at time of index PCI. Information presented per patient as mean ± SD or n (%). CAD: coronary artery disease; HDP: hypertensive disorder of pregnancy; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

	Preeclampsia (n = 566)	Non-PE hypertension (n =275)	Normotensive (n = 5224)
Age, years	53.0 ± 7.2	54.8 ± 6.5	55.3 ± 6.3
Diabetes mellitus	144 (25.5)	67 (24.7)	743 (14.3)
Hypertension	345 (61.4)	175 (64.8)	2154 (41.9)
Dyslipidemiea	193 (34.6)	99 (37.2)	1538 (30.0)
Current smoker	169 (30.8)	89 (34.4)	2446 (48.5)
Prior MI	20 (3.6)	16 (6.0)	198 (6.3)
Indication for PCI			
STEMI	182 (32.2)	100 (36.4)	1935 (37.0)
NSTEMI	77 (13.6)	31 (11.3)	724 (13.9)
Unstable CAD	193 (34.1)	84 (30.6)	1672 (32.0)
Stable CAD	91 (16.1)	49 (17.8)	732 (14.0)
Other	23 (4.1)	11 (4.0)	161 (3.1)
Year of index PCI			
2006–2009	150 (26.5)	92 (33.5)	1319 (25.3)
2010–2013	190 (33.6)	98 (35.6)	1762 (33.7)
2014–2017	226 (39.9)	85 (30.9)	2143 (41.0)

Clinical restenosis following percutaneous coronary intervention

In total, 345 cases (3.7%) of restenosis occurred during 16 084 segment-years of follow-up. Figure 12 shows the cumulative incidence of restenosis, indicating a lower unadjusted rate of restenosis in women with a history of term PE. Table 13 shows the HRs for restenosis by HDP history. A history of term PE was associated with a lower risk of restenosis following first PCI (adjusted HR 0.45, 95% CI: 0.21–0.94). No association was seen between the other exposure categories and restenosis. Results were similar in the complete case analysis (Supplemental Table 2 in online appendix of Paper III).

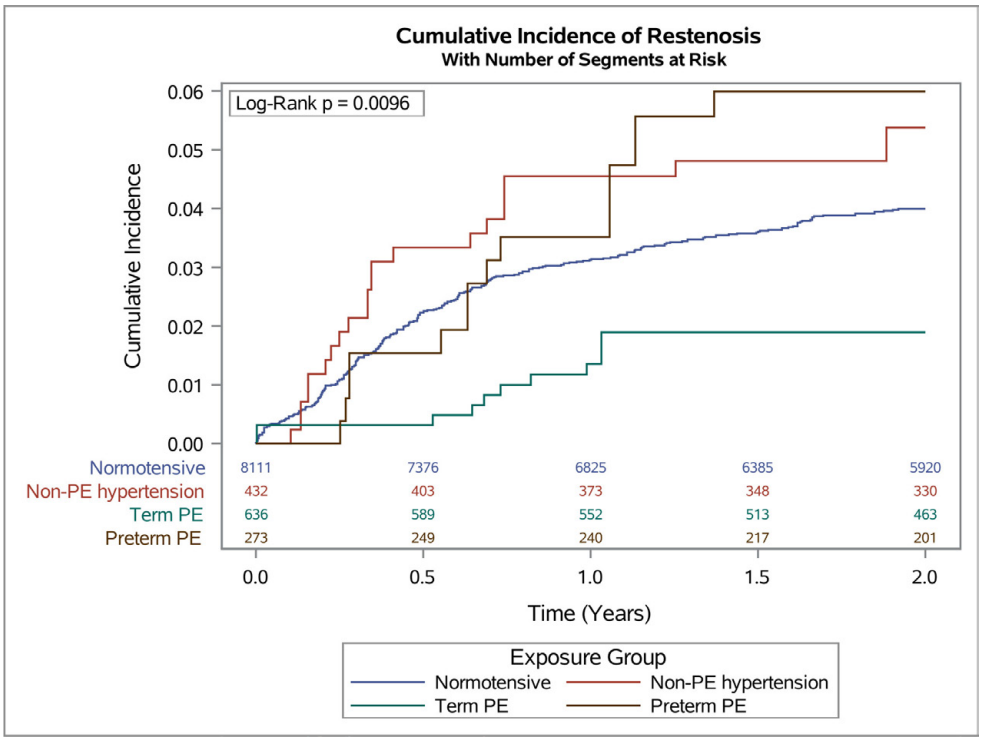


Figure 12. Cumulative incidence of restenosis by HDP history
The unadjusted rate of restenosis by history of HDP. Event rates were estimated using the Kaplan-Meier method and comparisons made using the log-rank test. HDP: hypertensive disorders of pregnancy. Adapted from figure by Lin, et al. © 2022 Lin, et al. Reprinted under the CC BY license (https://creativecommons.org/licenses/by/4.0/).

Table 13. Restenosis by history of HDP (N = 9452)
Restenosis following percutaneous coronary intervention by history of hypertensive disorders of pregnancy. Per-segment analysis. CI: confidence interval; HDP: hypertensive disorder of pregnancy; HR: hazard ratio; PE: preeclampsia.

HDP history (events/ segment-years)	**Model I** HR (95% CI)	*p*	**Model II** HR (95% CI)	*p*	**Model III** HR (95% CI)	*p*
Normotensive (297/13758)	1 (reference)		1 (reference)		1 (reference)	
Non-PE hypertension (22/753)	1.34 (0.75-2.40)	0.33	1.20 (0.67-2.16)	0.53	1.15 (0.64-2.07)	0.64
Preeclampsia (26/1573)	0.73 (0.42-1.25)	0.25	0.77 (0.45-1.32)	0.34	0.71 (0.41-1.23)	0.22
Term PE (11/1104)	0.45 (0.22-0.95)	0.03	0.47 (0.23-0.98)	0.04	0.45 (0.21-0.94)	0.03
Preterm PE (15/469)	1.33 (0.62-2.86)	0.47	1.47 (0.68-3.15)	0.33	1.28 (0.59-2.80)	0.53

Target lesion revascularization following percutaneous coronary intervention

In total, 383 women (6.3%) experienced a TLR during 10 174 patient-years of follow-up. Figure 13 shows the cumulative incidence of TLR by HDP history, indicating a potential higher unadjusted rate of TLR in women with a history of non-PE hypertension. However, proportional hazards regression showed no association between any exposure category and TLR after first PCI (Table 3 in Paper III). Results were similar in the complete case analysis (Supplemental Table 3 in online appendix of Paper III).

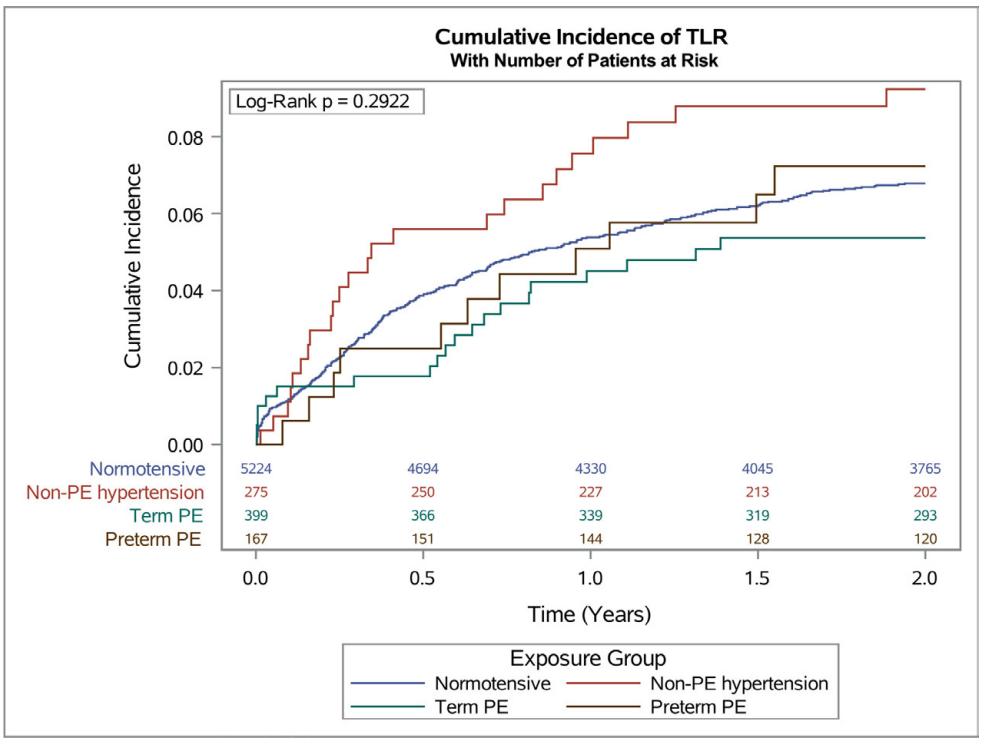


Figure 13. Cumulative incidence of TLR by HDP history

The unadjusted rate of restenosis by history of HDP. Event rates were estimated using the Kaplan-Meier method and comparisons made using the log-rank test. HDP: hypertensive disorders of pregnancy; TLR: target lesion revascularization. Adapted from figure by Lin, et al.

All-cause mortality following percutaneous coronary intervention

In total, 166 (2.7%) deaths occurred during 10 684 patient-years of follow-up. Proportional hazards regression showed no association between mortality following first PCI and a history of PE (adjusted HR 1.06, 95% CI 0.62–1.80; data not shown) or a history of non-PE hypertension (adjusted HR 1.21, 95% CI 0.62–2.38; data not shown).

Paper IV

In a national study sample of 8320 women with first time MI, 1301 women (15.6%) had a history of PTD. Table 14 shows patient characteristics at first MI by PTD history. Women with a history of PTD were younger and more likely to present with diabetes, hypertension, and/or treatment for dyslipidaemia at time of first MI compared to women with no history of PTD. For patient characteristics by HDP and SGA history, please see Table 1 in Paper IV. In short, women with a history of HDP presented with MI at a younger age, and were more likely to present with diabetes, hypertension, treatment for dyslipidaemia, and a higher BMI at time of first MI compared to women with no such history. Women with a history of SGA were more likely to be active smokers at time of first MI compared to women with no history of SGA.

Table 14. Characteristics of study sample in Paper IV by history of PTD (N = 8320)
Clinical patient characteristics of study sample in Paper IV at time of first MI. Information presented as mean ± SD or n (%). BMI: body mass index; MI: myocardial infarction; PTD: preterm delivery.

	Ever preterm delivery (n = 1301)	Never preterm delivery (n = 7019)
Age, years	55.0 ± 7.2	56.3 ± 6.8
Diabetes mellitus	296 (22.8)	1047 (14.9)
Hypertension	545 (41.9)	2683 (38.2)
Dyslipidemiea	206 (15.8)	902 (12.8)
Current smoker	582 (44.7)	2963 (42.2)
BMI, kg/m2	28.0 ± 5.8	27.9 ± 5.6

Clinical characteristics of first myocardial infarction

Table 15 shows the association between APOs and STEMI at the time of first MI. A history of SGA was associated with STEMI at the time of first MI (adjusted odds ratio (OR) 1.30, 95% CI 1.13–1.50), as was preterm PE (adjusted OR 1.40, 95% CI 1.05–1.87). No association was found between a history of PTD or HDP overall and STEMI.

Table 16 shows the association between APOs and invasive revascularization at the time of first MI. Women with a history of SGA were more likely to undergo invasive revascularization at time of first MI (adjusted OR 1.20, 95% CI 1.04–1.39), as were women with a history of preterm PE (adjusted OR 1.43, 95% CI 1.07–1.92). A history of PTD was not associated with invasive revascularization at time of first MI, nor was a history of HDP overall.

Table 15. STEMI at first MI by APO history (N = 8320)
Association between adverse pregnancy outcome history and STEMI among women presenting with first myocardial infarction. Data for subgroups of PTD not shown. APO: adverse pregnancy outcome; CI: confidence interval; HDP: hypertensive disorder of pregnancy; MI: myocardial infarction; OR: odds ratio; PE: preeclampsia; PTD: preterm delivery; SGA: small for gestational age; STEMI: ST-segment elevation myocardial infarction.

	Model I		**Model II**	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Preterm delivery				
Never PTD	1 (reference)		1 (reference)	
Ever PTD	0.99 (0.87-1.12)	0.84	0.98 (0.87-1.11)	0.76
Small for gestational age infant				
Never SGA	1 (reference)		1 (reference)	
Ever SGA	1.40 (1.22-1.61)	<0.001	1.30 (1.13-1.50)	<0.001
Hypertensive disorders of pregnancy				
Normotensive	1 (reference)		1 (reference)	
Ever HDP	0.95 (0.83-1.09)	0.48	1.07 (0.94-1.23)	0.31
Preterm PE	1.18 (0.89-1.57)	0.24	1.40 (1.05-1.87)	0.02
Term PE	0.88 (0.73-1.06)	0.17	0.98 (0.81-1.18)	0.81
Non-PE hypertension	0.95 (0.76-1.18)	0.63	1.06 (0.85-1.33)	0.61

Table 16. Revascularization at first MI by APO history (N = 8320)
Association between adverse pregnancy outcome history and invasive revascularization among women presenting with first myocardial infarction. Data for subgroups of PTD not shown. APO: adverse pregnancy outcome; CI: confidence interval; HDP: hypertensive disorder of pregnancy; MI: myocardial infarction; OR: odds ratio; PE: preeclampsia; PTD: preterm delivery; SGA: small for gestational age; STEMI: ST-segment elevation myocardial infarction.

	Model I		**Model II**	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Preterm delivery				
Never PTD	1 (reference)		1 (reference)	
Ever PTD	1.01 (0.89-1.15)	0.82	1.01 (0.89-1.15)	0.91
Small for gestational age infant				
Never SGA	1 (reference)		1 (reference)	
Ever SGA	1.30 (1.12-1.50)	<0.001	1.20 (1.04-1.39)	0.01
Hypertensive disorders of pregnancy				
Normotensive	1 (reference)		1 (reference)	
Ever HDP	0.91 (0.79-1.05)	0.19	1.03 (0.89-1.19)	0.69
Preterm PE	1.21 (0.90-1.61)	0.20	1.43 (1.07-1.92)	0.02
Term PE	0.80 (0.66-0.98)	0.03	0.89 (0.73-1.09)	0.27
Non-PE hypertension	0.92 (0.73-1.16)	0.50	1.04 (0.82-1.31)	0.76

Even though no association was found between any of the exposures and log z-score troponin at time of first MI (See Table 4 in Paper IV), a history of SGA was associated with particularly high troponin value at time of first MI (adjusted OR 1.18, 95% CI 1.01–1.38; see Table 5 in Paper IV). However, when stratifying by STEMI or NSTEMI, no association remained between any APO and high troponin levels (Table 17 and Table 18). Results were similar in the complete case analyses (data not shown).

Table 17. High troponin at first MI by APO history, only STEMI cases (N = 3128)
Association between APO history and high troponin in women with STEMI at first myocardial infarction. Data for subgroups of PTD and HDP not shown. APO: adverse pregnancy outcome; CI: confidence interval; HDP: hypertensive disorder of pregnancy; MI: myocardial infarction; OR: odds ratio; PTD: preterm delivery; SGA: small for gestational age; STEMI: ST-segment elevation myocardial infarction.

	Model I		**Model II**	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Preterm delivery				
Never PTD	1 (reference)		1 (reference)	
Ever PTD	0.98 (0.80-1.19)	0.80	0.98 (0.81-1.19)	0.84
Small for gestational age infant				
Never SGA	1 (reference)		1 (reference)	
Ever SGA	1.05 (0.85-1.30)	0.66	1.05 (0.85-1.30)	0.64
Hypertensive disorders of pregnancy				
Normotensive	1 (reference)		1 (reference)	
Ever HDP	1.02 (0.82-1.26)	0.87	1.03 (0.83-1.28)	0.80

Table 18. High troponin at first MI by APO history, only NSTEMI cases (N = 5192)
Association between APO history and high troponin in women with NSTEMI at first myocardial infarction. Data for subgroups of PTD and HDP not shown. APO: adverse pregnancy outcome; CI: confidence interval; HDP: hypertensive disorder of pregnancy; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; OR: odds ratio; PTD: preterm delivery; SGA: small for gestational age.

	Model I		**Model II**	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Preterm delivery				
Never PTD	1 (reference)		1 (reference)	
Ever PTD	0.99 (0.79-1.25)	0.96	0.99 (0.78-1.25)	0.93
Small for gestational age infant				
Never SGA	1 (reference)		1 (reference)	
Ever SGA	1.06 (0.80-1.40)	0.70	1.06 (0.80-1.40)	0.70
Hypertensive disorders of pregnancy				
Normotensive	1 (reference)		1 (reference)	
Ever HDP	1.15 (0.91-1.47)	0.24	1.19 (0.93-1.52)	0.16

Secondary analyses

To assess if the association seen between a history of SGA and STEMI at time of first MI may be due to a history of HDP, a secondary analysis was performed with a sample restricted to women without HDP where a history of SGA remained associated with STEMI at time of first MI (Table 19).

Table 19. STEMI at time of first MI by history of SGA, no history of HDP (N = 7242)
Association between SGA history and STEMI among women presenting with first MI. No history of HDP. CI: confidence interval; HDP: hypertensive disorder of pregnancy; MI: myocardial infarction; OR: odds ratio; SGA: small for gestational age; STEMI: ST-segment elevation myocardial infarction.

	Model I		**Model II**	
Small for gestational age infant	OR (95% CI)	*p*	OR (95% CI)	*p*
Never SGA	1 (reference)		1 (reference)	
Ever SGA	1.47 (1.25-1.72)	<0.001	1.34 (1.13-1.57)	0.001

When grouping PTD by HDP history, neither a history of normotensive PTD, nor a history of hypertensive PTD were significantly associated with any of the outcomes at time of first MI (Supplemental Table 6–9 in supplemental appendix of Paper IV). However, the estimates for hypertensive PTD appeared to be elevated, consistent with the observation in Table 12 that preterm PE was associated with STEMI (adjusted OR: 1.22, 95% CI 0.96-1.54). When additionally adjusting for parity in model I in all analyses, the results were similar to those of the main analyses (data not shown). In an additional analysis highlighting the effect of smoking status on the association between preterm PE and STEMI, preterm PE was associated with STEMI (OR 1.35, 95% CI 1.02-1.81) when adjusting for smoking status in addition to HDP history and age at MI in a separate model (Table 20). This is reflected in Paper IV where Table 1 shows that women with a history of preterm PE were less likely to be active smokers at time of first MI compared to normotensive women.

Table 20. STEMI by history of HDP, smoking in separate model (N = 8320)
Association between HDP history and STEMI among women presenting with first MI. Adjustment for smoking status in addition to HDP history and age at MI in model II. CI: confidence interval; HDP: hypertensive disorders of pregnancy; MI: myocardial infarction; OR: odds ratio; PE: preeclampsia; STEMI: ST-segment elevation myocardial infarction.

	Model I		**Model II**		**Model III**	
HDP history	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Normotensive	1 (reference)		1 (reference)		1 (reference)	
Ever HDP	0.95 (0.83-1.09)	0.48	1.05 (0.91-1.20)	0.52	1.07 (0.94-1.23)	0.31
Preterm PE	1.18 (0.89-1.57)	0.24	1.35 (1.02-1.81)	0.04	1.40 (1.05-1.88)	0.02
Term PE	0.88 (0.73-1.06)	0.17	0.95 (0.79-1.15)	0.60	0.98 (0.81-1.18)	0.81
Non-PE hypertension	0.95 (0.76-1.18)	0.63	1.03 (0.82-1.29)	0.79	1.06 (0.85-1.33)	0.61

Discussion

Composition and distribution of coronary artery disease

Results from Paper I showed that women with a history of PTD had a higher risk of MACE and mortality following a first coronary artery stenting compared to women with no such history. As mentioned before, the underlying association between PTD and future maternal CHD is still not clear, and we can therefore only speculate on the pathophysiological basis of the results presented in Paper I. A recent study on APOs and CAD assessed by coronary computed tomography angiography showed an association between a history of PTD and a higher coronary artery calcium score in middle-aged women.(111) Coronary artery calcium score is primarily used to assess a patient's risk of cardiovascular events in a primary preventive setting.(115) By quantifying the amount of calcium present in the coronary arteries, a coronary artery calcium score can be calculated, where a higher coronary artery calcium score is associated with an increased risk of future coronary events. However, a higher degree of calcification in coronary plaques has also been shown to be associated with an increased risk of adverse events following PCI.(177, 178) As such, the results presented in Paper I could, to some extent, be dependent on a higher coronary artery calcium score in women with a history of PTD compared to women with no history of a PTD.

The results in Paper IV showed that both a history of preterm PE and a history of delivering an SGA infant were associated more severe disease manifestation, indicating a higher risk of a greater myocardial injury, in women with a first time MI. As both PE and delivering an SGA infant are associated with persistent endothelial dysfunction post-partum,(136, 142) it is tempting to think of some sort of common pathophysiological pathway of PE and SGA in the development of future CHD in parous women as the reason for this. However, regardless of the underlying pathophysiological pathway of CHD in these women, the results could reflect a similar underlying CAD in women with a history of preterm PE or a history of SGA. The above-mentioned study on APOs and CAD assessed by coronary computed tomography angiography in middle-aged women showed an overall association between a history of APOs and future CAD in parous women.(111) More specifically, it showed that women with a history of HDP and women with a history of SGA, but not women with a history of PTD, had a different distribution of CAD, compared to women with no history of APOs. It also showed that women

with a history of APOs had a higher prevalence of proximal coronary atherosclerosis and atherosclerosis located to the left anterior descending artery (LAD), compared to women with no history of APOs. In patients with MI, lesion localization is associated with patient outcome, where specific locations of coronary lesions, such as the proximal lesions, are known to be associated with more adverse outcomes following MI.(68, 85, 179) For example, a major part of STEMIs stems from a thrombotic occlusion of the LAD,(179) and a proximal occlusion of the LAD is associated with a worse outcome after MI compared to distal LAD occlusions or other coronary artery occlusions.(180) Also, when comparing men and women with LAD MIs, women have been shown to have worse outcomes following PCI compared to men.(179) Taken together, this could possibly indicate that women with a history of HDP and/or SGA might present with a more severe disease at time of CHD presentation, compared to women with no such history, as seen in Paper IV.

Vascular dysfunction as a possible pathway

In Paper II and Paper III, the aim was to examine a possible association between APOs and clinical restenosis following PCI. The hypothesis that APOs might be associated with a higher risk of restenosis post-PCI was mainly based on previous studies regarding a history of PE. As already presented in the background section, restenosis is partly dependent on neoatherosclerosis, and in turn on endothelial dysfunction.(76) Apart from being associated with CHD events in general,(77) it has also been suggested that endothelial dysfunction plays a part in the development of future CHD seen in women with APOs, particularly in women with a history of PE and in women with a history of SGA.(136, 142) In addition to this, animal models have shown that an over-exposure to the Sflt1 receptor, a PE-associated antagonist to vascular growth factors, possibly interferes with the vascular response following vascular injury.(12) However, none of the studied APOs in Paper II and Paper III were associated with a higher risk of restenosis. Instead, results showed that women with a history of term PE had a lower risk of restenosis compared to normotensive women. A possible explanation for this could be that something hindering normal placentation in women who suffer PE during pregnancy in turn protects them from future development of restenosis.

Matrix metalloproteinases (MMPs) are involved in both normal and pathological processes, functioning as tissue modifying enzymes.(181) MMP-9 is one of the MMPs known to be associated with angiogenesis,(181) and previous studies have shown that elevated MMP-9 activity, both pre- and post-PCI, is associated with restenosis development.(182, 183) Interestingly, an opposite relationship between MMP-9 and PE could potentially exist.(184) Studies have shown PE to be associated with a dysregulation of MMP-9, some studies showing a possible

association between lower concentrations of MMP-9 and PE in pregnant women. During pregnancy, MMP-9 is known to have an important role in placental implantation through vascular remodelling. A dysregulation of MMP-9 could therefore be associated with placental dysfunction and consequently PE. Speculatively, genetics resulting in a decreased expression of MMP-9 could possibly explain the lower risk of restenosis in women with a history of term PE observed in Paper III.

In Paper IV, a history of preterm PE and a history of delivering an SGA infant were both associated with STEMI and invasive revascularization at the time of MI. As previously described, PE and delivering an SGA infant are both associated with persistent endothelial dysfunction post-partum.(136, 142) Even though no pathophysiological conclusions are possible in these studies, the fact that both a history of PE and of delivering an SGA infant are associated with persistent endothelial dysfunction could potentially indicate a common pathophysiological pathway for how these women develop, and later present, with future CHD. The difference in results observed in Paper IV between term PE and preterm PE could potentially stem from a difference in PE pathophysiology,(150) and will be further discussed below.

Timing of pregnancy complications

Paper I showed an association between a history of PTD in women and MACE following first coronary artery stenting. However, in a subgroup analysis, this association was only present in women with a history of late PTD, though the 95% CI of early PTD included the estimate of the main result. To evaluate a true difference between subgroups of PTD in the analysis, a secondary analysis was conducted with late PTD as the reference group. This showed that women with a history of early PTD had a lower risk of MACE following a first coronary artery stenting compared to women with a history of late PTD. Previous studies have shown that women with a history of an earlier PTD have a higher risk of developing future CVD compared to women with a history of a later PTD.(9, 122) As such, the results presented in Paper I are contradicting this previously observed dose-effect association. When looking at the clinical characteristics of the study sample in Paper I, the prevalence of traditional CVD risk factors was fairly similar between subgroups of PTD, and when analysing mortality following coronary artery stenting by subgroups of PTD, the estimates were similar for both subgroups. Taken together, this suggests that there was not any major difference in comorbidity in the two groups at time of coronary artery stenting. As presented in the background, the underlying association between a history of PTD and future maternal CHD is not yet fully understood, and it is therefore hard to speculate what this observed difference in subgroups of PTD could be due to.

In Paper III, results showed that a history of term PE, but not preterm PE, was possibly associated with a lower risk of restenosis following PCI, and the results from Paper IV indicated that a history of preterm PE, but not term PE, was associated with a more severe myocardial injury at time of first MI. Taken together, these results suggest a possible heterogeneity by type of PE regarding the association between PE and presentation and outcome of future CHD in women. PE, regardless of delivery timing, is thought to be a result of placental dysfunction,(131, 150) and from what was presented in the background section, one could therefore possibly imagine similar paths to future CHD for both subgroups of PE. However, the causes of the placental dysfunction are thought to possibly differ in regard to the timing of PE.(150) Placental dysfunction in preterm PE is thought to depend mainly on abnormal placentation, whereas in term PE, it is thought to possibly depend on either pregnancy burden or premature placental ageing. As the results presented in this work are based on clinical registry data, it is hard to draw any conclusions regarding the pathophysiological pathway. Though one could speculate that the differences observed between preterm and term PE could be due to a difference in PE pathophysiology and potentially future CHD development.

Clinical relevance

Previous studies on PTD and future maternal CVD are sometimes based on singleton deliveries, normotensive PTDs, and/or spontaneous PTDs, hence excluding women with multiple gestation pregnancies, women with a history of HDP, and/or women with medically indicated PTDs.(129) In this work, all APOs have been defined based on a woman's whole pregnancy history up until an index event, and PTD has been kept as a whole variable in the main analyses, not excluding women with multiple gestations, HDP, or women with medically indicated PTDs. This has been a conscious decision to maintain a higher level of clinical relevance. It is arguably more likely for a physician to ask about APOs, and for the patient to be able to answer it, if the question can be asked as simply as possible, e.g. have you ever delivered preterm? In 2015, Carter et al. presented a questionnaire for maternal recall of APOs associated with future CVD risk.(181) They showed that the maternal recall approximately four years post-partum was high in regard to infant birth weight and gestational age at delivery, though only modest in regard to HDP, and that the recall varied in regard to how the questions were asked.

Despite the modest nature of the associations reported in this thesis, one could still argue for a clinical relevance. The results reported in Paper I indicate that a history of PTD might not only be relevant in a primary prevention setting, but also in a secondary prevention setting, and studies like Paper II and Paper III could be clinically relevant in the long run even though mostly no associations were reported

here. As patients who develop restenosis often present with ACS,(74) studies that in any way contribute to a better understanding of outcomes after PCI in patients with an increased CVD risk can in turn contribute to a better patient outcome. The same goes for the results presented in Paper IV.

However, I would argue that the primary clinical significance of this thesis lies in emphasizing that a woman's pregnancy history is not only relevant to obstetrician-gynaecologists but also merits broader attention among clinicians.

Methodological considerations

This work does not aim to draw any conclusions about causal relationships between APOs and CHD, but instead aims to describe possible associations between APOs at time of pregnancy and future maternal CHD. In this work, we lack data on pre-pregnancy confounding factors. Because of this, confounding adjustment in the traditional sense has not been possible. To be able to establish causality between an exposure and an outcome you need to control for background variables either by adjusting for them in your analysis or by controlling for them in your study design.(182) These background variables can be grouped into confounders, colliders, and mediators. Confounders are variables that predict both the exposure and the outcome, and by controlling for them, you are excluding other possible causes of the association between your outcome and your exposure. Colliders, on the other hand, are variables that are influenced by both the exposure and outcome and should not be controlled for, as controlling for them introduces bias. Mediators are variables part of the causal pathway from the exposure to the outcome, i.e. they are affected by the exposure and also affect the outcome. When interested in the total effect an exposure of interest has on an outcome, adjusting for mediators will underestimate the total effect, and this is referred to as over-adjustment bias. As APOs are associated with future development of CHD risk factors,(118, 133) the adjustment for CHD risk factors in the papers presented in this thesis could be considered over-adjustment for mediators. However, post-pregnancy CHD risk factors are also likely markers of risk factors at the time of pregnancy to some extent. The most apparent example of this would be in Paper IV where adjustment for smoking could be an example of controlling for smoking at the time of pregnancy, as smoking is known to both reduce the risk of PE and increase the risk of STEMI.(183, 184)

In addition to traditional CHD risk factors, analyses in papers I–III have also been adjusted for predictors of the outcome. However, neither cardiac function (LVEF) nor renal function (creatinine) at time of coronary artery stent/PCI have been included as covariables in any of the analyses, even though they are both known predictors of worse outcome following PCI.(67) The decision not to include these

parameters stems from the prespecified variable check presented in the methods section (Table 3). As both measurements of cardiac and renal function had >10% missing in the datasets used for papers I–III, neither were included in the final analysis. A possible solution to this could have been to conduct secondary analyses on complete case samples to assess the effect of additionally adjusting for cardiac and renal function at the time of coronary artery stent or PCI. Another factor that could possibly be associated with the outcome after PCI is antithrombotic treatment before, during, and after the procedure. Antithrombotic treatment before and during the revascularization procedure was not included as a covariable in the main analyses of papers I–III. As APOs are not part of any PCI guidelines, we can assume that the APO history has not affected the treatment plan, and antithrombotic treatment after the revascularization procedure is hard to adjust for, as the data does not include information on compliance. In Paper I, an additional analysis was conducted, additionally adjusting for antithrombotic treatment before and during coronary artery stent, and the results from this analysis were very similar to those of the main analysis.

In Paper IV, estimates for the association between APOs and clinical characteristics of a more severe myocardial injury are presented as ORs, though one could argue for the use of risk ratios (RRs) instead. In the presence of a rare outcome, ORs and RRs are somewhat interchangeable.(185) However, in the case of a common outcome, ORs and RRs start to diverge, and interpreting ORs as RRs will overestimate the effect in the presence of a common outcome. Even though the outcomes were common, as the aim of Paper IV was to investigate the association between APOs and certain clinical characteristics of MI, and not to investigate the risk of said characteristics, I have chosen to present the estimates for these associations as ORs. As prior studies on the same topic have also used ORs,(14, 15) it makes comparisons with previous results easier, although the associations can be more difficult to interpret than if they were to be presented as RRs. However, I have only aimed to study the association between APOs and clinical characteristics of MI, and from the results in Paper IV, I cannot draw any conclusions on what could potentially lower, or increase, the risk of these characteristics. So, by choosing to only report ORs, I also only report associations.

Strengths and limitations

The main strength of this thesis is the use of nationwide samples in all papers. Extensive information on women's reproductive history collected over several decades, together with data on several covariables from well-known registers, resulted in comprehensive samples with very few exclusions. Another strength is the use of multiple imputation to account for missing data, with corresponding

complete case analyses with very similar results. In addition to this, the proportion of missing data was relatively small in all papers.

However, this thesis also had some limitations. In all papers, only women under or equal to the age of 65 years were included due to reasons already explained in the methods section. As no data on CHD risk factor status at time of delivery was available, adjustment for possible confounders in the traditional sense has not been possible in any of the papers. In papers I to III, women with coronary artery stent (Paper I) or PCI (Paper II and Paper III) before 2006 were excluded due to uncomplete variable collection until then. The same goes for women in Paper IV with MIs before 2007. As pregnancy dating using ultrasound was not used clinically in Sweden until the 1970s, pregnancies from the early days of the MBR are at risk of being misclassified regarding pregnancy dating. As incident restenosis events are relatively rare, the results from Paper II and Paper III do not exclude small or moderate associations for all exposures. In Paper IV, patient transfers between hospitals and wards presents a risk of peak troponin values being inaccurately recorded. Also, the relative ethnic homogeneity of the samples in all papers could affect the generalization of the results.

Conclusions

Paper I

A history of PTD was associated with worse prognosis following coronary artery stenting in women ≤65 years of age. Following these results, a history of PTD warrants consideration as a risk factor also in a secondary prevention setting.

Papers II and III

None of the studied aspects of pregnancy history, including PTD, were associated with an increased risk of clinical restenosis or TLR following PCI in women ≤65 years of age. Instead, the results pointed to a decreased risk of restenosis in women with a history of term PE. However, because of the small absolute numbers of restenosis events, even larger studies are needed to obtain more precise estimates.

Paper IV

Among women ≤65 years of age with first MI, a history of preterm PE and a history of delivering an SGA infant were associated with STEMI and revascularization. No associations were observed in women with a history of PTD. The extent to which these findings are explained by divergent CHD development among these subgroups of women warrants further study.

Future perspectives

Previous studies have repeatedly described the association between APOs and future CHD.(7) This work adds to these previous results by showing a potential association with worse outcome after coronary artery stenting and a more adverse clinical presentation of MI in women with a history of APOs. However, we lack information on how these women would respond to already existing primary and secondary preventive measures. For example, how would the risk of MACE following coronary artery stenting in women with a history of PTD be affected by secondary preventive measures? Studies like these would expand even further on the knowledge of APOs and future CHD and could potentially influence primary and secondary CVD prevention in women.

This work has observed a potential difference in adverse outcomes following PCI in women with a history of APOs by onset of the APO. Results from Paper I showed that women with a history of early PTD had a lower risk of MACE following coronary artery stenting compared to women with a history of late PTD. Paper III showed that a history of term PE was associated with a lower risk of restenosis following PCI, but not a history of preterm PE, and Paper IV showed that a history of preterm PE was associated with STEMI and invasive revascularization at time of MI, but not term PE. These results indicate that a difference in how women with a history of APOs develop, and eventually present with CHD could potentially exist in regard to the onset of the APO. As previously discussed, it is hard to say what this potential difference is due to, and further studies on the aetiology of CHD in regard to APO history are needed in general, but also to understand if these results represent an actual difference in risk between APO subgroups.

In a broader perspective, one could also highlight the need to spread knowledge regarding APOs and future CHD. We do not yet fully know how APOs affect CHD development and presentation, but even so, being aware of the association between APOs and future CHD could still be important in clinical decision making, as it gives a more comprehensive picture of the patient. I would also like to stress that systematic documentation of APOs in cross-clinic records could potentially be helpful and improve the cardiac care of women. However, maybe most importantly, a higher knowledge level in regard to APOs and future CHD could potentially influence the cardiovascular research field. Overall, taking female-specific or female-dominating CVD risk factors into account more frequently in cardiovascular research would likely result in more evidence-based cardiac care in women.

Acknowledgements

My name is on the cover of this thesis, but like many things in life, it is really a group effort, and I would like to thank a few people.

Firstly, thank you to my main supervisor, **Simon Timpka**. I have very much appreciated your ever-present support and guidance during these last four years. Thank you for pushing me when needed and taking a step back when the time has been right. Thank you for letting me think that I have been the one in control. Also, thank you for believing in me from the start – it made me believe in myself.

My co-supervisor **Mats Pihlsgård**, thank you for your vital support. You, and your minilectures, have been a lifeline to me when trying to understand the ins and outs of medical statistics. Thank you for always patiently answering the same questions over and over again. I can't promise you that you will never receive an email from me ever again. You see, I might need to understand model controls once again somewhere down the line.

My co-supervisor **Andreas Edsfeldt**. Thank you for always taking time out of your busy schedule, and for always doing it with a smile on your face. Your positive attitude towards research has been truly inspiring, and I am grateful that you have been part of my PhD journey.

Abigail Fraser, **Janet Rich-Edwards**, **Giovanna Sarno**, and **Isabel Gonçalves**. I am very grateful for having the opportunity to work with you and learn from you these last four years. Thank you all for your invaluable input on the manuscripts included in this thesis.

The members of **PACE**, thank you for creating a space in which I have been able to grow as a researcher. We may not have seen each other very often, but it has certainly been a comfort to me knowing that I have been a small part of your experienced and knowledgeable context.

Annie Lin, thank you for trusting me with your work – I am truly honoured.

My wonderfully talented friend **Anna Jonsson**. Firstly, thank you for creating the cover of this book and making my thesis look good. Secondly, thank you for taking on the role of professional photographer and making me look good. Lastly, thank

you for your support and for making me have a good time once in a while during these last four years.

My **old colleagues** at the women's clinic emergency department in Malmö. Thank you for inspiring me to start going down this path. My **new colleagues** at the women's clinic in Malmö. Thank you for inspiring me to continue on this path. I am, as always, in awe of your hard work.

My friends. Thank you for your support. **Nathalie**, for being my personal helpdesk in writing, science, and life overall. **Alice L**, for the help during my half-time review and the many discussions. **Leah**, for being my constant partner in crime. **Victoria and Johan**, for the safe space and many late conversations. **Kajsa**, for always picking up the phone and telling me the truth. **Alice W**, for the genuine interest and for always having a bed for me in your home. **The book club girls**, for the well-needed brakes and many laughs. And **every other friend** not mentioned who has supported me during these years, it has meant the world to me.

My family. Thank you. Mamman **Maria**, for everything. Look mum – we did it! Pappa **Ulf**, for your enthusiasm. My brothers **Adam** and **Gustav**, for being self-appointed presidents of my fan club. Farmor **Gunnel**, for being the best role model for a small girl. Mormor **Hanne**, for the unfiltered temperament, it has very much gotten me to where I am today. Uncle **Jens**, for your support in writing, for your big brotherly advice, and for letting me treat your home as my own. And all of **my extended family** who have all been there for me.

My dear husband **Gustav**, thank you to both of us for always supporting each other. Thank you for grounding me when I need it. Thank you for listening to me and laughing with me. Thank you for laughing at me. Love, thank you for being you.

Lastly, I want to express my extreme gratitude to all the women that came before me. I am well aware that I would not be in the position I am today if not for your persistence and hard work. Thank you.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982-3021.
2. Institute for Health Metrics and Evaluation (IHME). GBD Results [Internet]. Seattle, WA: IHME, University of Washington, 2020 [cited 2023 - 12 - 20]. Available from: https://vizhub.healthdata.org/gbd-results/.
3. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. Circulation. 2015;132(11):997-1002.
4. Yandrapalli S, Nabors C, Goyal A, Aronow WS, Frishman WH. Modifiable risk factors in young adults with first myocardial infarction. J Am Coll Cardiol. 2019;73(5):573-84.
5. Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized With Acute Myocardial Infarction. Circulation. 2019;139(8):1047-56.
6. Vogel B, Acevedo M, Appelman Y, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. The Lancet. 2021.
7. Okoth K, Chandan JS, Marshall T, et al. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. BMJ. 2020;371.
8. Wu P, Gulati M, Kwok CS, et al. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. J Am Heart Assoc. 2018;7(2):e007809.
9. Crump C, Sundquist J, Howell EA, McLaughlin MA, Stroustrup A, Sundquist K. Pre-term delivery and risk of ischemic heart disease in women. J Am Coll Cardiol. 2020;76(1):57-67.
10. Kunadian V, Qiu W, Lagerqvist B, et al. Gender differences in outcomes and predictors of all-cause mortality after percutaneous coronary intervention (data from United Kingdom and Sweden). Am J Cardiol. 2017;119(2):210-6.
11. Ray JG, Booth GL, Alter DA, Vermeulen MJ. Prognosis after maternal placental events and revascularization: PAMPER study. Am J Obstet Gynecol. 2016;214(1):106. e1-. e14.
12. Pruthi D, Khankin EV, Blanton RM, et al. Exposure to experimental preeclampsia in mice enhances the vascular response to future injury. Hypertension. 2015;65(4):863-70.

13. Countouris ME, Koczo A, Reynolds HR, et al. Characteristics of Premature Myocardial Infarction Among Women With Prior Adverse Pregnancy Outcomes. JACC Adv. 2023:100411.
14. Grand'Maison S, Pilote L, Schlosser K, Stewart DJ, Okano M, Dayan N. Clinical features and outcomes of acute coronary syndrome in women with previous pregnancy complications. Can J Cardiol. 2017;33(12):1683-92.
15. McDonald EG, Dayan N, Pelletier R, Eisenberg MJ, Pilote L. Premature cardiovascular disease following a history of hypertensive disorder of pregnancy. Int J Cardiol. 2016;219:9-13.
16. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165.
17. Visseren FL, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2021;42(34):3227-337.
18. Ohuma EO, Moller A-B, Bradley E, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. The Lancet. 2023;402(10409):1261-71.
19. Criado Perez C. Invisible Women: Exposing Data Bias in a World Designed for Men. First ed. London: Vintage Books; 2020.
20. Cleghorn E. Unwell Women: A Journey Through Medicine and Myth in a Man-Made World. First ed. London: Weidenfeld & Nicolson; 2022.
21. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143-57.
22. van Oosterhout RE, de Boer AR, Maas AH, Rutten FH, Bots ML, Peters SA. Sex differences in symptom presentation in acute coronary syndromes: a systematic review and meta-analysis. J Am Heart Assoc. 2020;9(9):e014733.
23. Ludvigsson JF, Berglind D, Sundquist K, Sundström J, Tynelius P, Neovius M. The Swedish military conscription register: opportunities for its use in medical research. Eur J Epidemiol. 2022;37(7):767-77.
24. Jin X, Chandramouli C, Allocco B, Gong E, Lam CS, Yan LL. Women's participation in cardiovascular clinical trials from 2010 to 2017. Circulation. 2020;141(7):540-8.
25. Food and Drug Administration Gender Studies in Product Development: Historical Overview [Internet]. 2018 [updated 2018-02-16; cited 2023 - 11 - 08]. Available from: https://www.fda.gov/science-research/womens-health-research/gender-studies-product-development-historical-overview.
26. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. Womens Health Issues. 2013;23(1):e39-e45.

27. Yoon DY, Mansukhani NA, Stubbs VC, Helenowski IB, Woodruff TK, Kibbe MR. Sex bias exists in basic science and translational surgical research. Surgery. 2014;156(3):508-16.
28. Söderström M. Därför uteslöt forskarna kvinnor ur sina studiepopulationer. Lakartidningen. 2001;98(13):1524-28.
29. National Institutes of Health History of Women's Participation in Clinical Research [Internet]. 2023 [cited 2023 - 11 - 01]. Available from: https://orwh.od.nih.gov/toolkit/recruitment/history.
30. Hamulyák EN, Brockmeier AJ, Killas JD, Ananiadou S, Middeldorp S, Leroi AM. Women's health in The BMJ: a data science history. BMJ open. 2020;10(10):e039759.
31. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol. 2014;11(5):276-89.
32. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016;4(13).
33. Jensen RV, Hjortbak MV, Bøtker HE, editors. Ischemic heart disease: an update. Semin Nucl Med; 2020: Elsevier.
34. Hjärt- Lungfonden Sjukdomar som gäller oss alla [Internet]. 2023 [cited 2023- 10 - 23]. Available from: https://www.hjart-lungfonden.se/sjukdomar/.
35. Socialstyrelsen. Statistik om dödsorsaker 2022. Stockholm: Socialstyrelsen; 2023. Report No.: 2023-6-8606.
36. World Health Organization Cardiovascular diseases [Internet]. 2023 [cited 2023 -10-17]. Available from: https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1.
37. Socialstyrelsen. Statistik om dödsorsaker år 2021. Stockholm: Socialstyrelsen 2022. Report No.: 2022-6-8020.
38. Björkegren JL, Lusis AJ. Atherosclerosis: recent developments. Cell. 2022.
39. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56.
40. Botts SR, Fish JE, Howe KL. Dysfunctional vascular endothelium as a driver of atherosclerosis: emerging insights into pathogenesis and treatment. Front Pharmacol. 2021;12:787541.
41. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2020;41(3):407-77.
42. Byrne RA, Rossello X, Coughlan J, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2023;44(38):3720-826.
43. Bergmark BA, Mathenge N, Merlini PA, Lawrence-Wright MB, Giugliano RP. Acute coronary syndromes. The Lancet. 2022;399(10332):1347-58.

44. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64.
45. Vogel B, Claessen BE, Arnold SV, et al. ST-segment elevation myocardial infarction. Nat Rev Dis Primers. 2019;5(1):39.
46. Giannitsis E, Steen H, Kurz K, et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. J Am Coll Cardiol. 2008;51(3):307-14.
47. Khullar N, Buckley AJ, O'Connor C, et al. Peak troponin T in STEMI: a predictor of all-cause mortality and left ventricular function. Open Heart. 2022;9(1):e001863.
48. Chia S, Senatore F, Raffel OC, Lee H, Wackers FJT, Jang I-K. Utility of cardiac biomarkers in predicting infarct size, left ventricular function, and clinical outcome after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2008;1(4):415-23.
49. Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. Nat Rev Cardiol. 2010;7(4):216-25.
50. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation. 2012;125(8):1043-52.
51. Roth Gregory A, Mensah George A, Johnson Catherine O, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019. J Am Coll Cardiol. 2020;76(25):2982-3021.
52. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: a compass for future health. American College of Cardiology Foundation Washington DC; 2022. p. 2361-71.
53. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. The Lancet. 2004;364(9438):937-52.
54. Khan SS, Ning H, Wilkins JT, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. JAMA Cardiol. 2018;3(4):280-7.
55. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. Eur J Clin Nutr. 2010;64(1):16-22.
56. Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. Res Integr Peer Rev. 2016;1(1):1-9.
57. Regitz-Zagrosek V, Gebhard C. Gender medicine: effects of sex and gender on cardiovascular disease manifestation and outcomes. Nat Rev Cardiol. 2023;20(4):236-47.
58. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

59. Conrad N, Verbeke G, Molenberghs G, et al. Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK. The Lancet. 2022;400(10354):733-43.
60. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-54.
61. Marx N, Federici M, Schütt K, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). Eur Heart J. 2023;44(39):4043-140.
62. Khan SQ, Ludman PF. Percutaneous coronary intervention. Medicine. 2022;50(7):437-44.
63. 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: the Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2021;42(14):1289-367.
64. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol. 2021;21(1):1-18.
65. Kosmidou I, Leon MB, Zhang Y, et al. Long-term outcomes in women and men following percutaneous coronary intervention. J Am Coll Cardiol. 2020;75(14):1631-40.
66. Madan P, Elayda MA, Lee V-V, Wilson JM. Predicting major adverse cardiac events after percutaneous coronary intervention: the Texas Heart Institute risk score. Am Heart J. 2008;155(6):1068-74.
67. Bawamia B, Mehran R, Qiu W, Kunadian V. Risk scores in acute coronary syndrome and percutaneous coronary intervention: a review. Am Heart J. 2013;165(4):441-50.
68. Harjai KJ, Mehta RH, Stone GW, et al. Does proximal location of culprit lesion confer worse prognosis in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction? J Interv Cardiol. 2006;19(4):285-94.
69. Halkin A, Singh M, Nikolsky E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol. 2005;45(9):1397-405.
70. Buccheri D, Piraino D, Andolina G, Cortese B. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. J Thorac Dis. 2016;8(10):E1150.
71. Montalescot G, Öngen Z, Guindy R, et al. Predictors of outcome in patients undergoing PCI. Results of the RIVIERA study. Int J Cardiol. 2008;129(3):379-87.
72. de Mulder M, Gitt A, van Domburg R, et al. EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. Eur Heart J. 2011;32(11):1398-408.

73. Abbott JD, Ahmed HN, Vlachos HA, Selzer F, Williams DO. Comparison of outcome in patients with ST-elevation versus non–ST-elevation acute myocardial infarction treated with percutaneous coronary intervention (from The National Heart, Lung, and Blood Institute Dynamic Registry). Am J Cardiol. 2007;100(2):190-5.
74. Giustino G, Colombo A, Camaj A, et al. Coronary in-stent restenosis: JACC state-of-the-art review. J Am Coll Cardiol. 2022;80(4):348-72.
75. Nusca A, Viscusi MM, Piccirillo F, et al. In stent neo-atherosclerosis: pathophysiology, clinical implications, prevention, and therapeutic approaches. Life. 2022;12(3):393.
76. Otsuka F, Finn AV, Yazdani SK, Nakano M, Kolodgie FD, Virmani R. The importance of the endothelium in atherothrombosis and coronary stenting. Nat Rev Cardiol. 2012;9(8):439-53.
77. Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. Int J Cardiol. 2013;168(1):344-51.
78. Pelliccia F, Zimarino M, Niccoli G, et al. In-stent restenosis after percutaneous coronary intervention: emerging knowledge on biological pathways. Eur Heart J Open. 2023:oead083.
79. Moussa ID, Mohananey D, Saucedo J, et al. Trends and outcomes of restenosis after coronary stent implantation in the United States. J Am Coll Cardiol. 2020;76(13):1521-31.
80. Mosca L, Barrett-Connor E, Kass Wenger N. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124(19):2145-54.
81. Gonsalves CA, McGannon KR, Schinke RJ, Pegoraro A. Mass media narratives of women's cardiovascular disease: A qualitative meta-synthesis. Health Psychol Rev. 2017;11(2):164-78.
82. Haider A, Bengs S, Luu J, et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. Eur Heart J. 2020;41(13):1328-36.
83. Mehilli J, Presbitero P. Coronary artery disease and acute coronary syndrome in women. Heart. 2020.
84. DeVon HA, Mirzaei S, Zègre-Hemsey J. Typical and atypical symptoms of acute coronary syndrome: time to retire the terms? J Am Heart Assoc. 2020;9(7):e015539.
85. Grayson A, Moore R, Jackson M, et al. Multivariate prediction of major adverse cardiac events after 9914 percutaneous coronary interventions in the north west of England. Heart. 2006;92(5):658-63.
86. Redfors B, AngerAas O, RAamunddal T, et al. Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish web system for enhancement of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). J Am Heart Assoc. 2015;4(7):e001995.

87. Nguyen HL, Saczynski JS, Gore JM, Goldberg RJ. Age and sex differences in duration of prehospital delay in patients with acute myocardial infarction: a systematic review. Circ Cardiovasc Qual Outcomes. 2010;3(1):82-92.
88. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016;133(9):916-47.
89. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. Circulation. 2020;142(25):e506-e32.
90. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev. 2015(3).
91. Gleicher N, Barad DH. Gender as risk factor for autoimmune diseases. J Autoimmun. 2007;28(1):1-6.
92. Altemus M, Sarvaiya N, Epperson CN. Sex differences in anxiety and depression clinical perspectives. Front Neuroendocrinol. 2014;35(3):320-30.
93. World Health Organization Preterm birth [Internet]. 2023 [updated 2023-05-10; cited 2023- 10-20]. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth.
94. Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reproductive health. 2013;10(1):1-14.
95. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
96. Socialstyrelsen. Fakta och statistik [Internet]. 2019 [updated 2020-11-09; cited 2023-10-20]. Available from: https://www.socialstyrelsen.se/meranbaramamma/statistik/.
97. Moutquin JM. Classification and heterogeneity of preterm birth. BJOG. 2003;110:30-3.
98. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. N Engl J Med. 2010;362(6):529-35.
99. Simhan HN, Canavan TP. Preterm premature rupture of membranes: diagnosis, evaluation and management strategies. BJOG. 2005;112:32-7.
100. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med. 2000;342(20):1500-7.
101. Blumenshine P, Egerter S, Barclay CJ, Cubbin C, Braveman PA. Socioeconomic disparities in adverse birth outcomes: a systematic review. Am J Prev Med. 2010;39(3):263-72.
102. Thomson K, Moffat M, Arisa O, et al. Socioeconomic inequalities and adverse pregnancy outcomes in the UK and Republic of Ireland: a systematic review and meta-analysis. BMJ open. 2021;11(3):e042753.
103. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):643-50.

104. Clausson B, Lichtenstein P, Cnattingius S. Genetic influence on birthweight and gestational length determined by studies in offspring of twins. BJOG. 2000;107(3):375-81.
105. Aughey H, Jardine J, Knight H, et al. Iatrogenic and spontaneous preterm birth in England: A population-based cohort study. BJOG. 2023;130(1):33-41.
106. Purisch SE, Gyamfi-Bannerman C, editors. Epidemiology of preterm birth. Semin Perinatol; 2017: Elsevier.
107. Valencia CM, Mol BW, Jacobsson B, et al. FIGO good practice recommendations on modifiable causes of iatrogenic preterm birth. Int J Gynecol Obstet. 2021;155(1):8-12.
108. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. Am J Obstet Gynecol. 2006;195(6):1557-63.
109. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG. 2006;113:17-42.
110. Nardozza LMM, Caetano ACR, Zamarian ACP, et al. Fetal growth restriction: current knowledge. Arch Gynecol Obstet. 2017;295:1061-77.
111. Lawesson SS, Swahn E, Pihlsgård M, et al. Association between history of adverse pregnancy outcomes and coronary artery disease assessed by coronary computed tomography angiography. JAMA. 2023;329(5):393-404.
112. Grandi SM, Filion KB, Yoon S, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications: systematic review and meta-analysis. Circulation. 2019;139(8):1069-79.
113. Catov JM, Wu CS, Olsen J, Sutton-Tyrrell K, Li J, Nohr EA. Early or recurrent preterm birth and maternal cardiovascular disease risk. Ann Epidemiol. 2010;20(8):604-9.
114. Kessous R, Shoham-Vardi I, Pariente G, Holcberg G, Sheiner E. An association between preterm delivery and long-term maternal cardiovascular morbidity. Am J Obstet Gynecol. 2013;209(4):368 e1-8.
115. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol. 2018;72(4):434-47.
116. Auger N, Potter BJ, He S, Healy-Profitós J, Schnitzer ME, Paradis G. Maternal cardiovascular disease 3 decades after preterm birth: longitudinal cohort study of pregnancy vascular disorders. Hypertension. 2020;75(3):788-95.
117. Bergman L, Nordlöf-Callbo P, Wikström AK, et al. Multi-fetal pregnancy, preeclampsia, and long-term cardiovascular disease. Hypertension. 2020;76(1):167-75.
118. Crump C, Sundquist J, Sundquist K. Preterm Delivery and Long-term Risk of Hypertension in Women. JAMA Cardiol. 2022;7(1):65-74.
119. Catov JM, Lewis CE, Lee M, Wellons MF, Gunderson EP. Preterm birth and future maternal blood pressure, inflammation, and intimal-medial thickness: the CARDIA study. Hypertension. 2013;61(3):641-6.
120. Tanz LJ, Stuart JJ, Williams PL, et al. Preterm delivery and maternal cardiovascular disease risk factors: the nurses' health study II. J Womens Health. 2019;28(5):677-85.

121. Lykke J, Paidas M, Damm P, Triche E, Kuczynski E, Langhoff-Roos J. Preterm delivery and risk of subsequent cardiovascular morbidity and type-II diabetes in the mother. BJOG. 2010;117(3):274-81.
122. Tanz LJ, Stuart JJ, Williams PL, et al. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. Circulation. 2017;135(6):578-89.
123. Haug EB, Markovitz AR, Fraser A, et al. The role of cardiovascular risk factors in maternal cardiovascular disease according to offspring birth characteristics in the HUNT study. Sci Rep. 2021;11(1):1-9.
124. Markovitz AR, Haug EB, Horn J, et al. Normotensive preterm delivery and maternal cardiovascular risk factor trajectories across the life course: The HUNT Study, Norway. Acta Obstet Gynecol Scand. 2020.
125. Catov JM, Bodnar LM, Ness RB, Barron SJ, Roberts JM. Inflammation and dyslipidemia related to risk of spontaneous preterm birth. Am J Epidemiol. 2007;166(11):1312-9.
126. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342(12):836-43.
127. Minissian MB, Kilpatrick S, Eastwood J-A, et al. Association of spontaneous preterm delivery and future maternal cardiovascular disease. Circulation. 2018;137(8):865-71.
128. Catov JM, Dodge R, Barinas-Mitchell E, et al. Prior preterm birth and maternal subclinical cardiovascular disease 4 to 12 years after pregnancy. J Womens Health. 2013;22(10):835-43.
129. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? Epidemiol Rev. 2014;36(1):57-70.
130. Metoki H, Iwama N, Hamada H, et al. Hypertensive disorders of pregnancy: definition, management, and out-of-office blood pressure measurement. Hypertens Res. 2022;45(8):1298-309.
131. Magee LA, Nicolaides KH, von Dadelszen P. Preeclampsia. N Engl J Med. 2022;386(19):1817-32.
132. Skogsdal Y och Conner P och Elvander L, Storck Lindholm E, Kloow M, Algovik M, Petersson K, Svanvik T, Granfors M på uppdrag av Graviditetsregistret. Graviditetsregistrets Årsrapport 2022. 2023.
133. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28(1):1-19.
134. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2):e003497.
135. Ray JG, Austin PC, Park AL, Cohen E, Fang J, Chu A. Severity of obstructive coronary artery stenosis after pre-eclampsia. Heart. 2023;109(6):449-56.

136. Weissgerber TL, Milic NM, Milin-Lazovic JS, Garovic VD. Impaired flow-mediated dilation before, during, and after preeclampsia: a systematic review and meta-analysis. Hypertension. 2016;67(2):415-23.
137. Bdolah Y, Lam C, Rajakumar A, et al. Twin pregnancy and the risk of preeclampsia: bigger placenta or relative ischemia? Am J Obstet Gynecol. 2008;198(4):428. e1-. e6.
138. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.
139. Maršál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr. 1996;85(7):843-8.
140. McCowan L, Horgan RP. Risk factors for small for gestational age infants. Best Pract Res Clin Obstet Gynaecol. 2009;23(6):779-93.
141. Sankaran S, Kyle PM. Aetiology and pathogenesis of IUGR. Best Pract Res Clin Obstet Gynaecol. 2009;23(6):765-77.
142. Hillman SL, Kubba T, Williams DJ. Delivery of small-for-gestational-age neonate and association with early-onset impaired maternal endothelial function. Ultrasound Obstet Gynecol. 2017;49(1):150-4.
143. Lv H, Wu H, Yin J, Qian J, Ge J. Parity and cardiovascular disease mortality: a dose-response meta-analysis of cohort studies. Sci Rep. 2015;5(1):1-9.
144. Li W, Ruan W, Lu Z, Wang D. Parity and risk of maternal cardiovascular disease: A dose–response meta-analysis of cohort studies. Eur J Prev Cardiol. 2019;26(6):592-602.
145. Sanghavi M, Kulinski J, Ayers CR, et al. Association between number of live births and markers of subclinical atherosclerosis: The Dallas Heart Study. Eur J Prev Cardiol. 2016;23(4):391-9.
146. Rosendaal NT, Pirkle CM. Age at first birth and risk of later-life cardiovascular disease: a systematic review of the literature, its limitation, and recommendations for future research. BMC Public Health. 2017;17(1):1-15.
147. Chen X-K, Wen SW, Fleming N, Demissie K, Rhoads GG, Walker M. Teenage pregnancy and adverse birth outcomes: a large population based retrospective cohort study. Int J Epidemiol. 2007;36(2):368-73.
148. Schummers L, Hacker MR, Williams PL, et al. Variation in relationships between maternal age at first birth and pregnancy outcomes by maternal race: a population-based cohort study in the United States. BMJ open. 2019;9(12):e033697.
149. van Baar PM, Welters SM, Ravelli AC, de Boer MA, de Groot CJ. Cardiovascular mortality risk a decade after twin and singleton pregnancies complicated by hypertensive disorders of pregnancy. Pregnancy Hypertens. 2022;28:9-14.
150. Dimitriadis E, Rolnik DL, Zhou W, et al. Pre-eclampsia. Nat Rev Dis Primers. 2023;9(1):8.
151. Cho L, Davis M, Elgendy I, et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(20):2602-18.

152. Markovitz AR, Stuart JJ, Horn J, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. Eur Heart J. 2019;40(14):1113-20.
153. Stuart JJ, Tanz LJ, Cook NR, et al. Hypertensive disorders of pregnancy and 10-year cardiovascular risk prediction. J Am Coll Cardiol. 2018;72(11):1252-63.
154. Timpka S, Fraser A, Schyman T, et al. The value of pregnancy complication history for 10-year cardiovascular disease risk prediction in middle-aged women. Eur J Epidemiol. 2018;33:1003-10.
155. Gogineni VSM, Manfrini D, Aroda SH, et al. Variations in awareness of association between adverse pregnancy outcomes and cardiovascular risk by specialty. Cardiology and Therapy. 2021;10(2):577-92.
156. Wu P, Mamas MA, Gulati M. Health Care Professional's Knowledge of Pregnancy Complications and Women's Cardiovascular Health: An International Study Utilizing Social Media. J Womens Health. 2022;31(8):1197-207.
157. Aslam A, Perera S, Watts M, et al. Previous pre-eclampsia, gestational diabetes and hypertension place women at high cardiovascular risk: but do we ask? Heart Lung Circ. 2021;30(1):154-7.
158. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
159. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart. 2010;96(20):1617-21.
160. Cnattingius S, Källén K, Sandström A, et al. The Swedish medical birth register during five decades: documentation of the content and quality of the register. Eur J Epidemiol. 2023;38(1):109-20.
161. Ludvigsson JF, Almqvist C, Bonamy A-KE, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31:125-36.
162. Statistics Sweden. History of Statistics Sweden [Internet]. 2023 [cited 2023 - 12 - 21]. Available from: https://www.scb.se/en/About-us/main-activity/history-of-statistics-sweden/.
163. Statistics Sweden. About Statistics Sweden [Internet]. 2023 [cited 2023 - 12 - 21]. Available from: https://www.scb.se/en/About-us/.
164. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32:765-73.
165. Socialstyrelsen. National Patient Register [Internet]. 2019 [updated 2022-01-14; cited 2023 - 10 - 31]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/.
166. Walani SR. Global burden of preterm birth. Int J Gynaecol Obstet. 2020;150(1):31-3.

167. Members WC, Lawton JS, Tamis-Holland JE, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(2):e21-e129.
168. Mantel Ä, Holmqvist M, Jernberg T, Wållberg-Jonsson S, Askling J. Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term outcome. Eur Heart J. 2015;36(48):3413-22.
169. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338.
170. Hughes RA, Heron J, Sterne JA, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. Int J Epidemiol. 2019;48(4):1294-304.
171. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the Child Health and Development Studies pregnancy cohort. Circulation. 2015;132(13):1234-42.
172. Swedish Authority for Privacy Protection The GDPR fundamental principles [Internet]. 2021 [updated 2021 - 09 - 22; cited 2023 - 10 - 24]. Available from: https://www.imy.se/en/organisations/data-protection/this-applies-accordning-to-gdpr/the-gdpr-fundamental-principles/.
173. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movment of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) [Internet]. OJ L 119, 04.05.2016; cor. OJ L 127, 23.5.20182016 [cited 2023 - 10 - 24]. Available from: https://gdpr-info.eu/art-14-gdpr/.
174. Socialstyrelsen. Sekretessprövning hos Socialstyrelsen [Internet]. 2018 [updated 2022 - 12 - 09; cited 2023 - 10 - 24]. Available from: https://bestalladata.socialstyrelsen.se/data-for-forskning/sekretessprovning/.
175. Socialstyrelsen. National Medical Birth Register [Internet]. 2019 [updated 2022 - 01 - 14; cited 2023 - 10 - 24]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-medical-birth-register/.
176. World Medical Association (WMA) WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [Internet]. 1964 [updated 2013 Oct.; cited 2023 - 10 - 24]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
177. Guedeney P, Claessen BE, Mehran R, et al. Coronary calcification and long-term outcomes according to drug-eluting stent generation. JACC Cardiovasc Interv. 2020;13(12):1417-28.

178. Généreux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes: pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials. J Am Coll Cardiol. 2014;63(18):1845-54.
179. Entezarjou A, Mohammad MA, Andell P, Koul S. Culprit vessel: impact on short-term and long-term prognosis in patients with ST-elevation myocardial infarction. Open Heart. 2018;5(2):e000852.
180. Elsman P, van't Hof AW, Hoorntje JC, et al. Effect of coronary occlusion site on angiographic and clinical outcome in acute myocardial infarction patients treated with early coronary intervention. Am J Cardiol. 2006;97(8):1137-41.
181. Carter EB, Stuart JJ, Farland LV, et al. Pregnancy complications as markers for subsequent maternal cardiovascular disease: validation of a maternal recall questionnaire. J Womens Health. 2015;24(9):702-12.
182. Etminan M, Brophy JM, Collins G, Nazemipour M, Mansournia MA. To adjust or not to adjust: the role of different covariates in cardiovascular observational studies. Am Heart J. 2021;237:62-7.
183. Wang J, Yang W, Xiao W, Cao S. The association between smoking during pregnancy and hypertensive disorders of pregnancy: A systematic review and meta-analysis. Int J Gynaecol Obstet. 2022;157(1):31-41.
184. Björck L, Rosengren A, Wallentin L, Stenestrand U. Smoking in relation to ST-segment elevation acute myocardial infarction: findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions. Heart. 2009;95(12):1006-11.
185. Cummings P. The relative merits of risk ratios and odds ratios. Arch Pediatr Adolesc Med. 2009;163(5):438-45.