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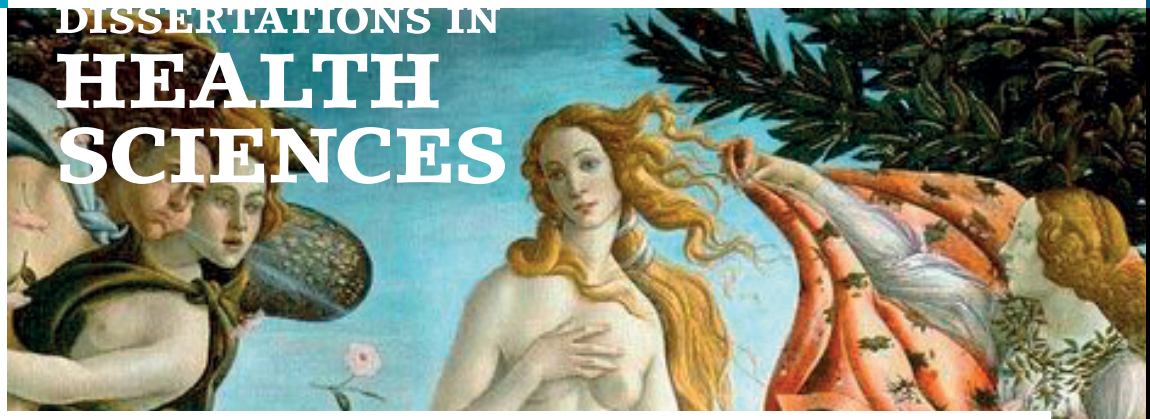

Hanna-Riikka Lehto

Gender Differences in the Occurrence, Prognosis and Risk Factor Control of Cardiovascular Disease

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UNIVERSITY OF
EASTERN FINLAND

HANNA-RIIKKA LEHTO

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Author's address: Institute of Clinical Medicine, School of Medicine
University of Eastern Finland
KUOPIO
FINLAND

Supervisors: Professor Veikko Salomaa, M.D., Ph.D.
National Institute for Health and Welfare
HELSINKI
FINLAND

Docent Seppo Lehto, M.D., Ph.D.
Institute of Clinical Medicine, School of Medicine
University of Eastern Finland
KUOPIO
FINLAND

Aki Havulinna, D.Sc. (tech.)
National Institute for Health and Welfare
HELSINKI
FINLAND

Reviewers: Docent Hannu Vanhanen, M.D., Ph.D.
National Insurance Institute, KELA
Health Department
HELSINKI
FINLAND

Docent Olli Anttonen, M.D., Ph.D.
Päijät-Häme Central Hospital
LAHTI
FINLAND

Opponent: Docent Mikko Syvänne, M.D., Ph.D., FESC
Finnish Heart Association
HELSINKI
FINLAND

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ABSTRACT

Cardiovascular diseases (CVDs) have remained the main cause of death in Finland. CVDs, especially coronary heart disease (CHD), have traditionally been considered to be diseases predominantly affecting men. However, each year more women than men die from CVD both in Finland and globally. In western countries women also surpass men in the absolute numbers of hospitalisations due to stroke and heart failure. While average cholesterol and blood pressure levels have declined in Finland, some CVD risk factors that are more detrimental to women, such as type 2 diabetes and obesity, have become more prevalent. Technical developments in diagnostics, such as the adoption of troponin measurement and improvements in treatments, may also have an impact on CHD occurrence and prognosis. Therefore, it was decided to examine, whether these changes in risk factors and technical development have affected CVD occurrence in women.

The aim of this study was to examine gender differences in CVD occurrence and preventive treatments in Finland. It was studied 1) whether the incidence, mortality and attack rate of acute coronary events have declined differently in women than in men in Finland from the mid-1990s to the beginning of 2000s; 2) whether the prognosis of acute coronary events has improved similarly in both genders in this time period; 3) are there gender differences in the prevalence of high CVD risk and in risk factor management among high-risk subjects and 4) whether the genders differ in incidence and in proportions of different clinical presentations of CVD. Data was utilized from two national CVD registers, FINAMI and CVDR to identify acute coronary events. The events were compared between two time periods: 1992-1994 and 2000-2002. Risk factors and high-risk subjects were identified from the FINRISK Surveys using years 1992-2007. All analyses were also performed in different age groups: in subjects <55 years and ≥55 years old.

The incidence, attack rate and mortality of acute coronary events declined from the mid-1990s to the 2000s and the prognosis improved. Nonetheless this improvement was slower among young, middle-aged (<55 years old) women. The slower pre-hospital case-fatality decline among younger women explained the slower overall case-fatality decline. Furthermore, high CVD risk was not efficiently recognised in young women. The overall risk factor treatment among high-risk individuals, especially among high-risk young women was not optimal, and the recommended target risk factor levels were poorly achieved. The incidence of CVD events was higher among men, as expected; only the incidence of heart failure was equal in men and women. The most common incident CVD event was a non-fatal CHD event in men, and heart failure among women.

National Library of Medicine Classification: WG 120, WG 210, WA 105, WA 309, QZ 53
Medical Subject Headings: Cardiovascular Diseases; Coronary Disease; Myocardial Infarction; Acute Coronary Syndrome; Heart Failure; Stroke; Prognosis; Epidemiology; Incidence; Prevalence; Mortality; Sex Factors; Age Factors; Risk Factors; Women; Men; Cohort Studies; Retrospective Studies; Registries; Finland

Lehto, Hanna-Riikka
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TIIVISTELMÄ

Sydän- ja verisuonisairaudet ovat edelleen suomalaisten yleisin kuolinsyy. Perinteisesti etenkin sepelvaltimotautia on pidetty miesten sairautena. Suomessa, kuten maailmanlaajuisestikin, naisia kuolee kuitenkin vuosittain näihin sairauksiin suhteellisesti enemmän kuin miehiä. Naiset ovat myös enemmistönä aivohalvaukseen sairastuneista sekä käyttävät suurimman osan sydämen vajaatoiminnan hoitopäivistä. Keskimääräiset kolesteroliarvot ja verenpainetasot ovat parantuneet viime vuosikymmenien aikana. Samaan aikaan tyypin 2 diabetes ja lihavuus ovat kuitenkin yleistyneet suomalaisessa väestössä, ja näiden riskitekijöiden on todettu olevan haitallisempia naisille kuin miehille. Lisäksi sydäntautien diagnostiikassa ja hoidossa on viime vuosikymmenien aikana tapahtunut muutoksia, joilla on vaikutuksia sydän- ja verisuonisairauksien esiintymiseen ja ennusteeseen.

Tutkimuksen tavoitteena oli selvittää sukupuolten välisiä eroja sydän- ja verisuonisairauksien esiintyvyydessä, ennusteessa sekä ehkäisevien hoitojen käytössä. Tutkimme 1) akuuttien sepelvaltimotautikohtauksen ilmaantuvuuden, kohtaustaajuuden ja kuolleisuuden laskun eroja 1990-luvun puolivälin ja 2000-luvun alun välillä 2) ennusteen muutoksia näiden aikajaksojen välillä molemmilla sukupuolilla 3) onko korkean sydän- ja verisuonitautiriskin esiintymisessä eroja sukupuolten välillä, ja 4) onko ensimmäisen sydäntautitapahtuman ilmaantuvuudessa eroja sekä eroaako tautitapahtumien kliininen kirjo naisilla ja miehillä. Akuutit sepelvaltimotautitapahtumat tunnistettiin käyttämällä kahta valtakunnallista sydän- ja verisuonitautirekisteriä, FINAMIa ja SYVEä. Tautitapahtumien muutoksia vertailtiin vuosijaksojen 1994-1996 ja 2000-2002 välillä. Riskitekijätasot ja korkean riskin henkilöt tunnistettiin FINRISKI-tutkimukseen vuosina 1992-2007 osallistuneista. Analyysit tehtiin erikseen myös ikäjaottelulla alle 55-vuotiaat ja ≥ 55-vuotiaat.

Tutkimuksessa todettiin akuuttien sepelvaltimotautitapahtumien ilmaantuvuuden, kohtaustaajuuden ja kuolleisuuden laskeneen tutkimusajanjaksolla. Nuorilla naisilla lasku oli hitaampaa kuin muilla ryhmillä. Lisäksi nuorten naisten ennuste oli parantunut tällä ajanjaksolla muita vähemmän, mikä johtui sairaalan ulkopuolisen kohtaustappavuuden hitaammasta laskusta. Kokonaisuudessaan korkean riskin potilaiden riskitekijöitä koskevien hoitotavoitteiden saavuttamisessa on edelleen parantamisen tarvetta. Etenkin nuorten naisten korkeaa riskiä ei myöskään tunnisteta riittävän hyvin. Ensimmäisen sydäntautitapahtuman ilmaantuminen on miehillä tunnetusti yleisempää, mutta sydämen vajaatoiminnan ilmaantuminen on molemmilla sukupuolilla yhtä suurta. Ensimmäinen sydäntapahtuma on naisilla useimmiten sydämen vajaatoiminta, ja miehillä ei-tappava sepelvaltimotautitapahtuma.

Luokitus: WG 120, WG 210, WA 105, WA 309, QZ 53
Yleinen suomalainen asiasanasto: sydän- ja verisuonitaudit; sepelvaltimotauti; sydäninfarkti; sydämen vajaatoiminta; epidemiologia; esiintyvyys; kuolleisuus; sukupuoli; sukupuolierot; riskitekijät; naiset; miehet; kohorttitutkimus; rekisterit; Suomi

"Medicine is a social science, and politics is nothing else but medicine on a large scale."

- Rudolf Virchow (1848)

To women with cardiovascular disease

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I express my deepest gratitude to my principal supervisor Professor Veikko Salomaa, MD, National Health Institute for Health and Welfare, Helsinki. His extensive knowledge in the field of clinical and cardiovascular epidemiology and his logical thinking have been essential in clarifying the outlines and key issues of this thesis. I would also like to thank Aki Havulinna D.Sc. (tech.), National Health Institute for Health and Welfare, Helsinki, for the statistical analyses and for his expertise in this field. He has also helped in preparing the thesis though his detailed critical feedback – it was helpful and made this thesis clearly defined. Both Veikko and Aki's accuracy and punctuality have been priceless.

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Kuopio, August 2013

Hanna-Riikka Lehto

List of the original publications

This thesis is based on the following original publications, which will be later referred by their Roman numerals I-IV. Additionally some previously unpublished data are presented.

I Lehto H-R, Lehto S, Havulinna AS, Ketonen M**,** Lehtonen A, Kesäniemi YA, Airaksinen J, Salomaa V; FINAMI Study Group. Are coronary event rates declining slower in women than in men - evidence from two population-based myocardial infarction registers in Finland? *BMC Cardiovasc Disord 12;7:35, 2007.*

II Lehto H-R, Lehto S, Havulinna AS, Ketonen M, Lehtonen A, Kesäniemi YA, Airaksinen KJ, Salomaa V. Sex differences in short- and long-term case-fatality of myocardial infarction. *Eur J Epidemiol 26: 851-861, 2011.*

III Lehto H-R, Lehto S, Havulinna AS, Jousilahti P, Salomaa V. Gender differences in the prevalence, causes and treatment of high cardiovascular risk: findings from the FINRISK Survey. *Eur J Cardiovasc Prev Rehabil 19: 1153-1160, 2011.*

IV Lehto H-R, Lehto S, Havulinna AS, Salomaa V. Does the clinical spectrum of cardiovascular diseases differ between men and women? *Eur J Prev Cardiol, 2013. Published online.*

Contents

Abbreviations

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AHA	American Heart Association
BMI	Body mass index
CABG	Coronary artery by-pass grafting
CDR	Causes of Death Register
CEE	Conjugated equine estrogen
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase isoenzyme MB
CK-MBm	Creatine kinase isoenzyme MB mass (concentration)
CVD	Cardiovascular disease
CVDR	Cardiovascular disease register
DALYs	Disability adjusted life-years
DBP	Diastolic blood pressure
DRR	Drug Reimbursement Register
ECG	Electrocardiogram
EF	Ejection fraction
EUROASPIRE	European action on secondary prevention through intervention to reduce events
ESC	European Society of Cardiology
GP	General practitioner
HDL	High-density lipoprotein
HDR	Hospital Discharge Register (HILMO)
HERS	Heart and Oestrogen/progestin Replacement Study
HF-PEF	Heart failure with preserved ejection fraction
HF-REF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HRT	Hormone replacement therapy
ICD	International Classification of Diseases and Health Related Problems
ID	Identity code
LDL	Low-density lipoprotein
MI	Myocardial infarction

MONICA	MONItoring Trends and Determinants in Cardiovascular Disease
MPA	Medroxyprogesterone acetate
N/A	Not available
NHANES	National Health and Nutrition Examination Surveys
NS	Not significant
OCs	Oral contraceptives
OECD	Organisation for Economic Cooperation and Development
OR	Odds Ratio
PCI	Percutaneous coronary intervention
PCOS	Polycystic ovary syndrome
RR	Relative risk, i.e. Risk Ratio
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation System
STEMI	St-elevation myocardial infarction
UAP	Unstable angina pectoris
WHO	World Health Organisation

1 Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality in both genders not only in Finland but throughout Europe. Previously, CVDs have typically been considered as "male diseases". The lifetime risk of CVDs among women has often been underestimated, and a common belief has been that the effects of estrogen protect women against CVDs during their fertile years. However, since 1984 more women than men have died of CVDs in the United States, and currently 52% of women's deaths and only 42% of men's deaths are due to CVDs in Europe (1, 2). Coronary heart disease (CHD) and stroke are the two main forms of CVD. CHD was considered as a disease of working-aged men in Finland 30-40 years ago, as was the case in the other western countries. Subsequently, the age-standardised CHD and CVD mortality rates have declined considerably, and general life-expectancy has increased among both genders in Europe, including Finland (3). On average women have 6 to 8 years longer life-expectancy than men. Because of the considerable decline in CVD occurrence among working-aged people, the burden of CVDs has shifted from working-aged to elderly subjects, of whom women constitute the majority. However, CHD, and CVD are not exclusively a problem of elderly women. Recently, the CHD and stroke mortality rates among young women have been failed to decline, plateauing and even started to increase among young middle-aged women in the United States (4, 5). In addition, the prognosis of CHD has been postulated to be worse among women than in men in this age group (6). The theory of "estrogen explaining it all, and the provision of (estrogen/progesterone) hormone replacement therapy for postmenopausal women have failed to provide any protection against CVD (7). The focus of attempts to explain gender differences in CVD has changed to research elucidating differences in major CVD risk factors; high blood cholesterol and blood pressure levels, diabetes and smoking and their prevalence in communities.

Differences between men and women have proved a fascinating topic for speculation throughout the history of mankind. However, taking gender differences into account is a fairly new approach in the field of medical research. In cardiovascular medicine, gender differences have been examined since the mid-1980s (8). Nonetheless, women tend to be under-represented in clinical trials for heart disease treatments, which has in part hampered development of gender-specific treatment guidelines (9). The results both in clinical and epidemiological studies have usually combined genders, or have not given results on gender differences.

CVD trends are known to reflect the trends in the major risk factors, and the differences in the risk factor burden between men and women have been claimed to explain differences in incidence among young populations (10, 11). In Finland, the average cholesterol- and blood pressure levels as well as the prevalence of smoking have declined (12). Women have always smoked less than men in Finland. However, smoking increased among women during the latter half of the 1990s with this trend continuing until the beginning of the 2000s although it has recently started to decline again (12). At the same time, the prevalences of overweight, obesity and type 2 diabetes have increased (1). These risk factors have been postulated to have a stronger impact on CVD morbidity in women than in men (11). In addition to the changes in risk factors, the diagnostic and therapeutic

procedures for CVDs have improved during the past decades. More sensitive laboratory measurements, such as the analysis of cardiac troponins, were adopted during late 1990s in Finland to help in the diagnostics of acute coronary events. The adoption of troponin measurements has had an effect on CHD epidemiology (13). Also, more medicines, (i.e. statins and angiotensin-converting enzyme (ACE) inhibitors) have become available for prevention and treatment of CVD risk factors.

In Finland, there is a long history of epidemiological research on CVD, and in fact the National Institute for Health and Welfare currently maintains two CVD registers. The CVD register (CVDR) is based on an administrative nationwide registers. The data are collected from the Hospital Discharge Register (HDR), the Causes of Death Register (CDR) and from the Finnish National Insurance Institute's Drug Reimbursement data. The FINAMI register is a descendant of the FINMONICA register, which was operational in Finland during 1983-1992 as part of the global World Health Organisation's (WHO's) Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project. The FINAMI register has collected data since 1993; it covers four geographical areas in Finland and it aims to collate data on every CHD event in the registration area. Events collected in FINAMI are evaluated by trained personnel. The FINRISK Surveys continue the work of the WHO MONICA Project and the North Karelia project started in 1972. The FINRISK survey is a cross-sectional study, which collects data from six geographical areas regarding cardiovascular risk factors at 5 year intervals. The FINRISK survey is also maintained by the National Institute for Health and Welfare.

Due to the changes in CVD risk factor levels in Finland, which might have been more detrimental to women, and changes in the diagnostic procedures of CVD, it seemed reasonable (firstly) to evaluate whether the acute coronary event incidence-, attack-, and mortality rates have declined equally in both genders from the mid-1990s to the early 2000s. It was also decided to evaluate whether the adoption of troponin measurements had affected gender differences in the numbers of CHD events. Since mortality is associated both with changes in incidence and changes in case-fatality, it was further investigated, whether the case-fatality of acute coronary events had improved equally in men and women. Gender differences were also evaluated in the prevalence of high CVD risk, risk factor levels, and in the use of preventive medications among subjects at high risk of CVD. Furthermore, gender differences were estimated in the incidence of first major adverse CVD events (i.e. non-fatal CHD, fatal CHD, stroke and heart failure), and in the clinical spectrum of incident CVD events. Women and men were analysed in two different age groups, <55 years and ≥55 years.

2 Review of the Literature

2.1 Cardiovascular diseases

Cardiovascular diseases (CVDs), defined as diseases of the heart and circulatory system, are the main cause of death among both genders. Globally, CVDs cause 30% of all mortality (14). In Europe, 42% of total deaths in men and 52% in women were attributable to CVDs in 2011 (15). In the Finnish population, CVDs have been the leading cause of death for many decades. In Finland in 2011, a total of 40% of all deaths were due to CVD, and one out of every five deaths (22%) was due to coronary heart disease (CHD). CVDs were the most common cause of death in both genders in 2011. Proportionally, more women than men died of CVD in Finland; of all deaths 41% among women but only 38.7% among men were due to CVDs (16). CVDs have remained an important cause of death in working-aged subjects. In 2011, alcohol-related diseases and accidental alcohol poisoning were most common causes of death in the working-aged (15-64 years old) men (1114 deaths) and women (346 deaths) in Finland. However, CHD caused an almost equal number of deaths in men (1111 deaths), and thus when the two most important causes of CVD mortality - CHD and stroke - are combined, CVDs were the main cause of death in working-aged men (1368 deaths vs. 1114 deaths due to alcohol-related diseases and accidental alcohol poisoning). In working-aged women, CHD and stroke combined contributed to an almost equal number of deaths (=287) as the second most common cause of death, breast cancer (=293 deaths). Figure 1 shows total CVD mortality (excluding congenital heart defects) trends among both genders in the United States from 1979 to 2009 (17).

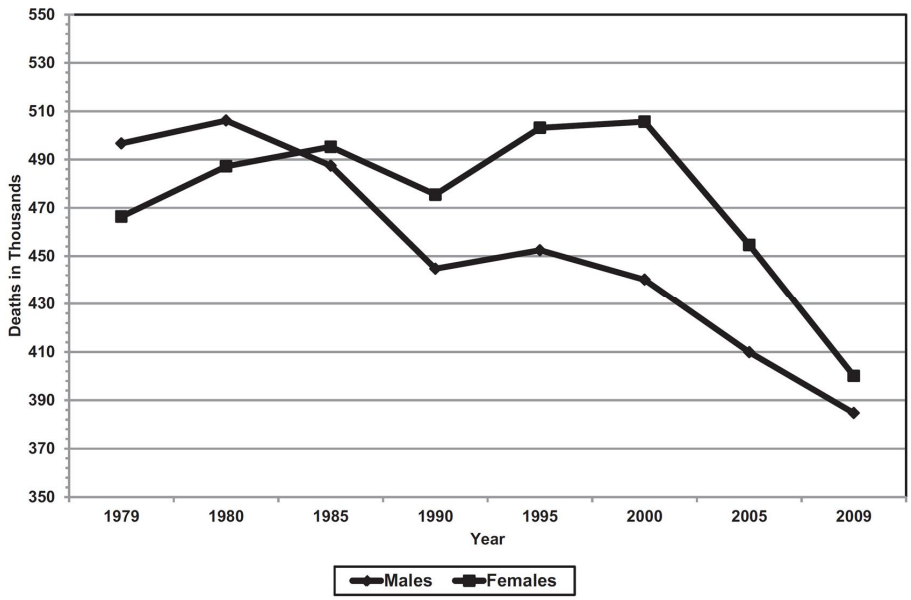


Figure 1. Total CVD mortality trends from 1979 to 2009 in United States among men and women. Reproduced with permission from Go AS et al. Circulation 2013;127:e6-e245.

CVD mortality is mainly due to CHD and stroke, which together account for two thirds of all cardiovascular deaths (14). In men, CHD evokes a larger proportion of CVD deaths than in women with CHD causing 46%, and cerebrovascular diseases 34% of all CVD-related deaths in men, and in women CHD is responsible for 38% and cerebrovascular diseases 37% of all CVD deaths (14).

The proportion of CVD mortality of all-cause mortality among working-aged men was the highest in Finland among all of the 21 countries participating in the World Health Organisation (WHO) MONItoring Trends and Determinants in Cardiovascular Disease (MONICA) Project during the 1980s. At the same time period (1985-1987), CVD mortality among Finnish women was the 5th highest among the MONICA populations (18). Age-standardised mortality rates from CVD have declined during the past 40 years in high-income countries including Finland. During the years 1969-71, the age-standardised CVD mortality rate in Finland was 680/100 000 among 35-64 year old men whereas in the year 2006 it had fallen to 172/100 000. In women, CVD mortality was 217/100 000 in the 1969-71 and 45/100 000 in 2006. Thus, among working-aged subjects, CVD mortality has declined by 75% in men and by 79% in women in the period from the beginning of the 1970s to 2006 (19). Table 1 shows the main CVD events: age-standardised mortality rates of CHD and stroke per 100 000 inhabitants in some Organisation for Economic Cooperation and Development (OECD) countries in the latest available year.

Table 1. Age-standardised[1] CVD death rates / 100 000 persons in the years 2007-2009 [(2)].

		CHD[2]		***Stroke***[2]	
	Year	***Men***	***Women***	***Men***	***Women***
Finland	*2009*	170	74	50	38
Sweden	*2008*	118	58	45	36
Estonia	*2009*	282	141	80	52
Netherlands	*2009*	62	27	35	32
Spain	*2008*	66	28	41	32
United States	*2007*	129	68	32	29
Japan	*2009*	38	17	53	30

[1] *Age-standardised to the 1980 OECD population*

[2]*Source:OECD Health Data 2011; IS-GBE, 2011. For CHD http://dx.doi.org/10.1787/888932523348 and for stroke http://dx.doi.org/10.1787/88893252367.*

Morbidity

Morbidity can be described using different measurements such as incidence, prevalence and hospital discharge rates. These are affected by national methods of reporting diseases, and cannot be considered as truly comparable across different countries in the same way as mortality rates. WHO Global Burden of Disease-project sums up the lost years of life due to premature death and lost years of healthy life due to disability (Disability-Adjusted Life Years i.e. DALYs). Globally, WHO estimates that CVDs cause 10% of the total disease burden measured by DALYs. In Europe, CVDs are responsible for 17% of the total disease burden and in the EU countries it is slightly less but still 14% (1, 20). In men, CHD is the second largest (6.8% of DALYs) and stroke (5.0% of DALYs) the third largest cause of disease burden globally after HIV and AIDS (7.4% of DALYs). In women, CHD account

for the third largest and stroke the fourth largest proportion of lost healthy life years (CHD 5.3% of women's DALYs and stroke 5.2% of DALYs), after HIV and AIDS (7.2%) and unipolar depressive disorders (8.4%) (20). Table 2 illustrates cardiovascular morbidity data and case-fatalities in some selected countries.

Table 2. Cardiovascular disease morbidity and case-fatality in selected countries in the years of 2007 - 2009.

	Year	**30-day in-hospital CF MI [1] (%)**	**30-day in-hospital CF Stroke [1] (%)**	**CHD DALYs[2] /100 000 in 2004**	**Stroke DALYs[2] /100 000 in 2004**	**Hospital Discharges/ 1000 population from CVD in 2007[3]**
Finland	*2009*	4.8	2.8	730	394	27
Sweden	*2007*	2.9	3.9	543	281	25
Estonia	-	N/A	N/A	1538	719	32
Netherlands	*2007*	5.3	5.7	417	291	17
Denmark	*2009*	2.3*	2.6*	551	358	20
U.K	*2009*	5.2	6.7	674	348	13
Spain	*2009*	5.6	6.1	401	276	13
USA	*2008*	4.3	3.0	715	327	20
Japan	*2008*	9.7	1.8	274	425	14

[1] Age- and gender standardised to the 2005 OECD population +45 years old

[2] Age-standardised Disability adjusted life years (DALYs) rate /100 000 population in 2004. According to the World Health Organisation Global Health Observatory Data Reposity.

[3] Source OECD Health Data 2011 http://www.oecd.org/els/health-systems/49105858.pdf

* The lowest in Europe

CF indicates case-fatality and N/A indicates not available

In 2003, 7.4% of the working-aged (ages 16-64 years) population in Finland were on disability pension. CVDs were the third most common cause of disability, after mental health problems and musculoskeletal diseases. In 2003, 8.7% of disability pensions were granted in men and 3.4% in women due to CVDs. The number of disability pensions due to CVDs has decreased substantially: in 2003 the proportion of disabilities due to CVDs was a mere one third of the level existing in the 1970s (21). Among the elderly (65-74 years old) CVDs are responsible for large proportion of disability (22).

CHD, stroke and heart failure are the main forms of CVD. More detailed information on those diseases and their gender differences are presented below.

2.2 Coronary heart disease

CHD is a clinical syndrome characterized by angina pectoris, namely myocardial ischemia due to atherosclerotic coronary artery disease, caused by the accumulation of fatty deposits in the intima of epicardial coronary arteries leading to impairment of blood flow. CHD is clinically manifested either as stable (chronic) CHD or acute coronary syndrome (ACS) which includes unstable angina (UAP), myocardial infarction (MI), or sudden death. The proportions of these clinical manifestations are known to differ between the genders. Men have more clinical events (MIs) and a higher rate of sudden deaths whereas

women express more angina pectoris (23). According to Framingham data (23) the incidences of these clinical manifestations differs considerably between the genders. Expressed per 1000 inhabitants among aged 35 to 84 years the clinical manifestations were in men: 14.1 for MI, 12.3 for angina and 3.1 for sudden death. In women, the corresponding rates were: 4.4, 8.3 and 1.1 (23).

CHD mortality is either due to sudden death or ACS, including UAP and MIs with different clinical presentations: non-ST-elevation and ST-elevation (STEMI) infarctions. CHD death does not necessary require that there is any objective evidence of a thrombus or myocardial necrosis as the actual lethal mechanism can be arrhythmic. Sudden death, most commonly defined as death occurring during the first hour after the onset of symptoms, accounts for approximately 30% – 50% of total CHD mortality, and can unfortunately be the first and only symptom of CHD (24, 25). Most of the CHD mortality (80%) occurs during the first day after the onset of symptoms, and over half of the CHD deaths occur in out of hospital circumstances (18). Gender differences are known to exist in the CHD mortality patterns. More men (74%) than women (61%) die in out of hospital circumstances (26). More women than men are unaware of the existence of CHD before sudden death: 50% of men, and 64% of women who die suddenly of CHD experience no previous symptoms of the disease (2).

2.2.1 Mortality

CHD is the main cause of CVD mortality and it is the most common cause of death. Globally, CHD is responsible for 12.8% of all deaths (14). In Europe CHD accounts for 20% of deaths in men and 22% in women, and in working-aged subjects CHD is the reason for 16% of all deaths in men and 10% in women (1). In Finland, CHD accounted for 23% of all deaths among men and 21% among women in 2011, and it was the second most common cause of death in working-aged men (16% of total deaths) and the seventh most common cause of death among working-aged women (5.3% of total deaths) (16). Trends in age-specific CHD mortality rates are similar in men and women except for the fact that women's mortality rates lag 10 years behind those of men (2).

In the United States, CHD mortality started to increase in the 1920s and in Europe during the 1950s. The male excess in CHD mortality was most prominent in the late 1970s, when 4-5 times more men died of CHD than women (19, 27). At the beginning of the 1970s, in the Seven Countries study, the age-standardised CHD mortality was the highest in working-aged men in North Karelia in Finland when they were compared to the other six participating countries. At that time, CHD mortality was 701/100 000 among working-aged men and 126/100 000 among working-aged women (19).

Since the early 1970s, age-standardised CHD mortality have shown a decline, and declining mortality rates have been seen both in national mortality statistics and in population-based cohort studies from different countries (2, 18, 28, 29). In the United States, CHD deaths have declined by 76% from 1963 to 2010 (2). Age-standardised CHD mortality declines according to the routine mortality statistics are shown for some selected countries in Table 3, and in some population-based register studies in Table 4. The decline in percentage terms may differ between the two different data sources due to different case definitions and lack of standardisation of the coding of causes of death in death certificates. Nevertheless, the CHD mortality declines have been faster among men than women in most studies and countries (Table 3, Table 4). In the study of Levi et al. (Table 3)

gender differences in the declines were not statistically tested (28). Gender differences in CHD event trends have been evaluated in only a few population-based studies. Gerber et al. found a total CVD mortality decline of 55% in men and 46% in women in the Olmsted County, Minnesota, between 1979 and 2003. These corresponded to an annual decline of 3.3% in men and 2.5% in women (p for gender differences 0.007). Unfortunately, CHD mortality decline gender differences *per se* were not reported in that study (29). Slower CHD mortality declines among women than among men have been described from the Olmsted County, Minnesota, between 1979 and 1994, and from New England communities between 1980 and 1991 (30, 31). In contrast, McGovern et al. reported similar CHD mortality declines in both genders in Minnesota from 1985 to 1997 (32). Among the MONICA populations, CHD mortality rate declined between 1983 and 1992 in working-aged persons equally, on average by 2.7%/year in men and 2.1%/year in women (33).

Table 3. Age-standardised[1] CHD mortality rates per 100 000 persons per year according to the national mortality statistics and CHD mortality change between 1985-1989 and 2000-2004 (28)

	Men				**Women**			
	1985-1989	1990-1994	2000-2004	*Change*[2]	1985-1989	1990-1994	2000-2004	*Change*[2]
Finland	248	209	140	*-43.7%*	98	86	61	*-37.7%*
Sweden	194	153	98	*-49.5%*	80	65	44	*-44.6%*
Estonia	381	378	282	*-26.1%*	206	185	133	*-35.5%*
Netherlands	143	113	67	*-52.8%*	55	46	29	*-47.0%*
U.K	281	184	112	*-48.7%*	95	83	50	*-47.4%*
Spain	71	67	56	*-20.6%*	28	27	22	*-21.2%*
USA	166	140	111	*-33.3%*	83	71	58	*-29.8%*
Japan	33	29	29	*-9.8%*	18	15	13	*-27.2%*

[1] *Age-standardised to the World Standard Population*
[2] *Change from 1985-1989 to 2000-2004*

Table 4. Age-standardised CHD mortality declines (%) according to the population-based registers

	Years	**Age group in years**	**Men (%)**	**Women (%)**
Finland **CVDR database** (34) [1]	*1991-2011*	25-74	62	70
United States **Ford et al.** (4)	*1980-2002*	≥35	52	49
Australia **O´Flaherty et al**. (35)	*1976-2006*	≥25	73	70
U.K. **O´Flaherty et al**. (36)	*1984-2004*	≥35	54.7	48.3
France **Wagner et al.** (37)	*2000-2007*	35-74	24	38
USA **Roger et al.** Olmsted County (31)	*1979-1994*	N/A	47	32

N/A indicates not available
[1] According to the cardiovascular disease register (CVDR) database, annual rates age-standardised to European population (34). Database accessed in June 2013.

In Finland, CHD mortality has declined equally in both genders from the early 1980s to the beginning of the 2000s. A study combining all Finland's MONICA areas for the time period 1983-1997 showed an average mortality decline of 6.4%/year (95%CI -5,4%, -7.4%)

in men aged 35-64 years and 7.0%/year (95%CI -4.7%, -9,3%) in women of the same age. According to the Cardiovascular Disease Register (CVDR), the CHD mortality decline between the years 1991 to 2001 was on average 5.2%/year in men (95 %CI -5.6%, - 4.8%) and 6.1%/year (95%CI -6.6%, -5.6%) in women aged 25 to 74 years (38). In the FINAMI register, during an almost similar time interval from 1993 to 2002, the CHD mortality decline in persons aged 35-74 years was similar between the genders, 5.3% in men (95%CI -6.6%, -3.9%) and 4.0% (95%CI -6.3%, -1.8%) in women (13).

Age-standardised CHD mortality rates may conceal age-dependent differences seen in some of the countries. In the United States, England and Wales, Australia and France CHD mortality was proposed to have levelled off between the end of the 1990s and the beginning of the 2000s, or even increased among middle-aged (<55 years old) subjects (4, 35-37). A recent study from France described an overall decline in women's CHD mortality, which was apparent among older, 55 to 74 years old women, whereas no decline was seen to occur in women aged 35-54 years (37). In the United States, CHD mortality even increased among 35-44 year old subjects during the period 1997 to 2002 (4). In contrast, no difference was detected between the genders in CHD mortality declines between 1980 and 2009 in the Netherlands (39). Bertuccio et al. used the WHO mortality database and reported that the average CHD mortality decline for young (35-44 years old) persons was -3.3% per year in men and -2.1% per year among women in the EU areas between 1980 and 2007. However, statistical differences between the genders were not estimated (40).

With respect to the mortality decline in MONICA from 1982 – 1992, two thirds was considered to be explained by the decline of event rates, and one third by the decline in case- fatality (33). Correspondingly, the decline in CHD mortality during 1980 to 1997 in Finland 53-72% was estimated to be due to a reduction of the risk factor levels with about 23% attributable to improved treatments (41). More recently, according to data from England in 2002-2010, it has been estimated that slightly over half of the mortality decline could be explained by the decline in event rates, and slightly less than half by the decline in case-fatality occurring during the first month after the event (42). Adverse changes seen in CHD mortality among middle-aged subjects are difficult to explain; however, it has been speculated that unfavourable changes in risk factor prevalence, in particular obesity and diabetes, among young persons would explain the slower CHD mortality decline.

According to the latest available year 2011 in the CVDR database, the age- standardised CHD mortality in Finland was 250/100 000 in men and 81/100 000 in women aged 35-84 years. In subjects aged 35-64 years, the age-standardised CHD mortality was 87/100 000 in men and 15/100 000 in women.

2.2.2 Case- fatality

Case-fatality refers to the percentage of subjects who die of an acute CHD event of all the subjects diagnosed with an acute CHD event (incident or recurrent) within a defined time period (fatality =100- survival %), whereas mortality describes acute CHD event deaths per population within a defined time period. The declines in case-fatality have been estimated to have had an impact of 23 - 48% on total CHD mortality decline (41, 42). The American Heart Association (AHA) estimates that revascularization and secondary preventive therapies after MI would have been responsible for a 11% decline, initial treatments for ACS for a 10% decline, heart failure treatments for a 9% decline,

revascularisation for chronic angina for a 5% decline, and finally antihypertensive and lipid-lowering therapies in primary prevention are believed to have achieved a 12% reduction (2). Unfortunately, case-fatalities differ in acute coronary events, according to time definition, study setting, and patient-related characteristics such as clinical presentation, age, gender and co-morbidities. The prognosis after an acute coronary event is often considered to be poorer in women; a higher proportion of women than men die within one year after MI. Approximately 26% of women and 19% of men aged ≥45 years hospitalized due to MI will die during the first year after the MI (2). This gender difference is considered to be due to the higher age of women at the time of acute coronary event. However, among the young, i.e. working-aged subjects, a recurrent event is more likely to be fatal in men as compared to women, despite the fact that there were equal numbers of recurrent events in both genders during their follow-up of almost 6 years (43). Nevertheless, the AHA statistics reported the median survival after the first MI to be worse among women aged <75 years than among men: in subjects aged 55 to 64 years, the median survival after the first MI was 17 years in men and 13.3 years in women. In the age group of 65 to 74 years, the remaining life expectancy after the first MI was estimated to be 9.3 years in men and 8.8 years in women. After the age of 75 years the estimated remaining life expectancy was 3.2 years in both genders (2). However, it is not clear whether the female gender is an independent predictor of poorer prognosis, or whether the worse prognosis after MI is related to certain age-groups in women (young vs. older women).

Short-term case-fatality

Age- and gender-standardised 30-day case-fatalities after hospital admission are shown in Table 1 for some selected countries. According to the WHO MONICA study, the median 28-day case-fatality for MI was 49% in men and 51% in women (44). The short-term case-fatality has declined since the 1980s, and in CVDR, the latest available age-adjusted case-fatalities for the year 2011 in persons aged 35-64 years were: 35% in men and 27% in women with the corresponding percentages for the age group of 35-84 years being 47% in men and 39% in women.

Results on gender differences in short-term prognosis have appeared to be conflicting depending on the adjustments made and on the study setting. Studies including patients admitted to hospital have found higher case-fatality for women (6, 45-49). In some studies women's higher age, higher number of co-morbidities, differences in clinical presentation, greater difficulties in reaching diagnosis, and lesser usage of reperfusion therapies have been shown to explain the higher case-fatality among women compared to men (47-49) whereas in other studies, these differences have remained after adjustments for these factors (6, 45, 46). Gender differences in studies recruiting only hospitalized patients may be distorted due to different proportion of pre-hospital deaths between the genders (50). Population-based studies from Scotland, Sweden and New Zealand, which evaluated overall case-fatality by taking the pre-hospital deaths into consideration, reported higher case-fatality among men in pre-hospital circumstances, higher case-fatality among women in in-hospital cases, and equal short-term case-fatality between the genders (51-54). In some studies, a gender difference in prognosis has been shown to exist, especially among young women (6, 53, 55). Vaccarino et al. described two times higher in-hospital case-fatality among <50 year old women in the United States, with this difference remaining also after adjustments for medical history, clinical severity and early management of coronary event (6).

In Finland, the overall 28-day case fatality was 38% in men and 25% in women in 1983-1987, then until the year 1997, case-fatality declined equally among both genders in persons aged 35-64 years (Table 5). During this time period, 74% of all fatal events among men occurred in pre-hospital circumstances, and 61% of women's fatal events were pre-hospital. A gender difference was seen in the location of case-fatality decline in 1983 - 1997: pre-hospital deaths declined significantly only among women, whereas in-hospital deaths declined only in men (26). More recently, between 1993 and 2002, the 28-day case-fatality declined only in men (Table 5). During this time interval, case-fatality for hospitalised acute coronary events declined in both genders, which may point to an unfavourable pre-hospital case-fatality trend occurring in women. Pre-hospital case-fatality data for the period 1993-2002 were not available (13).

Table 5. Average annual 28-day, pre-hospital and in-hospital case-fatality (CF) change (%) with 95 % confidence intervals in 1983- 2002 in Finland.

	Average annual change (%) in 28-day CF	**Average annual change (%) in pre-hospital CF**	**Average annual change (%) in in-hospital CF**
Salomaa et al. (26) 1983-1997[1]			
Men	-1.3 (-2.3 – -0.3)	-1.0 (-2.1, +0.2)	-2.7 (-4.7 – -0.8)
Women	-3.1 (-5.5 – -0.7)	-4.0 (-7.1 – -0.8)	-3.0 (-6.7 – +0.7)
Salomaa et al. (13) 1993-2002[2]			
Men	-2.4 (-3.8 – -0.7)	N/A	-3.3 (-5.9 – - 0.5)
Women	1.2 (-3.5 – +1.1)	N/A	-4.9 (-8.5 – -1.2)

[1] Age-group of 35-64 years old

[2] Age-group of 35-74 years old

N/A for not available

There has been a 56% improvement in the one month case-fatality in the United States between 1987 and 2006 (56). The temporal trends in 30-day case-fatality during this time period did not differ between the genders or age groups in the Olmsted, Minnesota, cohort (56). In 2002-2006, 30-day case-fatality for incident MI was higher among women, approximately 11%, as compared to 5% in men (56). Vaccarino et al. have detected an improvement especially in case-fatalities of young (<55 years old) women in the period from the 1990s to 2006 (57).

Long-term case-fatality

Overall 1- and 5-year case-fatality has declined by 55-69% from the 1960s to 1999 in the United States (58). According to the CVD register, in the year 2009 in Finland the 1-year age-standardised case-fatality among 28-day survivors aged 35-84 years old was 8% in men and 6% in women. Among 45-54 years old subjects, the case-fatality was 1% among men and 2% among women (34). Studies on long-term prognosis have revealed no gender differences in case-fatality after discharge from hospital (59), although some have described a better prognosis among women (60). Vaccarino et al. reported higher overall 2-year case-fatality among survivors of acute myocardial infarction in women (28.9%) compared to men (19.6%). This gender difference was shown to be age-dependent: only women <60 years old had higher 2-year case-fatality compared to men of a similar age (HR

1.40). This difference diminished with age, so that among 70 years old subjects, the HR was 0.95 between women and men. These differences still remained after adjustments for medical history, hospital treatments and procedures, co-morbidities (diabetes) and discharge treatments (61).

2.2.3 Incidence

CHD incidence, as well as CHD mortality increase with age. Among males, the incidence increases until the age of 45-55 years, and after that the increase levels off and then the rate is maintained throughout the remaining age bands. In women, the incidence remains low until the age of 65-74 years after which it rapidly increases, the gender gap in the incidence narrows with the rates becoming almost equal after the age of 75 years (23). Comparable rates of men and women are in general achieved 10 years later in women compared to men (62). Men have 2 to 6.5 times more CHD before the age of 64 (23). Among women, CHD incidence increases by a factor of 4 after menopause when compared to the situation in premenopausal women (23).

Age-standardised incident CHD event rates were ranked highest for men in North Karelia in Finland in the 1985-1989 period from all MONICA regions (18). At that time, the CHD incidence rate was 586/100 000/year in 35-64 year old men in North Karelia, and the rate for all CHD events (fatal, nonfatal, incident and recurrent) was 915/100 000/year. Women of a similar age in North Karelia had the fourth highest event rate of the MONICA regions. In women, the incident CHD event rate was 115/100 000/year, and the total CHD event rate was 165/100 000/year in North Karelia. Other MONICA registration areas in Finland, Kuopio and Turku-Loimaa, also ranked in the "top 10" regions in the CHD event rates (18).

In the United States, the age-and gender adjusted CHD incidence increased from 274/100000 in 1999 to 287/100 000 in 2000, but after that, the rate has declined to 208/100000 in 2008 (63). Gender differences in incident acute CHD events have also been reported. Hospitalisations in the Olmsted County, Minnesota, increased among women, especially among older women between the years of 1979 to 1994 while the numbers of hospitalisations remained the same in men (64). More recent incidence rates are affected by adoption of troponins. Between 1986 and 2006, the incidence of hospitalized MIs did not change significantly in the Olmsted County, Minnesota, cohort (56). However when the effect of the troponins in incidence was taken into account, the incidence was found to decline by 1.1% per year. It was stated that the incidence trends did not differ by age and gender (56). In the Atherosclerosis Risk in Communities cohort in the United States, age-adjusted MI incidence was reported to decrease by 4.3% annually among white men and by 3.8% in white women between the years of 1987 to 2008, when biomarker adjustments were taken into account. Gender differences in decline rates were not tested statistically and no age-dependent differences in incidence were reported (65).

2.2.4 Prevalence

The CHD prevalence is estimated to be 8.3% in men and 6.1% in women in the adult population of the United States and the corresponding prevalence of MI is 4.3% in men and 2.2% in women (2). In contrast to those figures, angina pectoris is more prevalent among women than men (4.0% vs. 3.8%), and furthermore, this excess prevalence of angina symptoms is known to exist in both pre-and postmenopausal women (2, 66). The prevalence of CHD increases with age in the United States; 6.0% of the population (both genders) aged 40-59 years has CHD, and among the population aged 60-79 years 23%, of men and, 14% of women have CHD. In the age group of >80 years, 36% of men and 21% of women have CHD (2).

Data from the National Health and Nutrition Examination Surveys (NHANES) have shown that over the past two decades, the prevalence of MI has increased among young and middle-aged women, while it has declined among men of a similar age (67). In the NHANES 1999-2004, MI prevalence was 2.2% in men and 1.0% in women aged 35-54 years. In the United States it has been estimated that by 2030 the overall CHD prevalence will increase by 16% from the level in 2010 (2).

In Finland, according to the Health 2000 Survey, the prevalence of persons with a history of MI was 2.2% in working-aged men, and 0.3% in working-aged women. In the population aged >65 years, the prevalence of MI was 15.4% in men and 6.8% in women. Angina symptoms were also more common among men; 3.1% of working-aged men and 1.1% of working-aged women suffered from angina. The corresponding numbers in the population aged >65 years were 27.9% and 20.3% (68).

The overall CHD prevalence has increased by 18% in Finland from the 1980s to the beginning of the 2000s (69). The most predominant patient group was 45-64 years old men in the 1980s, whereas in the year 2000 this first place position had been taken by over 75 year old women (69). The number of hospitalisations due to CHD among ≥75 year old subjects was higher among women than in men in 2011 (the total number of hospitalizations was 20190 in women, and 17600 in men) (34). Women have a longer life-expectancy than men in Finland. According to Statistics of Finland, the life-expectancy at birth in the 2011 was 84 years in women and 77 years in men. In 2011, 65-year old men were estimated to have a life-expectancy of 17 years i.e. five years less than the 22 years in women (70). The general life-expectancy has increased since the 1950s throughout Europe (3). In 2010 the gender gap in the western countries was 5.6 years. The life-expectancy difference between the genders has narrowed during the past 30 years. Men have gained higher increases in life-expectancy in most OECD countries and, a part of this improvement in life expectancy is due to the decrease in CVD occurrence among men (71).

2.2.5 Effects of troponins

ACS and the detection of MI have changed over time. Sensitive troponins became available for MI diagnostics in the 1990s and were adopted into clinical use in Finland in the late 1990s. Cardiac troponins are known to have higher sensitivity and better specificity to detect MIs than the older enzymatic biomarkers (creatine kinase (CK), its isoenzyme CK-MB, and CK-MBm). Troponin adoption has increased the estimates of the MI incidence compared to old biomarkers but has had no effect on acute coronary event mortality rates or case-fatalities (13, 56, 58, 65). Roger et al. reported similar effects of

troponin adoption on MI incidence rates in different age-groups and in both genders (56). However, in that study, the age- or gender differences were not analysed in detail. Salomaa et al. studied the effects of troponins in FINAMI study subjects for whom both old enzymatic biomarkers and cardiac troponins were available (13). Troponins were found to have exerted effect on the incidence in both genders and all ages, but the greatest effect of troponin adoption on MI event numbers was observed among the elderly (≥75 years of age) women (13). Troponins had no significant effect on case-fatality in either gender or in any special age group. Investigators of the Framingham Heart Study also reported similar trends in case-fatality of MI events detected by electrocardiogram (ECG) or by biomarkers (58). Troponins have only a small effect on acute coronary event mortality due to the large proportion of deaths occurring before any diagnostic testing (13).

The clinical presentation of MI has changed after the adoption of troponins. The number of non-ST-elevation MIs has increased whereas those of STEMIs have decreased (56). However, this change seems to be independent of the adoption of troponins (56). The prognosis of MIs has not changed due to the adoption of troponins, because the MIs detected by troponins only seem to have a poor prognosis (72) .

2.3 Stroke

The WHO defines stroke as: "rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin" (73). Most strokes are due to blockade in the arteries supplying the cerebrum (ischemic stroke), accounting for 87% of all stroke events, or due to a rupture of blood vessel in brain (hemorrhagic stroke), which makes up 10% of all stroke events. The third stroke type is subarachnoid haemorrhage, which constitutes approximately 3% of all stroke events (2). In Finland, the proportions of stroke types among hospitalised subjects have been 79% for ischemic strokes, 14% for intracerebral hemorrhages and 7% for subarachnoid haemorrhages (74). Ischemic strokes can be further divided on the basis of their cause to cardioembolic, large artery, and small artery infarcts, or as those of unidentified origin. Each of these subcategories is responsible for approximately one quarter of the total ischemic strokes.

Studies on gender differences of stroke are being published in increasing numbers. Most of the population-based studies have found controversial results on gender differences. However, most of the researchers are unanimous that women are older at the time of the first stroke as compared to men, and therefore have more co-morbidities and poorer functionality prior to the stroke (75, 76). Stroke aetiology, important when considering the preventive actions, has been shown to differ between the genders. In a systematic meta-analysis, Appelros et al. evaluated 17 community-based studies with 7783 strokes in men and 8371 strokes in women. Men had more incident ischemic and hemorrhagic strokes compared to women. Male/ female incidence ratios (stroke incidence in men divided by stroke incidence in women) adjusted for WHO world population was 1.55 for ischemic stroke and 1.60 for intracerebral hemorrhage. The male/female ratio for subarachnoid haemorrhage was 0.84, with 95% CI 0.69- 1.04. More men than women suffered large-vessel and small vessel strokes, i.e. mainly strokes caused by atherosclerosis, whereas women had more cardioembolic strokes (75). However, Petrea et al. published

controversial results from the Framingham cohort which found no differences in clinical stroke subtypes between the genders (76). Stroke occurrence is reviewed in detail below. Studies on age- dependent differences in stroke occurrence are still few in number.

2.3.1 Mortality

In Europe, stroke is responsible for 15% of all deaths among women and 10% of all deaths in men, and it is the leading cause of disability (15). Globally, stroke accounts for 10% of all deaths (77). Due to the higher proportion of women in the older population, and due to the increasing stroke risk with ageing, proportionally more women than men die of stroke: women account for 60.1% of all stroke deaths (2). In the United States, the age-adjusted to year 2000 standard, stroke mortality among adults was 82.4/100 000 in women and 84.8/100 000 among men between 1994 and 2004 in the white population (78). Age affects stroke mortality; before 45 years of age the mortality is similar in both genders, whereas in the age group 45-74 years, women have 20% lower stroke mortality compared to men (78). A population-based study from Scotland detected a lower stroke mortality among women until 84 years of age, but after that, women displayed a 15% excess in mortality as compared to men of a similar age (79). The authors concluded that even though the sex-by-year interaction was statistically significant for the study period of 1986-2002 i.e. revealing a slower decline in stroke mortality rate in women, the minor differences in percentages were of no practical importance due to the similar female-male relative risk (RR) over the whole study interval (79). Table 6 shows stroke mortality rates obtained from routine mortality statistics per 100 000/year in selected countries during the 1980s and 1990s and at the beginning of the 2000s (28).

Table 6. Age-standardised[1] stroke mortality per 100 000 inhabitants from routine mortality statistics in 1985 – 2004 in selected countries and the change (%) in mortality (28)

	Men				**Women**			
	1985 - 1989	1990 - 1994	2000 - 2004	*Change* (%)*	1985 - 1989	1990 - 1994	2000 - 2004	*Change* (%)*
Finland	69	63	41	*-40.8*	55	49	32	*-42.5*
Sweden	44	43	34	*-22.5*	37	34	28	*-24.0*
Estonia	149	154	110	*-26.0*	119	117	76	*-36.1*
Netherlands	45	43	33	*-26.8*	36	34	28	*-22.5*
United Kingdom	61	52	39	*-37.1*	54	45	34	*-36.2*
Spain	65	52	34	*-48.3*	42	33	26	*-51.3*
United States	35	31	26	*-25.5*	30	27	23	*-22.7*
Japan	75	58	45	*-39.7*	53	40	27	*-48.9*

[1] Age-standardised to the World Standard Population

* Change from the 1985-1989 time interval to 2000-2004

Similarly to the situation with CHD, Bertuccio et al. described a decline in stroke death rates based on routine mortality statistics among young subjects aged 35-44 years and found a similar -2.5% decline for both genders in the EU area (40).

In Finland, the stroke mortality trend has followed the overall decline in CHD event rates. The population-based FINSTROKE study reported an average decline of 3.7% per year in men and 4.1% per year in women aged 25-74 years in the 15 year period of 1983-1997 (80).

Pajunen et al. reported declines in all three stroke subtypes using CVDR data for the period 1991-2002. Ischemic stroke mortality had declined by 4.8% per year in men, and by 6.2% per year in women aged 35-74 years, and the mortality of intracerebral haemorrhage had declined by 2.8% per year in men and by 4.2% per year in women. The corresponding values for subarachnoid haemorrhage had declined by 5.0% per year in men, and by 1.9% per year in women (81). According to the latest available CVDR data (year 2011), stroke mortality was 55/100 000 persons among 35-74 year old men and 30/100 000 persons among women of a similar age. The stroke mortality rate was substantially higher among both genders in persons aged ≥75 years than among younger persons. However, in subjects ≥85 years old, the mortality rates were higher among women (34).

2.3.2 Case-fatality

Depending on the population the overall 1-month case-fatality in western countries for all stroke subtypes combined was 17-30% during 2000-2008 (82). Stroke subtype exerts a great impact on case-fatality, since haemorrhagic strokes have a higher case-fatality when compared to ischemic strokes. The 1-month case-fatality of ischemic stroke in western countries was in the range 13-23%. Similarly, case-fatality of intracerebral haemorrhage was 25-35%, and 25-35% for subarachnoid haemorrhage (82). Stroke case-fatality has declined in most western countries from the 1970s to 2008, and the latest 1-month case-fatalities for this time period were 14.3% for ischemic stroke, 41.0% for intracerebral haemorrhage and 30.0% for subarachnoid haemorrhage (82).

In Finland, the 28-day case-fatality did not decline significantly in either gender during 1983-1997 (80). However, more recently the 28-day case-fatality for all stroke subtypes has been reduced substantially in persons aged 35-74 years from 1991 to 2002: ischemic stroke 3.0% per year in men and 2.9% per year in women, and intracerebral haemorrhage 2.3% in men and 2.0% in women. The case-fatality of subarachnoid haemorrhage also declined significantly, 3.5% per year in men and 1.8% per year in women (81). According to the CVDR database, the 28-day case-fatality for all stroke subtypes combined in subjects aged 35-74 years was 10% in men and 8% in women in 2011. Case-fatality increased with age, and for subjects aged ≥85 years, the case-fatality was 37% in women and 27% in men (34).

There is a controversy about whether there are gender differences in stroke case-fatality. The WHO MONICA study found, on average, higher average 28-day case-fatality for women than men (31.8% vs. 28.7%). However, stroke case-fatality has varied between the populations, revealing either similar or higher case-fatality for women, depending on the population. In Finland, 28-day case-fatality was lower in women than men in all three MONICA areas (83). In the Framingham cohort including all age groups, case-fatality did not differ significantly between the genders, despite the large differences in the percentages between men and women: 30-day case-fatality was 21% in women and 15% in men, and 180-day case-fatality was 30% in women and 23% in men (76). A significant difference was found in the pooled results of 31 population-based analyses, which revealed a 1-month case-fatality that was 1.25 times higher in women than in men (95% CI 1.17- 1.34). The pooled 1-month case-fatality was 24.7% in women and 19.7% in men (75). The poorer prognosis for women was also reported in a Scottish study of hospitalised patients. Lewsey et al. reported a higher 30-day case-fatality in women over a 20-year study period. The gender difference was age-dependent, and the largest difference was seen in subjects 55-64 years old. In this age group, after adjustments for co-morbidities and socioeconomic differences, the 30-day case-fatality in women revealed an excess of 35%.

Moreover, this higher case-fatality was seen in all age groups, and the smallest difference, an excess of 9%, was seen among subjects ≥85 years old. Furthermore, the gender difference increased from 1980s to 2005, with the 30-day case-fatality being 20.6% for women and 14.7% for men aged 55-64 years in 2005 (79).

A German population-based study did not detect any gender differences in 1-year survival (84). According to the AHA statistics, gender differences in long-term prognosis depended on age. During the first year after incident stroke, deaths occurred in 35% of women and 31% of men ≥65 years old, whereas 21% of women and 16% of men <65 years old died (2).

Gender differences in stroke subtype may affect the case-fatality results, if indeed women have a higher rate of cardioembolic strokes, as is often – but not unanimously – reported (75, 78). This may distort the gender differences in case-fatality, since cardioembolic strokes are on average more severe than their atherosclerotic counterparts (75, 85). Some other reasons might also explain the possibly higher case-fatality among women; however, the findings are conflicting. Some researchers have reported longer waiting times before seeking treatment and more atypical symptoms among women (for example pain and lightheadness) compared to men, gender disparities in acute phase treatment, lower rate of diagnostic procedures in women (echocardiography and carotid artery evaluation), and furthermore, a lower rate of secondary preventive medication usage among women as compared to men (78, 86, 87).

Nevertheless, trends and gender differences in stroke case-fatality are important, because the MONICA study reported that in those countries where the stroke mortality had declined during the MONICA period, the decline was mostly (2/3) due to declines in stroke case-fatality (83). Moreover, even should the stroke event not be fatal, women are known to have poorer functional outcome. Women have been shown to have higher institutionalization rates and higher rate of depression after stroke, to suffer from lower quality of life, and to need more assistance after stroke than men, even when controlling for age and the pre-stroke functional capacity (76, 78).

2.3.3 Incidence

Similarly to the situation with stroke mortality, stroke incidence increases with age. Men have a higher incidence during midlife. However, after the age of 75 years, gender differences diminish, and after the age of 85 years women have a higher incidence (76). Due to the longer life-expectancy of women, the life-time stroke risk after the age of 55 years is higher in women (1:5 among women and 1:6 among men) (76). The Framingham investigators reported age-standardised stroke incidence of 407/100 000 person years in women and 496/100 000 person years in men (76). During the early mid-life (45-54 years), stroke incidence was 82/100 000 person years among women and 116/100 000 person years among men. Among individuals aged 75-84 years the incidence was 1209/100 000 person years in women and 1340/100 000 person years in men (76). The stroke incidence has declined by 42% in high-income countries since the 1970s, when the overall stroke incidence was 163/100 000 person years, compared to the 94/100 000 person years in 2000-2008 (82). In Finland, according to the CVDR database in the latest available year of 2011, the overall age-standardised stroke incidence was 197/100 000 among 25-74 years old men and 116/100 000 among women. In subjects ≥85 years old, the incidences were 2538/100000 in men and 2594/100 000 in women (34).

Studies on gender differences in the decline of stroke incidence are more concordant than those examining mortality; in most studies the declines in incidence have been discordant between the genders (85, 88). A population-based study from the years 1988-2002 in Canada found a lower incidence decline in women and, a similarly, lower stroke incidence decline was observed in the Framingham cohort in 1950-2004 (85, 88). The Framingham study reported that the incidence had declined by 30.3% in men but by 17.7% in women (88). Recent population-based studies have even shown an increasing stroke incidence in mid-life in women according to the NHANES data in the United States and Sweden (5, 89). A lower decline in stroke incidence was also seen in Scotland among middle-aged women (79). In the Framingham study, however, no increase in stroke incidence rate was seen among middle-aged women, but the numbers in this age group were small (76). The increasing stroke incidence has been postulated to be caused by the increases in the prevalence of obesity, adverse life-styles changes, metabolic syndrome and type 2 diabetes (89, 90).

2.3.4 Prevalence

In the United States, stroke prevalence has been reported to be 2.4% in adult white men and 3.3% in women (2). The prevalence increases with age among both genders: among subjects aged ≥65 years the prevalence was elevated to 8.3%, among the 45-64 years old 2.9%, and among persons aged <44 years 0.7% (91). The prevalence of silent strokes is estimated to be 6-28%, depending on the age group (2). Pooled analysis by Appelros et al. showed an average 41% higher prevalence in men as compared to women. The male/female prevalence ratio was the highest (male per female ratio of 1.56) in the age group of 65-74 years, and diminished with aging (75). In contrast, Reeves et al. reported higher prevalence of stroke among females than men after the age of 65 years, and after the age of 85 years the prevalence in women was twice that of men (78). Recently Towfighi et al. described data for the period 2005-2006 indicating that young (aged 45- 54 years) women had suffered 3 times more prior strokes than similarly aged men (92).

2.4 Heart failure

Heart failure can physiologically be defined as a state where defects in heart function or structure lead into failure of the heart to provide sufficient amount of oxygen to satisfy the needs of the metabolising tissues despite a normal filling pressure or only at the expense of increasing filling pressure. The European Society of Cardiology (ESC) defines heart failure more clinically: heart failure is a syndrome depicted with symptoms of shortness of breath, ankle swelling and fatigue and signs of elevated jugular venous pressure, pulmonary crackles and displaced apex beat, resulting from abnormality in heart structure and function (93). In epidemiological studies, heart failure has been defined mainly by using the Framingham Heart Study criteria (Table 7) or the ESC clinical criteria (93, 94).

Previously in clinical settings, and also in many clinical trials, the definition of heart failure has been connected to decreased left ventricular ejection fraction. Heart failure can be divided, according to findings in functional cardiac imaging, to heart failure with reduced ejection fraction (EF) (HF- REF reduced ejection fraction, commonly considered EF ≤ 40%) and heart failure with preserved EF (HF-PEF), also referred to as ´diastolic´ heart failure. According to the updated ESC 2012 heart failure guidelines, a heart failure diagnosis requires that there be symptoms and signs of typical heart failure, and an HF-REF-

diagnosis requires evidence of reduced ejection fraction, whereas diagnosis for HF-PEF requires symptoms, signs and functional cardiac imaging to show specified alterations in detail: 1) normal / mildly reduced left ventricular EF, and no dilatation of the left ventricle, 2) relevant structural heart disease (left ventricular hypertrophy/ left atrium enlargement) and / or diastolic dysfunction (reduced left ventricular passive filling i.e. reduced é or increased E/é ratio, i.e., active filling caused by left atrium systole divided by passive filling of the left ventricule during diastole) (93). Since heart failure is an end result of another underlying cause, this aetiological cause needs to be identified.

Table 7. Framingham Heart Study criteria for heart failure

Framingham criteria for Heart Failure
Major criteria
Paroxysmal noctural dyspnea or orthopnea
Neck vein distension
Rales
Cardiomegaly
Acute pulmonary edema
S3 gallop
Increased venous pressure ≥16 cm H_2O
Circulation time ≥25 seconds
Hepatojugular reflux
Minor criteria
Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity decreased one third from maximum
Tachycardia ≥120/min
Major or minor criterion
Weight loss ≥4.5 kg in 5 days in response to treatment
Heart failure is present if two major or 1 major criterion plus 2 minor criteria apply

Gender differences in heart failure are related to differences in the underlying aetiology, clinical characteristics and outcomes of heart failure. Women are more likely to have a non-ischaemic cause for heart failure than men, i.e. a higher prevalence of hypertension and valvular defects. Men have a higher rate of CHD before the heart failure diagnosis and men have more dilated cardiomyopathy than women (95-97). More women have a preserved ejection fraction, i.e. diastolic heart failure than men, whereas more men have reduced EF, i.e. systolic heart failure (96). As with other CVDs, women are older at the time of the heart failure diagnosis; on average 79 years vs. 73 years in men (95). Women have more diabetes and anemia compared to men, who are more likely to have chronic obstructive pulmonary disease, peripheral arterial disease and renal failure (96). During the 2000s, the age of onset of heart failure has increased, and the numbers of co-morbidities among heart failure patients have increased (98).

2.4.1 Mortality and prognosis

Heart failure has high a mortality, even though the prognosis has improved in parallel with introductions of modern drug therapy. Still, approximately 50% of people diagnosed with heart failure will die within five years after the diagnosis (95). The AHA statistics indicate overall age- and gender adjusted 30-day fatality of 10.4%, 1-year fatality of 22% and 5-year fatality of 42.3% (2). In a large population-based study from the United Kingdom with over 600 000 heart failure patients mainly from a primary care setting, the 3-year fatality after a definitive heart failure diagnosis was reported to be 54% in men and 47% in women. Mean survival was on average 22.9 months in men and 24.5 months in women (99). In some population-based studies the prognosis of heart failure is reported to be worse among men than among women (95, 100). No gender differences were seen in the Rotterdam study nor in the Framingham Heart Study in 1 to 5 year-prognosis of heart failure (94, 101). Van Jaarsveld et al. described an age- and gender dependent difference in 1 to 7 year-prognosis of heart failure: among <75 years old subjects the prognosis is worse among men, and after 76 years of age, no gender differences were seen in heart failure prognosis (102). Table 8 depicts the fatality proportions of heart failure in different population studies for both genders separately.

Table 8. Proportions of fatal outcome at 30-day, 1-year and 5-year time points, in different population-based studies

	Years	**Age group**	**30-day %**		**1-year %**		**5-year %**	
			Men	***Women***	***Men***	***Women***	***Men***	***Women***
Levy et al. Framingham (94)	1990-1999	65-74	11	10	28	24	59	45
Roger et al. Olmsted County (95)	1996-2000	mean age 75	6*	4	21*	17	50*	46
Jhund et al. Scotland[1](103)	1999 2003	N/A N/A	19.6 16.2	18.9 16.9	27.8 27.6	27.8 25.6	65.8 N/A	63.6 N/A
Vaartjes I et al. Netherlands [1] (100)	1997-2000	mean age 76	18**	27	38**	36	67**	66

[1] Hospitalised with first episode of heart failure. N/A indicates not available. * Significant ($p<0.001$) age-adjusted gender difference, towards higher fatal outcome in men. ** Significantly higher fatal outcome in men when adjusted for age and co-morbidities including diabetes mellitus

Population-based studies have detected an improvement in heart failure prognosis. The Framingham study reported an improvement in heart failure prognosis from 1950 to 1999 in both genders. The risk of death declined approximately by 12% per decade in both genders (94). Data from the Olmsted county, Minnesota, also revealed an improvement in prognosis between the two time periods of 1979-1984 and 1996-2000, although these improvements were greater in men and among younger subjects. Heart failure prognosis had improved by 52% in men and by 33% in women in the age group of 60-69 years, and by 41% in men and by 21% in women aged 70-79 years. For the eldest age group (≥80 years), no improvement was seen in women, whereas for men, the survival had improved by 28% (95).

2.4.2 Incidence

Heart failure incidence and its time trends depend on the definition of heart failure. Heart failure incidence increases with age, with men displaying a higher heart failure incidence in all age groups. According to the AHA statistics, incidences indicated as numbers per 1000 person years, are 9.2 in men vs. 4.7 in women in the age group of 65-74 years, 22.3 in men vs. 14.8 in women in the age group of 75-84 years, and 41.9 in men vs. 32.7 in women in subjects ≥85 years old (2). Population-based cohort studies using either the Framingham heart failure definition (Table 7) or clinical heart failure definition of the ESC have reported age-adjusted heart failure incidence of ~ 2-5 per 1000 person-years (94, 95, 101). In the Framingham study, the age-adjusted incidence was 564 per 100 000 person-years in men compared to 327 per 100 000 person-years in women (94). More similar incidences between the genders were reported by the Rotterdam study group: an age-adjusted incidence of 17.6 per 1000 person-years in men and 12.5 per 1000 person-years in women (101). In the Olmsted County study, the age-adjusted incidence was 378/100 000 in men and 289/100 000 in women (95). Most of the heart failure diagnoses (>70%) are, however, assigned in primary care by general practitioners (GPs) without applying the above mentioned strict criteria (99). A large population-based study from the United Kingdom reported an overall age-adjusted heart failure incidence of 9.3/1000 person-years, when most of the diagnoses were made by the GPs. Men had a higher incidence, but unfortunately that study did not report incidence rates separately for men and women (99).

The temporal changes in heart failure incidence rates have shown inconsistent results. The population-based study from the Olmsted County, Minnesota, showed no difference in heart failure incidence between the years 1979 and 2000 in either gender (95). A recently published population-based study from Spain, in which the Framingham case definition was used, reported a 32% increase in heart failure incidence from 2000 to 2007 (98). In this study, the incidence had increased in both genders. Data from the United States Medicare system found evidence for an increasing incidence among the 65-69 years old, but a declining incidence among subjects >75 years old during the period 1994-2003 (104).

2.4.3 Prevalence

Heart failure prevalence in the adult population is estimated to be 2-3% (2, 105). The prevalence increases with age, to reach over 8.4% in the population aged >75 years, and then up to 17.4% in subjects aged ≥85 years (101, 105). Only half of the patients with moderate or severe ventricular dysfunction receive a heart failure diagnosis, suggesting that asymptomatic heart failure is as prevalent as symptomatic heart failure (105). In the Rotterdam study, the heart failure prevalence was 3.9% with no gender differences, with 60% of the persons who were considered to have left ventricular systolic dysfunction in echocardiography exhibiting no symptoms or signs of heart failure (106). Heart failure prevalence has increased over the past decades (101, 104). It has been claimed that the increasing prevalence is due to several factors i.e. improvements in CHD and heart failure treatments, increasing awareness, and the aging of the population. In Finland, the heart failure prevalence was higher among women than in men (9% of women and 5% of men) among subjects ≥65-years old according to data from the Health 2000 survey. The prevalence was similar in working-aged people, of whom 0.2% of women and 0.5% of men were assessed to have heart failure in a doctor's examination. Compared to the values above obtained from the clinical evaluation, a higher proportion of subjects appeared to have heart failure according to the self-reporting: 1.4% of working-aged men and 1.1% of

working-aged women had heart failure (p for gender difference not significant (NS)). Similarly, 14.1% of men and 15.5% of women over 65 years old have reported that they have heart failure (p for gender difference NS) (68).

2.5 Risk factors

2.5.1 Cardiovascular disease risk factors

Traditionally CVD risk factors have been divided into non-modifiable and modifiable factors. The non-modifiable risk factors are age, gender, family history and genetic contributions. The modifiable, behavioural, risk factors, namely tobacco use, physical inactivity, unhealthy diet and excess use of alcohol are associated with four independent, major risk factors for CVD: high total blood cholesterol level, elevated blood pressure, smoking and diabetes (107). These main risk factors are same for both genders, although some gender differences have been shown to exist in prevalences of the main risk factors and their significance (11). In addition, women have some unique gender-related risk factors: menopause, polycystic ovary syndrome (PCOS), usage of oral contraceptives (OCs), and pregnancy-related disorders such as pre-eclampsia, gestational hypertension and gestational diabetes (108). These risk factors, their effects and possible gender differences in CHD and stroke (Table 9 and Table 10) are presented in detail below.

Age

Aging increases the risk for CVD; women develop CVD approximately 10 years later in life compared to men (11). The average age of the first MI is 64.5 years in men and 70.3 years in women (2). Most of this difference is due to the higher prevalence of risk factors among men in the younger age groups (11). In Finland in 2002 the mean age of having the first MI was 70.2 years in men and 80.0 years among women (CVDR database accessed 2005). The average age of an incident stroke in the Framingham cohort was 75 years in women and 71 years in men (76).

Family history

Family history of CVD increases the risk for CVD independently of traditional risk factors. The greatest risk, doubling the risk for offspring, is when a first degree relative (parent, offspring or sibling) has had an early-onset CVD (<55 years old in men and <65 years old in women) (109, 110). Some studies have indicated that family history is a stronger risk factor for women than for men (111). In particular in females a maternal history of CVD may predict CVD more strongly than a paternal history (112). However, the INTERHEART study reveal to show any difference in maternal vs. paternal family history of MI among the offspring with MI events (109).

Socioecomic status

Socioeconomic status refers to a person´s social status relative to other members in their society. Socioeconomic status is often evaluated using education, income or employment status as indicators. High social standing is known to protect from CVD events: in the Whitehall Study cohort, subjects (i.e. male civil cervants) in the lowest social group were 3.6 times more likely to die of a CHD event than those in the highest social group (113). Socioeconomic factors have been postulated to exert a higher impact on a woman's CVD risk. However, in some studies there are methodological issues, such as using the woman´s partner's income or whole household income to evaluate woman´s socioeconomic status (114, 115). Results from NHANES, in a prospective follow-up setting,

indicated that education had a gender specific role as a risk indicator for CHD; women with a low level of education had a 61% increase in their risk for incident CHD as compared to women with high education, while men with a low level of education had only a 29% increase in risk compared to men with high education (116). These analyses were adjusted for smoking, diabetes, cholesterol and blood pressure, i.e. indicators which are known to be worse in persons with a low level of education. Low socioeconomic status, measured as the subject´s own level of education, pointed to a twofold increase in the risk for CHD mortality among 30-59 years old women, whereas in men of the same age, the increase in risk was only 55% when compared to those males with a high level of education (117). In the NHANES low income (adjusted as above) displayed no significant gender differences with low income status increasing the risk of CHD events for both men and women (116). Socioeconomic status has also been studied using FINMONICA data of 25-64 years old men and women. In that study, low levels of occupation, education and income were associated with an increased risk of CVD in both genders. In women, the family income was also an important factor contributing to the risk (114).

Elevated blood cholesterol

A strong association has been found for total blood cholesterol, especially low-density lipoprotein (LDL) cholesterol to increase the risk for CVD and this relationship exists in both genders (10, 118-120). CHD is known to be rare among the population with total cholesterol less than 3-4 mmol/l, even in the presence of other risk factors (121). Most of the cholesterol in plasma is carried in the form of LDL, and total and LDL cholesterol have been shown to display a graded, positive association to CVD risk (119). The adverse effect of high LDL cholesterol is clinically evident in patients with heterozygote familial hypercholesterolaemia; in these individuals CHD has been found already in men at the age of 17 years and in women at the age of 25 years (122). Apoprotein B is a major protein component of apolipoprotein B, which carries LDL, intermediate-density lipoprotein and very-low density lipoprotein, which in turn are the atherogenic components, whereas apoprotein A1 is the main protein in high-density lipoprotein (HDL) particles and is considered to be antiatherogenic (121). Tables 9 and 10 show odds ratios (ORs) of ApoB/Apo A1 for CHD and stroke for both genders according to the INTERHEART and INTERSTROKE studies. However, in the routine clinical work, total cholesterol, or the ratio of total cholesterol and HDL cholesterol are measured and used for risk prediction (121).

Gender differences due to aging can be observed in cholesterol values. In men, total cholesterol values tend to be higher than in women until the age of 50 years, whereafter women tend to have higher values. HDL cholesterol levels decline in men at puberty, and in women after menopause. Thus, the gender difference in the total cholesterol per HDL cholesterol ratio diminishes with aging (62). Blood lipid analyses from the Framingham Offspring cohort have shown that premenopausal women have a less atherogenic lipid profile when compared to men of a similar age. Furthermore, premenopausal women had lower LDL cholesterol and triglyceride levels, and higher HDL-cholesterol values compared to men of a similar age. (123). Blood total cholesterol level might be a more important risk factor in men compared to women. In a Swedish population study of middle-aged women, those with a total cholesterol level above 8 mmol/l, had a double risk of future CHD death compared to women with cholesterol below 6 mmol/l (120). In middle-aged men, the risk of death is doubled, when the total cholesterol increases from 5.0 mmol/l to 6.5 mmol/l, and is increased 4 fold when the total cholesterol concentration is above 8.0 mmol/l (124). Data from the Finnish MONICA cohorts showed that a total

cholesterol increase of 1 mmol/l was associated with increases in CHD mortality by 36% in men and by 21% in women (10). However, the Finnish MONICA study recruited 25-64 year old women, and in the Swedish study the follow-up was 19 years and women recruited in this study were mostly under 55 years old. Thus, the subjects in both of these studies were mainly under 75 years old (10, 120). Since cholesterol levels increase later in life among women, and most of the CHD events occur after the 7th decade of life in women, the impact of hypercholesterolaemia on CHD mortality might be underestimated among elderly women (120). Total cholesterol levels have been shown to predict CHD events among young individuals, whereas hypertriglyceridemia (triglycerides ≥1.7 mmol/l) has been proposed to be a stronger predictor among old, postmenopausal women when compared to their premenopausal counterparts in whom the triglyceride concentration displayed no predictive value for MI or CHD death (125). In the Framingham study, a low HDL cholesterol level was a stronger predictor of CHD in women than in men (23).

The WHO estimates that globally 1/3 of CHD, and 4.5% of total deaths are due to high cholesterol levels. In 2008, the prevalence of hypercholesterolaemia, defined as total cholesterol ≥5.0 mmol/l or having medication for high cholesterol, was globally found in 40% of adult women and in 37% of adult men (14). The prevalence of hypercholesterolaemia was highest in the European region, 54% of Europeans, of both genders, had either medication for hypercholesterolaemia or total cholesterol ≥5.0 mmol/l. Globally, total cholesterol levels have not changed considerably; from 1980 to 2008 there was a 0.1 mmol/l decrease per decade (14). In Finland in 1972, the mean total cholesterol was 6.92 mmol/l in men and 6.81 mmol/l in women, but subsequently it has declined by 21% in men and 23% in women (Figure 2). In 2007, the mean cholesterol was 5.39 mmol/l in men and 5.18 mmol/l in women when all FINRISK areas were pooled (12). In 2007 33-41% of men and 42-49% of women had a total cholesterol level <5.0 mmol/l (12). More recently, FINRISK 2012 reported that the mean cholesterol levels had increased in the Finnish population. According to FINRISK 2012 the mean cholesterol level was 5.34 mmol/l (+ 0.05 mmol/l from 2007 level) in men and 5.31mmol/l (+0.13 mmol/l from 2007 level) in women. These increases were significant in both men (p for increase 0.0054) and women (p for increase p<0.001) (126) .

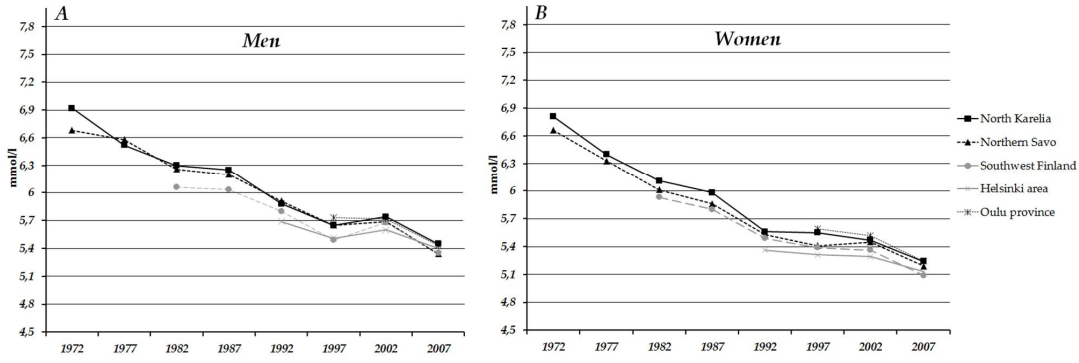


Figure 2. Total cholesterol levels between 1972-2007 in men (A) and in women (B) aged 30-59 years in FINRISK areas (19).

Elevated Blood Pressure

Optimal blood pressure is considered to be <120/80 mmHg, whereas prehypertension is considered as the range of systolic blood pressure (SBP) 120-139 mmHg and diastolic blood pressure (DBP) 80-89 mmHg. Hypertension is defined as SBP ≥140 or DBP ≥90 mmHg. For subjects with diabetes and individuals with renal disease, lower values of SBP >130 or DBP >85 mmHg are considered as hypertensive (2). Elevated blood pressure is one of the main risk factors for CHD, heart failure, stroke and other CVDs, with up to 2-3 fold higher risk on average detected in both hypertensive men and women (127). The ORs of CHD event and stroke due to hypertension are shown in Table 9 and Table 10. The risk for both CHD and stroke increases linearly and progressively from SBP values as low as 115 mmHg and DBP 75 mmHg (128). Blood pressure exhibits a continuous relationship, without any significant cutpoint, to CVDs. Every 20 mmHg increase in SBP or 10 mmHg increase in DBP doubles the risk for a CVD event (128).

There is known to be a gender difference in blood pressure from adolescence, men having 6-7 mmHg higher SBP and 3-5 mmHg higher DBP than women throughout their adult life. In men, SBP rises throughout the adult life with DBP reaching its' highest level at 60 years, whereas in women DBP peaks 10 years later at the age of 70 years, whereafter DBP starts to decline (121, 129). Women have more isolated systolic hypertension, and some differences in the pathophysiology of hypertension have been discovered: women have more labile blood pressure, a higher rate of white coat hypertension, and they are more likely to have salt-sensitive hypertension, and high volume hypertension in comparison to men (129). Women also are subject to unique hypertension-inducing conditions, i.e. pregnancy, menopausal hormonal changes and usage of OCs. OCs may cause mild blood pressure elevation: in a cross-sectional survey from the United Kingdom low-dose estrogen containing OCs users had significantly ($p<0.001$ for both SBP and DBP) higher blood pressure values when compared to non-users; the difference was 2.3 mmHg in SBP mmHg and 1.6 mmHg in DBP between OCs users and non-users (130). However, blood pressure usually descends back to the normal range within 6 months after drug withdrawal. Pregnancy- and menopause-related changes in blood pressure will be described in more detail later in the chapter "Unique risk factors for women".

Globally, as many as 40% of adults have high blood pressure (14). In the United States, one out of three adults has high blood pressure (2). The prevalence of high blood pressure is higher among men than women before the age of 45 years old. After that, the prevalence hypertension is similar in both genders, and later after the age of 64 years, the prevalence becomes higher in women (2). In 1972 in North Karelia, the mean SBP was 149 mmHg in 30-59 year old men and 153 mmHg in similar aged women, and the mean DBP 92 mmHg in men and 92 mmHg in women. In FINRISK 2007 in subjects aged 30-59 years, the mean SBP was 138 mmHg in men and 130 mmHg in women, and the mean DBP 83 mmHg in men and 77 mmHg in women (12). Overall, blood pressure levels have declined in Finland since the 1970s (Figure 3). In the FINRISK 2012 survey, mean SBP among 25-64 years old participants was 134 mmHg in men and 127 mmHg in women; SBP has declined both in men and women from the year 2007 (131, 132). The mean DBP was 84mmHg in men aged 24-64 years and 78 mmHg in women of a similar age (131). In fact, DBP has increased in both genders since 2007 (132). The prevalence of hypertension (SBP ≥140mmHg or DBP≥90mmHg or medication to hypertension) has declined in both men and women from the 1980s, however that decline levelled off in the late 1990s. The prevalence of hypertension did not change between 2007 and 2012 in men, and in women hypertension

prevalence has not declined in the past 10 years (132). In FINRISK 2012, the prevalence of hypertension was 47% in men and 27% in women (132).

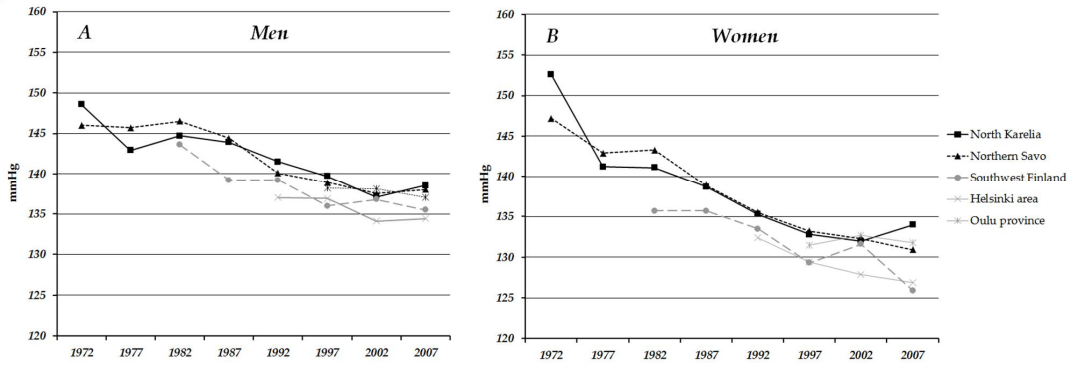


Figure 3. Mean systolic blood pressure levels in FINRISK areas between 1972-2007 among men and women aged 30-59 years old (19).

Smoking

Smoking is the second most important risk factor after dyslipidemia for MI, and one of the leading preventable causes of CHD in both genders (133). The INTERHEART Study estimated that 29% of all MIs in western Europe could be blamed on smoking (133). European Heart Network Statistics 2012 indicated that 20% of CVD deaths in men and 3% in women were due to smoking in Europe (1). ORs with 99% confidence interval (CI) for first MI and stroke due to smoking are shown in Table 9 and Table 10. In the Systematic Coronary Risk Evaluation System (SCORE) project, the 10-year risk of fatal CVD event is considered to be doubled in smokers in comparison to non-smokers (134).

Smoking does not only speed up the development of atherosclerosis, but it also is a major risk factor for coronary thrombosis and sudden death and this is true in both genders (135, 136). Smoking is known to display a dose dependent relationship with the MI risk: the OR for MI in individuals smoking 1-9 cigarettes per day was 1.63 (95% CI 1.45- 1.82) and those who smoked >20 cigarettes per day had a strikingly high OR of 4.59 (95% CI 4.21-5.00). A similar dose-dependence has also been reported in women. In the Nurses' Health Study, the women who were the heaviest smokers (>20 per day) had a 6 times higher risk for CVD compared to non-smokers (137). In fact, smoking has been found to be more detrimental in women than men: in a systematic meta-analysis analysing 2.4 million participants and 75 cohorts, the currently smoking women had a 25% increased risk for CHD compared to the currently smoking men (138). The smoking-associated CHD risk is postulated to be more harmful to younger people, and smoking has been reported as the greatest risk factor for MI in young, <45 years old subjects (139). In younger 35-39 year old subjects with non-fatal MI, 81% of men were smokers whereas only 45% of 60-64 years old subjects with the same condition were smokers. The corresponding numbers for women were 77% and 36% (140).

Regular exposure to secondhand smoke has also been shown to increase CVD risk by 15% in women (141). A population-based register study from the United States described a decline in MI incidence after the implementation of smoke free laws in workplaces (142). In addition to additive effects to other CVD risk factors, smoking has some gender specific

adverse effects: smoking decreases endogenous levels of estrogen and increases the risk for premature menopause.

In 1972 in North Karelia, 52% of men and 10% of women were smokers (12). Figure 4 shows the smoking prevalence in men and women in the period from 1972 to 2007 in the FINRISK areas. The proportions of never smokers has declined and ex-smokers have increased since then (19). However, in 2011 20% of Finnish adults still smoked on a daily basis. Smoking has declined among men, in 1990 32% of men smoked daily, compared to 22% in 2011. Historically, fewer women than men have smoked in Finland. However, the rate of decline rate has been slower for women: in 1990 20% of women were daily smokers, compared to 15% in 2011 (143). According to FINRISK 2012, the prevalence of smoking was 25% in men aged 25-64 years old and 20% in similar aged women (144).

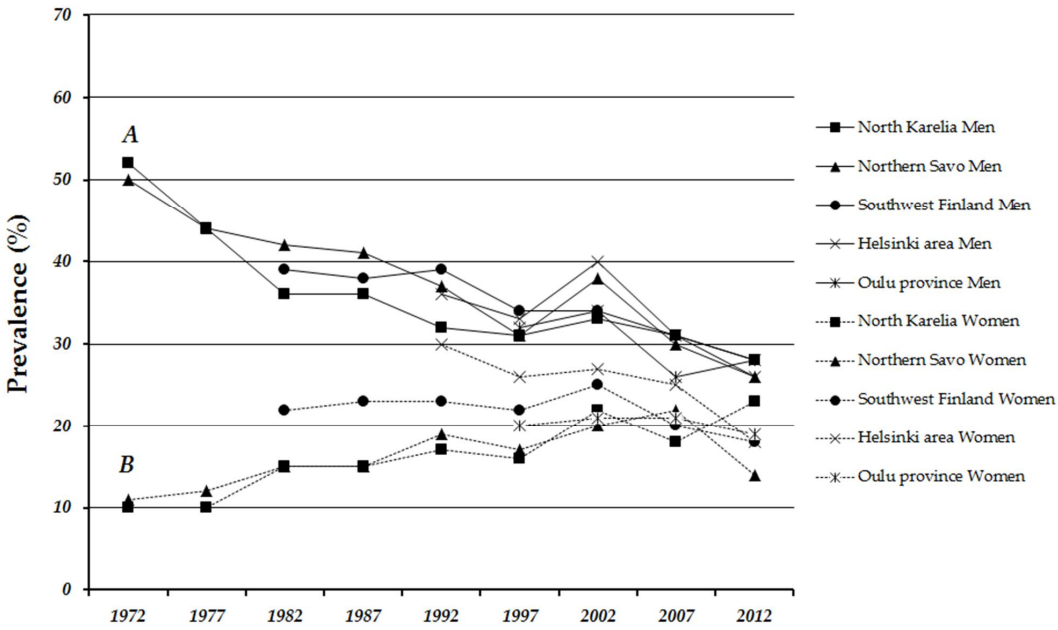


Figure 4. Smoking prevalence (%) in men (A) and women (B) aged 30-59 years between 1972-2012 in the FINRISK areas (19).

Diabetes

Diabetes is a major risk factor for CVD, and traditionally the risk for a CHD event or stroke is considered to be elevated by two to three fold in diabetic persons (14, 78, 145, 146). In type I diabetes, the CVD risk is almost entirely confined to patients with renal disease, whereas in type 2 diabetes, all patients display an increased risk (121). Subjects with diabetes also have poorer prognosis after an acute CHD event compared to their non-diabetic counterparts, and this prognosis is known to be worse among diabetic women than men with diabetes (14, 147). Diabetes is known to abolish the general gender-related difference in CVD risk and diabetes is considered to be more detrimental in women. In the Nurses' Health Study, age-adjusted RR for CHD mortality in diabetic women was 8.7 compared to healthy women and the RR for a fatal CHD event was 25.8 in women with

known CHD and diabetes in comparison to healthy women (148). In the INTERHEART study, which had a cross-sectional case control design, the OR for a CHD event was 4-fold among women and 3-fold among men with diabetes compared to subjects without diabetes (11). In the meta-analysis published by Huxley et al. the age-adjusted RR for CHD was 3.69 in women and 2.16 in men with diabetes. The RR was reduced to 3.12 in women and 1.99 in men after multiple adjustments for other risk factors: weight, hypertension and lipid abnormalities which often cluster in these diabetic persons (149). In the meta-analysis conducted by Huxley et al. the high RR for CHD morbidity among women was apparent even after these adjustments and women had a higher RR also for fatal CHD events (149). In the meta-analysis of Kanaya et al. the gender difference, not in favour of women, was related to the increased risk factor burden in diabetic women and thus the gender difference was not statistically significant after adjusting for other traditional risk factors (146). There has been a debate about, whether this difference is due to the higher prevalence of risk factors and co-morbidities among women with diabetes; the alternative is that gender has an independent effect on morbidity (146, 150). Some studies have also hinted at poorer risk factor treatment among women with diabetes in comparison to men (147, 150). Nevertheless, women with diabetes are known to suffer their first MI at the same age as men with diabetes, i.e. there is an evident risk for premature CHD (151).

According to WHO statistics, the prevalence of diabetes was 10.9% among adult men and 9.6% among adult women in Europe in 2008. It has been estimated that the prevalence of diabetes will increase by 20% until the 2030s (14). In the FIN-D2D survey in Finland, the prevalence of type 2 diabetes (established diagnosis) was 7.4% in men and 4.3% among women aged 45–74 years, and previously undiagnosed type 2 diabetes was found in an additional 8.3% of men and 6.9% of women. The prevalence of abnormal glucose regulation (high fasting glucose, impairment in glucose tolerance or type 2 diabetes) was very high; 42% in men and 33% in women (152).

Obesity, waist- hip ratio and the metabolic syndrome

Obesity increases the risk for CHD, stroke, heart failure and total CVD mortality in both genders, this being mainly attributable to the effect on other traditional risk factors, i.e. hypertension, type 2 diabetes and alterations in blood lipid levels (153, 154). The association of weight with CVD mortality has been shown to be J-shaped (154). Total CVD mortality is known to increase by 34% in men and by 29% in women with every 5 unit increase of body mass index (BMI) (154). The Nurses' Health Study reported that obesity increased CVD risk in a dose response manner, with the risk in the heaviest category (BMI $\geq$40 kg/m^2) being 3-fold higher than that of women in the leanest category (BMI in a range of 18.5-22.9 kg/m^2) (155). Waist-hip ratio, a marker of visceral fat amount, has been proposed to predict CVD risk better than BMI alone (156). Some cohort studies have suggested that an increase in waist-hip ratio increases CVD risk irrespective of overall body weight or BMI, and that there are gender differences depending on the evaluation method of obesity. (157, 158). In men, the waist-hip ratio was shown to be associated with increased CVD incidence only in normal weight men, and no additive effect of waist-hip ratio was seen among overweight or obese men, whereas in women, the CVD risk increased in parallel with the increasing waist-hip ratio irrespective of BMI (157, 159). In the INTERHEART study, abdominal obesity i.e. waist-hip ratio, was related to MI three times more strongly than when BMI was used as the variable (156). A large systematic meta-analysis of prospective studies, including 56% of women, revealed the equal importance of BMI, waist-hip ratio and waist circumference in prediction of CVD events (160).

The prevalence of obesity (BMI ≥30 kg/m²) has doubled during the past 20 years: in 1980 only 5% of men and 8% of women were obese worldwide, but in 2008 10% of men and 14% of women were obese (15). According to FINRISK 2012, the mean BMI was 27.1 kg/m² among working-aged men and 26.0 kg/m² among similar aged women in Finland, and thus 66.3% of adult men were overweight (BMI ≥25 kg/m²) and 20.4% were obese, similarly 46.4% of adult women were overweight and 19.0% were obese. Thirty-one percent of the working-aged men had a waist circumference > 100cm and 29.7% of women had a waist circumference >90 cm (161). Figure 5 shows the prevalence of obesity in FINRISK areas between 1972 and 2007.

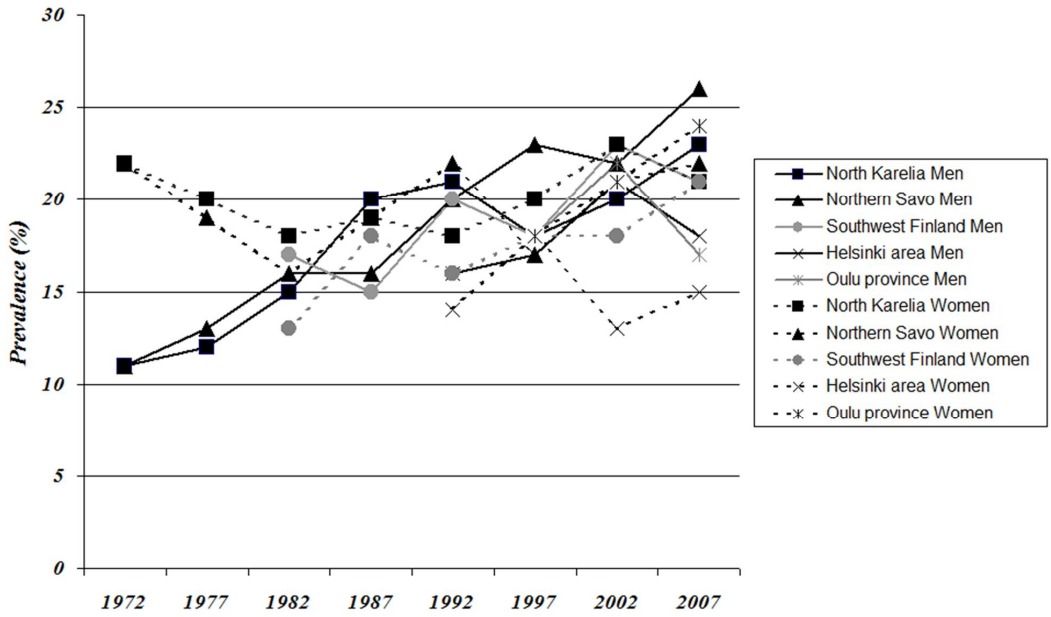


Figure 5. Prevalence of obesity (BMI ≥30 kg/m²) in FINRISK areas 1972-2007 in men and women aged 30-59 years (19).

The metabolic syndrome is a cluster of risk factors for CVD and type 2 diabetes. The metabolic syndrome includes central obesity (waist ≥94-102 cm in men and ≥80-88 cm in women), impaired glucose regulation, elevated triglyceride levels, reduced HDL and hypertension. Different clinical definitions for metabolic syndrome exist; of these the definition of NCEP-AT III is most often used in clinical work (121). It is controversial, whether metabolic syndrome predicts CVD risk more efficiently and independently than the individual components of metabolic syndrome. In the European action on secondary prevention through intervention to reduce events (EUROASPIRE) - study the prevalence of metabolic syndrome was 56% in women and 40% in men (162). In Finland, the prevalence of metabolic syndrome has increased significantly (P=0.003) among women from the year 1992 to 2002, from 32.2% to 39.1%, and non-significantly in men from 48.8% to 52.6% (163). It has been suggested that metabolic syndrome would be a stronger risk factor for CVD in women compared to men. In a meta-analysis by Agassi et al., the overall RR for CVD risk was 1.61 (with 95% CI of 1.42-1.83), and gender-specific analyses showed

a higher RR for CVD in women; 2.10 (with 95% CI 1.79-2.45) vs. 1.57 (with 95% CI 1.41-1.75) in men (164). Recently, metabolic syndrome has been suggested to associate with subclinical progression of atherosclerosis independently of hypertension, waist circumference, hyperlipidaemia, BMI and age, but only among women (165).

Physical activity

Regular physical activity and aerobic exercise training is associated with beneficial effects on cardiovascular health in both genders and all ages by reducing CVD and CHD mortality (166, 167). CVD prevention guidelines of the WHO recommend at least 2.5 hours of moderate physical activity (3-5.9 times the intensity of rest measured as energy expenditure) or 75 minutes of vigorous activity (≥6 times of intensity of rest measured as energy expenditure) per week for both genders (166, 168). The 2008 Physical Activity Guidelines for Americans have concluded that the physically most active persons enjoy a 30-35% risk reduction in developing CHD when compared to the least active individuals (14). The beneficial effect has been proposed to be somewhat stronger among women; Shiroma and Lee concluded in an evaluation of prospective cohort studies, that the median risk reduction was 40% among women and 30% among men when comparing those subjects with the least physical activity to those with the highest physical activity (169). Physical activity, especially good aerobic fitness, may reduce some of the increased risk of CVD events related to being overweight or obese (155, 170). The Women's Health Initiative indicated that for postmenopausal women brisk walking was as beneficial in risk reduction as more vigorous exercise (171). A systematic review showed a dose-dependency for the effects of physical activity: a 33% decline in CVD-related death for most active women and protective effects were seen for as little as walking 1 hour a week (172). Physical activity has been shown to have beneficial effects also among premenopausal women: it lowers the blood pressure, improves insulin sensitivity, increases HDL cholesterol and improves lipid profile by lowering total and LDL cholesterol (173). In addition to lowering the prevalence of obesity and type 2 diabetes, physical activity has also been shown to improve coronary blood flow and enhance endothelial function (174).

When asked: "How often do you exercise or play sports", 39% of participants in an EU survey answered never, and 21% responded that they exercised ≥3 times a week. At least once a week was reported by 43% of men and 37% of women. Regular non-sport activities (cycling, walking, gardening) were reported by 27% of men and women. When sufficient physical activity was considered as 30 minutes of moderate exercise 5 times a week, or 20 minutes of vigorous exercise 3 times a week, then it was found that 38% of Finnish adults could be considered to be insufficiently physically active; when divided by gender 41% of Finnish men and 35% of women exercised less than the amounts mentioned above (1).

Psychosocial stress

Depression has been the most commonly studied psychosocial stress factor, and observational studies have shown that depression increases the risk for incident CHD. A large meta-analysis reported the hazard ratio (HR) of depression for fatal CHD or MI of 1.81 (1.53-2.15) (175). This risk was greatly reduced, but still significant, after adjusting for traditional risk factors. The Women's Health Initiative detected a higher CVD mortality and all-cause mortality among postmenopausal women with depressive symptoms (176). A study of a Finnish cohort also pointed to a small increase in the RR of CVD events in women with depressive symptoms; the RR was 1.09 (CI 95% 1.06-1.11) when prevalent CVD was excluded and with adjustment for traditional risk factors, but no increase was

seen in men (177). Moreover, the Nurses' Health Study reported the strongest association of depressive symptoms with fatal CHD events, and this was mainly thought to be due to an increasing effect of antidepressant use and the risk of sudden cardiac death (178). The effect of psychosocial stress on CHD has also been studied. It has been believed commonly that work-related stress predicts CHD events in men, whereas stress at home and in relationships increases the risk in women. However, in a recent meta-analysis of 13 European cohort studies, work-related stress increased the risk of incident CHD events equally in both genders (age-and gender adjusted work-stress vs. no work-stress HR 1.23) (179). A comparable risk increase was also reported from another recent meta-analysis of 6 prospective cohort studies of general perceived stress: The RR for CHD event was 1.27 (95% CI 1.12-1.45) after adjustment for traditional risk factors (180). Stress was evaluated by assessing the level of stress in life in general with no difference being found between the genders (180). In the INTERHEART Study, psychosocial stress had a stronger impact on women´s CHD risk (11).

2.5.2 Coronary heart disease risk factors

The INTERHEART study was a large cross-sectional case-control study of 27 098 participants from 52 countries, 6787 of whom were women. Nine different risk factors explained >90% of acute MI events. The population attributable risk for these nine risk factors together was 96% in women and 93% in men (133). The ORs of these risk factors are shown in Table 9 for both genders separately and pooled. Current smoking was more strongly associated with MI in men than in women, but there was no statistically significant gender difference. When comparing the risk factor associations between younger (<60 years old) and older (≥60 years old) age groups in both genders, the INTERHEART study found a stronger association of traditional risk factors - ApoB/ApoA, hypertension, diabetes and current smoking - among younger women compared to older women. In men, ApoB/ApoA, current and former smoking, hypertension, and abdominal obesity, but not diabetes, were more strongly associated with acute MI among the younger age group than in the older age group (11).

In the Framingham cohort among persons aged 30 – 74 years, the RRs for CHD with the following risk factors were: hypertension 1.93 (95% CI 1.28-2.92) among men and 1.24 (95% CI 0.69-2.24) in women, diabetes 1.69 (95%CI 1.11- 2.57) in men and 2.38 (95% CI 1.40-4.06) in women, current smoking 2.65 (95% CI 1.77-3.97) in men and 2.07 (95%CI 1.60-2.68) in women, total cholesterol in the range of 5.0-6.1 mmol/l (when compared to subjects with cholesterol values in the range of 4.1-5.0 mmol/l) 1.77 (95% CI 1.23-2.50) in men and 1.55 (95% CI 0.81-2.96) in women (181). Moderate alcohol consumption was found to have a protective effect against CHD event (Table 9), but the effect of alcohol is known to be J-shaped (166). Women are recommended to limit alcohol intake to a maximum of one glass/day (10 g of alcohol), in men the limit intake is double, 20 g alcohol/ day (166).

Table 9. Factors that influence the risk of acute myocardial infarction according to INTERHEART study (11, 133)

Risk factor	OR (99% CI) [1]	OR (95% CI) [2]		
	Both genders	**Men**	**Women**	**p[3]**
Increasing risk				
ApoB:ApoA1 ratio	4.73 (3.93-5.69)	2.87 (2.63-3.13)	3.30 (2.85-3.82)	0.20
Smoking (current vs. never)	2.87 (2.58-3.19)	3.04 (2.84-3.26)	2.86 (2.47-3.32)	0.06
Psychosocial factors	2.67 (2.21-3.22)	2.58 (2.11-3.15)	3.49 (2.40-5.09)	0.02
Diabetes [4]	2.37 (2.07-2.71)	2.67 (2.43-2.94)	4.26 (3.68-4.94)	<0.0001
Hypertension[4]	1.91 (1.74-2.10)	2.32 (2.16-2.48)	2.95 (2.66-3.28)	0.0001
Abdominal Obesity	1.62 (1.45-1.80)	2.24 (2.08-2.42)	2.26 (1.98-2.57)	0.03
Decreasing risk				
Alcohol consumption ≥3 times a week [4]	0.91 (0.82-1.02)	0.88 (0.82-0.94)	0.41 (0.34-0.50)	<0.0001
Regular physical exercise [4]	0.86 (0.76-0.97)	0.77 (0.71-0.83)	0.48 (0.41-0.57)	<0.0001
Daily fruit and vegetable consumption	0.70 (0.62-0.79)	N/A	N/A	N/A

ApoB/ApoA1- ratio is given as a comparison of upper tertile to the lowest tertile. Abdominal obesity is gender specific and the odds Ratios (ORs) are for the comparison of upper tertile to the lowest tertile of waist-hip ratio. Individuals were considered to have psychosocial stress, if at least one of the stress components were present (i.e. depression, global stress, financial stress, locus of control or other stresses (separation, job loss, family conflict). Diabetes and hypertension were self-reported. Subjects were considered to be physically active if they did moderate (walking and cycling) / strenuous exercise ≥4 hours / week.

[1] Yusuf et al. Lancet 2004 (133)

[2] Anand et al. Eur Heart J 2008 (11)

[3] p- value for gender interaction

[4] There was a gender difference in the ORs and the risk predictors were more powerful among women

N/A indicates not available

2.5.3 Stroke risk factors

Established stroke risk factors are hypertension, hyperlipidaemia, diabetes, atrial fibrillation, MI, smoking, waist-hip ratio, metabolic syndrome, excess alcohol consumption and carotid artery disease (87). In the Framingham cohort, the RRs for stroke were 1.16 for 10 mmHg increase of SBP, 1.82 for atrial fibrillation, 1.41 for diabetes 1.41, and for smoking 1.69 (182). No gender-specific RRs were reported.

The INTERSTROKE study, which was an extension of the global INTERHEART study, evaluated global associations of traditional and emerging risk factors for stroke. INTERSTROKE was conducted in 2007-2010 in 22 different countries, with 3000 strokes matched to 3000 controls. A minority of the subjects (37%) were women (183). The stroke types evaluated were ischemic (78% of all strokes) and haemorrhagic (22% of all strokes) strokes; subarachnoid haemorrhages were excluded from this study (183). The ORs for strokes combined for both genders are shown in Table 10, as well as genderwise, when available. Hypertension was the strongest predictor of stroke, and it was more strongly associated with stroke among young (<45 years old) subjects with OR of 8.53 (99% CI 5.39-13.49). The population attributable risk for all strokes, both genders combined, was 80%

when five risk factors were included: hypertension, smoking, abdominal obesity, diet and physical activity. Population attributable risk for all stroke increased to 90.3% when hypertension, current smoking, abdominal obesity, diet, physical activity, diabetes, excess alcohol intake, cardiac causes and ApoB/A1 were taken into account (183). At present no gender-specific population attributable risk analysis from the INTERSTROKE data has appeared.

Table 10. Risk factors for stroke according to the INTERSTROKE study (183)

	Both genders OR (99% CI)	**Men OR (99% CI)**	**Women OR (99% CI)**
Increasing risk			
Hypertension	3.89 (3.33-4.54)	3.88 (3.22-4.68)	4.89 (3.79-6.32)
Cardiac causes	2.38 (1.77-3.20)	N/A	N/A
Smoking (current vs. never)	2.09 (1.75-2.51)	2.46 (2.02-3.01)	1.56 (1.03-2.36)
ApoB:ApoA ratio	1.89 (1.49-2.40)	N/A	N/A
Abdominal Obesity	1.65 (1.36-1.99)	1.25 (0.99-1.59)	2.70 (1.95-3.74)
Diabetes	1.36 (1.10-1.68)	N/A	N/A
Psychosocial stress	1.30 (1.06-1.60)	N/A	N/A
Decreasing risk			
Regular physical exercise	0.69 (0.53-0.90)	N/A	N/A
Increased consumption of fruit	0.61 (0.50-0.73)	N/A	N/A
Increased consumption of fish	0.78 (0.66-0.91)	N/A	N/A

Hypertension was defined as self-reported hypertension or measured blood pressure ≥160/90 mmHg. ApoB/ApoA1- ratio was based on a comparison of highest tertile to the lowest tertile. Abdominal obesity was based on the comparison of gender specific highest tertile to lowest tertile of waist-hip ratio. Individuals were considered to have psychosocial stress if at least one of the stress components was present (i.e. global stress, financial stress, locus of control or other stresses (separation, job loss, family conflict). Diabetes was self-reported. Cardiac causes included atrial fibrillation, flutter, previous myocardial infarction, rheumatic valve disease or prosthetic valve replacement. Subjects were considered as physically active if they did moderate (walking and cycling) or strenuous exercise ≥4 hours / week. N/A indicates not available.

2.5.4 Heart failure risk factors

Heart failure has various causes; CHD, hypertension, cardiomyopathies, valvular and congenital causes, infectious diseases, arrhythmias, cardiotoxic substances (for example alcohol, anthracyclines) but the most common cause is considered to be CHD. Data from NHANES in the United States showed CHD to have a 61.6% population attributable risk for heart failure (184). In the Framingham heart study, 59% of men and 48% of women had CHD and 70% of men and 78% of women had hypertension as the underlying aetiology for heart failure (185). Valvular disease was found in 31% of women and 22% of men (185). Diabetes and valvular disease were proposed to exert a stronger impact on women´s risk of heart failure in the Framingham cohort, however the gender comparison was not statistically evaluated (Table 11) (186). Among younger men (<65 years old), hypertension and diabetes were both separately associated with a 4-fold increased risk for heart failure, and among younger women (<65 years old) hypertension was linked with a 3-fold, and diabetes with a 8-fold risk for heart failure. Among older subjects these risk

factors remained associated with heart failure, although their impact was less dramatic (185).

Table 11. The impact of risk factors for developing heart failure in subjects without heart failure at baseline

	Both genders [1]*	**Men** *	**Women** *
Hypertension	1.40 (1.24-1.59)	2.1 (1.3-3.2)[2]	3.4 (1.7-6.7) [2]
CHD	8.11 (6.95-9.46)	4.63 (3.52-6.10) [3]	4.64 (3.42-6.31)[3]
Left ventricular hypertrophy	N/A	2.2 (1.5-3.2) [3]	2.9 (2.0-4.1)[3]
Diabetes	1.85 (1.51-2.28)	1.27 (0.90-1.79) [3]	4.17 (2.91-5.97) [3]
Obesity	N/A	1.90 (1.30-2.79)[4**]	2.12 (1.51-2.97)[4**]
Valvular heart disease	1.46 (1.17-1.82)	2.43 (1.73-3.41) [3]	3.47 (2.46-4.92) [3]

* Relative risk ** Hazard ratio [1] According to NHANES (184) [2] Mosterd et al. 2007 (187) [3] Kannel WB et al. 1999 (186) [4] Kenchaiah et al. 2002 (188)

2.5.5 Unique risk factors for women

In addition to the above presented traditional risk factors, women have some unique CVD risk factors, some of which are related to normal physiological female aging, such as menopause, some related to therapeutical interventions provided only for women, such as OCs and hormone replacement therapy (HRT), some related to disease conditions, such as polycystic ovary syndrome (PCOS), monosomal X-syndrome and some are related to pregnancy. Normal pregnancy and the peripartum period (= 6 weeks after delivery) increase the stroke risk by 2.4-fold (189). Normal pregnancy does not increase the CVD risk later in life. However, pregnancy complications such as pre-eclampsia, gestational diabetes, preterm labour and third trimester bleeding have been shown to increase the risk of suffering future CVD events (108). Women with pre-eclampsia in combination with poor fetal growth or intrauterine death are considered to be at the greatest risk (190). These risk factors should to be taken into account when evaluating the CVD risk in women (191).

Menopause

Menopause is determined as the loss of ovarian function, permanent cessation of menses for at least 12 months, and subsequent deficiency of endogenous estrogens (192). In Finland, the average age of natural menopause was 51 years in 2007, and the mean menopause age has increased during the last decade (193). CVD incidence is substantially lower among women than men during the fertile age, but CVD morbidity increases after menopause. Even though studies have failed to show abrupt changes in CVD morbidity rates at menopausal age, the hypothesis of protective effects of estrogen is generally accepted. The overall epidemiological evidence is controversial, as to whether the increased risk is caused by the age at menopause per se, or chronological aging itself which affects CVD risk; this is probably due to the alterations of ovarian function years before the actual menopause (=perimenopause). In the Nurses' Health Study, which was a prospective cohort study, women with natural menopause who had not taken estrogens did not have any increased risk for CHD when compared to premenopausal women (age and smoking adjusted RR 1.2; 95% CI 0.8-1.8) (194). A meta-analysis of 18 studies confirmed this result; pooled RR after adjustments for age and smoking was 0.96 (95% 0.77-1.12) (195). However, women with premature (<40 years old) or early menopause (<45 years old, affecting approximately 5% of the female population) have an increased risk for

death (RR 1.04; 95% CI 1.00-1.08), which is mostly due to the increased risk for CVD (196). Premature and early menopause increased the risk for CHD death by 80% in comparison to women with normal menopause (197). In a meta-analysis, early menopause exhibited an RR of 1.25 (95% CI 1.15-1.35) (195). In the Nurses' Health Study, surgical hysterectomy with bilateral oophorectomy among women under 45 years old increased the risk for fatal and non-fatal CHD event risk by 17% after adjustments for traditional CVD risk factors and the use of estrogen replacement therapy; the younger the age at the time of the surgery, the greater the risk was increased (198). The North American Menopause Society has recommended that subjects with early and premature menopause should receive estrogen replacement therapy until the median age of natural menopause. This recommendation is based on some beneficial findings, although not from randomized clinical trials, on estrogen's effects in relieving menopausal symptoms, preventing osteoporosis, and possibly also preventing in CVD and dementia (199).

Estrogens are known to have regulating effects on several metabolic factors, such as lipids, inflammatory markers, and the coagulation system. These sex hormones have a direct vasodilating effect through α- and β- adrenoceptors on blood vessel wall, and estrogen is also known to prevent coronary artery spasms (200). The loss of estrogen can evoke several disadvantageous changes in major CVD risk factors, as detailed in Table 12. The lipid profile is known to change to be more atherogenic after the menopausal transition i.e. an increase in total and LDL cholesterol levels, and changes in HDL to a smaller particle size have been shown to occur within one year after the last menstruation (201). This is considered to some extent to be due to the loss of estrogen's effect on hepatic apolipoprotein gene expression (200). Plasma cholesterol levels peak in women at the age of 55-65 years old (which is 10 years later than in men) (202). The changes in other CVD risk factors are more controversial. The prevalence of hypertension is higher in men of the same age when compared to premenopausal women; and after menopause, the prevalence of hypertension is greater among women than in men. According to the NHAHES data on 55 to 64 years old individuals, 56% of women and 47% of men had hypertension and a total of 75% of postmenopausal women were hypertensive in 1999-2002 (203). In addition to aging itself, the increase in blood pressure is considered to be due to changes (partly via unknown mechanisms) in the blood vessel walls, partly due to the effects of hormonal changes in renin-angiotensin-aldosterone-system, sympathetic nervous activity, and fat distribution (from gynoid to abdominal) (200, 203). The changes in blood pressure levels occur during the decade following after the menopause (203).

In women, the body fat distribution is linked to ovarian function, and thus the premenopausal gynoid fat distribution (hips and gluteus) changes to a android pattern (abdominal) after menopause. The weight gain after menopause, 0.5 kg annually on average, is due to aging rather than the menopause itself (204). Loss of estrogen is known to reduce glucose-induced insulin secretion, and to reduce peripheral insulin sensitivity (200), which are factors increasing the risk for impaired glucose intolerance and type 2 diabetes. It is not clear whether these changes and the elevated risk for metabolic syndrome and type 2 diabetes are indirectly caused by the changes in body fat composition, or by direct effects of menopause itself. However, changes in blood glucose levels have been shown to occur later, years after the menopausal transition (205).

While postmenopausal ovaries continue to produce small amounts of estradiol and estrone, they produce significant amounts of androgens: testosterone, androstenedione and dehydroepiandrosterone, which are converted to estrogen peripherally, which may

explain some of the differences seen in surgical versus natural menopause in CVD risk. Furthermore, testosterone levels, the estradiol-testosterone ratio and alterations in sex hormone-binding globulins may exert some consequences on metabolic activities and CVD morbidity (206). Further studies on menopause, hormonal changes and changes in risk factors are thus needed.

Polycystic ovary syndrome, PCOS

PCOS is a complex reproductive endocrine disorder characterised by ovarian dysfunction; oligo-or amenorrhoea, oligo/anovulation, hyperandrogenism and polycystic ovaries. Although the precise definition is still controversial (207). PCOS is one of the most common hormonal disorders among women; its prevalence is estimated to be 7-10% in the female population (208). Women with PCOS are affected by various metabolic disorders and risk factors for CVD including insulin resistance, metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, obesity and non-alcoholic fatty liver disease (209-211). Metabolic syndrome, a cluster of CHD risk factors, is common among PCOS women. A study by Ehrmann et al. found that ≥3 metabolic syndrome criteria were fulfilled in 33.4% of PCOS women (210).

A recent meta-analysis showed increased levels of potentially adverse vascular biomarker levels (CRP, homocystein) in PCOS women (212), and women with PCOS have been shown to exhibit more subclinical vascular disease than normal women (213). Although these risk factors are known to increase the risk for CVD and CHD events, evidence of PCOS's independent role as a CVD risk factor remains unclear. Wild et al. retrospectively studied women with PCOS in the United Kingdom from 1979 to 1999, and showed that despite their higher CHD risk factor prevalence compared to non-PCOS women, they had a similar CHD incidence and mortality: OR for CHD was 1.5 (95% CI 0.7-2.9). PCOS women had a higher rate of cerebrovascular disease (OR 2.8 with 95% CI 1.1-7.1) (214). Nevertheless, a recent consensus statement advised that PCOS women should be screened for glucose intolerance by an oral glucose tolerance test, and for dyslipidemia, and given advice about the benefits of weight control and a healthy lifestyle (215).

Table 12: *Direct and indirect consequences of estrogen and other hormonal or metabolic alterations in menopause, and subsequent systemic effects relevant to CVD health*

		Menopausal alterations	Systemic effects of hormonal changes menopause	Changes in CVD risk factors after menopause
Indirect changes	**Lipids**	Estrogen alters hepatic expression of apolipoprotein genes, reduces hepatic triglyceride lipase, and estrogen deficiency downregulates LDL receptors in liver(200)	Total and LDL cholesterol increases, HDL decreases(201)	An increase in LDL cholesterol by 0.05 mmol/l /decade in ages of 40-60 years (216). *Changes during early menopause, within 1 year*
	Blood pressure	Changes in RAA system and in autonomic nervous system (sympathetic tonus) (200)	Systolic and diastolic blood pressure increase	Hypertension prevalence is higher among women in postmenopausal years (203) *Changes within 1 decade after menopause*
	Glucose metabolism	Glucose dependent insulin secretion decreases, peripheral sensitivity decreases(200)		Increased risk for impaired glucose tolerance and type 2 diabetes *Changes within 5 years after menopause (205)*
	Weight gain	Fat distribution from gynoid (hips and gluteus) to android (abdominal fat) (204)	Weight gain of 0.5 kg / year (204).	Increased risk for metabolic syndrome
Direct changes	**Vasodilation**	Estrogen causes endothelium dependent (NO) vasodilation (200)	Vasoconstriction and increasing blood pressure	
	Coagulation	Estrogen affects hepatic gene expression of coagulation and fibrinolytic proteins (200)	Blood coagulation increases	
	Endothelial repair	Estrogen accelerates endothelial cell growth and rapid re-endothelization in response to injury (200)	Increasing injuries in endothelium	
		Estrogen inhibits vascular smooth muscle cell proliferation	Progression of atherosclerosis	

RAA indicates renin-angiotensin-aldosterone system and NO indicates nitric oxide.

Pre-eclampsia

Pre-eclampsia is a syndrome characterised by the appearance of hypertension and proteinuria after the 20th week of gestation, but the pathogenesis behind pre-eclampsia remains unknown. Pre-eclampsia is estimated to affect 3-5% of all pregnancies. However, eclampsia, i.e. the development of seizure(s) due to pre-eclampsia, is a rare complication in the western world (217). A meta-analysis by MacDonald et al. detected an increased CVD risk later in life among women with pre-eclampsia, 5-15 years after pregnancy; the RR for CHD was 2.33 (95% CI 1.95- 2.78), for cerebrovascular disease 2.03 (95% CI 1.54- 2.67) and for CVD mortality 2.29 (95% CI 1.73- 3.04) (190). The severity of pre-eclampsia increased the risk, such that those who had preterm delivery, poor fetal growth or fetal death, had the highest risk (190). CVD events have also been shown to occur early in life among pre-eclamptic women. Ray et al. found only a median of only 8 years after pre-eclamptic pregnancy, and the mean age of 38.3 years old for experiencing the first CVD event or revascularization (218). Recently, pre-eclampsia and other placental syndromes have also been connected to an increased risk for developing of heart failure later in life. Ray et al. analysed retrospectively 1 130 764 women having delivered, and the placental syndrome, mainly gestational hypertension and pre-eclampsia, was considered to have occurred in 75 242 women (6.7% of all women). After adjusting for traditional CVD risk factors and excluding those women with known CHD or thyroid dysfunction, the HR for heart failure and dysrhythmias was 1.51 (95% CI 1.26-1.80) and even higher in those women with preterm delivery or poor fetal growth (HR 2.42, 95% CI 1.25- 4.67) (219). It is unknown whether pre-eclampsia and other placental disorders independently increase the risk for CVD, for example by inducing harmful effects to entire vascular endothelial function, whether pre-eclampsia is an early presentation of CVD due to the similar risk factors shared by both pre-eclampsia and CVD, or whether it is a combination of both of these conditions (191, 220).

Gestational diabetes

Gestational diabetes is defined as any degree of glucose intolerance which is recognised for the first time during the pregnancy (221). Gestational diabetes is mainly caused by the pregnancy-related increase in insulin resistance. Gestational diabetes has been shown to affect 2-4% of pregnant women (222). In Finland, the prevalence of abnormal glucose values during pregnancy is increasing; in 2006, abnormal glucose levels were found in 8.4% of pregnant women, and insulin therapy was required in 2.1% cases, whereas in 2010, abnormal glucose levels were found in 11.2% of pregnancies (223). Gestational diabetes is diagnosed with an oral glucose tolerance test and fasting glucose ≥5.3 mmol/l, 1- hour glucose level ≥10 mmol/l or 2- hour glucose level ≥8.6 mmol/l are all considered abnormal (221). The oral glucose tolerance test is performed for all pregnant women in the 1st trimester if there is a known increased risk for gestational diabetes (such as obesity or PCOS), or more commonly in the 3rd trimester. Gestational diabetes is known not only to increase risk for pre-eclampsia and other pregnancy- and birth-related disorders, but it also has long-term consequences for both mother and infant. For example, gestational diabetes is a risk factor for developing diabetes: 20-60% of mothers with gestational diabetes develop type II diabetes in the future (224). Diabetes itself is a major risk factor for CVD, however, gestational diabetes also increases the risk for other CVD risk factors; obesity, hypertension, dyslipidemia and the metabolic syndrome (225). In a case-control study from Canada, women with gestational diabetes were at an increased risk for suffering future CVD events with a HR of 1.71 (95% CI 1.08-2.69); the increased CVD risk was mainly mediated by the increased risk of type 2 diabetes (226). Women with previous

gestational diabetes, independently of their current BMI and metabolic abnormalities, display more endothelial dysfunction and increased levels of inflammatory markers as well as subclinical atherosclerosis as assessed via the carotid intima-media thickness (227).

Gestational hypertension

Gestational hypertension refers to hypertension detected for the first time during the second half of the pregnancy without proteinuria. Blood pressure values are considered as high if SBP ≥140 or DBP ≥90 mmHg. Increased blood pressure is the most common gestational complication affecting 4-10% of pregnant women (228). A recently published cohort study of 12 055 women from northern Finland with an average follow-up of 39 years showed that gestational hypertension increased the subsequent risk for overall CVD, the HR being 1.45 (95% CI 1.29- 1.63), for CHD the HR is 1.44 (95% CI 1.24-1.68), for fatal CHD the HR is 3.00 (95% CI 1.98-4.00), for heart failure the HR is 1.79 (95% CI 1.43-2.21), for stroke the HR is 1.59 (95% CI 1.24-2.04) and for hypertension the HR is 2.53 (with 95% CI 2.25-2.84) even after adjustments for diabetes, smoking and socioeconomical status. The mean age of these events were low, 58 years for CVD events, 61 years for CHD, 67 years for fatal CHD events, 58 years for heart failure, 67 years for stroke and 50 years for hypertension (229). In this cohort, the prevalence of gestational hypertension was 17% of all pregnancies and of these, 30% had a CVD event before the late 6th decade, and 3% died of MI. The authors concluded that CVD risk assessments are needed later in life for women with hypertensive pregnancies (229).

Hormone-replacement therapy

Observational studies from the beginning of the 1990s suggested that estrogen hormone replacement therapy (HRT) might be beneficial for CHD prevention in women. A large meta-analysis combining these results showed that post-menopausal HRT was associated with a 37% risk reduction (RR 0.63, 95% CI 0.55-0.72) in fatal CHD, and estimated that this benefit of HRT would prevent more deaths than the increased risk of breast cancer and uterine cancer due to HRT might cause combined (230). At the same time, the American College of Physicians published counselling guidelines for postmenopausal women about preventive hormone therapy recommending HRT for women in order to prevent CVD (231). In the mid-1990s, the rationale was to recommend HRT, and the provision of estrogen was one of the criteria used to evaluate the quality of medical care (232).

The first randomised clinical trial aiming to evaluate the "benefit" of estrogen therapy was launched in 1993. The Heart and Oestrogen/progestin Replacement Study (HERS) aimed to evaluate whether conjugated equine estrogen (=CEE 0.625 mg/day) with medroxyprogesterone acetate (=MPA 2.5mg) therapy would reduce CHD events in women with prevalent CHD compared to placebo. The HERS included 2763 postmenopausal women (mean age 67 years old) with an intact uterus and known CHD. The trial was terminated in 1998 after an average follow-up of 4.1 years. No overall difference between the study groups was seen in the primary endpoint of nonfatal MI and CHD death combined (HR 0.99 95% CI 0.81-1.22). However, there were significant reductions in the LDL level and an increase in that of HDL. During the first study year, there was a 52% significant excess of CHD events in the HRT group (233). In addition to other critical comments raised from the HERS results, it was speculated about whether the HRT was started too late as the HERS subjects already had established CHD. The Women's Health Initiative was initiated to evaluate the effects of HRT in healthy postmenopausal women. In total, 16 608 women with a uterus were randomized into groups receiving either a CEE 0.625 mg/day plus MPA 2.5 mg or placebo. Another group

of 10 739 women without uterus were randomized to receive either CEE 0.625 mg without progesterone, or placebo. Due to safety reasons, i.e. risks exceeding the benefits, the CEE + MPA study arm was stopped after an average follow-up of 5.6 years. The increased risk for CHD was apparent almost immediately after starting the medication, as the HR for CHD was 1.29 (95% CI 1.02-1.63). Furthermore, only 2 years after the initiation of HRT; the stroke risk was elevated (HR 1.41; 95% CI 1.07- 1.85), and risks for pulmonary emboli and for breast cancer were also increased (7). The CEE only arm was stopped due to the increased risk for stroke, and with no benefits being detected for CHD after an average of 6.8 year follow-up (234).

Questions remained after these clinical trials, for example should the HRT regime doses should be lowered, whether the oral or transdermal administration route would be more effective, what are the correct formulas and hormone administering timing, what is the optimal total duration for HRT, and whether natural menopause is equal to the surgical salpingo-oophoroectomy. One particularly important topic was the timing of HRT after menopause; in most observational studies women were starting HRT soon after menopause to relieve menopausal symptoms. In the Women' s Health Initiative, the mean age of the women was 63 years, and it was estimated that only 10-17% of randomised women had started HRT within 5 years from menopause (235). Subsequent subgroup analyses of Women's Health Initiative have supported the hypothesis of timing; older women who had started HRT ≥20 years after menopause had an increased CHD risk HR 1.28 (95% CI, 1.03-1.58). Women starting HRT less than 10 years from menopause displayed no significant difference or excess in CHD events (235). However, the increased risk of stroke by HRT seemed to exhibit no difference with respect to HRT timing (236). The controversy regarding benefits and harms of HRT still remains unsolved. Basic research and animal models have suggested that HRT might prevent atherosclerosis and reduce CHD events. However, randomised clinical trials have shown a lack of benefit, or even harm associated with HRT use. Thus, today clinical recommendations do not support the HRT use as a means of CVD prevention, and the current clinical rationale is to use HRT in the lowest possible dose and as a short duration as possible, if needed to relieve menopausal symptoms (237).

Oral contraceptives

Combined estrogen and progestagen OCs are associated with an increase risk for thromboembolic events: MI, stroke, and venous thrombosis. The risk for venous thrombosis came apparent shortly after OCs came to market in the early 1960s. These first OCs contained many times higher estradiol doses (50-150ug/day) compared to modern OCs with an estradiol content on average of 20-30ug/day. Even with today's lower hormone dosage and more careful patient selection, a recent meta-analysis revealed a doubling of the risk for current use of low-dose OCs for CVD, OR for MI was 1.84 (95% CI 1.38- 2.44) and 2.12 (95% CI 1.56- 2.86) for ischemic strokes. With third-generation OCs, the risk for ischemic stroke was only apparent with OR of 2.03 (95% CI 1.15-3.57) (238). The Nurses' Health study found no connection of past use OCs with the risk of a suffering a CHD event (239).

Currently it is believed that there is little or no risk associated with the current use of newer generation OCs in healthy low-risk women. Women with increased risk for CVD, i.e. having hypertension, smoking, having diabetes, and (migraine for stroke), may experience a modest to highly significant increase in their CVD risk and OCs are contraindicated in these high risk groups, especially after the age of 35 years (240).

2.6 Total risk evaluation

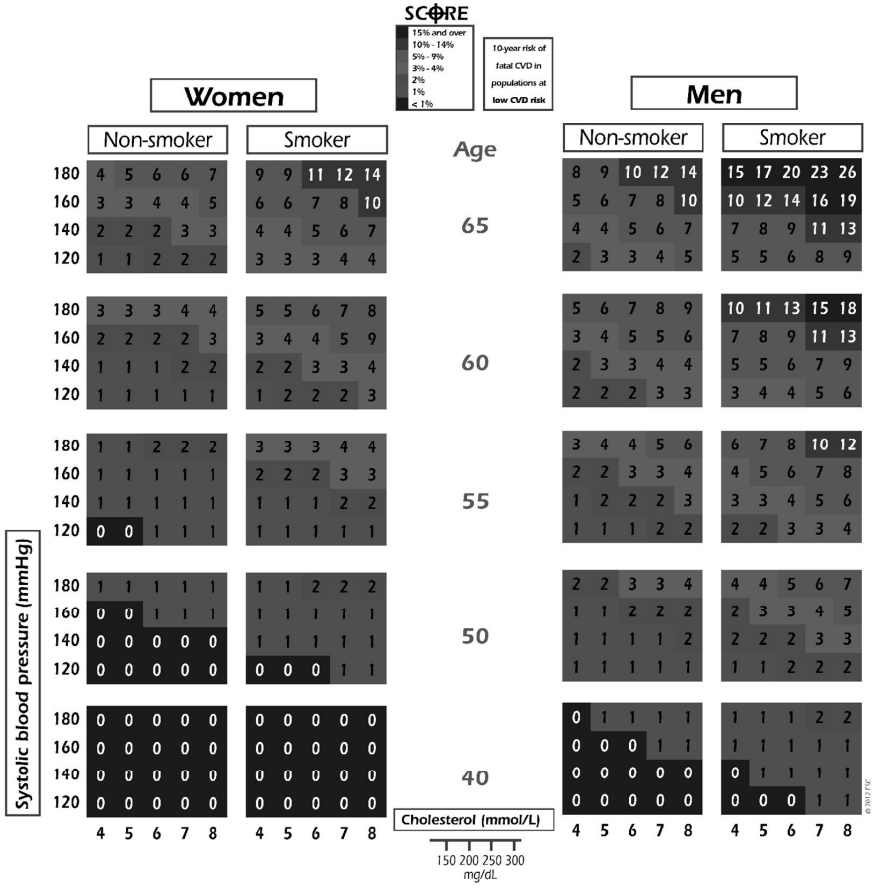
In Finland CVD prevention recommendations are based on the European Guidelines on Cardiovascular Disease Prevention (166). These guideline apply similarly to both genders and at the time of writing the latest version of ESC Guidelines on cardiovascular disease prevention in clinical practise appeared in 2012 (166). The AHA has published its own guidelines for women since 2007 with the latest update being published in 2011 (191).

The CVD risk evaluation is based on a total risk estimation, which is an estimated sum of several individual CVD risk factors acting additively together, predicting a person's future risk for suffering a CVD event over a given time period, e.g. 10 years. The current ESC guidelines recommend that risk factors should be screened from all men ≥40 years old and all postmenopausal or ≥50 years old women. The risk estimation should also be performed if a subject requests it, has a history of premature CVD in the family, or has at least one major risk factor, or the subject has symptoms suggestive of CVD, or has been diagnosed with obstructive sleep apnoea or erectile dysfunction. The total risk estimation is not needed in subjects with an established atherosclerotic manifestation or other manifestations listed in the very high risk group below, since they already are in high risk group for experiencing a CVD event due to these diseases.

The total risk estimation is based on different risk estimation charts with the most commonly used ones being the SCORE (Systematic Coronary Risk Evaluation System) and Framingham Risk evaluation (Figure 6), which are presented in more detail below (166, 241). The total risk can also be estimated using the FINRISK Risk function, which has been based on the FINRISK Survey years of 1982, 1987 and 1992 among 25 to 64 years old subjects. It estimates the absolute risk of having either a CHD event or stroke and the risk of these end-points combined during the next 10 years. The FINRISK risk function gives an estimation of person's total risk using data on gender, smoking, blood pressure, total- and HDL cholesterol levels, diabetes and family history. In FINRISK function, the risk is considered high if the total risk is ≥10% over 10 years. This corresponds approximately to the 5% risk in SCORE. The FINRISK risk calculator is available online (http://www.thl.fi/finriski-laskuri) (242).

The SCORE is based on data from 12 European cohort studies with 2.7 million years of follow-up and 7934 CVD deaths among 25-64 years old subjects. Different charts are recommended to be used in low-, and high risk countries. Previously Finland has been considered as a high-risk country, but currently the low-risk SCORE chart is recommended (166) for use in Finland (Figure 6). The SCORE evaluates a subject's total risk for having a fatal first event during next the 10 years using 5 different risk factors (age, gender, SBP, smoking and total cholesterol or total cholesterol/ HDL ratio). SCORE and ESC guideline recommendations subdivide the general population to four different risk categories (166).

A) Very high risk if the calculated SCORE is ≥10%, or the subject has documented atherosclerotic manifestation (CHD, stroke, peripheral artery disease, abdominal aneurysm) or revascularisation or type I or type II diabetes with either one or more CVD risk factors and/ or target organ damage such as microalbuminuria, or the subject has severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m^2).



CVD Points for Women

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic
−3				<120			
−2		60+					
−1		50–59			<120		
0	30–34	45–49	<160	120–129		No	No
1		35–44	160–199	130–139			
2	35–39	<35		140–149	120–129		
3			200–239		130–139	Yes	
4	40–44		240–279	150–159			Yes
5	45–49		280+	160+	140–149		
6					150–159		
7	50–54				160+		
8	55–59						
9	60–64						
10	65–69						
11	70–74						
12	75+						
Points allotted							Total

SBP indicates systolic blood pressure.

CVD Risk for Women

Points	Risk, %
≤−2	<1
−1	1.0
0	1.2
1	1.5
2	1.7
3	2.0
4	2.4
5	2.8
6	3.3
7	3.9
8	4.5
9	5.3
10	6.3
11	7.3
12	8.6
13	10.0
14	11.7
15	13.7
16	15.9
17	18.5
18	21.5
19	24.8
20	28.5
21+	>30

Figure 6. SCORE Low-Risk Chart, and Framingham Risk point charts. Reproduced with permission from Perk et al. Int J Behav Med 2012 (166), and Mosca et al. Am Coll Cardiol 2011 (191).

B) High risk if the calculated SCORE is ≥5% and <10%, or the subject has any substandially elevated single risk factor (for example familial dyslipidemia, severe hypertension), or diabetes mellitus type I or type II without CVD risk factors or target organ damage, or moderate chronic kidney disease.
C) Moderate risk: subjects with the SCORE index ≥1% to <5%.
D) Low risk: individuals who have <1% SCORE index.

The Framingham Risk algorithm is based on age, gender, total cholesterol, HDL cholesterol, smoking status, SBP, hypertension treatment and diabetes. These risk factors are "summed up", and the algorithm estimates the subject's total risk for either having an event, or for dying from a CVD event in the following 10 years. The Framingham risk chart is based on Framingham Heart Study and Framingham Offspring study of 3969 men and 4522 women aged 30-74 years with a follow-up of 12 years (241). The Framingham risk score divides subjects into 3 different risk categories for having an event in the next 10 years: low <10% risk, intermediate 10-20% risk, and high >20% risk. The high-risk in SCORE (≥5% risk) to die in 10 years equals the 10 to 25% Framingham risk depending on chosen risk function version in Framingham (166). In addition to the above risk categories, the AHA has adopted a concept of "ideal CVD health" which includes meeting the criteria of no smoking, having normal weight, optimal blood pressure, total cholesterol <5.0 mmol/l, fasting blood glucose <5.5 mmol/l and having a healthy lifestyle with recommended amount or more exercise (150 min/wk of moderate exercise or 75min/week vigorous exercise) and use of Dietary Approaches to Stop Hypertension (DASH) -like diet (fish 2 times a week, fruits and vegetables ≥4.5 cups a day, saturated fat <7% of total energy intake, alcohol ≤1 portion/day, sodium <1500 mg/day, no trans-fatty acids, nuts, legumes and seeds ≥4 servings/week, fiber 30g/day). Only 4% of women in the United States were estimated to fulfil these criteria of ideal CVD health (191).

The Framingham and SCORE risk algorithms suffer limitations in risk prediction in young subjects. These risk algorithms are intended to predict the absolute risk for having an incident CVD event (in following 10 years for example) and this is low in young persons. Nonetheless, those young persons with CVD risk factors (i.e. very high LDL or total cholesterol, smoking, blood pressure) may have a high RR for CVD event when compared to a healthy person of similar age. Since the development of the atherosclerosis behind CVD is a life-time continuum, different methods (RR chart, extrapolation to a higher age and the risk-age concept) have been developed to evaluate a younger person's risk and to help clinicians in advising about life-style choices. Using the risk age, a RR chart or extrapolating the risk to a higher age are not recommended for clinical use when considering medical treatment since this might lead to overmedication (166). The SCORE chart has been criticised that it may underestimate a woman's risk, as the absolute risk is substantially lower among premenopausal and early postmenopausal women when compared to men of similar age, and large increases in RR may not be taken into account. The SCORE may also underestimate the risk for subjects with abdominal obesity, premature CVD in the family, and for subjects with features associated with the metabolic syndrome (166). It has been suggested that women's risk evaluation should be extended to higher ages (70 years instead of 60 years old). However, extrapolation is recommended to be used only in life-style intervention (243).

Since most middle-aged individuals (especially women) falling into the low and intermediate risk groups, the additional risk evaluation methods (CRP, other biomarkers, family history, detection of subclinical atherosclerosis) have been proposed to be used for

re-evaluation of the person's risk score (166). Ridker et al. published a gender-specific risk score which included gender, age, SBP, smoking, CRP, total cholesterol, HDL cholesterol, family history of premature MI, and HbA1c if the subject had diabetes (244). This Reynolds Risk Score has been developed from two different gender-specific cohort studies; the Physician´s Health Study (10 724 men) and Women´s Health Study (24 558 women). The Reynolds Risk Score has been postulated to estimate a woman´s CVD risk better than other total risk estimation tools. However, the Reynolds Risk Score is a new risk estimator, and the role of CRP role in CVD prediction is not yet clear, and thus the Reynolds Risk Score needs to be further validated.

2.6.1 Cardiovascular disease prevention and treatment goals

CVD prevention has two complementary approaches. Population prevention strategies are intended to prevent CVD events in the whole population by affecting national health policies, legislation and health education. Population strategies are needed, because most events occur in those who have low-or moderate risk for CVD, simply because those groups are more numerous than the high-risk subjects. The total risk estimation is used in high-risk strategy to set treatment targets and to assist clinicians to target more aggressive treatments, including medications and more intense lifestyle support to those individuals with a high CVD event risk. Table 13 shows the treatment goals of the ESC at the population level, and specifically for the high and very high risk subjects (166).

Table 13. Treatment targets according to the European Society of Cardiology (ESC) Guidelines on cardiovascular disease (CVD) prevention in clinical practise in 2012 (166)

Treatment targets according to ESC Guidelines for CVD prevention (2012)	
For the general population	**For subjects with high or very high risk [1]**
No smoking	No smoking
Healthy diet	Healthy diet
Physical activity of 2- 2.5 h a week, preferably at least 30 minutes a 5 times a week	30 minutes of exercise ≥3 times a week
Avoid obesity, BMI[2] <25 kg/m^2	Avoid obesity, BMI <25 kg/m^2
Blood pressure <140/ <90 mmHg	Blood pressure in a range of 130-140/80-85 mmHg
Total cholesterol <5.0 mmol/l	Total cholesterol <4.5 mmol/l
LDL cholesterol <3.0 mmol/l	LDL cholesterol high-risk <2.5mmol/l , very high-risk <1.8 mmol/l
Blood fasting glucose <6.0 mmol/l	Blood fasting glucose <6.0 mmol/l HbA1c <7.0% and if safely possible HbA1c <6.5%
Avoidance of excess stress	

[1] Very high risk: Established coronary heart disease, stroke, peripheral artery disease or revascularisation, SCORE (Systematic Coronary Risk Evaluation System) ≥10%, type I or type 2 diabetes with either one or more risk factor, severe kidney disease and High risk: SCORE ≥5%, diabetes mellitus, elevated single risk factor or moderate chronic kidney disease

[2] BMI indicates body-mass index

2.6.2 Risk factor treatment among high-risk subjects for CVD

Women have been under-represented in most cardiovascular clinical drug trials. Nonetheless, some important observations on gender differences have been emerged from pooled meta-analyses. The ESC and AHA are trying to promote the enrolment of more women into drug trials and for gender-specific results to be published.

Blood pressure

The recommended blood pressure in the general population is below 140/90 mmHg. If SBP is >160 mmHg or DBP >100mmHg, antihypertensive medication is recommended. Lower blood pressure levels of 140/90 mmHg for starting the treatment are applied if the subject has diabetes, renal disease, has had a CVD event, or has signs of organ damage due to elevated blood pressure; in these cases, the treatment target for blood pressure is ≤130/80 mmHg and even lower target values are recommended, if renal disease is combined with proteinuria. It is known that lowering the SBP by 10 mmHg and DBP by 5 mmHg reduces the risk of stroke by 30-40% and acute coronary events by 16% over 5 years (166). The blood pressure treatment goals and medications recommended to lower blood pressure are similar in both genders (166). The major antihypertensive drug classes, i.e. diuretics, ACE inhibitors, calcium antagonists, angiotensin (AT) II receptor antagonists and beta-blockers, do not significantly differ in their blood pressure lowering efficacy and any of these can be used in the initiation of treatment of high blood pressure (166). ACE inhibitors are recommended as the primary choice for subjects with diabetes. ACE inhibitors and AT II receptor antagonists are contraindicated in pregnancy, and should be used with caution in women who may become pregnant (191).

According to the EUROASPIRE III study, carried out in 2006-2007 in 66 general practices in 12 European countries, 71% of patients had blood pressure above the target values (≥140/90 mmHg or ≥130/80 mmHg if diabetic). Furthermore, of those who had medication for hypertension, only 26% had achieved the blood pressure treatment goal (245).

Women with pre-eclampsia and gestational hypertension are known to have a doubled risk of suffering CVD events 5-15 years after pregnancy (246). The AHA guidelines for prevention of CVD in women recommend that a referral to primary care physician or cardiologist should be considered by the obstetrician in the postpartum unit in order to provide risk factor monitoring and control. The ESC guidelines for CVD prevention do not discuss gender-specific risk factors. The Finnish Current Care Guidelines for Hypertension in 2009 have recommendations for management of hypertension during pregnancy (247). However, these guidelines do not give recommendations for follow-up or total risk estimation for women who have had a hypertensive pregnancy.

Lipids

The goal is that there should be a total cholesterol level <5.0 mmol/l and LDL <3.0 mmol/l in the general population, with even lower values for those who are at high-risk. The recommended levels are similar for both genders (Table 13). The benefit of cholesterol lowering therapy depends on the total risk, and it has no gender-related differences. Medication, primarily a statin if possible, should be considered if life-style intervention is not sufficient to achieve the targets set by the total risk estimation in the primary prevention. Based on Collaborative AtoRvastatin Diabetes and Heart Protection studies, the ESC 2012 Guidelines recommend statins for subjects with diabetes in order to decrease

the CVD risk regardless of the baseline cholesterol, and the same principle is applied also for subjects with familial hypercholesterolemia (166).

In the EUROASPIRE III study 66% of the subjects had elevated total cholesterol (≥5.0 mmol/l and ≥4.5mmol/l in subjects with diabetes). An elevated total cholesterol level was found in 60% of men and 71% of women. Furthermore, only 31% of subjects with lipid-lowering medication achieved the total cholesterol treatment goals (<5.0 mmol/l or <4.5 mmol/l if diabetes). The recommended total cholesterol values were achieved by 40% of men compared to 29% of women. Statins had been prescribed for 47% of subjects with hyperlipidemia. 2.6% were using fibrates and 2.7% were taking other lipid-lowering drugs (245).

Smoking

Cessation of smoking decreases the risk for thrombosis in the short-term, and CVD risk approaches the risk of never-smokers in 10-15 years although without ever quite reaching the same level. The guidelines advise that all smokers, regardless of gender or age should be encouraged to quit smoking and non–smokers should avoid passive smoking. Firm and explicit advice from a physician will increase the odds of success in the cessation process. Nicotine replacement therapy has been shown to be more effective when compared to abstinence (166).

In the EUROASPIRE surveys I-III the prevalence smoking has remained at almost 20%. In the latest EUROASPIRE III, 17% of high-risk subjects were smokers. Smoking prevalence was 23% in men and 13% in women (245). The proportion of female smokers under 50 years of age has increased from EUROASPIRE I 1995-1996 to EUROASPIRE III in 2005-2006 (245, 248).

Diabetes

Glycemic control in diabetes reduces microvascular complications and it has a lowering effect on the macrovascular complications of diabetes in both genders (166). The 2012 ESC Guidelines set a general glycemia target of HbA1c <7.0% (<53 mmol/mol) to prevent CVD. A further reduction in HbA1c below 6.5% may be useful at the time of diagnosis. For patients with long-term diabetes, this target may be useful in prevention of microvascular complications, but strict glucose control achieved rapidly during a few months has been shown to be detrimental if the baseline HbA1c has been >7.0% (166). Metformin is recommended as the first-line therapy if tolerated and not contraindicated (166). Glucose-lowering drugs have no gender-specific recommendations. However, women may have a higher risk of fractures in long-term use of thiazolidinediones, and this effect needs to be further investigated (9).

In the EUROASPIRE III the prevalence of self-reported diabetes was 30%, and the prevalence of previously undetected diabetes was 13%. Only 7% of self-reported diabetic subjects achieved the recommended fasting glucose level ≤6.0 mmol/l, and 40% had HbA1c ≤6.0 mmol/l (245).

Acetylsalicylic acid

Whether acetylsalicylic acid has a beneficial effect in patients without established CVD (although at high-risk for CVD events) has remained unclear. Furthermore, the effect of acetylsalicylic acid on CVD prevention has been shown to exhibit gender differences. In the Antithrombotic Trialist`s Collaboration study, acetylsalicylic acid achieved a 12% risk

reduction in vascular events, but no change in stroke and no effect on total CVD mortality. Moreover, major gastrointestinal and extracranial haemorrhages increased significantly, by 0.03% per year. A meta-analysis by Berger et al. of 6 randomised controlled trials with >95 000 subjects detected a 12% reduction in CVD events with a 17% reduction in stroke, no effect on prevention of CVD death or MI events in women. In men, acetylsalicylic acid reduced CVD events by 14% with a 32% reduction in MI, but it exerted no effect on stroke or total CVD mortality (249). The reason for this gender difference in the effects of acetylsalicylic acid is unclear.

The ESC 2012 Guidelines do not recommend acetylsalicylic acid for persons without established CVD due to the increased risk of bleeding (166). The recommendation of acetylsalicylic acid use has been revised from the previous guidelines and acetylsalicylic acid is no longer recommended in the primary prevention of subjects with diabetes due to the excess risk of bleeding complications (166). The AHA Guidelines for Prevention of CVD in Women - update 2011, still recommends acetylsalicylic acid for women with diabetes, unless contraindicated, and also for ≥65 year old women in ischemic stroke and MI prevention if blood pressure is under control; it is believed that the benefits of stroke prevention outweigh the risk of bleeding (191). Routine use of acetylsalicylic acid is not recommended by AHA guidelines for <65 year old women (191).

2.6.2 Risk factor treatment among subjects with CVD

Blood pressure
The target level of blood pressure for subjects with established CVD is recommended to be near 130 /80 mmHg. Multiple drugs are often required to achieve this target. Beta-blockers are recommended for all patients, unless contraindicated, with established CHD during the hospital stay and their use should be continued thereafter. ACE inhibitors are recommended to be administered during the first 24 hours after the MI and their use should be maintained thereafter, unless contraindicated (166).

Beta-blockers were prescribed equally to both genders according to an interview conducted in EUROASPIRE III in the subjects with CHD: 81% of women and 79% of men had been provided with beta-blocker treatment after hospitalisation. Women had a lower rate of ACE inhibitor use compared to men (59% vs. 60%, p=0.01), whereas more women had angiotensin II receptor antagonist (15% vs. 11%, p <0.0001). Women were also more likely to have received calcium antagonists and diuretics. Despite the greater drug use among women, their mean blood pressure was higher than that of the men, and the proportion of women above the recommended blood pressure target was higher in comparison to the men: 55% of women and 49% of men had blood pressure levels ≥140/90 mmHg (p=0.010)(250).

Smoking
Giving up stop smoking after MI is considered to be the most effective of all preventive measures, similarly in both genders, with a mortality benefit of 36% (HR 0.64 with 95% CI 0.58-0.71). Subjects with prevalent CVD should be recommended to avoid passive smoking. Medications and therapies follow the same principles as in high-risk subjects.

In the EUROASPIRE III 19% of men and 11% of women hospitalized due to CHD were current smokers (p=<0.0001 for gender difference). According to the data from EUROASPIRE III advice to stop smoking was given equally in both genders (250).

Lipids

A 1 mmol/l reduction in LDL cholesterol is considered to be associated with a corresponding reduction of 20-25% in CVD mortality and non-fatal MI events (166). The target level for LDL is <1.8 mmol/l or a reduction by ≥50% is the aim if that target cannot be achieved (Table 13). High-dose statin treatment is recommended to be started early in subjects hospitalised with ACS. Blood lipids should be controlled after 4-6 weeks and the medication or dose should be changed if the target is not achieved. Statin treatment should also be started for subjects with a history of non-cardioembolic ischemic stroke or transient ischemic attack, for secondary prevention. Guidelines recommend avoiding statin treatment after hemorrhagic stroke unless there is evidence of atherosclerotic disease or of a high CVD risk (166).

In the EUROASPIRE III study, statins were prescribed equally in both genders among subjects with CHD and thus almost 80% of men and 76% of women received a statin in the secondary prevention. Nonetheless, the management of high cholesterol was better among men: 61% of women and 52% of men had not achieved the LDL cholesterol target of ≤2.5 mmol/l (p <0.0001), and women also had higher LDL cholesterol on average (250).

Acetylsalicylic acid and other antithrombotic drugs

The current ESC guidelines recommend dual antiplatelet therapy with ticagrelor or prasugrel to be added to acetylsalicylic acid in the acute phase of ACS and to be continued for the following 12-months, unless contraindicated due to a high risk of bleeding. Previously, clopidogel was recommended to be added with acetylsalicylic acid: however, prasugrel and ticogrelor have been shown to be more advantageous without causing significantly more bleedings when compared to clopidogrel (166). Continuing the treatment with acetylsalicylic acid only is recommended after one year from the event. The Antithrombotic Trialist's Collaboration meta-analysis showed that the total mortality was reduced by 10%, and furthermore the absolute risk for CHD and stroke was reduced, but major bleedings were increased. Nevertheless, the benefits of acetylsalicylic acid exceeded the bleeding hazards (166). In patients with prior non-cardioembolic ischemic stroke either dual therapy with dipyridamol and acetylsalicylic acid, or clopidogrel alone is recommended. In cases of intolerance for dipyridamol or clopidogrel, acetylsalicylic acid is recommended alone (166).

In the EUROASPIRE III study among subjects with established CHD, acetylsalicylic acid and other antiplatelet treatments were prescribed significantly (p=0.03) less frequently to women than to men (88% women vs. 91% men) (250).

2.6.3 Heart failure treatment

Heart failure treatment goals are intended to relieve symptoms, and to reduce mortality and hospital admissions. The ESC 2012 Guidelines for heart failure treatment do not have any gender-related issues with all recommendations being the same for men and women (93). The recommended therapy is based on whether the person has HF-REF or HF-PEF. In heart failure with reduced EF, the treatment is based on beta-blockers, ACE inhibitors, mineralocorticoid receptor antagonists and diuretics. The pooled data on beta-blockers

have shown that they decrease mortality among both genders having heart failure (251). There is believed to be less benefit with ACE inhibitors in women than in men. In an analysis of 30 clinical ACE inhibitor trials, men were shown to display a 37% decrease in heart failure mortality compared with the 22% (non-significant) decrease among women (252). The reason for the lesser benefit for women is unclear, and needs further investigation. Nevertheless, the recommendation for ACE inhibitor usage is similar in both genders and guidelines indicate that one should add an ACE inhibitor to the beta-blockade for all subjects with reduced EF ≤40% (93). Mineralocorticoid receptor antagonists/ aldosterone receptor antagonists are recommended to be provided to subjects with persistent symptoms after treatment with beta-blockers and ACE inhibitors (93). Aldosterone-antagonists have not been shown to exert different efficacies in men or women; survival benefits have been similar. The effect of diuretics on mortality and morbidity in heart failure has not been evaluated. However, diuretics relieve heart failure symptoms, and are therefore recommended for heart failure patients for this reason.

No treatment has yet been shown to reduce mortality and morbidity among subjects with HF-PEF. The ESC guidelines encourage the use of diuretics to reduce symptoms, and it is recommended that there should be adequate control of hypertension and myocardial ischemia (93).

In the EUROHEART Failure Survey II no gender differences were reported in the use of ACE inhibitors and beta-blockers upon hospital admission due to heart failure. Women had a higher rate of receiving digitalis treatment compared to men (prevalence on admission 29.1% in women vs. 25% in men, OR 1.34 with 95% CI 1.13-1.60). At discharge no gender differences were seen in the drug usage between the genders: approximately 90% of both genders were using diuretics, 70% of both genders were on ACE inhibitors, and 60% of both genders received beta-blockers (96).

3 Aims of the Study

The main aim of the study was to investigate gender differences in the occurrence, prognosis and risk factors of acute manifestations of CVDs. Secondary analyses were performed in different age groups to evaluate the differences between younger and older women as compared to men. The specific aims of the individual studies were:

(I) To examine whether declines in the incidence, attack rate and mortality of ACS have been different among women than in men in Finland from 1994-1996 to 2000-2002 and, secondarily, whether the use of troponins in the diagnosis of ACS has changed the proportions of MI diagnoses between the genders.

(II) To examine gender differences in the case-fatality of ACS and changes in case-fatality from 1994-1996 to 2000-2002 using three time windows: pre-hospital case-fatality, 28-day case-fatality and 1-year case-fatality.

(III) To examine whether cardiovascular risk factor levels and treatment of high cardiovascular risk differ between the genders.

(IV) To examine gender differences in the incidence and clinical spectrum of the first major adverse cardiovascular disease events, i.e., CHD, stroke and heart failure, among subjects with no previous CVD events.

4 Material and Methods

4.1 Data sources, registers and register linkage

4.1.1 Administrative registers and register linkage

Hospital Discharge Register (HDR)
In Finland, all hospitalisations have been collected in a nationwide register since 1967. The National Institute for Health and Welfare maintains the register (253). The register collects data primarily for administrative purposes. It includes data on the hospital and its ward, the patient's discharge diagnoses, surgical procedures, dates of the hospital admissions and discharges. The hospitalisations are coded according to the International Classification of Diseases and Health Related Problems -codes (ICD codes). The first diagnosis listed is the principal cause of hospitalisation, and up to three additional codes are registered. Clinicians responsible for the patients' care assign both the diagnoses and ICD codes for the hospitalisations. In Finland, the 8th version of the ICD was used from 1968 until 1986, the 9th version used from 1987-1995 and since 1.1.1996 the 10th version has been used.

Causes of Death Register
Causes of Death register (CDR) is maintained by Statistics Finland. Data from death certificates has been collected in Finland since 1936 (254). If a person has been treated in a hospital or in an outpatient clinic, the physician responsible for the patient's care at the time of death defines the diagnosis for the cause of death and assigns the corresponding ICD codes in the death certificate, or decides whether autopsy is required for determining the causes of death. The death certificate has the following strict format: the main causes of death are categorised into a.) the immediate cause of death, b.) intermediate cause of death, and c.) the underlying cause of death. Thereafter, other causes which have contributed to the death, but have no causal connection to the main responsible causes (a-c) are determined. Death certificates are inspected by local health authorities at the Regional State Administrative Agencies, and since 2010, the certificates have been sent to the National Institute for Health and Welfare, where they are inspected, and indefinite cases are further evaluated by a specialist in forensic medicine. Once accepted, the data are sent to Statistics Finland and are further checked for completeness from the Population Information System. An autopsy has to be performed, if the circumstances preceding the death are unclear, the death was unpredictable regarding the existing clinical condition, the causal relationships of the illnesses are unclear, or if the death has occurred suddenly or in a public place without preceding significant illnesses.

Drug Reimbursement Register
The National Insurance Institute (KELA) maintains a drug reimbursement register (DRR). Information on the persons entitled to drug reimbursement has been collected and registered since 1964. Special reimbursements are available on medicines for severe and long-term diseases, and are granted if certain disease-specific indications are fulfilled. The physician responsible for patients care writes a medical certificate based on signs, symptoms and medical findings, and based on the certificate, a physician in the National Insurance Institute decides whether the reimbursement will be granted. The National

Insurance Institute also registers pharmacy data using anatomic therapeutical classification (ATC) codes. All prescribed drugs purchased by patients have been registered in the pharmacy database since 1995.

Register linkage
All permanent residents in Finland have a unique personal identity (ID) code. A system of unique personal identification numbers was launched in 1964 and by 1968 all permanent residents and Finnish citizens had been allocated their own numbers. The Finnish Population Register Centre and the Local Register Offices maintain the Population Information System and admit the ID codes. Computerised data from the administrative registers has been available since 1969 (HDR, CDR and DRR (since 1964), Pharmacy database (1995) and Population Information System) and can be linked based on the personal ID code. The ID code includes a character for internal validity check, which minimises the risk of registering a faulty personal ID. The HDR register has been validated frequently. Also the register linkage between the HDR and MI register FINAMI has been validated and showed to improve: in 1991 0.26% of the personal ID codes were imperfect, and in 2002 less than 0.08% of codes were incomplete. None of the personal ID codes in CDR were imperfect (255). Register linkage between the HDR and CDR showed less than 0.5% of ID codes to be incomplete and in 0.2% (358 cases during the years 1991-2001) of deaths did the date of death differ between the HDR and CDR (38). The National Cardiovascular Disease Register (CVDR) links data from the HDR, CDR, and from National Insurance Institute. After linkage, the data are added to the CVDR database and anonymised. The CVDR summary data are available at the website of the National Institute of Health and Welfare (http://www.thl.fi/cvdr/). In the FINAMI register, collected data are cross-checked for completeness with the HDR and CDR using the personal ID numbers. The FINRISK database has been linked to all of the above mentioned administrative databases from the year 1969 onwards. Further characteristics of the CVDR, FINAMI and FINRISK databases are described in the following paragraphs.

4.1.2 Cardiovascular disease registers

FINAMI-register
The FINAMI register is a population-based register aiming to evaluate all events suspected to be a MI event or CHD death among permanent residents of the four study areas. The FINAMI register follows similar procedures as the FINMONICA MI register, which was the Finnish contribution to the WHO MONICA Project, which operated in Finland in 1983-1992 (256). The FINAMI register covers the following geographical areas: The city of Turku in south-western Finland, the city of Kuopio in eastern Finland, the city of Joensuu and surrounding rural areas of Ilomantsi, Juuka and Lieksa in the former province of North Karelia and the city of Oulu in north-western Finland. Oulu joined the register later, and has collected data for the years 1993, 1997, 1999, and 2001 – 2007. Due to practical reasons and workload, the Kuopio area lacks data for the year 1998 and Turku for the year 1999. This is not believed to have any effect on these results since the beginning and the end of the monitored time interval are included. All other areas and years have been covered since 1993. Data from on the persons older than 75 years have been registered since 1995. The average population at risk aged ≥35 years in FINAMI areas was ~ 313 000 in the study periods 1993-2002.

The FINAMI register's primary sources for case finding are hospital admission diagnoses and death certificates of each area. Trained nurses, supervised by register physicians, collect the information from hospital documents, death certificates and autopsy reports onto a data collection form on a laptop. Local registration teams send the data to the coordinating centre at the National Institute for Health and Welfare in Helsinki, where data are checked for logical errors. Data are cross-checked annually with CDR and HDR for completeness. The ICD codes used in FINAMI case finding and cross-checking with administrative registers are shown in Table 14. Events that are not included in the register are sent back to the local registration teams which evaluate the event according to the study protocol for possible inclusion in the register.

In FINAMI the ACS events were classified into diagnostic categories according to symptoms, signs, biomarker and ECG findings, and in fatal cases also according to the autopsy findings using the guidelines as suggested in the AHA Scientific Statement in 2003 (257). The classification categories for non-fatal MI were 1) definite MI, 2) probable MI, 3) possible MI, 4) non CHD event. Fatal events in hospital circumstances are classified as 1) definitive fatal MI, 2) probable fatal MI and 3) possible fatal coronary event 4) non-CHD death and in out-of-hospital circumstances 1) definitive fatal MI, 2) definitive fatal CHD, 3) possible fatal CHD, 4) non-CHD-related death. The biomarkers in each case (if taken) were determined according to the usual practice in each register hospital. The concentrations of troponin T or I were classified as diagnostic, normal or missing on the basis of the limits set by the laboratory of the hospital in question. The local register physician evaluated the clinical relevance of troponin value from the clinical information. If the troponin value was considered to be non-relevant (for example because of kidney failure, or because of false timing of sampling) it was recorded as missing. Other biomarkers (CK, CK-MB and CK-MBm) were classified according to the principles of the WHO MONICA Project using the limits set by the local laboratories (258). The time period for one event was considered to be 28 days, during which the most severe findings were recorded.

The FINAMI register has been approved by the ethical committee of the National Institute for Health and Welfare.

National Cardiovascular Diseases Register (CVDR)

The CVDR has been set up to cover the whole Finland and identify all Finnish residents with a CHD event or cerebrovascular disease event. The register has been compiled using data from three different nationwide administrative data sources (presented above); HDR maintained by the National Institute for Health and Welfare, CDR maintained by Statistics Finland and National Insurance Institute´s records on individuals receiving reimbursements for CVD medications. The National Institute for Health and Welfare in Helsinki maintains the register. At the time of this present study, CVDR data were available for the years 1991-2007. Data on hospitalisations due to CHD in the HDR were linked to the CDR using personal ID numbers. ICD codes used for case identification in the CVDR are shown in Table 14; all codes were accepted as main or side diagnosis. ICD-9 and ICD-10 coding systems were used in Finland during the study periods. The corresponding codes from the ICD-8 were used for identification of prior cases. In fatal cases, the CVDR included CHD, if the codes were as an underlying or as an immediate cause of death, or if MI (ICD-9th version code 410 or ICD-10th version I21-I22) was identified as a contributing cause of death.

Table 14. International Classification of Diseases (ICD) -codes used in substudies (I-IV) for case definition from different registers and time periods.

	ICD-9* 1986-1995		ICD-10 since 1996	
		STUDY I		
FINAMI and CVDR				
Nonfatal CHD events[1]				
	410[2]	Acute myocardial infarction	I200[2]	Unstable angina pectoris
	4110[2]	Unstable angina pectoris	I21[2]	Acute myocardial infarction
			I22[2]	Subsequent myocardial infarction
Fatal CHD events[1]*	410[2]	Acute myocardial infarction	I20	Unstable angina pectoris
	411	Other acute and subacute forms of ischemic heart disease	I21	Acute myocardial infarction
	412	Old myocardial infarction	I22	Recurrent myocardial infarction
	413	Angina pectoris	I23	Certain complications of recent acute myocardial infarction (Heart ruptures and bleedings due to acute myocardial infarction)
	414	Other forms of chronic ischemic heart disease	I24	Other acute ischemic heart diseases (Dressler´s syndrome and coronary occlusion without infarction)
			I25	Chronic ischemic heart disease
			I46	Asystole (Cardiac arrest)
			I461	Unspecified sudden cardiac death
			I469	Unspecified cardiac arrest (asystolia)
	798 (not 798A)	Sudden death with unknown origin (not sudden infant death syndrome)	R96	Sudden death with unknown origin
			R98	Unwitnessed death
		STUDY II		
FINAMI and CVDR				
Fatal CHD events[3]	410-414, 798 (not 798A)	see above	I20-I25, R96, R98, I461, I469	see above
		STUDY III #		
Hospital Discharge				

Register (HDR)				
		Study III # continued		
	ICD-9* **1986-1995**		**ICD-10** **since 1996**	
CHD	410, 4110	see above	I200, I21-I22	see above
Stroke	431	Intracerebral hemorrhage	I61	Intracerebral hemorrhage
	4330A	Basilar artery occlusion with infarction	I63 (not I636)	Ischemic stroke (not nonpyogenic cerebral venous thrombosis)
	4331A	Carotid artery occlusion with infarction		
	4339A	Occlusion of other pre-cerebral artery with cerebral infarction		
	4340A	Occlusion of cerebral arteries with cerebral infarction	I64	Stroke, not specified as haemorrhage or infarction
	4341A	Cerebral embolism with cerebral infarction		
	4349A	Occlusion of cerebral artery non-specified with cerebral infarction		
	436	Acute but ill-defined cerebrovascular disease		
Diabetes[4]	250	Diabetes mellitus	E10	Type I diabetes
			E11	Type II diabetes
			E12	Diabetes mellitus due to malnutrition
			E13	Other diabetes
			E14	Unspecified diabetes
		STUDY IV[5]		
National Hospital Discharge Register, Causes of Death Register, National Drug Reimbursement Register				
Nonfatal CHD events	410, 4110	see above	I200, I21-I22	see above
Fatal CHD events	410-414, 798 (not 798A)	see above	I20-I25, I46, R96, R98	see above

	ICD-9* 1986-1995		ICD-10 since 1996	
		Study IV[5] continued		
Stroke	431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436	See above	I61, I63-I64, (not I636)	See above
Heart failure[6]	42700	Oedema cardiac origin	I50	Heart failure
	42710	Acute pulmonary oedema		
	4029B	Hypertensive heart disease with heat failure	I110	Heart failure due to hypertension
	4148	Other definite ischeamic heart diseases, including heart failure	I130	Hypertensive heart failure with kidney disease
	428	Heart failure	I132	Heart and kidney failure due to hypertension

* ICD-9 and ICD-10 coding systems were used in Finland during the study periods. The corresponding codes from ICD-8 was used to prior case identification in studies I, II and IV.

[1] ICD codes used for cross-checking the FINAMI register data from Causes of Death register and Hospital Discharge Register to evaluate the completeness of data.

[2] ICD codes used for cross-checking the Cardiovascular Disease Register database from Hospital Discharge register.

[3] Deaths in which listed ICD codes were mentioned as underlying or immediate cause of death and also deaths where MI was a contributing cause of death (ICD-10: I21-I22, ICD-9: 410). Except for ICD-10 codes: I46, R96, R98 which were included only for immediate cause of death.

[4] Diabetes was also considered if the subject was entitled to reimbursement for diabetes medication or the subject had purchased drugs prescribed for diabetes least 3 times since 1995 to the end of the follow-up. However, drugs bought for gestational diabetes were not considered here. For prevalent diabetes, also self-reported information was considered.

[5] Subjects with prior CVD event were identified using these ICD codes from Hospital Discharge Register and excluded from the follow-up. Incident events during the follow-up were obtained from the above mentioned registers.

[6] In study IV a heart failure event was also considered if subject was entitled to drug reimbursement for heart failure or the subject had purchased at least 3 times furosemide since 1995 to the end of the follow-up.

Coronary revascularisations were identified using the codes of the Nordic-Medico-Statistical Committee or earlier with the codes of the Finnish Hospital League.

Similarly to FINAMI, the time period for one event was 28 days. The CVDR and the underlying administrative databases have been validated repeatedly (255, 259). CVDR has shown to have 83% sensitivity and 90% of positive predictive value against the FINAMI register with the AHA 2003 definition (255).

The CVDR has been approved by the ethical committee of the Institute for Health and Welfare.

FINRISK

The National FINRISK Survey aims to monitor the levels of cardiovascular risk factors in Finland (12). FINRISK is a population-based health examination survey, which has been conducted at five year intervals since 1972. The first two surveys were carried out in North Karelia and Kuopio provinces as the basis for evaluation of the North Karelia Project (260). Between the years 1982 and 1992, the surveys were conducted as a part of the WHO MONICA project (18). During the years 1992-2007, the study has been carried out in four geographical areas in Finland: North Karelia and Kuopio provinces in eastern Finland, Turku and Loimaa areas in South-western Finland and the metropolitan area of Helsinki and Vantaa in Southern Finland. The fifth area, Oulu province in North-western Finland, has been included since 1997. In 2002, the province of Lapland was also included.

The FINRISK survey is a cross-sectional study: In each study-year, a sex and 10-year age group stratified random sample of inhabitants have been drawn from the Finnish Population Information System. In 1992, subjects aged 25-64 years were invited to the survey. In 1997, similarly, 25-64 years old persons were invited, although not in two areas: North Karelia and the metropolitan area of Helsinki-Vantaa, where the age-range was 25-74 years and the number of 65-74 year old men was twice the number of participants in the other strata. Since 2002, subjects aged 25-74 years have been included in the survey in all areas. Sampling has been stratified according to sex, 10-year age group and study area. Between the years 1992 and 2002, 250 subjects in each sex and 10-year age group have been sampled from each study area. In 2007, the corresponding number was 200. Table 15 shows sample size separately in men and women, and participation rates percent to health examination.

Table 15. Samples and health examination participation rate (%) of men and women aged 25-64 years old in 1992-2012*.

Year	Men (n)	Participation rate (%)	Women (n)	Participation rate (%)
1992	3965	72	3962	81
1997	5000	68	5000	75
2002	4972	59	4980	70
2007	3983	56	3979	66
2012	3960	52	3961	60

* Including North Karelia, Kuopio provinces, Turku/Loimaa, Helsinki/Vantaa and Oulu province.

The methodology has been kept as similar as possible over the study years. The WHO MONICA protocol has been used since 1982, although in 2002 the methodology was revised to comply with some detailed recommendations from the European Health Monitoring Project (258, 261). Risk factor information was collected from a self-administered questionnaire, and from a clinical examination including physical

measurements and laboratory tests. The questionnaire and invitation to the health examination were sent by mail to the subjects. Specially trained nurses carried out the blood sampling and physical measurements in local health centres or other survey sites. Blood pressure was measured from the right arm after a ≥5 minutes' rest using a mercury sphygmomanometer. The first phase of Korotkoff sounds was recorded as the SBP and the fifth phase as the DBP.

Blood sampling has been done in a comparable manner over the study years. Venous blood samples have been drawn with the subject in a sitting position after at least 4 hours of fasting between 11 am and 6 pm. Samples were centrifuged in the survey site and mailed daily for total cholesterol, HDL cholesterol and triglyceride measurements to the laboratory of the National Public Health Institute. In 2007, the sera was frozen and sent packed in dry ice to the laboratory once a week. The total cholesterol concentration has been measured using an enzymatic method since 1982. In 2007, serum total cholesterol was measured using an enzymatic assay (Abbott Diagnostics Europe, Wiesbaden, Germany). LDL cholesterol has been obtained indirectly, using the Friedewald equation: LDL cholestrol (mmol/l) = Total cholesterol (mmol/l) - HDL cholesterol (mmol/l) – 0.4545 x (Triglyceride (mmol/l). The equation is considered to be valid if the triglyceride level is <4.52 mmol/l. The laboratory methods, reagents and instruments have been described in detail elsewhere (262).

Smoking was assessed by a questionnaire based on the subjects' answers. Current smokers were defined as those who had smoked regularly ≥1 year. Ex-smokers were those who had smoked regularly, but had stopped 6 months or more before the survey and never smokers were those who had never smoked regularly. Physical activity was assessed by a self-administered questionnaire. Low physical activity was defined as no leisure-time physical activity, or less than 4 hours of light physical activity (e.g walking) per week.

The FINRISK surveys were each approved separately by the local ethics committee at National Institute for Health and Welfare, Helsinki, Finland and/or the coordinating ethics committee of the Helsinki and Uusimaa Hospital District.

FINRISK cohort follow-up

Participants of the FINRISK surveys are followed up (since FINRISK 2002 only if the participant has given written informed consent) by annual record linkage by the participants' personal ID code to the HDR, CDR and DRR of the National Insurance Institute. New CVD events during the follow-up are identified using the case definitions explained in detail below with the ICD codes being followed shown in Table 14.

4.1.3 Definitions of events and covariates in the registers

Diagnoses in the HDR, CDR and CVDR are recorded using the ICD codes. In FINAMI the completeness of data are checked using the ICD codes for case finding from HDR and CDR.

MI event classifications in FINAMI

ACS diagnosis is based on symptoms, ECG findings, and elevation of biomarkers, and in the fatal cases on autopsy findings using adapted AHA case definitions (257).

Non-fatal events

A. **Definitive MI.** Evolving ischemic changes in ECG *or* diagnostic biomarkers

B. **Probable MI**. Positive ECG findings + cardiac symptoms or signs+ missing troponin *or* positive ECG findings and equivocal enzymatic markers
C. **Possible MI**. Equivocal enzymatic markers + nonspecific ECG findings *or* equivocal enzymatic markers + cardiac symptoms or signs *or* missing troponin or enzymatic markers + positive ECG
D. **Non-CHD event.**

Fatal events (hospitalised patients)

A. **Definitive fatal MI.** Death within 28 days of hospital admission and defined as definitive before death *or* post-mortem finding consistent with MI in 28 days
B. **Probable fatal MI**. Death within 28 days of hospital admission and defined as probable before death *or* death within 6 hours of hospital admission with cardiac symptoms and/or signs. Other confirmatory data (biomarkers, ECG) are absent or not diagnostic.
C. **Possible fatal coronary event.** Death within 28 days of hospital admission in cases defined as possible before death *or* defined as UAP when alive (new cardiac symptoms with positive ECG findings with normal biomarkers, changing symptom pattern and positive ECG findings with normal biomarkers *or* stable angina when alive (cardiac symptoms in a pattern that remains constant in presentation, frequency, character and duration over time) *or* post-mortem findings show old infarct and / or ≥50% atherosclerotic narrowing of coronary arteries.
D. **Non-CHD event.**

Fatal events (out of hospital)

A. **Definitive fatal MI.** Documented definitive, probable or possible MI within the previous 28 days and no evidence of non-coronary cause of death, or autopsy evidence of coronary occlusion or MI <28 day old.
B. **Definitive fatal CHD.** Either: A) History of CHD and /or documented cardiac pain within 72 hours before death and no evidence of non-coronary cause of death in autopsy; B) Autopsy evidence of chronic CHD, including coronary atherosclerosis and myocardial scarring.
C. **Possible fatal CHD.** ICD codes classified in Table 14 and no evidence of non-coronary cause of death.
D. **No CHD-related death or insufficient information.** Evidence of non-coronary cause of death or insufficient information to determine whether the death was a CHD death or a non-cardiac death.

Incident event

Incident event means the first event for the patient in question. In the FINAMI register, an event was considered as incident, if hospital records or other documents did not show any previous clinically recognised CHD events in the patient's history. In CVDR, an event was considered as incident if that person had no record of ACS in the HDR during the preceding seven years. The most severe diagnosis during the 28-day period was used.

All events

The time frame for one event was 28 days. If a patient had recurrent symptoms and signs within this time frame, they were considered to belong to the same event. New symptoms and signs >28 days after the onset of the previous event were considered as a recurrent event. The same ICD codes as for the incident events, listed in Table 14, were used for recurrent events. The attack rate was calculated as the sum of incident and recurrent events i.e. all events during a specified time period and in a specified population.

Fatal events
An event was considered as fatal if the patient died within 28 days after the onset of the event and the cause of death (immediate, underlying or contributing cause of death) was any of the ones listed above (Table 14).

Case-fatality
Case-fatality is defined as the proportion of fatal events from all events within a given time period. The 28-day period for one event was defined according to the WHO MONICA Project (33). The day of symptoms' onset was defined as day 0, and the last day was the day 27 after the onset of symptoms. The pre-hospital case-fatality was defined as the proportion of cases which did not reach a coronary care unit or hospital ward alive. These subjects died either in out-of-hospital circumstances or in the emergency room. In calendar time, their survival was less than one day. In-hospital deaths were considered to occur after the incoming phase to a hospital, in calendar time during the days 2-27 after symptom onset. In practice, deaths occurring after the discharge from a hospital but within the 28-day time frame were also included in the in-hospital case-fatality. The 1-year case-fatality was the proportion of events that ended fatally at any time from the beginning of symptoms to the end of the 364 th day.

High-risk subject
In study III, a person was considered to have a high risk of CVD if he/she had had either a prior diagnosed CVD event (see diagnoses detailed in Table 14), had a revascularisation, i.e. percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) in the HDR, had prevalent diabetes, or had a calculated CVD risk $\geq$20% based on the Framingham risk function (241). The Framingham risk function adopted from (241) was used in this study. Beta-coefficients used in the Framingham equation were estimated from FINRISK data using Cox proportional hazards regression.

Hypertension
The diagnosis of hypertension was defined in study III as the use of antihypertensive medication according to the self-administered questionnaire, or blood pressure ≥140/90 mm Hg or ≥130/80 mmHg if the subject had diabetes.

Diabetes
The diagnosis of prevalent diabetes was defined in study III as either self-reported or confirmed from the HDR (Table 14), pharmacy database for purchase of hypoglycaemic drugs and from the DRR if the subject had the right to special reimbursement for diabetes.

High cholesterol
In study III, among high-risk subjects (Framingham 10-year risk ≥20%, prevalent CVD or diabetes) cholesterol was considered high if the total cholesterol concentration was >4.5 mmol /l and/or LDL cholesterol >2.5 mmol/l (263).

Smoking
Smoking was assessed by a questionnaire based on the subjects' answers. Persons who had smoked regularly ≥1 year and during the past 6 months were considered as current smokers. Ex-smokers were those who had smoked regularly and had quit >6 months before the survey, and never smokers were those who had never smoked regularly.

Heart failure
Heart failure was identified in study IV from the HDR and CDR using the ICD codes shown in Table 14. Heart failure cases were also identified from the DRR of the Finnish National Insurance Institute. If a participant was entitled to special reimbursements for heart failure medications, he/she was considered to have heart failure or if a participant had at least 3 times purchased furosemide since 1995 to the end of follow-up in study IV he/she was considered to have heart failure. This definition of heart failure has been recently validated and found to have high specificity, but only modest sensitivity (264).

4.2 Study population in different studies (I-IV)

Study I
ACS events were collected from the FINAMI and CVDR for two time periods, in 1994-1996 (prior troponins) and 2000-2002 (post-troponins). A total of 4586 (2370 among men and 2216 among women) CHD events were found from the FINAMI register among persons aged ≥35 years for the time period 1994-1996 and 5564 (2882 in men and 2682 in women) for the time period 2000-2002. Correspondingly, a total of 72 699 CHD events (38 849 in men and 33 850 in women) were found from CVDR in the first period, and 76474 (39 860 in men and 36 614 in women) in the later time period. The total numbers of events are shown by event type, study period and gender in Table 1, Publication I.

Study II
A total of 6342 incident ACS events were found from the FINAMI register for two time periods, 1994-1996 and 2000-2002, combined and 117 632 from the CVDR. The numbers of incident events and fatal events are shown in Table 1 of Publication II.

Study III and IV
The participation rates in FINRISK survey are shown in Table 15. Some baseline characteristics of the participants in the FINRISK surveys are shown in Table 16.

Study III were included those FINRISK participants for whom the relevant risk factor measurements were available, i.e. clinical evaluation done and total cholesterol measurements. A total of 13 991 men and 15 281 women aged 25-74 were included. Of these, 3057 high-risk men and 1365 high-risk women were identified when the FINRISK survey years of 1992, 1997, 2002 and 2007 were pooled together. The numbers and the mean ages of groups are shown in Table 1 of Publication III.

In study IV, a total of 13 999 men and 15 286 women who had given permission for record linkage of their examination data to the national health care registers were included. Subjects with a prior major adverse CVD event (MI, stroke or heart failure) found from the HDR (n=1388, 936 men and 452 women) were excluded from the follow-up. Thus, 13 063 men and 14 834 women who were healthy at the time of baseline investigation were followed- up until the end of 2010.

Table 16. Characteristics of participants in the FINRISK surveys

		Men					Women			
	Total	1992	1997	2002	2007	***Total***	1992	1997	2002	2007
All subjects with relevant risk factors available (Study III[1])										
25-54 years old	***8820***	2137	2490	2560	1633	***10348***	2399	2827	3142	1980
55-74 years old	***5171***	707	1735	1439	1290	***4933***	781	1336	1483	1333
All subjects participated and allowed register linking (Study IV)										
25-54 years old	***8825***	2137	2490	2557	1641	***10353***	2399	2827	3138	1989
55-74 years old	***5174***	707	1735	1439	1293	***4933***	781	1336	1481	1335
All high-risk subjects[2]										
25-54 years old	***451***	102	125	136	88	***384***	73	99	127	85
55-74 years old	***2606***	297	968	680	661	***981***	95	279	281	326
10-year risk >20% according to Framingham score										
25-54 years old	***107***	31	30	37	9	***3***	0	1	1	1
55-74 years old	***1900***	215	746	472	467	***553***	43	152	150	208
Subjects with prevalent CVD[3]										
25-54 years old	***163***	38	43	51	31	***82***	10	29	30	13
55-74 years old	***773***	95	272	209	197	***370***	38	110	121	101
Subjects with diabetes[4]										
25-54 years old	***273***	52	81	78	62	***361***	70	89	118	84
55-74 years old	***636***	64	199	148	225	***511***	59	142	144	166

[1] Equal to the total participant number in study III

[2] Framingham 10-year risk >20%, history of any of the following: CHD, stroke, diabetes

[3]In study III. History of any of the following: myocardial infarction, revascularisation, stroke or heart failure.

[4] Prevalent CVD not excluded

4.3 Statistical methods

Data analyses were performed with SAS software, version 8 (study I) and version 9 (studies II-IV) (SAS Institute Inc, Cary, NC, USA) or R version 2.5.1 (study I), version 2.9.2 (studies II, III) or version 2.14 (study IV) (R Foundation for Statistical Computing, Vienna Austria). Statistical significance was based on the level of p <0.05 and two-tailed tests. Age-group specific analyses were performed for two different age groups: younger, 25-54 years old, and older, ≥55 years old.

In study I, all FINAMI areas were pooled together. The Oulu area had data for the years 1993 and 1997 in the first period and 2001-2002 in the later study period. All other study areas had full three year time periods of 1994-1996 and 2000-2002. The incidence rate was defined as the number of first events per 100 000 persons per year. The attack rate was

defined as the sum of incident and recurrent events per 100 000 persons per year. Age-standardisation for event rates was conducted according to the direct method using 5-year age groups and the European standard population *(http://seer.cancer.gov/stdpopulations/)*. The population counts used for the denominators of the event rates were obtained from the Finnish National Population Information System. The 95% CIs for the event rates were calculated assuming a Poisson distribution for the annual number of events. In FINAMI, the significance of changes of age-adjusted rates for both genders separately were done using 100 000 simulated Poisson-draws from each age group and using direct age standardisation to obtain representative samples for both time periods and both genders. In CVDR, this was not needed as the differences between study periods were self-evident.

In the FINAMI and CVDR the comparisons of the gender differences in the event rate changes were done using negative binomial regression models, as Poisson regression models showed overdispersion. The models for incidence, mortality and attack rate were adjusted for age in 5-year groups with gender interaction and the comparisons of trends being conducted using interaction terms with the effect of the year in two age groups <55 years and ≥55 years separately. The relative differences in event trends between the genders in two time periods were normalised by their respective rates during the first study period.

In study II, all FINAMI areas were pooled and the same time periods were used as in study I. Age-standardisation for incident ACS case-fatality was done using weights based on the combined age distribution of cases in the MI and stroke registers of the WHO MONICA Project. Weights (beginning from the age group 35-39 years old and ending with the age group of 85+ years old) were for each 5-year age groups: 5, 9, 16, 26, 42, 56, 75, 93, 100, 100, 100. The case-fatalities were expressed as percents: the number of deceased cases were divided by the number of all incident cases and multiplied by 100. Logistic regression analyses were used to evaluate gender differences in the pre-hospital, 28-day and 1-year case-fatality and Cox proportional hazards regression analyses in the 28-364 day time interval. In all regression models the study period (later vs. earlier), sex (as baseline difference women vs. men), history of diabetes and its interaction with sex (men=0, women=1) were used as explanatory variables. In the Cox regression analyses, the entry was day 28 after the onset of the event and non-fatal events were censored at the day 364. Deaths due to causes other than CHD were censored at day of death.

In study III data from all FINRISK study regions and survey years 1992, 1997, 2002 and 2007 were pooled. Logistic regression analyses were used to test the significance of gender differences for discrete risk factors and linear regression for continuous risk factors. Models were adjusted for baseline age and study area (East: North-Karelia, Kuopio, Oulu vs. West: Helsinki-Vantaa and Turku-Loimaa).

In study IV, data were similarly pooled as in study III and the same survey cohorts were analysed. The age-standardisation for event rates was done similarly as described above in study I. Event rates were compared using male/ female ratios. They were obtained by dividing age standardised incident event rates in men by event rates in women. To investigate the effect of age, all male/female comparisons were repeated separately for the younger (25-54 years) and the older (≥55) age group. The 95% CIs of age-adjusted rates and rate ratios were calculated using methods described in (265).

5 Results

The gender-specific age effect was linear with 5-year age groups with a significant ($p<0.001$) change point (interaction) in women at the age of 55-59 years old (Figure 7).

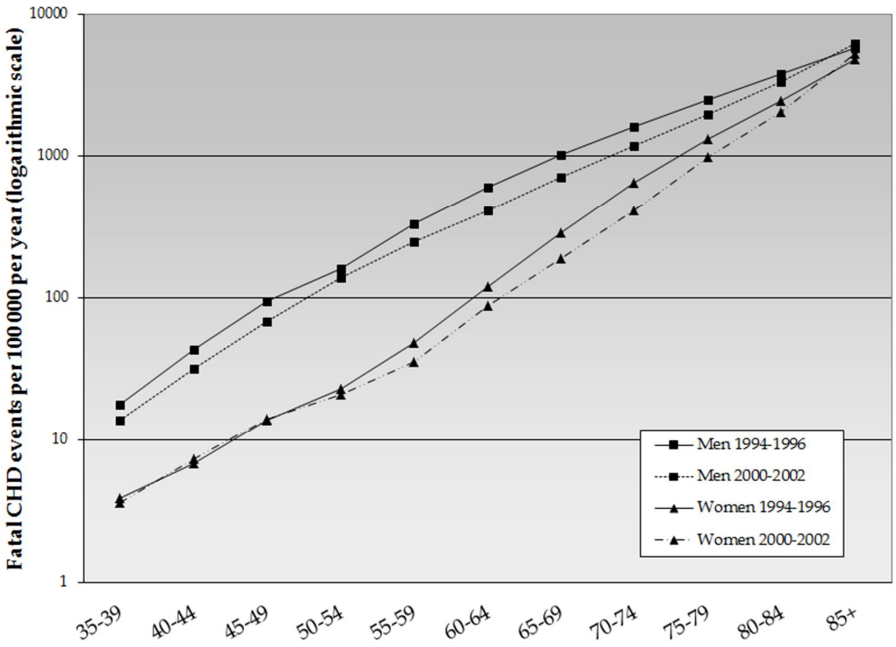


Figure 7. Fatal coronary heart disease (CHD) events in 5-year age groups per 100 000 inhabitants per year in men and women in 1994-1996 and 2000-2002 in the Cardiovascular Disease Register (CVDR). In the logarithmic scale a straight line corresponds to a multiplicative effect on the relative risk (RR). Unpublished data from study I.

5.1 Gender differences in the incidence-, mortality-, and attack rates of ACS from 1994-1996 to 2000-2002 (Study I)

The gender differences in average age-standardised ACS incidence, mortality and recurrent event rates per 100 000 inhabitants per year in the two time periods with 95% CIs are shown in Figure 8.

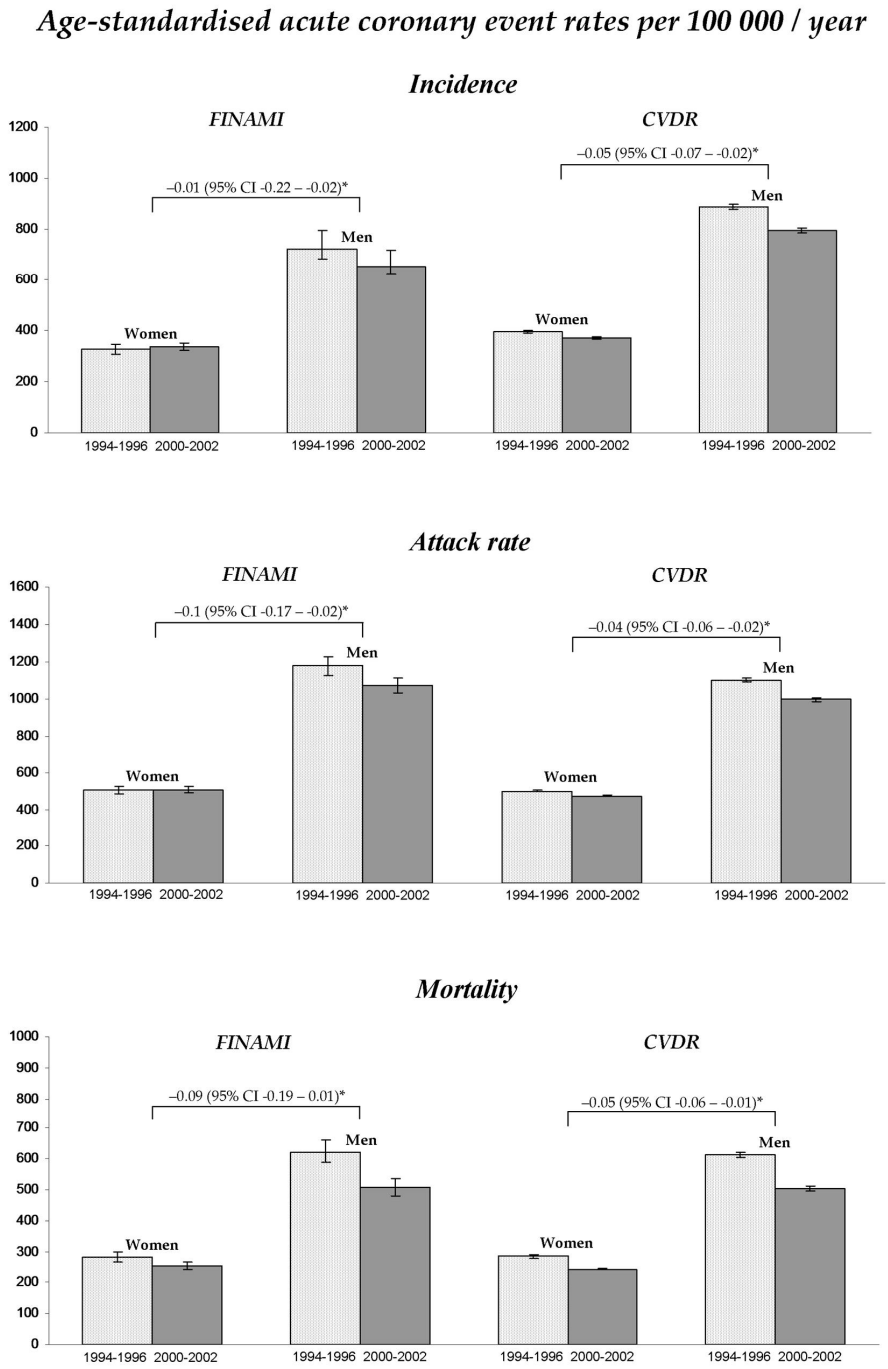


Figure 8. Average age-standardised acute coronary event incidence, mortality and attack rates per 100 000 in the FINAMI and CVDR registers in 1994-1996 and 2000-2002. The error bars denote 95% CIs of the event rates. * Male-female difference in gender-specific relative (to the 1st time period) changes of age-adjusted event rates. Adapted from Lehto H-R et al. BMC Cardiovasc Disord 12;7:35, 2007.

Table 2 in Publication I reveals the male-female differences in gender-specific relative (to 1st time period) changes of age-adjusted event rates. Significant differences between the genders were seen in the relative decline in incident and recurrent events and also in mortality in CVDR. In the FINAMI register, the relative changes differed significantly between the genders in incident and recurrent events (Figure 8).

Further analyses with a negative binomial regression model in CVDR confirmed that the incidence, attack rate and mortality had generally declined between the study periods (Table 3 in Publication I). However, when evaluating the decline rate differences between the genders in two different age groups (subjects of 35-54 years old and subjects ≥55 years old), the relative changes seen in younger (<55 years old) women were smaller than in similarly aged men and older women. No differences were seen between older (≥55 years old) women and men. The gender by year interaction expressed as RR in the younger age group was 1.04 for incidence (p=0.01), 1.04 (p=0.01) for attack rate and 1.04 (p=0.03) for mortality rate. The results from negative binomial regression models are shown in Publication I Table 3.

In the FINAMI register, negative binomial regression models produced results that were generally consistent with the findings in the CVDR, but the year by gender interaction among age group <55 years old failed to reach statistical significance, probably due to the small numbers of ACS events in women aged <55 years old in the FINAMI data.

The proportion of definitive MIs increased after adoption of troponins in both genders. In women, the proportion of definitive MIs changed from 40% in the first period to 60% in the second period. Among men, the proportion of definite MIs was higher than the corresponding value in women in the first study period 54% (vs. 40% in women) but increased to 75% in the second period. The changes in different MI subtypes are shown in Table 4 in Publication I.

5.2 Gender differences in the prognosis of ACS from 1994-1996 to 2000-2002 (Study II)

Generally the short- and long-term prognosis improved among both genders between the study periods. Age-standardised case-fatality percents for the three main indicators in two different time periods are shown in Table 17.

Figure 1 in Publication II shows the age-standardised case-fatality (%) with 95% CIs for both age groups in 1994-1996 and 2000-2002 in both FINAMI and CVD Registers.

Table 17. Age-standardised case-fatality (%) for incident acute coronary syndrome according to gender, age group and three case-fatality time windows in both study periods

	Pre-hospital		***28-day***		***365-day***	
	1994-1996	**2000-2002**	**1994-1996**	**2000-2002**	**1994-1996**	**2000-2002**
FINAMI						
Men[1]	***29.7***	***26.7***	***46.5***	***41.0***	***49.5***	***45.1***
<55 years old	27.4	27.0	34.1	29.2	35.9	30.2
≥55 years old	30.1	26.6	48.8	43.5	52.0	48.5
Women[1]	***24.1***	***25.6***	***53.5***	***48.6***	***59.4***	***54.4***
<55 years old	9.4	29.6	15.6	31.5	18.8	31.5
≥55 years old	24.4	25.5	54.4	49.1	60.3	55.1
CVDR						
Men[1]	***33.6***	***29.5***	***54.7***	***50.1***	***59.2***	***55.1***
<55 years old	30.8	29.2	36.1	33.7	37.5	34.8
≥55 years old	34.0	29.6	57.6	52.6	62.7	58.1
Women[1]	***27.0***	***24.4***	***58.9***	***54.6***	***65.7***	***61.8***
<55 years old	25.7	25.2	32.7	31.2	33.8	32.2
≥55 years old	27.1	24.3	59.6	55.2	66.6	62.6

[1] Subjects aged ≥35 years old

Short-term case-fatality

Generally, short-term case-fatality improved between the time periods. However, when comparing the case-fatality declines between the genders using logistic regression analyses, the results showed smaller declines in pre-hospital and 28-day case-fatality between the study periods among young (<55 years old) women when compared to men and older women. In FINAMI, the OR for pre-hospital case-fatality was 2.03 (sex by study period interaction in the age group of <55 years old) with 95% CI of 1.08-3.82, and correspondingly in CVDR, the OR was 1.35 with 95% CI 1.11-1.63. Similarly, for 28-day case-fatality, the OR was 2.04 (95% CI 1.14-3.64) in FINAMI and 1.80 (95% CI 1.50-2.16) in CVDR. All results from the logistic regression analyses are shown in Tables 2, 3 in the Publication II.

Interestingly, the decline in 0-27-day case-fatality was slower among women aged <55 years due to a slower decline in the pre-hospital case-fatality in this age group, whereas the in-hospital (2-27 day) case-fatality revealed no gender differences (Table 18). With respect to in-hospital case-fatality, the gender by study period interactions in FINAMI and CVDR, separately in the age group <55 years old, and in the age group ≥55 years were all statistically non-significant (Table 18).

Table 18. Odds ratios (95% confidence intervals) for in-hospital (2-27 day) case-fatality of incident coronary events in the FINAMI and CVD registers

	OR	***95% CI***	***p***
FINAMI[a]			
Study period (latter vs. former)	0.99	0.77 – 1.27	0.940
Age, per 5 years in men	1.13	0.85 – 1.51	0.384
Age, per 5 years in men ≥55 years	1.24	0.90 – 1.70	0.190
Age, per 5 years in women	1.30	0.59 – 2.85	0.517
Age, per 5 years in women ≥55 years	1.06	0.48 – 2.37	0.879
Gender by study period interaction in age group <55 years	0.73	0.20 – 2.72	0.639
Gender by study period interaction in age group ≥55 years	0.82	0.60 – 1.14	0.241
History of diabetes mellitus	1.49	1.11 – 2.01	0.008
History of diabetes mellitus in women	0.67	0.46 – 0.98	0.038
CVDR			
Study period (former vs. latter)	0.83	0.79 – 0.88	<0.0001
Age, per 5 years in men	1.25	1.11 – 1.41	0.0001
Age, per 5 years in men ≥55 years	1.01	0.90 – 1.15	0.851
Age, per 5 years in women	1.33	0.97 – 1.81	0.076
Age, per 5 years in women ≥55 years	0.92	0.67 – 1.26	0.590
Gender by study period interaction in age group <55 years	0.84	0.54 – 1.30	0.434
Gender by study period interaction in age group ≥55 years	0.98	0.90 – 1.06	0.557
History of diabetes mellitus	1.38	1.29 – 1.48	<0.0001
History of diabetes mellitus in women	0.95	0.87– 1.04	0.236

Long-term prognosis

Generally, the 1-year case-fatality improved between the time periods. The logistic regression analyses for 0-364 day case-fatality are shown in Table 19. The results differed between the registers. In FINAMI, no gender difference was seen in 1-year case-fatality for either of the age groups. In the CVDR, the 1-year case-fatality improved more among older women than among men and younger women, whereas in younger women the 1-year case-fatality seemed to decline more slowly compared to men and older women (Table 19). The 28-364 day case-fatality interval showed no differences between the genders in the CVDR in either age group. These results are shown in Publication II, Table 4. In FINAMI, the gender difference could not be tested in the younger age group because there were no deaths in that group of young women in the later study period. Gender differences were also tested during the time interval from the second day after the event to 364 days. No gender differences were seen in either of the studied age groups in both registers. The gender by study period interaction for the younger age group was statistically non-significant (OR 0.39, 95% CI 0.11-1.40) in FINAMI and OR 0.75, 95% CI 0.51-1.10 in the CVDR as well as for the older age group (OR 0.78, 95% CI 0.58-1.04) in FINAMI and OR 0.99, 95% CI 0.93-1.06 in CVDR. This indicates that a slower pre-hospital case-fatality decline was behind the slower 1-year case-fatality decline detected in younger women in the CVDR.

Table 19. Odds ratios (95% confidence intervals) for 1-year case-fatality of incident coronary events in the FINAMI and CVD registers

	OR	***95% CI***	***p***
FINAMI			
Study period (latter vs. former)	0.83	0.72 – 0.96	0.014
Age, per 5 years in men	1.06	0.95 – 1.19	0.314
Age, per 5 years in men ≥55 years	1.21	1.05 – 1.38	0.007
Age, per 5 years in women	0.95	0.71 – 1.28	0.727
Age, per 5 years in women ≥55 years	1.57	1.16 – 2.14	0.004
Gender by study period interaction in age group <55 years	1.68	0.95 – 3.00	0.078
Gender by study period interaction in age group ≥55 years	0.94	0.77 – 1.16	0.575
History of diabetes mellitus	1.26	1.05 – 1.52	0.016
History of diabetes mellitus in women	0.82	0.64 – 1.06	0.134
CVDR			
Study period (latter vs. former)	0.78	0.75 – 0.80	<0.0001
Age, per 5 years in men	1.00	0.96 – 1.04	0.952
Age, per 5 years in men ≥55 years	1.29	1.23 – 1.35	<0.0001
Age, per 5 years in women	0.68	0.61 – 0.75	<0.0001
Age, per 5 years in women ≥55 years	2.22	2.00 – 2.47	<0.0001
Gender by study period interaction in age group <55 years	1.87	1.56 – 2.24	<0.0001
Gender by study period interaction in age group ≥55 years	0.93	0.88 – 0.97	0.002
History of diabetes mellitus	1.23	1.18 – 1.29	<0.0001
History of diabetes mellitus in women	1.02	0.96 – 1.09	0.473

5.3 Gender differences in the prevalence, causes and treatment of high CVD risk (Study III)

The prevalence of high-risk subjects in FINRISK Surveys 1992-2007, defined here as the Framingham risk score ≥20% in 10 years, or prevalent CVD or diabetes, was almost equal in men and women in the age group of 25-54 years: 5.1% (n=451) in men and 3.7% (n=384) in women, whereas in the group aged 55-74 years, the high risk status was more common in men (50.4%, n=2606) than in women (19.9%, n=981). The difference was similar also in the FINRISK 2007 separately (Publication III, Web Supplement Table 1).

Among high-risk subjects, women had a significantly higher prevalence of diabetes than men in both age groups (94% vs. 60.5%, p <0.001 in younger age group) and 51.2% vs. 24.4%, p <0.001 in the older age group). More men had a history of a prior CVD event (29.3% vs. 7.8% in younger age group, p<0.001 and 23.5% vs. 18.9% in older age group, p=0.002). Smoking and former smoking were more prevalent among men than women in both age groups. The prevalence of selected risk factors is shown in Publication III, Table 3.

Generally, high-risk women in both age-groups had better lipid values and lower blood pressure levels, but higher BMI values than men. The average levels of measured risk factors in all high-risk patients are shown in Publication III Table 2. In the FINRISK 2007, mean cholesterol levels were lower as compared to the cholesterol levels in the pooled years and mean blood pressure values were lower in 2007 when compared to the blood pressure values in the pooled years whereas the mean BMI level and waist-hip ratio were higher in 2007 when compared to the results in pooled study years (Table 20 for results of the study in 2007 and for pooled years Table 3 of the Publication III). The proportion of high-risk subjects achieving blood pressure target values and recommended cholesterol level <4.5 mmol/l was higher in 2007 when comparing the results in the pooled years (Publication III Table 3). The prevalence of LDL level >2.5mmol/l had declined in 2007 when compared to the results in the pooled years, and the prevalence of high LDL (>2.5 mmol/l) was similar in both genders and in both age groups in 2007 (Table 20).

The use of medications to control the risk factor levels is presented in Publication III Table 4. If one considers the high-risk subjects, then it seemed that young women generally used preventive medications less than their age-matched male counterparts. In the older age group, this situation tended to be reversed.

Subjects with diabetes

Among diabetic subjects, the mean total cholesterol levels were equal in the younger age group (5.4 in men and 5.5 mmol/l in women), whereas in the older women the mean cholesterol level was higher in women than in men (5.7 mmol/l vs. 5.3 mmol/l, p ≤0.001). Men achieved the recommended level of total cholesterol <4.5mmol/l more often than women: in the younger age group 21% of men but only 14% of women achieved the recommended levels (p=0.01). Similarly in the older age group, 28% of men but 13% of women had total cholesterol less than 4.5mmol/l (p <0.001). Among young diabetic women, the prevalence of lipid treatment was 9% being much less than in men where the prevalence of lipid treatment was significantly higher (18%, p=0.001). This difference was no longer present in the older age group: 31% in men and 32% in women had lipid lowering treatment (p=NS). The mean blood pressure values were in men 137/85 mmHg and in women 134/80 mmHg in the younger age group (p=NS for SBP and p <0.001 for DBP, and 149/82 mmHg in men and 147/79 mmHg in women in the older age group (p=NS for SBP and p <0.001 for DBP). Among the older age group, the prevalence of blood pressure treatment was equally common: 51% of men and 52% of women were being treated for high blood pressure (p=NS). In the younger age group, women less often were receiving antihypertensive treatment than men (22% vs. 34%, p=0.01). Acetylsalicylic acid was more commonly used by men: 19% in young men vs. 7% young women (p ≤ 0.001) and among the older age group (44% in men vs. 36% in women, p=0.005). Beta-blockers were equally commonly used in both age groups: 21% in men and 13% in women in the younger age group, and 43% vs. 38% in the older age group, respectively (p= NS for both age groups).

Subjects with prevalent CVD

Subjects with prevalent CVD had similar mean total cholesterol levels in both genders. Mean total cholesterol was 5.5 mmol/l in men and 5.7 mmol/l in women in the younger age group, and 5.1 mmol/l and 5.2 mmol/l in the older age group; in both age groups there was no significant gender difference.

Table 20. Risk factors among subjects at high risk for CVD in the FINRISK 2007 Survey (shown as mean for continuous variables or percentage of the total for dichotomous variables)

	Young (25-54 years)							Older (55-74 years old)						
	Men			Women			p*	Men			Women			p*
	mean or %	SD	n (n total)	mean or %	SD	n (n total)		mean or %	SD	n (n total)	mean or %	SD	n (n total)	
Total Cholesterol(mmol/l)	5.2	1.1	88 (88)	5.3	0.9	85	*0.37*	5.1	1.1	661	5.3	1.0	326	*0.003*
LDL Cholesterol (mmol/l)	3.0	1.0	82 (88)	3.2	0.7	83	*0.29*	3.1	1.0	642	3.1	0.9	319	*0.36*
HDL Cholesterol(mmol/l)	1.2	0.3	88 (88)	1.4	0.3	85	*<0.001*	1.2	0.3	661	1.4	0.3	326	*<0.001*
Triglycerides (mmol/l)	2.2	1.3	88 (88)	1.5	1.2	85	*0.003*	1.8	1.1	661	1.8	0.9	326	*0.50*
% Cholesterol <4.5 mmol/L	23.9		21 (88)	20		17 (85)	*0.27*	31.3		207 (661)	21.2		69(326)	*0.001*
% LDL >2.5 mmol/L	69.5		57 (82)	80.7		67 (83)	*0.05*	68.1		437 (661)	72.7		232(319)	*0.16*
Systolic Blood pressure (mmHg)	136	18	88 (88)	130	18	84	*0.20*	152	22	660	153	22	325	*0.72*
Diastolic Blood pressure (mmHg)	85	12	88 (88)	80	11	84	*0.02*	82	12	660	78	11	325	*<0.001*
Blood pressure in target values**	40.9		36 (88)	63.1		53 (84)	*0.02*	25.0		165 (660)	25.5		83 (325)	*0.81*
Ex-smoking	33.0		29 (88)	20.0		17 (85)	*0.09*	46.4		307 (661)	14.4		47 (362)	*0.01*
Current smoking	37.5		33 (88)	21.2		18 (85)	*0.02*	21.2		140 (661)	17.2		56 (362)	*0.19*
BMI (kg/m^2)	29.6	4.9	88 (88)	30.6	7.7	85	*0.18*	28.9	4.4	661	30.3	5.3	326	*<0.001*
Waist-Hip Ratio	1.0	0.1	88 (88)	0.9	0.1	85	*<0.001*	1.0	0.1	654	0.9	0.1	322	*<0.001*
Low physical activity	72.7		64 (88)	65.9		56 (85)	*0.49*	79.6		526 (661)	75.5		246 (326)	*0.15*

* P for the difference between men and women. Linear regression analysis adjusted for age as a continuous variable (in years) and study area, East (covering North Karelia, Kuopio, Oulu) and West (covering Helsinki-Vantaa and Turku-Loimaa). Logistic regression analysis adjusted for age as a continuous variable in years and the study area, East (covering North Karelia, Kuopio, Oulu) and West (covering Helsinki-Vantaa and Turku-Loimaa).

Among subjects with prevalent CVD, the target cholesterol level of <4.5 mmol/l was reached by 22% of the younger men vs. 20% of younger women (p=NS). In the older age group, the corresponding numbers were: 29% vs. 25% (p=NS). No gender differences were seen in provision of lipid treatment: 42% of younger men received lipid lowering treatment vs. 27% of women (p=NS), and in the older age group: 51% of men and 54% of women (p=NS). Mean blood pressure levels and the prevalence of blood pressure treatment were similar between the genders (data not shown). A lower proportion of women were taking acetylsalicylic acid in the younger age group: 40% in women vs. 62% in men (p=0.03) and in the older group 59% in women and 68% in men were receiving acetylsalicylic acid (p=0.02). In contrast, beta-blockers were equally commonly used in the younger age group: 48% in men vs. 40% in women (p=NS) and 70% of men vs. 65% of women (p=NS).

5.4 Gender differences in the incidence and clinical spectrum of major adverse CVD events (Study IV)

A total of 27 897 subjects (13 063 men and 14 834 women) without prevalent CVD were identified at baseline when the FINRISK 1992-2007 surveys were pooled together. During a total of 292 316 person years of follow-up, 1599 incident major adverse CVD events were identified in men and 974 in women. The incident event numbers by clinical subcategory were: 173 fatal CHD events in men and 48 in women, 645 non-fatal CHD events in men and 222 in women, 318 stroke events in men and 219 in women, 463 cases of heart failure in men and 485 in women. The median follow-up time was 8.9 years (interquartile range 8.8 years). The mean age at the time of an incident major adverse CVD event was 65 years (standard deviation (SD) ±9.5) in men and 66 years (SD ±9.9) in women. The mean ages and detailed numbers of events and co-morbidities are shown in Publication IV Table 1.

The incidence of major adverse CVD event per 100 000 persons per year and the rate ratios according to the age group, gender and major adverse CVD event subgroup are shown in Figure 9. The incidence in men was almost double that encountered in women (rate ratio of 1.8 95%CI 1.6-2.0). Men had significantly higher incident CHD event rates, especially fatal CHD events and stroke compared to women. Men had four times more fatal CHD events, three times more non-fatal events and almost two times more stroke events than women. Both genders had an equal amount of heart failures. The rate ratios for younger and older age groups separately are shown in Figure 9.

The relative proportions of major adverse CVD event categories differed between the genders, but were similar in different age groups (Table 21).

The potential aetiological factors for heart failure were analysed further. In this analysis only prevalent heart failure cases were excluded. A total of 1195 incident heart failure cases (633 in men and 562 in women) were found during the follow-up period. Hypertension was the main factor preceding heart failure, in 83% of men and 76% of women. Prior CHD was found in 42% of men and in 24% of women. Diabetes had been diagnosed in 28% of men and in 24% of women. In addition in the younger age group, hypertension was a common preceding factor for heart failure; 83% in men and 62% in women, whereas CHD was found in 28% of men and in 12% of women, and diabetes in 27% of men and 21% of women.

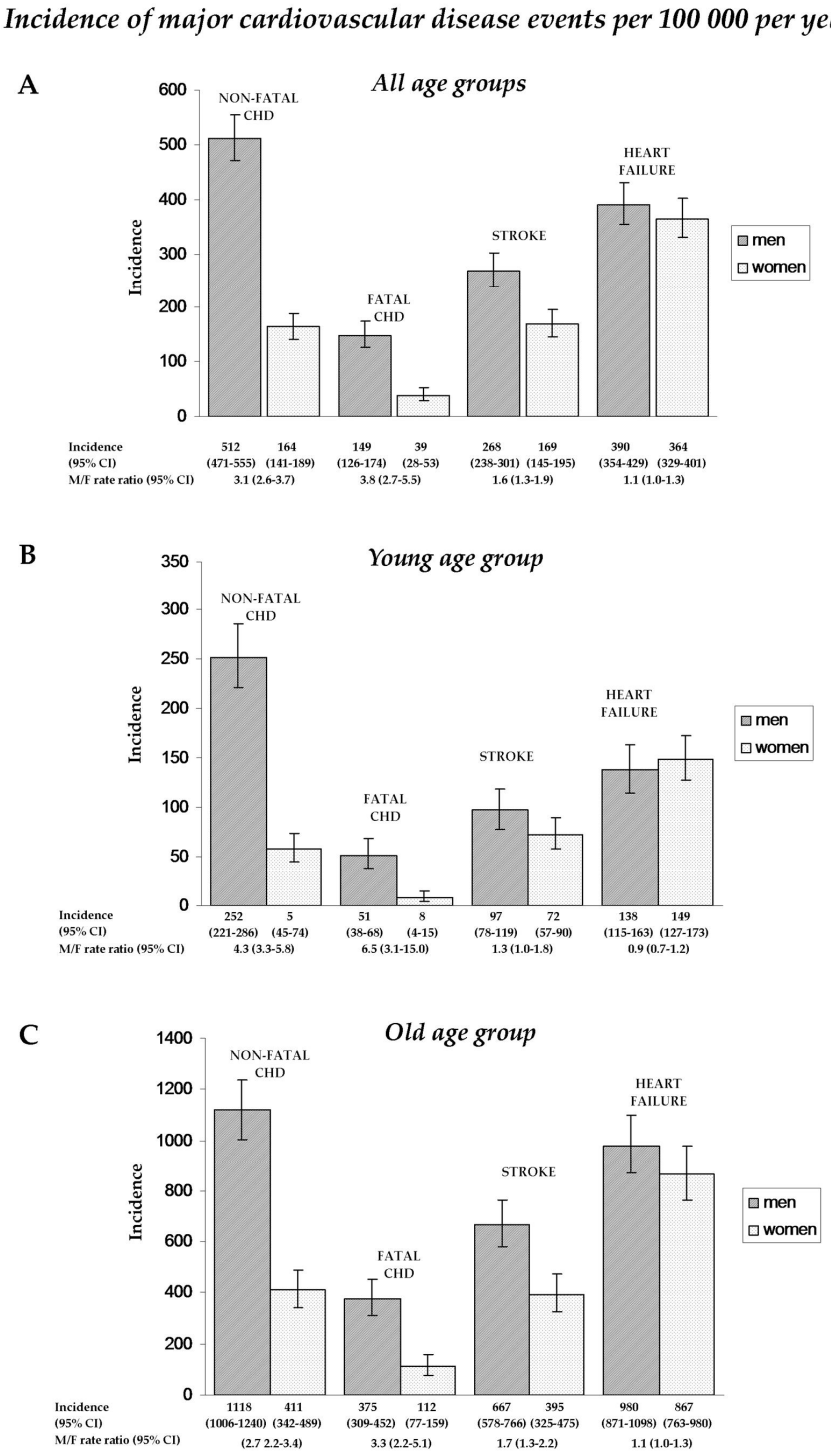


Figure 9. The incidence of major adverse cardiovascular disease events per 100 000 persons per year and the rate ratios according to the age group (A= 25-74 years old, B= 25-54 years old, C=55-74 years old), gender and major adverse cardiovascular disease subgroup. Adapted from Lehto H-R et al. Eur J Prev Cardiol, 2013. Published online.

In the older age group, hypertension preceded heart failure in 83% of men and in 82% of women. CHD had been diagnosed in 46% of men and in 29% of women. Diabetes preceded the heart failure diagnosis in 28% of men and 26% of women.

Table 21. Relative proportions of major adverse cardiovascular disease categories in the different age groups

All		**Young**		**Old**	
25-74 years old[1]		**25-54 years old[1]**		**55-74 years old[1]**	
Men	***Women***	***Men***	***Women***	***Men***	***Women***
1. Non-fatal CHD (38.8%)	1. Heart Failure (49.5%)	1. Non-fatal CHD (46.9%)	1. Heart Failure (51.8%)	1. Non-fatal CHD (35.6%)	1. Heart Failure (48.6%)
2. Hear Failure (29.6%)	2. Stroke (22.9%)	2. Heart Failure (25.6%)	2. Stroke (25.1%)	2. Heart Failure (31.2%)	2. Non-fatal CHD (23.0%)
3. Stroke (20.3%)	3. Non-fatal CHD (22.3%)	3. Stroke (18.0%)	3. Non-fatal CHD (20.3%)	3. Stroke (21.3%)	3. Stroke (22.1%)
4. Fatal CHD (11.3%)	4. Fatal CHD (5.3%)	4. Fatal CHD (9.5%)	4. Fatal CHD (2.8%)	4. Fatal CHD (12.0 %)	4. Fatal CHD (6.3%)

The sum of each column is 100%

1 Baseline age

6 Discussion

6.1 Summary of the main findings

The FINAMI and CVDR studies showed that the incidence, mortality and attack rate of coronary events have generally declined from 1992-1994 to 2000-2002 in Finland, and furthermore that the prognosis of ACS has improved between these time periods. However, the incidence and decline in mortality and the improvement in prognosis revealed a gender difference during this time interval. This was due to the slower decline in the incidence of ACS, mortality and attack rate among young (<55 years old) women compared with men and older women. Although the short- and long-term case-fatality of ACS has declined, the decline was slower among younger (<55 years old) women. This was mainly due to the slower decline in pre-hospital case-fatality in the younger women. In population-based FINRISK studies, it was found that the treatment of risk factors was less intensive in these young female high-risk patients when compared to men and older women. In the follow-up of initially healthy FINRISK participants, gender differences were seen in the incidence of CVD events. Men had a higher rate of non-fatal and fatal coronary events and stroke than women, whereas incident heart failure event rates were similar in both genders. Men and women also differed in the clinical spectrum of CVD events; in men the most common incident CVD event was a non-fatal ACS, whereas for women heart failure was the most common CVD. These differences were similar in all age groups.

6.2 Study population and methods

The subjects examined in studies I and II were obtained from two large population-based registers. CVDR is a nationwide register and it includes data mainly from the HDR and CDR registers which have been validated against the AHA 2003 definition. Together these registers showed a sensitivity of 80% and a positive predictive value of 90% for MI (255). Sensitivity improved from 1988 to 2002 in both genders, which was most likely due to the adoption of troponin into the diagnostic protocols. The diagnostic sensitivity and accuracy of MI seemed to be lower in women than in men. The accuracy of MI diagnosis between 1998 and 2002 (as acquired from the HDR and CDR registers) was tested against the AHA 2003 definition; the sensitivity was 81% and the positive predictive value 90% for men aged 35-74 years, the corresponding percents for women were 78% and 86%. When UAP was taken into account, sensitivity increased and positive predictive value decreased. In those subjects over 75 years old, the percentages were similar as those found in the younger groups. In fatal cases, sensitivity and positive predictive value were similar among both genders; sensitivity was 92% and positive predictive value 91-92% (255). In Finland, the frequency of autopsies in out-of-hospital deaths is high; more than 70% (50). The diagnosis of stroke, based on the HDR and CDR registers, was found to have a good positive predictive value (86%) for the first stroke event, and no gender differences were seen (266). The diagnosis of heart failure, according to the HDR, CDR, DRR and pharmacy prescription data had poor sensitivity (48.5%) but good positive predictive value (85.9%) against register-based clinical classification (264). No gender specific data quality analysis was reported (264).

The FINAMI register collects data mainly from urban areas (Kuopio, Oulu, Turku, Joensuu), and also from a few rural areas around Joensuu. FINAMI has a strict case definition coding, and the quality of ACS diagnosis is likely to be higher than in the CVDR register. However, FINAMI contains a smaller amount of coronary events, and due to this some gender differences, which were apparent in the CVDR, may not have been apparent in the FINAMI data. FINRISK is a unique survey of CVD risk factor trends in Finland, and has comparable data for over 30 years collected at 5 year intervals. The participation rate has been fairly good, ranging from 58% to 81% depending on the survey year and gender. Women had slightly higher participation rates than men in all survey years (19). The non-participants usually have higher risk factor levels, and their overall health may be poorer compared to the participants (267). The characteristics of non-participants have not been studied during the 2000s, but it is unlikely that gender would influence the non-participants differently.

Pre-hospital mortality in this study was defined as death in the same day as the symptoms had begun, which corresponds to a survival time of less than one day. In the FINAMI, register autopsies were performed on 64.9% of men in the first time period, and on 73.4% in the second period, and in women 33.9% and 43.3%, correspondingly. Due to the Finnish legislation concerning determination of the cause of death, it can be assumed that these percents are similar, or even higher among young subjects. In this study, the 28-day time period was considered to depict in-hospital mortality, and to consist of one single event in the registers. This definition has been adopted from the WHO MONICA criterion. The average hospitalisation period for ACS in Finland according to the CVDR database was 7.4 days among men aged 35-84 years old in 2010 and 8.1 days among similar aged women.

Unrecognised MIs could not have been registered as MI cases in CVDR or FINAMI registers. The amount of unrecognised MIs is known to be higher among women than in men (34% of all MIs in women vs. 27% in men) (23, 268). This may underestimate the incidence of ACSs among women, and this in turn would widen the gender differences. However, it is not likely that unrecognised MIs would change ACS mortality rates, as the cause of death still needs to be identified.

Aging is known to affect CVD rates exponentially. Women are known to have low rates of CVD events before the menopause, and after menopause the male-to-female ratio starts to decrease. In women, the increasing effect of age on CHD mortality is more pronounced than in men. CHD mortality increases up to 2.3 -2.7 fold per every decade of life among men compared to the greater, 2.9- 3.7 fold, increase in women (269). The epidemiological evidence is controversial i.e. is it the menopause *per se* rather than age that carries an association with CHD. In a meta-analysis, the pooled RR of CVD in postmenopausal women was 1.36 (95% CI 1.15-1.60), however when this was adjusted for age and smoking, the difference between pre-and postmenopausal women became non-significant (RR 0.96 95% CI 0.77-1.21) (195). However, in this meta-analysis of 18 studies, early menopause was identified as a risk factor (RR 1.38, with 95% CI 1.21-1.58) after adjusting for age and smoking (195). A study from the Netherlands which included 824 CVD deaths revealed a reduced RR of 0.98 for a CVD event per each year of delay of menopause, and the inverse relation was greater at younger ages (270). Surgical menopause had a pooled RR of 4.55 (95%CI 2.56-8.01) (195).

The relationship between menopause and age has also studied in mathematical analysis of modelling longitudinal mortality data from three birth cohorts from England and Wales, and the United States; in these no acceleration of CVD mortality was seen at the menopause age group (45-55 years old), whereas the increase in breast cancer mortality was shown to significantly decelerate after the age of 45 years. In men, a rapid increase in CVD mortality has been shown to occur as they reach young adulthood this being followed by a slower increase after the age of 45 years (271). The authors concluded that deceleration of the increase in CVD mortality in men explained the gender differences better than the postmenopausal estrogen deficiency in women (271). Menopausal changes occur transitionally during perimenopause, and the changes in lipid metabolism as well as some effects on blood pressure occur during one to ten years after the menopause. Aging itself has also effects on CVD risk factors and the changes caused by menopause are difficult to differentiate from those attributable to aging. It has even been suggested that the increased levels of CVD risk factors might have an effect on menopause age rather than the other way around (272). In the CVDR, fatal CHD events had a significant changing point at the age group of 55-59 years in women, and therefore 55 years was selected as the cut point between the two age groups. No significant change was seen in the average menopause age in the 50-51 years old. Our data from FINAMI and CVD registers do not include information of menopause status *per se*, nor the time point of loss of menstruation. It is possible that this change among age group of 55-59 years old, is due to the aging, and possibly to some extent this could have influenced effect of menopausal changes on risk factors. It also might be that these early menopausal women are not considered to be at risk for CHD, and thus remain underdiagnosed and treated, leading to a change in mortality. The cutpoint of 55 or 60 years have been used in other population-based studies also (23, 37, 273).

CHD has different clinical presentations, and women are known to suffer more from angina, and men more from clinical events as the clinical presentation of CHD (23). In this study, the FINAMI register collects all acute coronary events and deaths in the register areas. Thus stable angina is not included in the registration in either FINAMI or in CVD register. Non-fatal events and stable angina are problematic, since they invariably depend on the classification, methods and diagnostic tools used in determining the diagnoses. In the SCORE project, the outcome was a fatal CVD event, because data on fatal events are more robust and better comparable over different time periods than data on non-fatal events in different European countries (166). Stable angina is also a problematic clinical presentation of CHD: especially among women in whom, despite the poor prognosis related to stable angina, CHD with occluding atherosclerosis is more rarely identified in coronary angiography (274). In a large cohort study of 375 886 patients from the United States, the risk-adjusted OR for significant coronary stenosis was only 0.34 in women with stable angina compared to men with stable angina, but at the same time, the in-hospital mortality was significantly higher in the women (274). The present method of collecting data on acute coronary events, can be assumed to have good specificity and, due to gender differences in the clinical spectrum of CHD (women having lower rate of events compared to men), it is possible that the results on acute events alone might actually underestimate the overall occurrence of CHD in women. Due to the lower rate of diagnostic testing in women, it is also likely that only the most severe cases of CHD were detected.

6.3 Gender differences in the incidence-, mortality - and attack rate trends of ACS (Study I)

In general, the incidence, attack rate and mortality of CHD declined between the time periods 1994-1996 and 2000-2002. This decline is consistent with other reports of CHD trends in western countries and Finland during the past decade (13, 28, 29). The rate of the decline differed between genders; a slower decline among women was seen in the incidence and the attack rate in both registers, and a slower decline in mortality among women was seen in the CVDR register. A slower decline in mortality from total CVD events was also seen in the Olmsted County, Minnesota, cohort (29). A slower mortality decline in women, without age-grouping, was also shown in two other studies from the United States; however, both of these studies evaluated time periods before the mid-1990s (30, 31). In the present study the slower decline in mortality was age-dependent in women since it was only seen in young women. Similarly, more recent studies from the United States, France, Australia, England and Wales, have pointed to a slower decline in CHD mortality among younger, middle-aged subjects (4, 35-37). In France, Wagner et al. reported a slower decline in the mortality of CHD among young women during 2000-2007 (37). Ford et al. reported a levelling off in the CHD mortality decline in both genders, even an increase in mortality seemed to occur among young (aged 35-54) women from 2000 to 2002 (4). Contrary to this report and these present results, Vaartjes et al. described an attenuation in the decline of CHD mortality decline among young 35-54 years old subjects and there were no gender differences in this respect in the Netherlands between 1972-2007 (273).

The slower decline in CHD mortality among young women - who have the lowest absolute risk - is difficult to explain. In general, changes in mortality are due to changes in incidence and case-fatality and, moreover, incidence changes are associated with changes in diagnostics or risk factor levels. In the present study, the decline in CHD incidence was slower among young women compared to men and older women according to both the FINAMI and the CVDR registers. This gender difference could either be attributed to the adoption of troponins in Finnish hospitals during the study periods, or to changes in the development of risk factors in Finland. The effects of troponins on the incidence of CHD have been previously studied using data from the FINAMI register. Salomaa et al. described a declining trend in incidence (-2.0% per year) between 1993 and 2002 in men aged 35-74 years in Finland, whereas a non-significant 1.0% decline was seen among women of the same age. However, when the effect of troponin measurements in the diagnostics were taken into account, the decline among women in the age group of 35-74 years was changed to being statistically significant, i.e. - 2.7% per year (13). Furthermore, the adoption of troponin measurements was shown to have the greatest effect on the number of events among the elderly, ≥75 year old women (13). In the present study, the slower decline in incidence was seen among young, <55 year old, women. Thus it is unlikely that the adoption of troponin measurements would entirely explain those changes in the incidence. The gender difference seen in the decline of CHD mortality is not explained by troponins, since most of the CHD deaths occur suddenly in out-of-hospital circumstances, i.e., before any laboratory measurements can be taken or before the blood concentration of troponin has become elevated (18).

Since many of the first CHD events are fatal, it maybe that it is changes in risk factor levels in Finland that account for the gender difference seen in the declines of incidence and

mortality. Traditional risk factor levels have been monitored in Finland at five-year intervals since 1972. Jousilahti et al. showed that differences in risk factor levels, especially in the HDL cholesterol levels and smoking, explained nearly half of the difference in CHD risk between the genders (10). It is likely that detrimental movements in risk factors explain these gender differences. Mean cholesterol levels have declined among both genders. However, during the time period 1992-1997 cholesterol levels remained the same among women, but after that cholesterol levels have started to decline again. In 2002 the mean total blood cholesterol was 5.7 mmol/l in men and 5.5 mmol/l in women (12). Similarly, the SBP among women stayed at the same level between the years 1997 and 2002, whereas DBP was declining in both genders until 2002 (12).

The most adverse changes were, however, seen in smoking, and the increasing prevalence of obesity and diabetes. In Finland, women have traditionally smoked much less than men, but smoking increased in women until 2002 and has stayed at the 2002 level until 2007. After that, smoking has declined among women. In men, the prevalence of smoking decreased from the 1970s to 1997, when smoking prevalence seemed to increase until 2002, but it has been declining since that time (12).

The most prominent risk factor change from the 1970s is the increasing obesity in Finland, as in other western countries, among both genders. Globally 33.6% of men and 35% of women are overweight, and 9.8% of men and 13.8% of women are obese based on the definition of BMI $\geq 30 kg/m^2$(14). From 1978 to 2001 in Finland, the prevalence of obesity has increased more in men; from 11% to 21% compared to a change from 18% to 24% in women. The mean BMI increased more in men during this time period. However, changes in the fat distribution may well have been more disadvantageous in women, since the waist circumference has increased by 4.3 cm in women but only by 2.7 cm in men in the past decades (275, 276). The prevalence of obesity has increased even further since 2001, and the latest FINRISK 2012 findings have suggested that 66.3% of men and 46.4% of women are overweight in Finland (1, 161). Abdominal obesity was shown to have a small, but significantly greater effect on CHD events in women than in men in the INTERHEART study (11).

The prevalence of diabetes has increased, and in 2008 it was estimated that diabetes prevalence was 10% globally (1). According to FIN DM II data currently there are 300 000 diabetic persons in Finland, and an additional 200 000 persons are believed to have unrecognised diabetes (277). From the mid-1990s to 2007, the prevalence of type 2 diabetes increased by 5.5% annually. The encouraging news for women was that the proportion of women has declined among subjects with type 2 diabetes; from 55.9% in 1997 to 50.1% in 2007 (277). The population attributable risk of CHD event due to diabetes is, however, significantly greater in women (19.1 women vs. 10.1% men, $p < 0.0001$). Overall, risk factors related to metabolic syndrome explained 73% of women´s CHD events and 68% of men´s events in the INTERHEART study (11).

The potential changes in case-fatality in explaining the slower mortality decline will be discussed in detail below.

The declines in CHD event rates between the study periods in men and women showed some inconsistency between the registers: the incidence and attack rate did not decline in women according to the FINAMI register. In CVDR, declines were seen among both genders in incidence, attack rate and mortality. This discrepancy is partly due to the

differences in registers; in FINAMI, the register areas are mainly cities, and the hospitals are large university hospitals (Kuopio, Turku, Oulu), with one large central hospital (Joensuu). As the CVDR covers the whole country, including a large proportion of smaller hospitals, it is likely that the adoption of troponins occurred gradually in different hospitals, at first in larger hospitals in the late 1990s and then later in the smaller hospitals. The effect of troponins has been shown to have a greater impact on women's MI diagnosis than men's (13). Moreover, in the FINAMI register, the event numbers were low with respect to young women in both time periods, and therefore the FINAMI register was underpowered to reveal changes in this group between these time periods.

6.4 Gender differences in the prognosis of ACS (Study II)

Short-term and 1-year case-fatality improved among both genders from the mid-1990s up to 2002. Pre-hospital case-fatality declined more slowly in young (<55 years old) women when compared to men and older women. The slower decline in pre-hospital case-fatality was also reflected in a slower decline in 28-day case-fatality in young women. The reduction in-hospital (2-27 day) case-fatality was similar in both genders and age groups (<55 years and ≥55 years), as was the decline in 28-364 day case-fatality.

This slower decline in early case-fatality may explain the slower mortality decline seen in study I. Almost 50% of total CHD mortality change has been shown to be due to the changes in case-fatality (42). The present results are similar as those reported in population-based studies from the United States, New Zealand and Scotland, including both pre-hospital and in-hospital deaths (29, 53, 54, 278). Those study settings which examine only hospitalised subjects may distort the results of gender differences as pre-hospital case-fatality is higher in men than in women (26).

There may be several explanations for the slower decline of pre-hospital case-fatality in young women. First, pre-hospital deaths due to incident events are considered to depict the efficacy of primary prevention in the population, and as revealed in Study III, the high-risk situation is not always recognised and appropriately treated in women (discussed in detail below) even though most of the women who will die of CHD have at least a one elevated CVD risk factor (279). The high-risk situation needs to be recognised, since 64% of women who die suddenly, do not display any prior symptoms (2). The prevalence of smoking was increasing in women in the 1990s and this trend continued at the beginning of the 2000s, and smoking is known to be one of the most important risk factors for sudden death in women (135). Population-based preventive actions and campaigns to increase knowledge on heart disease among women are important if one wishes to reduce CHD mortality in women (191).

Secondly, the clinical presentation and symptoms are more complex among women, and non-invasive diagnostic tests are known to have lower reliability and this may lead to poorer CHD recognition among women, especially among pre-menopausal women. Women report more unusual prodromal symptoms before an acute coronary event such as: fatigue, sleep disturbances and shortness of breath (62). It is not clear whether women experience less or a similar rate of chest pain during an acute event as men. However, women are more likely than men to report fatigue and shortness of breath and other heart failure symptoms as one of the symptoms during the acute coronary event (280). Women also report more angina evoked from emotional stress, men more often display exertional

angina (62). The symptoms poorly predict obstructive CHD, especially among premenopausal women. In the Women's Ischemia Syndrome Evaluation i.e. WISE study, signs of obstructive CHD were found in 21% of women having typical symptoms, in 17% of women with atypical symptoms and in 21% with non-angina symptoms among the 45-55 years age group. In post-menopausal women, symptom prediction for obstructive CHD was better, but still less than for men of same age (62). Diagnostic testing, such as exercise ECG evaluation, shows poorer reliability in women, especially among premenopausal women, among whom angina and ischemia symptoms may vary depending on the phase of the menstrual cycle. In the luteal phase, when estrogen levels are low, ischemia and angina symptoms may be provoked more easily. Overall, exercise ECG, taking ≥1mm ST-depression as a marker of ischemia, has ~ 60% sensitivity and ~ 70% specificity for significant obstruction in a coronary artery in women, compared to the ~ 80% diagnostic sensitivity and specificity reported in men (62). Single-photon emission tomography and pharmacologic stress testing have been proposed to have higher sensitivities and specificities for prediction of obstructive CHD (62).

Women with stable angina are admitted to diagnostic tests and to coronary angiography less often than men in stable angina (281). Daly et al. estimated that there was 2-times higher risk of death in 1-year follow-up in those women with stable angina compared to men, even after adjustments for clinical characteristics, severity of CHD, revascularisation and usage of drugs (281). Theoretically, some restrictions are associated in the search for obstructive CHD, as 15% of subjects with diagnosed non-ST-elevation MI exhibit non-obstructive CHD in angiogram (280). In women diagnosed with STEMI, 10.2% have normal or no obstruction in coronary arteries, compared to 6.8% of men (p=0.02 for gender difference) (282). Women account for the majority of subjects with angina symptoms, suspected ischemia and non-obstructive CHD in coronary angiography, also named as cardiac syndrome X (274). This status has commonly been considered as a benign state. However, data from the Women's Ischemia Syndrome Evaluation study has shown that women with persistent angina symptoms without obstructive CHD or normal coronary arteries are twice as likely to suffer CVD events, including non-fatal MIs, strokes, heart failure and CVD deaths when compared to those women without angina symptoms in 5-year follow-up (283). This non-obstructive CHD has been further investigated recently; most of these women have been shown to have an abnormal coronary flow reserve and endothelial dysfunction (62, 283).

A recently published study from Japan reported that in women with angina and non-obstructive CHD, an intracoronary acetylcholine provocation test revealed epicardial coronary artery vasospasm to be the cause of ischemia in 49.3% of cases and microvascular coronary artery vasospasm in 21.3% of the cases, whereas a non- ischemic cause was found in 18.5%, and 10.9% of cases could not be classified. In the same study, microvascular coronary artery spasm was found significantly more frequently in women than men (21.3% vs. 3.1%, $p<0.0001$) (284). Vasospasms evoke stress on the endothelial cells and erosions leading to thrombus formation, and this may trigger an acute coronary event. Women are known to have more superficial erosions, and men to have more deep plaque ulcerations in the lipid core (285). Endothelial dysfunction has been proposed to be the cause of symptoms encountered in non-obstructive CHD, and to be a cause of microvascular disease (62, 274, 284). However, knowledge of these disease states is scarce; more information on prognosis, risk factors and benefit of medications would be clearly desirable. However, the Red Alert project has recommended to evaluate and treat risk factors in these women (286).

Thirdly, women have anatomical and physiological differences which may be responsible for the poorer short-term prognosis. Women have a high risk for spontaneous coronary dissection due to their thinner coronary artery walls, and more women suffer heart muscle ruptures due to MI than men (287, 288). Women also have been postulated to react differently to ischemia via autonomic nervous system: in premenopausal women the stronger vagal reflexes protect them from ventricular fibrillation, but on the other hand, extreme vagal activation can evoke asystole and hemodynamic instability (289).

Fourthly, women have higher rate of co-morbidities, especially diabetes, which may interfere with symptom recognition, or may even mean that the acute coronary event remains undiagnosed (268).

There were no gender differences detected in in-hospital (2-27 day) case-fatality changes between the time periods of 1994-1996 and 2000-2002. Several prior studies from other countries have shown poorer in-hospital prognosis in women, especially young women, compared to men and older women (6). However, more recent data has shown that this difference has narrowed from the 1990s to 2006, although it still is apparent (57). The lower rate of revascularisation procedures (PCI or CABG), and higher mortality related to these procedures have been considered to explain this gender difference in the in-hospital case-fatality (290). However, the gender gap related to PCI and CABG outcomes has now narrowed between the genders (291). Current ESC non-ST-elevation MI Guidelines of 2011 do note that women with non-ST-elevation MI are less likely to receive evidence-based medicine and diagnostic procedures including revascularisation (280). The long-term benefit of invasive vs. conservative strategy in women has been highlighted in a Cochrane meta-analysis, although with an early increased hazard. The guidelines now recommend to consideration of early invasive strategy for women according to the same principles as for men (280).

There were no gender differences in the changes in long-term prognosis (28-364 days) in this study. Commonly, women have been perceived to enjoy a better long-tem prognosis (280). Nonetheless, register studies on long-term prognosis have shown controversial results. Vaccarino et al. described an age-dependent difference in long-term prognosis; poorer 2- year prognosis was seen in young women compared to men and older women (61). A recurrent MI event, non-fatal or fatal, has been reported to occur during the subsequent 5 years in 22% of women and in 15% of men <50 years old, but in 22% of both genders in subjects ≥65 years old (2).

In this present study diabetes was associated with a lower risk of pre-hospital case-fatality, although the long-term prognosis was not advantageous. Women with diabetes are probably recognised by themselves and their physicians to be a high risk group for a CHD event, and thus may have a shorter delay in contacting the health care system.

The adoption of troponins does not explain the difference seen in case-fatality changes between the genders. In the pre-hospital deaths, troponins do not play any role in diagnosis, since samples for troponins have been taken yet, or the time to troponin elevation (at least 4 hours in old troponins) is too short that it has not occurred before death. In addition, troponins have been shown to have no effect on 1-month case-fatality trends in either of the genders (13, 56).

6.5 Gender differences in the prevalence, causes and treatment of high CVD risk (Study III)

Prevalence of high CVD risk was almost the same in men and women in the age group of 25 to 54 years, but in the older (55-74 years) age group, the high-risk situation was more common among men than in women. Diabetes was the main cause for a high-risk to be present in young persons. In young women, diabetes was the most common cause, whereas in men a high Framingham risk score and prevalent CVD also seemed to have an important role. In older age-groups, diabetes was the main cause among women, whereas in men the proportions of diabetes, prior CVD event and high Framingham risk score were more evenly distributed. The use of preventive medication differed between the genders. In the younger age group, women received less preventive medications, whereas in the older age group women received more preventive medications than similarly aged men.

In publication II, it was concluded that the pre-hospital case-fatality had declined more slowly among <55 year old women from the mid-1990s to the 2000s. As stated earlier, pre-hospital mortality is considered to be an indicator of prevention, especially of primary prevention. In addition to the population prevention approach affecting the whole population through health education, legislation and tax policies, also a high-risk approach is needed to identify those individuals at high-risk for suffering a CVD event since it is the best way to target intensive therapy as effectively as possible. In the present study the prevalence of high-risk was almost the same in young women as in similarly aged men, and this was mostly due to diabetes. Here, the prevalence of high-risk was close to the diabetes prevalence reported among the working-aged subjects (1). As could have been expected in the younger age group, only a few (0.03% of young women and 1.2% of young men) high-risk subjects could be identified using the Framingham risk score (>20% absolute risk to either die or to have CHD or stroke event within the next 10 years). It is well known that absolute risk charts may seem to indicate a low risk even though young subjects may have a high relative risk. Clearly, prevention would be efficient in these younger subjects. However, it has been also suggested that risk scores have a lower sensitivity of high-risk identification in females. Ketola et al. studied risk prediction models among >25 000 subjects aged ≥40 years and without prior CVD in the FINRISK Survey years 1972-1992. The subjects were followed for 10 years, and CVD events were identified from administrative registers. The Framingham risk score >20% to predict CVD events had 47% sensitivity and 79% specificity among men, whereas the sensitivity was only 7% in women with specificity of 98%. The same study also showed 88% sensitivity and 40% specificity for CVD mortality among <55 years old men with Framingham score >10%, and the corresponding numbers for women <55 years were 41% and 84% (292). This indicates that the Framingham score has good or even high specificity among women, but at the same time low sensitivity to identify those women with an increased risk to experience a CVD event or to die of a CVD event.

High-risk status identified from chart algorithms often is used as a guide for the initiation of preventive medications. However, it has been reported that physicians assign a lower risk category to women than men with similar Framingham risk scores, and these risk classifications also are known to influence their treatment decisions (293). It has been claimed that physicians use these risk classification charts insufficiently in primary care,

mostly since they are concerned of exaggerating the need for medical therapy and perhaps partly due to the lack of time. The ESC guidelines working group reported that 85% of cardiologists and physicians knew they should base CVD risk assessment on the evaluation of overall CVD risk. But nonetheless, only 62% of them used those scores (166). One in every four men aged ≥40 years have been estimated to belong to the high-risk group when the Framingham risk score >20% equation is used, compared to a mere 2% of women (292). When estimated at the age of 40 years the actual remaining lifetime risk for CHD is one in three for women, and one in two for men (2).

In order to improve high-risk prevention and identification in young individuals, the ESC has launched relative risk charts, and AHA has introduced the concept of vascular age (166, 191, 241). The use of relative risk chart and extrapolation to higher ages are advised to be used only in targeting lifestyle intervention, but not to be considered as a basis for initiating medication (166). The use of these tools may help to identify women with unhealthy lifestyle, and to guide in lifestyle management before the absolute risk score is fulfilled at high-or intermediate risk level.

CVDs are mostly due to an unhealthy lifestyle, and the pathogenesis of CVDs is a continuum of decades or a lifetime, and therefore, the prevention should also be equally long-sighted. Women are considered to be protected during their fertile years, and only to be at risk after that period. This concept is based on event numbers, and does not take into account the fact that atherosclerosis develops over decades. In women, the risk factor levels present at a young age, i.e. prior menopause, have been suggested to predict the vascular risk 20-30 years later, and subclinical atherosclerosis has been shown to be as prevalent among women with an early menopause as it is in men matched for age and traditional risk factors (294, 295). The optimal timing of the lifestyle guidance for women should be further refined. Lifestyle guidance would probably be more beneficial when given to women prior to, or early in the menopausal transition, since physiological changes increase the risk factor levels during the menopausal transition and in the following decade. In addition, atherosclerosis rapidly progresses in women after the menopause. Now the ESC guidelines of 2012 consider that in women aged ≥50 years or who are postmenopausal, the CVD risk should be evaluated to determine whether or not the person has a high-risk (166).

Currently, none of the risk estimating tools includes risk factors specific for women, namely, early menopause, pre-eclampsia or gestational hypertension or gestational diabetes in the total risk estimation. The AHA guidelines for women include pre-eclampsia, gestational hypertension and gestational diabetes as risk factors and for these women the overall risk estimation is recommended (191). With increasing knowledge of the gender difference in CVD prevention, gender-specific guidelines may become available in the future.

In this study, the overall risk factor target levels were poorly achieved. High-risk young men were more often achieved lipid targets, but the levels of other risk factors were poorer compared to similarly aged women. Women received less preventive medications compared to men. This overall excess of risk factors has been shown to explain almost completely the overall higher CVD morbidity in men when compared to women (10, 11). Among the older age group, the target values were achieved equally in both genders, and more women used preventive medications than men. The overall risk factor treatment has been shown to be poor among high-risk subjects throughout Europe (245). In this study,

acetylsalicylic acid was less often used by young women who were at a high-risk for CVD compared to men of a similar age, but more equally between men and women in the older age group. Current ESC guidelines do not recommend the use of acetylsalicylic acid in subjects without established CVD due to the increased risk of bleeding (166). In the meta-analysis by Berger et al. acetylsalicylic acid prevented CVD events, with the risk of bleeding being similar in both genders. The clinical end-point that was prevented differed between the genders. In men acetylsalicylic acid prevented MI events, and in women it inhibited stroke events, but had no effect on MI prevention (249).

Here those subjects with prevalent CVD, i.e. subjects in secondary prevention, risk factor treatment was applied equally insufficiently in both genders. Current ESC guidelines recommend that initial treatment should be with beta-blocker, statin, ACE inhibitor/ angiotensin receptor II blockers and acetylsalicylic acid, unless contraindicated, in subjects with ACS (166). In subjects with ischemic stroke, acetylsalicylic acid plus dipyridamol or clopidogrel are recommended. There was no information available on the use of dipyridamol or clopidogrel in this study. EUROASPIRE III and REACH register studies, with larger cohorts than here, confirmed the lower use of antithrombotic agents in women (250, 296). Acetylsalicylic acid use has been confirmed to be beneficial in both genders in subjects who already suffered had a CVD event (166). Lipid lowering drugs were used in our study equally in women and men. However, the numbers of women were small. In larger register studies, the results are conflicting: in EUROASPIRE III, statins were reported to be prescribed equally commonly but in the REACH register study, women had a lower chance receiving lipid-lowering medication (250). A German register study pointed out a 74% reduction in total mortality among subjects who used optimal medical therapy (listed above) over 1-year after ACS. This reduction was similar in both genders and in subjects with diabetics (297). Interestingly, the REACH register study reported similar rates of the combined endpoints of CVD death, MI and stroke in both genders despite the lower use of preventive medication and overall poorer risk factor management in women. The REACH study authors concluded that if secondary prevention could be improved in women, this might well reduce event rates (296).

Diabetic subjects were divided into two-groups in the ESC 2012 guidelines, i.e. subjects with very -high or high -risk. A very high-risk was considered to be present if in addition to diabetes there were one or several other CVD risk factors (hypertension, smoking, hyperlipidaemia) or a target organ failure. The other diabetic subjects were considered to be at a high risk. The AHA Guidelines for CVD prevention in women consider diabetes as a high-risk feature without any other requirements (166, 191). In this study, diabetes was considered as a high-risk feature, in line with those recommendations used in 2010-2011 and we did not further classify diabetic persons as high and very high risk. Nevertheless, young women with diabetes were being treated with significantly less preventive medications compared to men, a fact which was not apparent in the older age group. The current guidelines recommend statin therapy regardless of gender and baseline LDL, targeting LDL cholesterol levels to <1.8mmol/l in individuals in this very-high risk group. With respect to the diabetics in the present study, LDL was >2.5 mmol/l in 80% of young women (vs. 66% of young men) and in 68% of older women vs. 48% in men according to FINRISK survey of 2007. Acetylsalicylic acid is no longer recommended for diabetic persons without established CVD or other high-risk features (166). Under-treatment of blood pressure and blood cholesterol levels, especially among diabetic women has been also detected in other studies (298).

6.6 Gender differences in the incidence and clinical spectrum of major adverse CVD events (Study IV)

As was expected, men experienced two times more incident major adverse CVD events compared to women. Men suffered four times more fatal CHD events, and three times more non-fatal CHD events. The male/ female ratio was larger in the younger age group (seven times more fatal and four times more non-fatal events in men). In the older age group, the differences were evident, but smaller (three times more fatal and non-fatal events in men). In the Framingham study, gender differences in CHD were examined in detail, and in the 26-year follow-up the male-to-female ratio was ~ 6.5 in the age group of 35-44 years old, ~ 3.2 among 45-54 years old, ~2.2 among 55-64 years old, but after that the ratio was equal (23). In fact the ratio became reversed among subjects >75 years old (23). Wagner et al. recently reported male to female ratio of 3.4 for fatal CHD among 35-54 year old subjects and 2.4 for subjects aged 55-74 years in France, evidence for smaller gender differences in fatal CHD between the genders than in Finland (37). As already mentioned, the risk factors explain most of the observed gender differences (10, 11). In France, the average blood cholesterol levels in population are comparable to those in Finland. The mean blood pressure is slightly lower, but the prevalence of obese subjects is slightly higher than in Finland. Furthermore, the prevalence of smoking is higher among women in France, and it increased from 16.6% from the end of 1980s to 21.5% in 2007 among 45-54 year old women (1, 37).

Non-fatal CHD events were the most common CVD presentation in the men in both age groups, as was expected. Fatal CHD events occupied the 4th place in the clinical spectrum in all groups. Twelve percent of first CVD events were fatal in 55-74 years old men and the value was 10% in younger men. The high-risk situation is probably identified more readily in men than in women, but the general risk factor levels are poorly treated, and improvement is needed in both genders. Even though in women the proportion of fatal events were substantially lower than in men, 2.8% of women´s first CVD events were fatal CHD events in the young age group and 6.3% in the older age group. Due to the possibility of the lack of symptoms prior to the first clinical event, which may be fatal, total risk estimation and risk factor identification are important if one wishes to change this situation. This is even more so in women, in whom a larger proportion than men do not have any symptoms suggestive of CHD before death (2). Nevertheless, if one wishes to avoid fatal events then both the high-risk approach and the population level approach are needed in prevention. These male-female ratios do not depict the overall CHD burden, since stable angina was not included; if it had been, the ratios might have been closer to each other.

The incidence of heart failure did not differ between the genders in this study, and it was the most common first CVD presentation in women in both age groups. The heart failure incidence numbers differ between the sources: the present incidence numbers were consistent with those reported by Roger et al. from the Olmsted County cohort, Minnesota (95). In that study both Framingham criteria and clinical criteria were used in the heart failure diagnosis, and men were found to have higher heart failure incidence than women (95). In a study from the United Kingdom, the rate-ratio was 1.4 for men in heart failure diagnoses made by GPs (99). However, it is likely that women are diagnosed with heart failure less often than men, since women have more HF-PEF, the diagnostic criteria of which have only recently been established. Mosterd et al. reported an equal prevalence of

heart failure in both genders in the general population of the Netherlands when the clinical definition for HF was used (106).

Hypertension was the most common predisposing factor preceding heart failure in the present study, but in men CHD preceded heart failure more commonly than in women. In general, a total of 75% of all heart failure cases have been estimated to have preceding hypertension (2). The Rotterdam study suggested that hypertension had a stronger role as a contributing factor in women than in men (106). Dunlay et al. evaluated population attributable fractions of heart failure using Olmsted County, Minnesota and Rochester Epidemiology Project resources, and concluded similarly that hypertension had a larger role in heart failure in women. Population attributable fraction of heart failure due to hypertension was 28% in women and 20% in men (299). The gender differences in blood pressure levels are multifactorial and poorly understood. Women have lower rate of hypertension until the age of 45. At the age of 45 to 64 years men and women have similar rates of hypertension, whereas after the age of 65 years more women (69 %) than men (64%) have hypertension (2). In the United States, the prevalence of hypertension is estimated to be 34% among adult males and 33% among adult women (2). The prevalence of hypertension in Europe has been reported to be higher. Wolf-Maier et al. studied blood pressure values in several European countries, and found that the overall prevalence of hypertension was 44% in adult population in Europe (300). Finland was also included in that study, and had one of the highest blood pressure levels and prevalence among subjects aged <60 years old (300). The prevalence of hypertension in Finland among the working-aged population was 49%, (55.7% in men and 42% in women). The study of Kastarinen et al. revealed, that working-aged women had better awareness of high blood pressure, they were more likely to be using antihypertensive medications and a higher proportion of them reached target levels than men (awareness 73%, treatment 55%, control 40% in women vs. 63%, 49%, 34% in men) (301). Respectively, in the United States, where among adults a lower prevalence of hypertension than in Finland has been reported, the proportion of subjects aware of hypertension is higher (79.6%), and 70.9% hypertensive subjects are being treated and almost one in every two (47.8%) have their hypertension under control (2). This indicates that more efficient measures are needed in this field in Finland. In addition, the increasing prevalence of obesity, which is a risk factor for heart failure, also after adjustment for hypertension, may have an impact on the similar heart failure incidence in women and men, since obesity may be a stronger risk factor in women than in men (188). Dunlay et al. studied temporal trends in heart failure risk factors, and when comparing the 1970s to the 2000's they emphasized the increasing significance of obesity and hypertension as predisposing factors (299).

The unique risk factors for heart failure in women are the pregnancy-related disorders. Ray et al. retrospectively combined women with different placental syndromes during pregnancy and compared the risk for being hospitalised due to heart failure or dysrhythmias to women with a normal pregnancy, and found that there was a 1.5 times higher risk in women with the history of placental syndrome to be hospitalised during a median follow-up time of 7.8 years (219). The mean age at the time hospitalisation was <40 years (219). In this respect, prospective studies of maternal complications and the risk for subsequent heart failure are needed. However, a recent systematic review revealed that women with pre-eclampsia had double the risk for early cardiac, cerebrovascular and cardiovascular mortality, including fatal heart failure, when they were compared to women without pre-eclampsia (190). Chronic hypertension is a risk factor for pre-eclampsia and certain blood pressure medications are contraindicated during pregnancy.

However, pre-eclampsia had a separate independent role beyond hypertension in the later risk for CVD (190, 219, 302, 303). One of the potential mechanisms for this could be the endothelial dysfunction associated with pre-eclampsia but there has also been speculation on the role of possible damage to the kidneys caused by pre-eclampsia (190, 304, 305).

When considering all age groups in the whole population, CHD plays the largest causal role in heart failure development, and explains 60% of heart failure cases in general population and 23% of heart failure cases in men (299). It is also possible, that due to the high prevalence of heart failure during the acute presentation of ACS among women, and due to more atypical symptoms in women compared to men, underlying CHD might remain undiagnosed (62). During an acute CHD event, women have been reported to have a higher rate of heart failure and prior heart failure diagnoses (6, 57, 62).

The incidence and prevalence of heart failure has not changed; it may even have increased due to the aging of western populations, and increasing prevalence of known predisposing factors such as: diabetes, obesity and excess alcohol consumption (1, 95, 98). In addition, better survival due to improved management of MI may be reflected in two ways; better survival increases the number of those who are at risk of subsequent heart failure and, on the other hand, due to better treatments MI events may not be so severe to evoke heart failure as frequently as earlier (306). The prevalences of obesity, diabetes and alcohol consumption have also increased in Finnish women (1). The finding that heart failure was the first incident CVD event among young women is alarming because of the high mortality related to heart failure. Unfortunately, clinical data on EF was not available in the present study population. Heart failure with preserved EF has been shown to be more common in women, and despite the better prognosis of this type of heart failure, the mortality is still high, and since there is no proven therapy for this type of heart failure the survival rates have not changed (93).

In this study, men had a 30-70% excess in the incidence of strokes, depending of age group, when compared to women. Stroke was the second most common adverse CVD event among young women, and the third most common in older women. Appelros et al. calculated the age-adjusted pooled incident male/ female rate ratio from 44 different population-based studies, and found a male excess of 33% (75). In this study, the male/ female rate ratio was higher, 1.6, in 25-74 year old subjects. However, this is explained by the age groups. The incidence peak of stroke is known to occur in the age group of over 75–years, and even higher incidence rates have been reported among women over 85 years old than in men (76). In Appleros's study, the pooled rate ratios among younger age groups (<55 years) were in a range of 1.42-1.49, which are in the same order of magnitude of the value of 1.3 found here in the younger age group (75). Hypertension is the most important risk factor for stroke, and the prevalence of hypertension in the general population is closely associated to stroke mortality (87, 300). In the study by Wolf-Maier et al., Finland had the highest stroke mortality out of eight countries studied in its working-aged population (300).

In summary, men suffer a higher incidence of major adverse CVD events, except for heart failure. Further studies are needed to clarify the gender differences in the relative burdens of different CVDs and their risk factors. If it were possible to understand the gender differences and the unique risk factors for women this could have important implications since it could lead to more focused CVD prevention, eventually achieving a reduction in the overall CVD burden.

7 Conclusions

I) ACS mortality, incidence and attack rate have declined more slowly among younger (<55 years old) women in Finland from 1994-1996 to 2000-2002 than older women and men. This slower decline in incidence may have partially been caused by technical advances, i.e. the adoption of troponin measurements. The slower mortality decline, however, cannot be explained by troponins since troponin evaluation does not play a major role in fatal cases.

II) The ACS case-fatality has declined among both genders between 1994-1996 and 2000-2002. The decline in ACS case-fatality was slower among <55 years old women than older women and in men. The slower pre-hospital and first day case-fatality declines among young women explained the gender differences detected in the 28-day and 1-year case-fatalities. The slower pre-hospital case-fatality decline may have been caused by risk factor changes in Finland, or by poorer detection and inadequate treatment of these high-risk younger women.

III) The prevalence of high CVD risk was almost the same in both genders in the FINRISK cohorts pooled for the years 1992-2007. The most common cause of high risk was diabetes among young subjects, whereas among older persons the proportions were more equally distributed between Framingham score >20%, prior CVD and diabetes. However, older men had more prior CVD events. The overall risk factor target levels were poorly achieved. Young women received fewer preventive medications than other groups. The high-risk status seemed to be poorly recognised among young women.

IV) As expected, men had a higher rate of all incident major adverse CVD events (non-fatal and fatal CHD events and stroke) than women. The incidence of heart failure was equal in both genders. Women and men differed in the clinical spectrum of the first CVD event: the most common incident event was a non-fatal CHD event in men and heart failure in women. This difference in the clinical spectrum was similar in both age groups (<55 years old and 55-74 years old).

8 Summary

This study was carried out to compare trends in incident fatal, and non-fatal acute coronary events, and to determine if there were differences in the prognosis of acute coronary events between the genders from the mid-1990s to the beginning of the 2000s. It was also decided to investigate gender differences in the prevalence of high CVD risk at the population level, attainment of the guideline- recommended treatment targets in major risk factors, and the use of preventive medications. In addition, male-female incidence ratios in major adverse CVD events (fatal and non-fatal CHD, stroke and heart failure) were estimated, and it was examined whether there were differences in the clinical spectrum of the first CVD event between the genders. The age groups were <55 years and ≥55 years.

In studies I and II the acute coronary events were identified from the FINAMI and CVD registers, and two time periods 1994-1996 (prior to troponins) and 2000-2002 (after the adoption of troponins) were compared. A total of 10 150 subjects ≥35 years old were included from the FINAMI register and 149 173 from CVDR. In study II when the two time periods were combined, a total of 6324 incident fatal acute coronary events were identified from the FINAMI register and 117 632 from the CVDR. In study III, the FINRISK years 1992-2007 were pooled, and a total of 29 272 subjects aged 25-74 years were included. We identified 3057 high-risk men and 1365 high-risk women. The high-risk status was considered to be present, if a subject either had a Framingham Score > 20% for 10 years, or had diabetes or a history of a prior CVD event. In study IV a total of 27 870 persons, who were healthy at the time of their participation in the FINRISK survey were followed to the end of 2010. The incident adverse CVD events were recorded from the Hospital Discharge Register and the Causes of Death Register. Heart failure diagnoses were also gathered from the National Insurance Institute's Pharmacy database and the Drug Reimbursement Register.

Study I: Generally, acute coronary event rates have declined in Finland between the study time periods. Incident events and all events declined more slowly among <55 years old women compared to men and older women according to both registers. Mortality declined more slowly in young women than other groups. Negative binominal regression models using CVDR data revealed significant gender by year interactions. When expressed as RR for the younger age group, then the RR was 1.04 for incidence (p=0.01), 1.04 (p=0.01) for attack rate and 1.04 (p=0.03) for mortality rate.

Study II: The prognosis of acute coronary events has improved during the study periods. The 0-27 day and 0-364 day case-fatalities declined more slowly among young (<55 years old) women than in men and older women. However, 2-27 day case-fatality changes were equal in both genders, as were the 2-364 day case-fatalities. This indicates that the slower pre-hospital mortality decline was responsible for the poorer improvement in the short- and long-term prognosis among young women. The OR of pre-hospital death was significantly elevated in young women: In FINAMI the sex-by-study-period interaction in the age group of <55 years old was 2.03 with 95% CI of 1.08-3.82, and correspondingly in CVDR, the OR was 1.35 with 95% CI 1.11-1.63.

Study III: A high CVD risk was almost as common in women as in men in the younger age group (5.3% in men vs. 4.3% in women). In the older age group, high-risk was more common in men (51.2%) than women (24.5%). In general, risk factor management was poor. Younger high CVD risk women used fewer preventive medications, whereas in the older age group women tended to use more medications than similarly aged men.

Study IV: Men had almost two times more incident major adverse CVD events than women. Men had almost four times more fatal CHD events, three times more non-fatal CHD events, and almost two times more strokes than women. The incidence of heart failure was similar in both genders (male/ female-rate ratio of 1.1 with 95% CI 0.9-1.2). The most common incident event was a non-fatal CHD in men and heart failure in women. This gender difference was similar in both age groups of 25-54 years and 55 -74 years.

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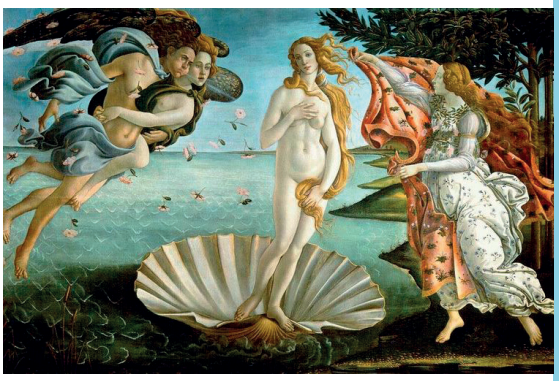
The picture on the cover of the thesis: "The Birth of Venus". Sandro Botticelli, ca. 1485-1486. Galleria degli Uffici, Florence, Italy.

Hanna-Riikka Lehto

Gender Differences in the Occurrence, Prognosis and Risk Factor Control of Cardiovascular Disease



Cardiovascular diseases (CVDs) have remained the main cause of death in Finland. CVDs, especially coronary heart disease, have traditionally been considered to be diseases predominantly affecting men. However, each year more women than men die from CVDs both in Finland and globally. The aim of this study was to examine gender differences in CVD occurrence, prognosis and preventive treatments in Finland.

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