# Heart disease in women and men

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# CHAPTER 1

General introduction

# EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE AND RISK FACTORS

## Cardiovascular disease and mortality

In 2016, the worldwide number of people who died from cardiovascular disease (CVD) was around 17.9 million, representing 31% of all global deaths[1]. From 1990 to 2013, population aging (55% increase from 1990) and population growth (25% increase from 1990) resulted in a 40% increase in the number of CVD deaths, despite an overall decrease in age-specific death rates[2]. Ischemic heart disease was the largest contributor to this increase in the number of CVD deaths (2.4 million of the overall increase of 5.0 million CVD deaths). Central and Western Europe were the only regions with a decrease in CVD deaths between 1990 and 2013, with declines of 5.2% and 12.8%, respectively[2]. Small relative gains in health, paired with a lower degree of population aging, resulted in this decline in total CVD deaths in Western Europe. In Europe, the number of deaths due to CVD was higher for women (2.1 million) than in men (1.7 million)[3]. CVD also accounted for a larger proportion of all deaths in women (49%) than in men (40%)[3].

Focusing on the Netherlands, sex differences in CVD mortality can be seen as well. In 2017, 20.039 women died because of CVD compared to 18.080 men, which account for 25% and 26% of the total mortality numbers[4]. Due to the higher number of women with an older age in the Netherlands, more women than men are dying from CVD in the Netherlands nowadays. From 1980, there is a decline in CVD mortality rate of 76% in men and 74% in women in the Netherlands[5]. However, this fall in CVD mortality is not going to persist[6] and is already slowing or even plateaued for young adults (<55 years)[5]. Also, sex-differences in clinical and procedural characteristics and outcome in individuals with ischemic heart disease are described in the Netherlands[7]. Women with ischemic heart disease more often have hypertension and diabetes compared to men, but have less extensive coronary artery disease and undergo less often coronary angiography. One-year mortality after ischemic heart disease is higher in women than in men[7].

## Cardiovascular risk factors and health behavior

Controlling cardiovascular risk factors together with the improvements in treatment of CVD resulted in a decline in CVD deaths since the early 1970s in the Netherlands[5]. However, there is still an expected rise in cardiovascular risk factors such as obesity and diabetes by 2030[8,9]. Important differences in the occurrence of cardiovascular risk factors are identified between European high-income and middle-income countries. For both men and women, the prevalence of hypertension is lower in high-income countries compared to middle-income countries. Smoking prevalence in men (but not in women)

is also lower in high-income countries compared to middle-income countries[3]. In the Netherlands, a large percentage of the adult population between 18 and 75 years is at risk for developing CVD since around 1.9 million, 2 million, 3 million and 2.5 million of these inhabitants have obesity, elevated cholesterol levels, hypertension or smoke, respectively[4]. The effect of these risk factors on CVD outcomes are largely similar between women and men, however prolonged smoking is significantly more hazardous for women than for men[10].

Besides these classical cardiovascular risk factors, several new risk factors have been identified in an effort to improve risk assessment for CVD. Resting heart rate is one of these potential cardiovascular risk factors of particular interest[11]. Elevated resting heart rate has been associated with higher risk of CVD and death in observational studies[12]. However, this association does not provide sufficient evidence for a shared or causal relationship. Additionally, during the last years, major developments in CVD risk prediction during the last years have been made by the identification of many single-nucleotide polymorphisms (SNPs) that are associated with cardiovascular risk factors or events. Based on these SNPs, genetic risk scores can be generated for improving (causal) risk prediction of CVD.

To conclude, the worldwide and nationwide burden of CVD is high, especially in women. The decline in CVD death is plateauing and the number of individuals with cardiovascular risk factors is high and expecting to rise. Primary prevention, in terms of lifestyle intervention and preventive medication, remains therefore an important target to reduce the incidence of CVD. Novel technologies, like genetic analyses, are of major importance for identifying individuals at risk and for determining causal relationships between (novel) risk factors and CVD.

## THE ELECTROCARDIOGRAM

The electrocardiogram (ECG) is an important tool for diagnosing CVD. The first step in the development of the ECG dated back to 1786 with the recording of an electrical current from skeletal muscles. In 1842, an electrical current was described that accompanied every heart beat in a frog. The first human ECG was reported by Augustus Waller in 1887. He showed that the electrical activity preceded ventricular contraction[13]. Willem Einthoven was able to demonstrate the ECG in five deflections, nowadays known as the P wave, QRS complex and T wave and was awarded the Nobel Prize in physiology for the invention of the ECG in 1924[13]. Since that time, many new technologies have been developed for the diagnosis of CVD. However, the ECG retains its central role. The

ECG is the most important test for interpretation of the cardiac rhythm, conduction system abnormalities and the detection of myocardial ischemia. The ECG is also of great value in the evaluation of other types of cardiac abnormalities including valvular heart disease, cardiomyopathy, pericarditis, and left ventricular hypertrophy (LVH). Finally, the ECG can be used to monitor drug treatment (specifically antiarrhythmic therapy) and to detect metabolic disturbances such as alternations in serum calcium and potassium concentrations.

Since 1960, is has been shown that ECG parameters differ between sexes[14]. For example, PR interval and QRS duration are longer in men compared to women[15]. In addition, men have higher Q, R and S wave amplitudes than women[15]. Therefore, it is crucial that detecting cardiac disorders with the ECG, such as LVH, takes these sex differences into account.

## (Unrecognized) myocardial infarction and the electrocardiogram

The ECG has a major role in diagnosing MI. ST-elevations on the ECG are highly sensitive for acute ST-elevation MI (STEMI) and have a leading role in determining further treatment[16]. Individuals with complains of angina and ST-elevations on the ECG should undergo percutaneous coronary intervention as soon as possible without the need for further diagnostic exploration[16]. In addition, the ECG is quick in diagnosing STEMI, available in ambulances all over the world, which makes it possible to diagnose STEMI before a patient reaches the hospital. The enormous decline of in-hospital mortality rates after STEMI (30% in 1950 to 4% in 2010) is therefore, in addition to the development of the critical care unit and reperfusion therapy, partly due to the possibility of quickly diagnosing of STEMI by the ECG[17].

Although major steps have been made in diagnosis and treatment of recognized MI, a large number of MIs remain unrecognized. These individuals with unrecognized MI are not treated at all. Earlier studies reported that 22% to 64% of the patients with coronary artery disease experience an unrecognized MI, with atypical or no symptoms of MI at all[18]. These patients do not receive secondary prevention and are at increased risk of clinical CVD compared to individuals without previous MI[19,20,21] and even compared to individuals in whom MI was recognized[22]. In addition, unrecognized MI has been associated with an increased risk for all-cause mortality[23]. It has been described that MIs in women are more associated with atypical symptoms compared to men, and are therefore at higher risk for remaining unrecognized[24]. Examples of atypical symptoms are nausea, dizziness and fatigue. With the help of the ECG there is a possibility to screen for individuals with unrecognized MI. The most prevalent sign of an old MI on the ECG is a pathological Q wave. This pathological Q wave can be seen as an electrical

hole in the heart, since scar tissue, developed as a result of a MI, is electrically dead. Diagnosing Q wave MI requires that pathological Q waves are present in at least two anatomically contiguous leads[25]. Large population based cohort studies are set up to evaluate the epidemiology of CVD and cardiovascular risk factors. Cohort studies, with available 12-lead ECGs, give the opportunity to search for unrecognized MI and related sex-differences in the general population. It is known that the sensitivity of the ECG for diagnosing old MIs is low and lies between 0.30 and 0.58[26]. However, due to the non-invasiveness and cost-effectiveness, the ECG remains an important tool for detecting unrecognized MI.

## Left ventricular hypertrophy and the electrocardiogram

LVH is a marker of the pathophysiologic response of the myocardium to chronic pressure or volume overload and is associated with future cardiovascular events[27]. Major risk factors of LVH are hypertension and aortic stenosis. Commonly used imaging techniques for detecting LVH are echocardiography and cardiac magnetic resonance imaging (MRI). Studies using echocardiographic criteria for detecting LVH reported a prevalence of 15% of LVH in men and 9% in women in the general population[28]. Besides imaging techniques, the ECG is a widely-used tool for detecting LVH. Increased left ventricular mass can be identified by the ECG according to high Q, R or S wave amplitudes and long QRS duration. So far, many ECG-LVH criteria are developed with different sums of amplitudes of different leads of the ECG, but these criteria show low sensitivity for detecting LVH as compared to echocardiography. The accuracy of the ECG for diagnosing LVH has been described to be less in women than in men[29], but LVH detected by the ECG is a stronger risk factor for incident CVD events in women than in men[30]. Antihypertensive treatment can decrease LVH and improve left ventricular dysfunction[31]. The higher chance of false negative findings of LVH in women may therefore lead to a higher rate of undertreatment of LVH and related cardiovascular events[32]. Existing ECG-LVH criteria are similar in men and women and most of these criteria do not have sex-specific cut-off points, suggesting that there is still some room for improvement.

To conclude, the ECG plays a central role in diagnosing CVD in the acute phase, but is also an important tool for detecting (unrecognized) cardiac disorders on population level. It is important to take sex-differences, which manifest on the ECG, into account.

# THIS THESIS

## Big data and study designs of this thesis

The increasing generation and development of digital data and computational science make it possible to gain new insights from enormous data sets, known as big data. In this thesis, big data of two large cohort studies are used: the Lifelines cohort study and the UK Biobank. In addition, data of the IADB.nl pharmacy database was used. The Lifelines cohort study is a contemporary population-based study, which was initiated in 2006 to improve our knowledge on (cardiovascular) healthy ageing[33]. The Lifelines cohort study includes over 167,000 individuals of the three northern provinces of the Netherlands and aims to follow them for 30 years. The PharmLines Initiative was started in 2017 to link data of the Lifelines cohort study to the University Groningen prescription database, IADB.nl. The IADB.nl database is a pharmacy database that contains prescription data from approximately 600,000 patients in the northern part of the Netherlands[34]. At the beginning of 2019, around 60,000 of the participants of the Lifelines cohort study, could be linked to the IADB.nl database. The UK Biobank is a population based prospective study established for investigating genetic and non-genetic determinants of diseases. Between 2006 and 2010, over 500,000 participants of the United Kingdom aged between 40 and 69 years were recruited[35]. Imaging visits of the UK Biobank were initiated in 2015. During these visits, cardiac magnetic resonance imaging (CMR) was performed, with the aim to scan over 100.000 participants[36].

Baseline characteristics of participants of these cohort studies were used in cross-sectional study designs to determine the prevalence of CVD and risk factors. A cross-sectional study design was also used for testing the accuracy, in terms of sensitivity and specificity, of diagnostic criteria for CVD. Follow-up data was used in longitudinal analyses to obtain incidence rates of CVD and to determine the predictors of incident CVD. Nested matched case-control designs were used for studies in which was focused on one specific CVD. The generation of a matched control group out of the total study population, enabled a comparison of risk factors among cases and controls with less confounding factors. Also, the use of nested case-control designs resulted in smaller sample sizes and enabled additional measurements in these individuals.

In the remaining chapters of this thesis, summary statistics of performed genome wide association studies (GWAS) on CVD and cardiovascular risk factors were used in Mendelian randomization (MR) analyses. Also, a GWAS meta-analysis was performed and described in one of the chapters of this thesis. MR analyses are designed to investigate the causal nature of the relationship between risk factors and outcomes

in observational data in the presence of confounding factors[37]. Using genetic variants as instruments, which are randomly assigned when passed from parents to offspring during meiosis, the genotype distribution in the population should be unrelated to the presence of confounders.

## Aim of this thesis

The first aim of this thesis is to evaluate the prevalence and pharmaceutical prevention of CVD and risk factors in the general population, especially the northern part of the Netherlands. Secondly, it is aimed to evaluate the occurrence of (unrecognized) MI detected by the ECG in women and men of the general population and to determine the predictors, related symptoms and association with mortality of (unrecognized) MI. Lastly, the performance of ECG criteria for detecting LVH is studied and these criteria are used for determining causal relationships between cardiovascular risk factors and LVH and between LVH and mortality and longevity.

### Part I: Prevalence and prevention of cardiovascular disease and risk factors

In part I, occurrence of CVD and risk in the general population are investigated. Due to changes in lifestyle and the ageing population, the prevalence of CVD and related healthcare costs are expected to increase. Epidemiologic studies are crucial to improve our understanding of the genetic, behavioral and environmental determinants associated with CVD and its risk factors. Epidemiologic studies in the past, including the Framingham Heart study initiated in 1948, have contributed enormously to our understanding of CVD and its risk factors. However, advances in treatment as well as changes in behavior and lifestyle have occurred and contemporary data is needed for determining the occurrence, pharmaceutical prevention and associates of CVD nowadays. A contemporary population-based cohort study is the Lifelines cohort study[33]. In **chapter 2** the prevalence of CVD, its risk factors and utilization of primary prevention by drug treatment in the Lifelines cohort study are presented. In **chapter 3**, the use of cardiovascular preventive medication is determined in individuals at risk for CVD (aged <70 years) based on the "European Society of Cardiology" (ESC) and "The Dutch College of General Practitioners" (Nederlands Huisartsen Genootschap (NHG)) guidelines using the PharmLines data. After the baseline visit of Lifelines, all participants and their general practitioners are informed about their individual health status, including their cardiovascular risk. Cardiovascular preventive medication usage is reported before and after the Lifelines baseline visit. In **chapter 4**, an overview is given about sex-specific population-based values of heart rate, P wave and QRS complex duration, PQ and QTc interval and the P, QRS and T axis measured by ECG. Additionally, the prevalence of abnormalities on the ECG in the Lifelines population free of CVD is

reported. In **chapter 5**, resting heart rate as a new potential cardiovascular risk factor is evaluated. Genetic variants associated with resting heart rate are determined in a GWAS meta-analysis of 835,465 individuals including 100 cohorts, and are used to test for a causal relationship with coronary artery disease and MI in MR analyses.

**Part II: Unrecognized myocardial infarction**

In **chapters 6** and **7**, individuals who have ECG signs of MI but are unaware of this are studied. In **chapter 6**, the prevalence of unrecognized MI in 152,124 individuals of the Lifelines cohort study is determined. During the baseline visit, a 12-lead ECG was made of all participants. A comparison is made between individuals with unrecognized MI and individuals with recognized MI and a generated matched control group. Risk factors related to unrecognized MI are determined and analyses are performed to determine whether a relationship exists between unrecognized MI and mortality. In **chapter 7**, incidence rate, symptomatology and predictors of unrecognized MI are described. 57,276 women and 39,927 men of the Lifelines cohort study with available baseline *and* follow-up ECG are included in this study. An *incident* unrecognized MI is defined when a participant has ECG signs corresponding to MI during follow-up in absence of a reported history of MI and pathologic ECG signs at the baseline ECG. Sex-differences in incidence of unrecognized MI are described, as well as the sex-specific predictors and symptomatology of unrecognized MI.

**Part III: Left ventricular hypertrophy**

In **chapter 8**, the accuracy of existing ECG voltage criteria for predicting LVH is described in 1,670 men and 1,962 women of the UK Biobank study with available CMR and 12-lead ECG data. In addition, the first sex-specific ECG criteria for detecting LVH using CMR are developed. In **chapter 9**, MR analyses are performed using summary statistics of GWAS to determine which cardiovascular risk factors causally lead to lager QRS amplitudes or longer QRS duration. Also, it is aimed to determine whether genetically predicted larger QRS amplitudes or longer QRS duration have a causal relationship with mortality and longevity. Finally, in **chapter 10**, MR analyses are performed to investigate whether causal relationships exist between systolic blood pressure and left ventricular structure and function, as determined by CMR.

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