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HYPERTENSION – EPIDEMIOLOGICAL STUDIES OF PREVALENCE, PREVENTION, TREATMENT AND PROGNOSES IN MEN AND WOMEN

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ABSTRACT

Background and aim Hypertension is ranked as the leading risk factor for mortality and the third most common factor leading to disability in the world. Detection, treatment, prevention and control are thus of high priority. The aim was to study the prevalence of both diagnosed hypertension and newly diagnosed high blood pressure and how well diagnosed hypertension is treated in Stockholm County. In addition, we aimed to find factors that might be helpful in the prevention and control of hypertension by studying factors associated with newly diagnosed high blood pressure, and factors associated with hypertension control. Finally, we aimed to study age-adjusted mortality in men and women with different baseline blood pressures during a 26-year follow-up.

Material and methods Two population-based samples were used in the studies. One comprising 4232 men and women aged 60 years was used for cross-sectional studies; the other comprised 2578 men and women with a 26-year follow-up in the National Cause of Death Register. The participation rate was high (≈80%) in both studies and study participants were thoroughly investigated, making adjustments for many variables possible. Blood pressure was measured on one occasion in both studies.

Results The total prevalence of hypertension (in 60-year-olds) was 62% among men and 45% among women. In Swedish-born individuals (n=3327) the prevalence was 61% in men and 44% in women, among Finnish-born individuals (n=327) it was 77% in men and 62% in women. Only 22% of the men and 33% of the women with diagnosed hypertension had a blood pressure below 140/90 mmHg. All individuals with diagnosed hypertension and a goal blood pressure had antihypertensive therapy. Both men and women had multiple cardiovascular risk factors in addition to their hypertension. Waist circumference ≥95 cm (quintiles 3–5) in men and ≥88.5 cm (quintiles 4–5) in women was associated with newly diagnosed high blood pressure. Secondary school was negatively associated in men, OR 0.73 (0.54–0.99), and university education was negatively associated in both men, OR 0.66 (0.52–0.85), and women, OR 0.45 (0.34–0.59). Regular physical activity was negatively associated in women OR 0.77 (61–0.99), and high alcohol consumption (> 30 g/day) was positively associated in men, OR 1.60 (1.22–2.09). Female gender was negatively associated with newly diagnosed high blood pressure, OR 0.50 (0.41–0.61). The 26-year follow-up revealed that the hazard ratio for all-cause mortality in those with very high blood pressure, ≥ 160 and/or 95 mmHg, was 1.93 (1.38–2.70) in men and 2.29 (1.42–3.69) in women. High blood pressure, ≥ 140 and/or 90 but < 160 and 95, and prehypertension ≥ 130 and/or 85 but < 140 and 90 were significant in women but not in men. Hypertension as a risk factor appears to be independent of healthcare needs, a proxy for co-morbidities.

Conclusion High prevalence and poor control of hypertension were found in this Swedish cohort, despite better opportunities for combating hypertension than are available in most parts of the world. Based on the findings in this thesis, prevention of hypertension needs to be gender specific, and should focus on physical exercise to reduce waist circumference in both men and women. Elevated blood pressure should be given just as high priority in patients with co-morbidities as in otherwise healthy individuals. Hypertension should receive more attention in Sweden; the high prevalence and poor control may otherwise lead to premature death, and unnecessary suffering and healthcare costs. Societal changes are needed as well as intensive screening, prevention and antihypertensive therapy.

To my mother and father

"The good life is one inspired by love and guided by knowledge."
Bertrand Russell (What I Believe, 1925)

Every morning in Africa, a gazelle wakes up.
It knows it must run faster than the fastest lion or it will be killed.
Every morning a lion wakes up.
It knows it must outrun the slowest gazelle or it will starve to death.
It doesn't matter whether you are a lion or a gazelle.
When the sun comes up, you better start running.
Ancient African proverb

"In the fields of observation, chance favours only the prepared mind."
Louis Pasteur (1822–1895)

LIST OF PUBLICATIONS

This thesis is based on the following original articles, which will be referred to in the text by their Roman numbers.

I   **Axel C Carlsson,** Per E Wändell, Ulf de Faire, and Mai-Lis Hellénius Prevalence of hypertension in immigrants and Swedish-born individuals, a cross-sectional study of 60-year-old men and women in Sweden. ***Journal of Hypertension,*** *2008; 26: 2295–2302*.

II   **Axel C Carlsson,** Per E Wändell, Gunilla Journath, Ulf de Faire, and Mai-Lis Hellénius. Factors associated with uncontrolled hypertension and cardiovascular risk profiles in hypertensive 60-year old men and women -a population-based study. ***Hypertension Research,*** *2009; 32:780–785.*

III   **Axel C Carlsson,** Per E Wändell, Ulf de Faire, and Mai-Lis Hellénius. Risk Factors Associated With Newly Diagnosed High Blood Pressure in Men and Women. ***American Journal of Hypertension,*** *2008; 21: 771–777.*

IV   **Axel C. Carlsson**, Holger Theobald, Mai-Lis Hellénius and Per E. Wändell. Cardiovascular and total mortality in men and women with different blood pressure levels – A 26-year follow-up. ***Blood Pressure,*** *2009; 18:105–110.*

LIST OF OTHER PUBLICATIONS BY THE AUTHOR

The thesis is not based on the following original articles to which the author contributed. In cases where they appear in the text they will be cited as references.

V **Axel C Carlsson**, Per E. Wändell, Mats Halldin, Ulf de Faire and Mai-Lis Hellénius. Is a Unified Definition of Metabolic Syndrome Needed? Comparison of Three Definitions of Metabolic Syndrome in 60-year-old Men and Women. ***Metabolic Syndrome and Related Disorders,*** *2009; 7: 231–241.*

VI Per E Wändell, **Axel C Carlsson** and H Theobald. The association between BMI value and long-term mortality. ***International Journal of Obesity,*** *2009; 33: 577–582.*

VII Per E. Wändell, **Axel C Carlsson** and Holger Theobald. Effect of heart-rate recovery on long-term mortality among men and women. ***International Journal of Cardiology****, published online ahead of print February 2009.*

VIII Per E Wändell, **Axel C Carlsson**, Ulf de Faire, and Mai-Lis Hellénius. Prevalence of blood lipid disturbances in Swedish and foreign-born 60-year-old men and women in Stockholm, Sweden. *Accepted for publication in* ***Nutrition Metabolism and Cardiovascular Disease****.*

IX Per E Wändell, **Axel C Carlsson**, Kristin Hjörleifsdottir Steiner. Prevalence of diabetes and metabolic syndrome among immigrants in the Nordic countries. Systematic review. *Submitted.*

X Gunilla Journath, Mai-Lis Hellénius, **Axel C Carlsson**, Per E. Wändell and Peter M. Nilsson, for the Hyper-Q and EKO Study Groups, Sweden. Physicians' gender is associated with risk factor control in patients on combined antihypertensive and lipid lowering treatment. *Submitted.*

XI **Axel C Carlsson**, Holger Theobald and Per E Wändell
Are Clinical Blood Pressure Decisions Based on the Best Available Blood Pressure Measure? Findings from a Long-term Mortality Follow-up of Mean, Mid and Pulse Pressure Compared with Clinical Guidelines. *Submitted.*

XII **Axel C Carlsson**, Holger Theobald and Per E Wändell.
Health factors and longevity in men and women. *Submitted.*

XIII Per Wändell, **Axel C Carlsson**, Katarina Andersson, Catharina Gåfvels and Lena Törnkvist. Tactile massage versus relaxation exercises as treatment for type 2 diabetes – a randomized controlled trial. *Submitted.*

CONTENTS

1 PREFACE

Hypertension is one of the four classical risk factors for cardiovascular disease. the other three are dyslipidaemia, smoking and diabetes [1, 2]. In my work as a community pharmacist, pharmacologically treated hypertensive patients are very common. I like to ask them if they have reached a goal blood pressure and I answer any questions that they may have regarding their hypertension and their therapy. I have noticed that many do not know if their blood pressure is under control and if they want, I measure their blood pressure. I have posed many questions to myself, and in this thesis I have managed to answer them to some degree.

How is hypertension treated and controlled in the population? How can hypertension be prevented? What risk factors do patients share who have uncontrolled, treated hypertension? Which individuals are at high risk? Is any immigrant group at risk, and could environment or genetics explain excess risks? How well does blood pressure predict future mortality?

I will try to provide answers to these questions from the literature and based on my findings in this thesis. The ideas leading to this project started while I was working at a pharmacy in Hallunda, a Stockholm suburb with many immigrants. I noticed that, contrary to what is recommended in the US, people of African origin received basically the same antihypertensive therapy as Swedish-born individuals. My main supervisor, Per Wändell was working part time as a general practitioner at the community medical clinic in Hallunda and I contacted him and asked if he was interested in doing hypertension research on immigrants. The papers in the present thesis are not primarily on hypertension in immigrants, but we have wide-ranging plans for future research together concerning hypertension and cardiovascular disease in immigrants. The papers in the present thesis focus more on the challenging situation regarding hypertension. I hope the thesis will contribute to a better understanding of how serious the situation regarding hypertension is in Sweden. Based on the improved knowledge concerning the situation in Sweden, further studies of specific groups such as immigrants from specific countries will be easier.

Axel C Carlsson

2 BACKGROUND

2.1 WHAT IS HYPERTENSION?

Arterial blood pressure is dependent on two things, the strength with which the heart pumps blood and the peripheral resistance in the blood vessels, mainly arterioles. Hypertension is often defined as elevated blood pressure above 140 mm Hg systolic and/or 90 mmHg diastolic, measured on three occasions. For individuals with diabetes, end organ damage or the metabolic syndrome, blood pressure levels as low as 130/80 mmHg are defined as hypertension [3].

In epidemiological studies, however, hypertension is commonly defined as above 140 and/or 90 mmHg measured on one occasion which overestimates the true prevalence. Blood pressure measured on one occasion is far better than self reported hypertension which greatly underestimates the prevalence. Blood pressure levels as low as 115/75 mmHg can be linked to cardiovascular events in middle aged and older individuals i.e. far below the treatment goal of 140/90 [4].

2.2 HOW COMMON IS HYPERTENSION IN THE POPULATION?

In populations with Western lifestyles the systolic blood pressure increases continuously with age, leading to a lifetime prevalence of hypertension of nearly 90% [5]. The relationship between diastolic blood pressure and age is not as prominent [6], and isolated systolic hypertension is the most common type of hypertension in individuals over the age of 60 [7].

The estimated total number of adults worldwide with hypertension in 2000 was 932 million, a number that is expected to grow dramatically with urbanisation and adaptation of the Western lifestyle in the developing world [8]. Nationwide American studies reported that the prevalence of hypertension in the adult population (individuals above 18 years of age) was nearly 30% [9, 10]. The prevalence is highly dependent on the age of the hypertensive patients [11], resulting in higher prevalence figures in countries with older populations. The prevalence is generally lower in women than in men up until menopause, when the prevalence increases to the level seen in men [3, 5]. Large scale population-based investigations are, however, still sparse and the true prevalence in the population is therefore not fully known [12]. In fact, hypertension awareness, treatment and control vary greatly in different studies from around the world [13], and in populations of different countries in the same study [14]. Variations in hypertension prevalence in different ethnic populations within a country have been studied in London, England [15] and in Pakistan [16]. The high prevalence figures for hypertension that have been reported in studies of immigrant groups may also be attributed to acculturation to Western society [17], implying psychosocial stress and unfavourable lifestyle changes such as physical inactivity and unhealthy diets.

2.3 WHAT ARE THE MAIN CARDIOVASCULAR RISK FACTORS?

2.3.1 Classical risk factors

The most established risk factors for coronary heart disease are hypertension, cholesterol and blood lipid disturbances, i.e. dyslipidaemia, tobacco smoking and diabetes [1]. Among individuals with coronary heart disease over 80% have at least one of these four risk factors [2]. This does not mean that other factors are less important, it merely means that they are very prevalent in individuals with coronary heart disease. The "INTERHEART study" was a case-control study of acute myocardial infarction performed in 52 countries. In addition to the four classical risk factors mentioned above, risk factors of importance were abdominal obesity and psychosocial factors, and health factors were regular physical activity and consumption of fruits, vegetables, and alcohol [18, 19]. The Copenhagen City Heart Study followed 12 000 men and women for 21 years [20]. The most important risk factors were diabetes, hypertension, smoking and physical inactivity.

Apart from being a major risk factor for coronary heart disease, hypertension is the most important factor predisposing to stroke, and it is present in more than 70% of all cases [21]. Other factors of importance for stroke from the Framingham Study are age, systolic blood pressure, diagnosed, treated hypertension, diabetes mellitus, cigarette smoking, coronary heart disease, cardiac failure, intermittent claudication, atrial fibrillation and left ventricular hypertrophy [22].

2.3.2 Emerging risk factors

Several other risk factors for cardiovascular disease are also emerging. These include C-reactive protein, fibrinogen and apolipoproteins [23]. Apolipoproteins have been proven to be stronger predictors of myocardial infarction in both a case-control (INTERHEART) and a cohort study (NHANES III) than conventional measures of blood lipids [24, 25]. The ratio ApoB/ApoAI has been suggested as the best measure of apolipoproteins, and there are cut off levels for high cardiovascular risk as well as very high cardiovascular risk [26]. This is a very robust method and the subject does not need to be in the fasting state. The apolipoprotein ratio therefore has the potential to replace total cholesterol, LDL, HDL and triglycerides in clinical practice.

C-reactive protein has recently received a great deal of attention as well. It was shown that individuals with normal or low levels of low density lipoprotein cholesterol and high C-reactive protein levels had large risk reductions with statin therapy in the JUPITER study [27]. However, there is a problem with causality in this study, as the participants had a high cardiovascular risk apart from their blood lipid levels. The evidence that C-reactive protein is being lowered by statin therapy is not sufficient. It may merely prove that lowering LDL beyond normal levels is beneficial in high risk individuals.

Elevated plasma fibrinogen was shown to independently predict future strokes in the Copenhagen Heart Study [28]. Fibrinogen is involved in the blood clotting process, which explains the association.

Another cardiovascular risk factor is a low heart-rate-recovery after exercise. Several recent studies have shown that it is independent of other cardiovascular risk

factors [29]. Heart rate at rest is easy to measure and there is convincing evidence that it is a risk factor. Higher risks have been seen in individuals, especially men, with heart rates exceeding 75 beats per minute [30-32].

2.4 A HEALTHY LIFESTYLE AND CARDIOVASCULAR DISEASE

A growing body of evidence supports the combined effect of healthy lifestyle factors in the prevention of cardiovascular disease [33-38]. There are five factors that repeatedly stand out in international studies and appear to have the power to prevent and postpone cardiovascular disease: physical activity, a prudent diet (including fruit, vegetables, legumes, whole grain, white meat and fish), normal weight / small waist circumference, moderate alcohol consumption and non-smoking. It may be argued that normal weight is more of a health factor than a lifestyle factor; however, the combined effects of these factors are dramatic. The traditional pattern of alcohol intake in Sweden with large amounts over a short period of time, i.e. binge drinking, has been shown to increase the risk of stroke [3] and coronary heart disease in a meta-analysis [39]. It is therefore debatable as to whether moderate alcohol consumption has any beneficial effects in the Swedish population.

2.5 HYPERTENSION AND THE METABOLIC SYNDROME

Hypertension is one of the features of the metabolic syndrome: the others are abdominal obesity, insulin resistance, hyperglycaemia and dyslipidaemia. This syndrome is a cluster of common cardiovascular risk factors that appear concomitantly in many hypertensive individuals. If one of these factors is diagnosed, the others should be screened for. An increased risk of developing type 2 diabetes, cardiovascular disease and all-cause mortality has repeatedly been seen in individuals with the metabolic syndrome, [40-42]. Views differ concerning the syndrome. One of the largest studies on the risk of cardiovascular disease in individuals with the metabolic syndrome concludes that by themselves, the individual risk factors provide more risk information than if the criteria for the metabolic syndrome are met based on any current definition [43]. This is also in agreement with a review article that focuses on therapeutic goal management of individual risk factors [44]. Physical activity, as well as aggressive drug treatment of hypertension and blood lipids, are therefore recommended in individuals with the metabolic syndrome. The syndrome has been defined differently by several organisations including the World Health Organisation, the International Diabetes Federation, the European Group for the study of Insulin Resistance and the National Cholesterol Education Program Adult Treatment Panel III. This is troublesome, as the different definitions identify different individuals, which makes it difficult to compare scientific findings [45]. We have chosen to use the National Cholesterol Education Program Adult Treatment Panel III definition as it is widely used, considers all factors equally and consists of factors measured in primary care [46].

2.6 WHAT HAPPENS IF HYPERTENSION IS LEFT UNTREATED?

In a study of malignant hypertension published as early as 1958, that showed a 7-year mortality of 62%, the authors concluded that "treatment should be withheld only in the most desperate circumstances" [47]. In a 20-year follow-up of 704 individuals concerning the natural history of hypertension (without antihypertensive treatment) that was published as early as 1974, higher than expected mortality rates were found in hypertensive individuals [48]. If the blood pressure is high, the pressure may ultimately cause damage to nearly all organs in the body, especially to the brain, eyes, kidneys and heart, thereby leading to disabilities and death. In fact, approximately two thirds of all strokes and half of all ischemic heart disease can be linked to non-optimal blood pressure [49, 50]. A study of nearly 60 000 Swedish participants revealed a dramatic risk for stroke in individuals with poorly controlled blood pressure [51]. Hence, pharmacological antihypertensive treatment and lifestyle changes are of crucial importance in reducing associated disabilities, morbidity, and mortality.

If hypertension is treated and controlled, however, the risk of cardiovascular morbidity and mortality decreases dramatically [3, 52, 53]. This applies to men and women, and to younger as well as older individuals [54, 55]. There is evidence supporting reduced risk and health benefits with large reductions in blood pressure, far lower than 140/90 mmHg, in hypertensive individuals [56]. Despite this finding, the conclusion of a recent Cochrane report was that there is no evidence to support lower blood pressure goals than we use today [57]. After the publication of this report, a randomized open label trial showed benefits of a lower than usual goal, 130 mmHg systolic blood pressure, in non-diabetic patients [58].

2.7 GENDER DIFFERENCES IN CARDIOVASCULAR MORTALITY AND HYPERTENSION

There are gender differences in cardiovascular risk and mortality, but these have not been thoroughly investigated. The reason for this is that many studies have not included women, while others analyse risk factors with adjustments for sex. Possible gender interactions and differences between men and women will be missed with such study designs.

In general, cardiovascular mortality and morbidity are two to three times higher in hypertensive men [59], and occurs earlier in men than in women. Age is of greater importance in women, where the risk increases greatly after menopause [3]. Because of this as well as other factors, the Framingham 10-year risk score is calculated using different equations for women and for men [60]. The age-adjusted annual risk of death due to coronary heart disease in individuals born in Sweden is three times higher in men than in women [61]. One of the main reasons for this may be the higher prevalence of hypertension in men [9]. Predictors of new-onset hypertension were studied with data from the Framingham Heart Study [62]. Male sex was a risk factor for isolated diastolic hypertension and female sex was a risk factor for isolated systolic hypertension. In contrast, combined systolic and diastolic hypertension did not differ significantly between sexes. Two separate meta-analyses of large-scale observational studies of antihypertensive therapies have shown that men and women have similar benefits regarding serious cardiovascular events [55, 63]. The differences in

cardiovascular risk between men and women are therefore unlikely to be caused by differences in response to therapy.

2.8 HYPERTENSION IN SPECIAL PATIENT GROUPS

According to the 2007 guidelines for the management of arterial hypertension [3], the cardiovascular disease risk increases with blood pressures exceeding 120/80 mmHg in patients with three or more cardiovascular risk factors*, metabolic syndrome, subclinical end organ damage, diabetes or established cardiovascular or renal disease. Blood pressures exceeding 130/85 mmHg add high or very high cardiovascular risk to these groups, and add cardiovascular risk to individuals with 1–2 cardiovascular risk factors.* Hence, lower goal blood pressure levels should be used depending on the overall cardiovascular risk for each patient. These recommendations are stricter than the current recommendations in Sweden.

2.9 CARDIOVASCULAR DISEASE AND HYPERTENSION IN DIFFERENT ETHNIC GROUPS IN SWEDEN

Many immigrant groups in Sweden have been shown to have an increased risk of cardiovascular disease [61, 64, 65]. The explanation for the higher mortality in certain groups is unknown, but may be due in part to differences in lifestyle [66]. The lifestyle differences may lead to a higher prevalence of cardiovascular risk factors such as dyslipidaemia (accepted manuscript), diabetes, where non-European immigrants, especially immigrants from the Middle East, have a higher prevalence of diabetes [67, 68], and hypertension, where Finnish-born individuals have a higher prevalence [69, 70]. These hypertension prevalence studies with findings in Finnish immigrants were not adjusted for covariate factors, and the higher prevalence that was shown may be due to socio-economic or lifestyle factors such as alcohol consumption, physical inactivity and unhealthy diet. The prevalence of hypertension in Finnish-born individuals in Sweden is also of interest as it involves persons from a country with a higher prevalence of hypertension and cardiovascular disease who are living in a country with a relatively lower level [12, 71], whereas the opposite is the rule in other migration studies [17]. It was also shown in a study of Finnish twins, where one twin had migrated to Sweden, that the endothelial function was better in the migrating twin [72]. This may be explained by a healthier lifestyle in the twin who migrated to Sweden.

2.10 HOW CAN HYPERTENSION BE PREVENTED?

Prevention of hypertension may be pursued through a change in alcohol habits, physical activity, weight loss and healthy dietary approaches, which are key tools for

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* Cardiovascular risk factors were: cigarette smoking, total cholesterol ≥ 5.2 mmol/L, HDL < 1.0 mmol/L, LDL ≥ 3.4 mmol/L, premature cardiovascular disease in a first degree relative (<65 years in women and <55 years in men), previous transient ischemic attack or stroke, established coronary or peripheral arterial disease.

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use alone [73, 74] or in combination with antihypertensive medication [75]. Alcohol consumption exceeding 30 g/day can cause hypertension [76], and a primary goal could be to decrease alcohol consumption in affected individuals. Physical activity has been shown to reduce mortality in hypertensive individuals [77], and they should be encouraged to find activities of interest. Salt (sodium) intake is of major importance in the development of hypertension, and salt restriction has been used as therapy for the treatment of high blood pressure [78]. Adherence to salt free diets is, however, poor, and one way to reduce the sodium intake is to switch to a mineral salt, where sodium is partly replaced by potassium and magnesium. A diet rich in vegetables and fruits that are low in sodium and high in potassium in combination with a low content of saturated fat and dairy products can be used as treatment for hypertension [79]. These dietary adjustments are referred to as the "DASH" (Dietary Approach to Stop Hypertension) diet, and robust follow-up mortality data favouring adherence have been published [80, 81]. Healthy lifestyle factors including, BMI<25, vigorous physical activity, use of non-narcotic pain relievers less than once a week, moderate alcohol consumption, adherence to a DASH-style diet, and intake of supplemental folic acid have been shown to have the power to prevent 78% of all new-onset hypertension among women [36].

Individuals could take more responsibility for their health to achieve better control of associated cardiovascular risk factors and to achieve better controlled blood pressure. This could probably be achieved with more public awareness of the risks of hypertension [82] and the overall cardiovascular benefits of a healthy lifestyle [35, 36]. Electronic blood pressure measurement devices are sold in pharmacies and home electronic stores. Since hypertension is so prevalent and it is so important that it is controlled, it would be worthwhile for most adults to have their own measurement device [83-85]. Guidelines on how to interpret home blood pressure are also available [86], which may facilitate implementation. Finally, education of primary care physicians has been associated with improvement in the rate of hypertension control [87].

2.11 LIFESTYLE INTERVENTIONS AS ANTIHYPERTENSIVE TREATMENT

The lifestyle factors that lower blood pressure or reduce cardiovascular risk in hypertensive individuals include weight reduction in overweight and obese individuals, moderation of alcohol consumption, physical activity, reduction in salt and saturated fat intake, increase in fruit and vegetable intake, and fish oil supplements [88]. Adherence to the lifestyle interventions as treatment for hypertension is unfortunately fairly low [3]. There is no convincing evidence for supplements of magnesium, potassium or calcium, or for relaxation therapies [88]. Smoking cessation may have the opposite effect on blood pressure because of weight gain, but should be encouraged in hypertensive individuals because it is the most documented lifestyle factor when it comes to reducing cardiovascular risk [1, 2]. Combined effects of lifestyle interventions in individuals with moderately elevated blood pressure that include dietary adjustments, reducing sodium, physical activity and weight loss were potent in the PREMIER study [89].

2.12 ANTIHYPERTENSIVE DRUG TREATMENT

Hypertension is treated today with five main groups of antihypertensive drugs: diuretics, where thiazide diuretics (for example, chlortalidone and hydrochlorethiazide) are best documented, beta-blockers (for example atenolol, and metoprolol), angiotensin converting enzyme inhibitors (for example, enalaprile and ramiprile), angiotensin receptor blockers (for example losartan, and candesartan), and calcium antagonists (mainly the dihydropyridines: for example amlodipine, and felodipine) [90]. These five groups have been tested extensively in clinical trials, and a main conclusion is that the most important goal is to reduce blood pressure effectively, because the reductions in serious cardiovascular events are related more to the reduction of blood pressure than to any particular antihypertensive drug [3, 52, 53]. However, beta blockers have been questioned in recent years and may not reduce serious cardiovascular events as other drugs do with the same reduction in blood pressure [91]. Special interest has focused on atenolol, which may be less effective than other antihypertensive drugs [92]. Combinations of these main drug classes are recommended and often needed to reach beyond goal blood pressure.

There are other treatment options when the main groups of antihypertensive drugs are not tolerated and/or effective enough to reach goal blood pressure. These are potassium saving diuretics (eplerenone, spironolactone and amiloride) [93], which may also be used to recapture potassium from urine in hypertensive patients treated with diuretics, centrally acting drugs (for example, hydralasine), and alpha blockers, which although widely used to treat enlarged prostate were shown to be less effective in reducing mortality in the ALLHAT trial [94].

Hence, the main problem in treating hypertension and controlling blood pressure is not the lack of drugs that can be used, but that the drugs are not sufficiently used and combined to control and battle hypertension in the population [87, 95-97].

It has also been suggested that hypertension is several different conditions that should be treated separately [98]. For example, low-renin hypertension which is salt sensitive and responds well to thiazide diuretics, and high-renin hypertension responds well to angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Perhaps there should be a recommendation to test the response to these two antihypertensive therapies in mono-therapy before combinational therapy is initiated.

2.13 PERSISTENCE AND SERIOUS SIDE EFFECTS OF ANTI-HYPERTENSIVE DRUGS

Many individuals discontinue their antihypertensive drug therapy [99]. There may be several reasons for this but no matter what the reason, any reduction in adherence or persistence to antihypertensive therapy is serious since it is so important that hypertension is treated. Random samples of 500 patients, with each sample prescribed a drug from one of the main antihypertensive drug classes, revealed that persistence was better with ARB and ACE inhibitors, followed by beta blockers, calcium antagonists and diuretics [100]. In general, persistence was lower in women. Reduced persistence may be caused by side effects such as calcium-antagonist induced ankle oedema or ACE-inhibitor induced cough. Neither one is lethal, but a change of drug is justified.

Metabolic side effects of the antihypertensive drugs are seldom noticed by the patient, but can predispose to type 2 diabetes and components of the metabolic syndrome [101]. The traditionally most used and recommended antihypertensive drugs in Sweden are beta-blockers and thiazide diuretics [102]. However, the risk of new-onset diabetes with these drugs [103, 104], and the resulting increased long-term cardiovascular risk has lately received attention. Consequently, their role as first line therapies is questioned. A sub study of ALLHAT (the largest randomized controlled trial concerning hypertension) concluded that the increased blood glucose found in subjects receiving chlorthalidone (thiazide diuretic) did not result in more serious cardiovascular events compared to subjects receiving lisinoprile (ACE-inhibitor) or amlodipine (calcium-antagonist) [105]. This is not surprising since the 5-year follow-up used in ALLHAT is too short to register cardiovascular events caused by new-onset diabetes, which may take 10 years or more [103]. New-onset diabetes has been shown to be less common with the beta-blocker carvedilol compared to metoprolol [106], which makes it a good treatment option when beta blockers are needed to control hypertension.

Other metabolic side effects include thiazide-diuretic induced elevation of uric acid. Uric acid is responsible for gout and is perhaps the most important antioxidant in plasma [107]. Increased levels are, however, independently associated with cardiovascular events in many cardiovascular cohort studies [108]. Whether uric acid is increased as an antioxidant defence mechanism remains unclear, but it has been shown to be decreased by the ARB losartan [109]. Less is known about the effects of other antihypertensive drugs effects on uric acid in plasma. Fibrinogen has been shown to be increased in relation to elevated levels of uric acid, and high fibrinogen levels have been found to be independent risk factors for future strokes [28]. Blood lipids are known to be unfavourably influenced by beta-blockers and diuretics [110]. This, in combination with the insulin resistance that these drugs may cause, contributes to the development of metabolic syndrome in individuals with pharmacological antihypertensive treatment.

2.14 SOME NON-CARDIOVASCULAR BENEFITS SEEN WITH ANTIHYPERTENSIVE DRUGS

Uric acid is decreased by the angiotensin receptor blocker losartan [109]. Losartan treatment of hypertension in individuals with hypertension and concomitant gout therefore seems logical.

Alpha blockers are not a first line treatment for hypertension because of a lower ability to prevent cardiovascular events [94]. They are instead mainly used for their effect on benign prostate hyperplasia [111].

Thiazide diuretic drugs are well documented antihypertensive drugs and they also have the ability to preserve bone mineralization and reduce hip fractures by up to 30% [112].

The dihydropyridine lercanidipine, with a long receptor half-life, reduces oxidation of low-density lipoproteins and significantly lowers total cholesterol and triglycerides in addition to its blood pressure lowering effects [113].

Studies have shown a lower occurrence of dementia in individuals with antihypertensive therapy [114]. A recently published paper suggests based on follow-up

data that therapy with angiotensin-converting enzyme inhibitors that pass the blood-brain barrier (ramipril and captopril) are associated with a lower incidence of dementia and cognitive decline [115]. The authors of the study conclude that a randomized controlled trial of angiotensin-converting enzyme inhibitors and their effects in cognitive decline and dementia is needed to confirm their positive results. However, since the angiotensin-converting enzyme inhibitor ramipril is one of the best documented antihypertensive drugs when it comes to preventing serious cardiovascular events [116, 117], it is a wise first-line antihypertensive choice. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors also reduce insulin resistance apart from their antihypertensive effects, and have been shown to reduce new-onset diabetes, making them a wise antihypertensive choice in patients with hypertension and concomitant metabolic syndrome, diabetes and obesity [118].

3 CURRENT HYPERTENSION GUIDELINES AND RECOMMENDED DOCUMENTS

I recommend the following documents for the interested reader:

I   Mancia G, De Backer G, Dominiczak A, et al. (2007) 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 28: 1462–1536.

II   Chobanian AV, Bakris GL, Black HR, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama* 289: 2560–2572.

III   Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J (2005) Global burden of hypertension: analysis of worldwide data. *Lancet* 365: 217–223.

IV   Chobanian AV (2009) Shattuck Lecture. The hypertension paradox – more uncontrolled disease despite improved therapy. *N Engl J Med* 361: 878–887.

V   Zanchetti A (2009) Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? *J Hypertens* 27: 1509–1520.

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4 AIMS

An understanding of the many factors involved in hypertension is of importance for understanding the burden of cardiovascular disease in the population. It may lead to hints concerning what we can do to better treat hypertension and prevent cardiovascular disease. The overall aim of the thesis was to study the prevalence, prevention, treatment and prognosis of hypertension in men and women. Hypertension research in general has been rather defective regarding gender differences, with many studies performed in men or adjusted for sex. We studied men and women separately to be able to find gender differences in all aspects of hypertension.

4.1 SPECIFIC AIMS

We aimed to estimate the prevalence of known hypertension, newly diagnosed hypertension and the two combined in 60-year-old men and women (I), and the extent to which known hypertension is controlled (II). We also aimed to see if any immigrant group in Sweden, such as the Finnish who have previously been shown have a high prevalence of hypertension, had a higher prevalence and if any higher prevalence of hypertension could be explained by adjustments for various explanatory factors (I). Other aims were to find factors associated with uncontrolled hypertension in participants with diagnosed hypertension using individuals with diagnosed and controlled hypertension as reference (II). We also aimed to find factors independently associated with newly diagnosed high blood pressure using individuals with normal blood pressure as reference (III). Yet another aim was to estimate the cardiovascular risk in hypertensive 60-year-old individuals based on their concomitant cardiovascular risk factors (II). Another aim was to study the relationship between clinically relevant blood pressure levels and risk of cardiovascular and total mortality adjusted for various explanatory factors (IV). Finally, we aimed to see if mortality in hypertension is independent of co-morbidities and if treated hypertension adjusted for blood pressure level is a risk factor for mortality (IV).

5 MATERIALS AND METHODS

Two population-based samples were used in the studies included in this thesis. One comprised 4232 men and women aged 60 years and was used for cross-sectional studies (I–III), and one included 2578 men and women with a 26-year follow-up and was used for a cohort study (IV).

The baseline investigations as well as follow-ups were approved by the ethics committee at the Karolinska Institutet and all participants gave their informed consent.

5.1.1 A Study of 60-Year-Old Men and Women in Stockholm County (I–III)

From August 1997 to March 1999, every third man and woman living in Stockholm County who was born between 1 July 1937 and 30 June 1938 was randomly selected from the database of the total population in Sweden and invited to participate in a thorough health screening study. The participants underwent a physical examination that included measuring the participant's height, weight, and waist. Systolic and diastolic blood pressures were measured after five minutes of rest. The mean values of two measurements were calculated. Fasting blood samples were taken and a comprehensive questionnaire was completed.

5.1.2 Study Population

A total of 5460 subjects, 2779 men and 2681 women, were invited, and 4228 individuals (77%) participated, 2036 men (73%) and 2192 women (82%). The response rate among immigrants (n =787) was somewhat lower (68%). Data regarding blood pressure and information about whether or not the subject had previously been diagnosed with hypertension or not was available for 1971 men, out of whom 503 had known hypertension, and 2133 women, out of whom 445 had known hypertension.

5.1.3 High blood pressure

Hypertension was defined as known hypertension reported in the questionnaire. Newly diagnosed high blood pressure was defined as systolic and/or diastolic blood pressure ≥140/90 mmHg measured at one occasion. Normal blood pressure was defined as <140/90 mmHg measured at one occasion.

Men and women were divided into 3 groups:

1. Known hypertension (503 men and 445 women)
2. Newly diagnosed high blood pressure (713 men and 510 women)
3. Normal blood pressure (755 men and 1178 women)

5.1.4 Anthropometric measures

In paper II, waist circumference was divided into quartiles and the relationship with uncontrolled hypertension was analysed. Based on this preliminary analysis we decided to dichotomize waist circumference in men at the median (97 cm) and at quartile 1 in women (78 cm) in the logistic regression models.

Waist circumference was analysed as quintiles (Q) in paper III, in men and women separately; men Q 1= 61.8–89 cm, Q 2=89.5–94.5 cm, Q 3=95–99.5 cm, Q 4= 100–105.5 cm, Q 5=106–153 cm and women Q 1= 60–76 cm, Q 2=76.5–82 cm, Q 3=82.5–88 cm, Q 4= 88.5–96 cm, Q 5=96.5–141 cm.

5.1.5 Blood Analyses

All blood samples were analysed consecutively during the study. Cholesterol and triglycerides in serum were analysed by enzymatic methods (Bayer Diagnostics, Tarrytown, NY, USA) [119, 120]. HDL-cholesterol in serum was measured enzymatically after isolation of LDL and VLDL (Boehringer Mannheim GmbH, Germany), and LDL-cholesterol was estimated using Friedewald's method [121]. ApoB and apoA-I were determined using an immunoturbidimetric method [122]. Serum glucose was measured with an enzymatic colorimetric test (Bayer Diagnostics, Tarrytown, NY, USA). Serum insulin levels were determined using the ELISA technique (Boehringer Mannheim GmbH, Diagnostica, Germany). Plasma fibrinogen was measured with a functional spectrophotometric test (Boehringer Mannheim, Germany) [123, 124]. Serum urate was measured by an enzymatic method (Bayer Diagnostics, Tarrytown, NY, USA) [120, 125]. Gamma glutamyltransferase in serum was determined by the enzymatic colorimetric test (Bayer Diagnostics, Tarrytown, NY, USA).

Insulin resistance was determined as HOMA-IR and was calculated by the HOMA2 model [126].

5.1.6 Blood lipids

The cut-off levels used were <5 mmmol/L for total cholesterol, <0.9 mmmol/L for HDL and <3.5 mmmol/L for LDL as well as <2.3 mmmol/L for triglyceride level (1997 therapy recommendations in Sweden, Apoteket 1997). We also used the apolipoprotein ratio, ApoB/ApoA-I, to estimate the cardiovascular risk [26]. Low risk for men was defined as ApoB/ApoA-I <0.7, medium risk as 0.7–0.9 and high risk as >0.9. For women, low risk was <0.6, medium risk 0.6–0.8 and high risk >0.8.

5.1.7 Medical history

The metabolic syndrome was classified using the revised NCEP ATP III definition [46]. This definition requires three of the following five risk factors: abdominal obesity, i.e. waist circumference > 102 cm for men and > 88 cm for women, fasting triglycerides $\geq$ 1.7 mmol/l, HDL cholesterol <1.03 for men and <1.29 for women, blood pressure $\geq$ 130/ $\geq$ 85 mm Hg, and fasting plasma glucose $\geq$ 5.6 mmol/l. In addition, drug treatment with fibrates and nicotinic acid to lower triglycerides or to increase HDL, and any drug treatment to lower blood pressure or blood glucose counts as having the respective risk factor.
A history of coronary heart disease, CHD, was reported in the questionnaire. Diabetes was defined as self-reported in the questionnaire (yes/no), and/or self-reported medication for diabetes, or a fasting morning serum glucose value $\geq$ 7.0 mmol/l.

5.1.8 Socio-economic factors

Civil status, cohabiting was defined as married/living together (yes/no). Housing conditions were defined as living in an apartment, in a block of apartments, or not (compared to living in a house). An employment variable was defined according to working status (yes, full or part-time/no). Financial satisfaction was rated on a scale from 1 to 7, with 1 being very bad and 7 being "could not be better". Answers 5–7 were defined as financially satisfied. No healthcare for financial reasons was defined as having refrained from healthcare or dental care within the past year on one or more occasions because of the cost.

Education level was defined as:

1. Lower level education, i.e. compulsory school
2. 9–12-year education, i.e. high school
3. >12-year education, i.e. university

5.1.9 Immigration and country of origin

An immigration variable was used (yes/no), and a statement of country of origin of both the responding subject and his or her parents. Regarding the immigrants (individuals not born in Sweden), the following areas and countries were represented:

Finland n 327
Northwestern Europe n 141
(Germany n 70, Norway n 19, Denmark n 14, United Kingdom n 14, Austria n 9, France n 6, Switzerland n 4, the Netherlands n 3, Belgium n 2).
Southern Europe n 86
(former Yugoslavia n 22, Croatia n 7, Bosnia n 6, Slovenia n 4, Greece n 15, Spain n 14, Italy n 13, Portugal n 4, Albania n 1).
Eastern Europe n 100
(Estonia n 29, Poland n 23, Hungary n 21, Romania n 7, Latvia n 4, Russia n 4, Czech Republic n 4, Bulgaria n 3, Slovakia n 2, Ukraine n 2, Lithuania n 1).
Non-European immigrants: n 123
Africa n 22
(Morocco n 4, Algeria n 3, Ethiopia n 3, Somalia n 3, Uganda n 2, Angola n 1, Egypt n 1, Equatorial Guinea n 1, Eritrea n 1, Swaziland n 1, Tunisia n 1, Zaire n 1)
North America (USA) n 8
Latin-America n 27
(Chile n 16, Colombia n 3, El Salvador n 2, Peru n 2, Bolivia n 1, French Guyana n 1, Trinidad and Tobago n 1, Uruguay n 1)
South- and East-Asia n 18
(China n 4, India n 3, Bangladesh n 2, Indonesia n 2, Thailand n 2, Vietnam n 2, Burma or Myanmar n 1, Philippines n 1, Singapore n 1)
Middle East including Iran and Turkey n 48
(Turkey n 17, Iraq n 13, Iran n 8, Syria n 7, Lebanon n 3)

5.1.10 Lifestyle Factors

Smoking habits was coded as current daily smoker, former smoker or having never smoked. Physical activity in leisure time the past year was asked for and grouped into the following categories: 1) inactive, 2) light activity at least two hours/week, 3) moderate activity 1–2 times/week, and 4) intensive activity ≥ 3 times/week. Categories 1 and 2 were classified as "inactive" and categories 3 and 4 were classified as "active".

Dietary intake was measured using a food frequency questionnaire that included 17 key questions, each with four answer alternatives. The questions used concerned the intake of fruit, vegetables, non-oily and oily fish, fried potatoes, sausage/bacon and eggs.

The questionnaire also included questions concerning the intake of beer (light, medium, and strong, with percentage of ethanol per volume of <2.5, 2.5–3.5 and >3.5, respectively), wine, and spirits. For example, for the question "How much strong beer do you usually drink?" the following alternatives were provided: "More than 1 bottle/day", "4–6 bottles/week", "2–3 bottles/week", "1 or less bottle/week", and "None at all" (1 bottle=0.45L). An average daily intake of alcohol was calculated and four categories of drinking groups were defined: no alcohol intake (0 g alcohol/day), low intake (0.1–10 g/day), moderate intake (10.1–30 g/day), and high intake (>30 g/day).

5.1.11 Statistical Methods

Calculations of statistical significance were performed by Student's T-test, analysis of variance (ANOVA), Chi-square-analysis and Fisher's exact test. Logistic regression was performed to determine odds ratios, (OR) with 95% confidence interval (CI). The fully adjusted logistic regression models were optimized and non-significant factors were not included in the models.

The significance level was set at $p<0.01$ to compensate for multiple testing except for logistic regression models where the significance level was set at $p<0.05$. P-values smaller than 0.1, were reported in the tables to show possible trends.

5.2 THE 26-YEAR FOLLOW-UP OF REBUS (IV)

5.2.1 Participants and methods

The baseline investigation was performed in 1969–70 to assess the healthcare needs in the population. The population of 25–64-year-olds in Stockholm County, excluding the city centre area, was 445 000 at the time. A random sample of 32 185 subjects was drawn from this population. All 32 185 subjects received a postal questionnaire with 30 questions regarding social difficulties in daily life and healthcare needs, and 87% responded. The sample was stratified into three age groups: 18–25 years, 26–45 years and 46–65 years. From the three age stratums, a random sample was drawn in a ratio of 3 to 2 to 1, respectively, resulting in half of all subjects being 18–25 years. This was done to include enough individuals with high healthcare needs in the younger age groups. The subjects in the three age groups were then divided into four groups

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according to their estimated need for healthcare services based on the questionnaire, hospitalization and sick leave registers. In a randomization procedure individuals with high needs were included in larger proportions and a group of 3064 individuals was obtained. These subjects were invited to participate in a thorough health screening: 2578 participated (84%) to some extent, and 2407 underwent an extensive health examination. The baseline investigation has been described previously [32, 127]. Due to missing blood pressure data some subjects were excluded, resulting in inclusion of 2280 participants (74%) in the thesis, 1130 men and 1150 women.

5.2.2 Investigated Blood Pressure Levels

After at least 20 minutes of rest with the subject lying down comfortably, the blood pressure was measured manually with a sphygmomanometer. The participants with diagnosed hypertension and concomitant antihypertensive treatment (from the questionnaire) had to be analysed with adjustments for blood pressure level, as their blood pressure levels despite therapy were in general very high. To achieve large enough groups for statistical comparison and clinically interpretable results, the following groups/blood pressure levels were chosen:

1. Very high blood pressure, above or equal to 160 mmHg systolic and/or 95 mmHg diastolic.

2. High blood pressure, above or equal to 140 mmHg systolic and/or 90 mmHg diastolic but lower than 160 mmHg systolic and 95 mmHg diastolic.

3. Prehypertension, above or equal to 130 mmHg systolic and/or 85 mmHg diastolic but lower than 140 mmHg systolic and 90 mmHg diastolic.

4. Normal/optimal blood pressure, lower than 130 mmHg systolic and 85 mm Hg diastolic, reference group.

5.2.3 Covariates

All Cox regression models were age-adjusted in 5-year intervals, as both mortality and blood pressure are highly age-dependent. This was also necessary in order to adjust for the age stratification in the baseline investigation. Blood samples were drawn in the fasting state and blood glucose was measured. High and low blood glucose levels were shown to carry an increased mortality risk in a previous study of this cohort [127]. Diabetes and fasting plasma glucose was divided into 4 groups: diabetes defined as diagnosed diabetes reported in the questionnaire, high fasting plasma glucose (FPG) >7.7 mmol/L, normal FPG 3.5–7.7 mmol/L (reference), and low FPG <3.5 mmol/L. Healthcare need is described above and may be regarded as a proxy for co-morbidities. It was divided into 4 groups: very high healthcare need, high healthcare need, normal healthcare need (reference), and unknown healthcare need. Body mass index (BMI) was calculated as weight (Kg) / height (m) x height (m), and divided into four groups: BMI 15–20, BMI 20–25 (reference), BMI 25–30 and BMI 30–40.

5.2.4 Twenty-Six-Year Follow-Up

The International Statistical Classification of Diseases, Injuries and Causes of Death (ICD), revisions 8 and 9, was used. It is based on physician-issued certificates and coded at Statistics Sweden. The models presenting death due to cardiovascular disease

used the codes from ICD 9, 391–459. All participants were followed in the Swedish National Cause of Death Register, which contains more than 99% of all deaths in the Swedish population and has been shown to be in almost complete accord (99.8%) with data from local hospitals [103].

The autopsy rate in Sweden was about 40% during the 26-year follow-up.

5.2.5 Statistical Analyses and Cox regression models

Hazard ratios (HR) with confidence intervals (CI) were calculated with Cox regression models. Separate models were made for total and cardiovascular mortality. The significance level was set at p=0.05. Due to poor hypertension control in subjects with diagnosed hypertension and treatment, we decided to adjust diagnosed treated hypertension for blood pressure level. Model 1 was adjusted for age, model 2 for age and diabetes/blood sugar levels, and model 3 added healthcare need to compensate for the selection of a population with greater healthcare needs and co-morbidities as well. Finally, model 4 was BMI-adjusted in addition to all other variables. The full table is presented in the results section in this thesis (age-adjusted model and full model in paper IV). Adjusting blood pressure for BMI may destabilize the model, as overweight and obesity have been shown to be strongly associated with high blood pressure levels [128]. Data on smoking was regrettably only available for 48% of the participants and could not be added to the models, as it would have excluded too many participants. The calculations were performed using the PHREG procedure in the SAS data package (SAS Institute Inc., Cary, NC, USA).

6 RESULTS

6.1 CHARACTERISTICS OF THE STUDY POPULATIONS (I–IV)

The baseline investigation of the 60-year-old men and women revealed that there was generally a high prevalence of many cardiovascular risk factors. As seen in Figure 1, the total prevalence of hypertension was 62% in men 45% in women. Dyslipidaemia, defined as an apolipoprotein ratio exceeding 0.9 in men and 0.8 in women, was seen in 27% of the men and 23% of the women. Ten percent of the men and 5% of the women had diabetes, and 20% of the men and 22% of the women were current smokers.

Figure 1: Hypertension prevalence and control in 60-year-olds in Sweden.
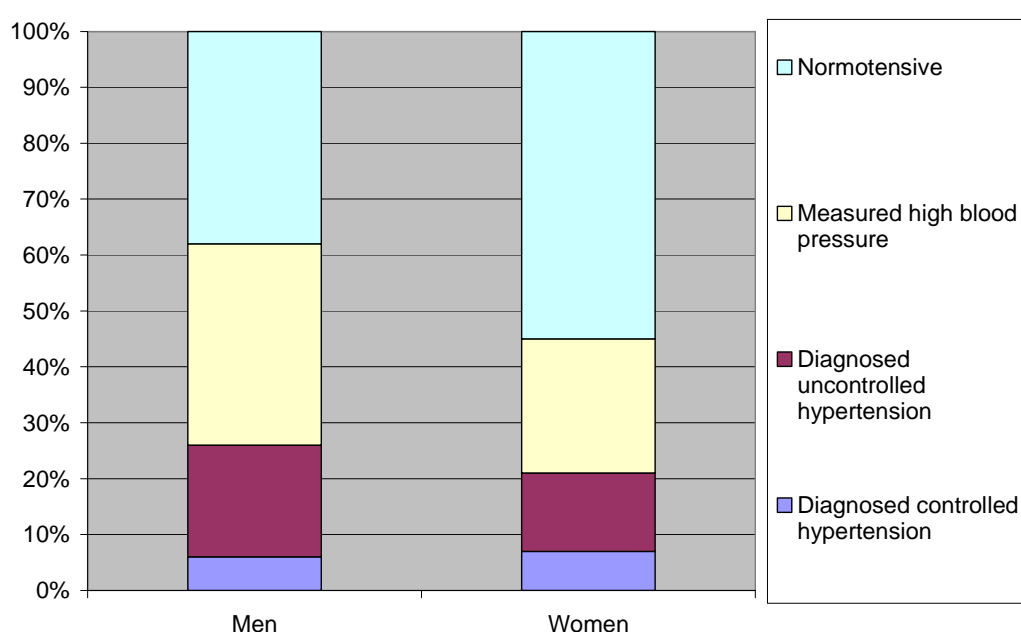
The above figure shows the percentage of 60-year-olds with a blood pressure <140 and/or 90 mmHg (Normotensive), a blood pressure ≥140/90 mmHg and no previous diagnosis (Measured high blood pressure), diagnosed hypertension and a blood pressure ≥140/90 mmHg (Diagnosed uncontrolled hypertension), and diagnosed hypertension and a blood pressure <140/90 mmHg (Diagnosed controlled hypertension).

In the healthcare need investigation from the 1970s, 1123 men and 1150 women participated and had blood pressure readings and mortality follow-up data. The different age groups were represented, with over 300 participating men and women. Among the participating individuals, 27% of the men and 26% of the women had a very high healthcare need. The hypertension prevalence was 34% among men and 26% in women. Diabetes or a fasting plasma glucose value exceeding 7.7 mmol/L was found in 1.4% of the men and 2.3% of the women. Obesity, defined as a BMI of 30 or more was seen in 3.9% of the men and 4.7% of the women. Data on smoking was available for about half of the individuals and among them 58% of the men and 46% of the women smoked.

6.2 HYPERTENSION IN IMMIGRANTS (I)

The descriptive statistics concerned metabolic, lifestyle and socio-economic characteristics in groups of immigrants and Swedish-born men and women. Statistically significant findings were detected in nearly all variables with a few gender and immigrant differences. The prevalence of hypertension was high, as 61% of the men and 44% of the women from Sweden were hypertensive. The prevalence of hypertension was highest among immigrants from Finland, comprising 77% of the men and 62% of the women, and lowest in non-European immigrants, comprising 51% of the men and 36% of the women. After adjustments for important factors by logistic regression, hypertension was associated with being born in Finland, diabetes, waist circumferences above 88 cm and high alcohol intake. Factors negatively associated with hypertension were female sex, being born outside Europe, college/university education, daily smoking and regular physical activity.

Table 1. Prevalence of hypertension in immigrant men and women using Swedish-born individuals as reference (presented as odds ratios with confidence intervals) and adjusted for socio-economic factors.

Analysis Variable	Men OR (95% CI)	Women OR (95% CI)	Both OR (95% CI)
Sex (women)	–	–	**0.47 (0.41–0.53)**
Sweden	1 (ref)	1 (ref)	1 (ref)
Finland	**1.85 (1.19–2.87)**	**2.06 (1.51–2.78)**	**1.98 (1.55–2.55)**
Northwestern Europe	0.85 (0.50–1.44)	0.78 (0.49–1.24)	0.82 (0.58–1.15)
Eastern Europe	1.51 (0.83–2.76)	0.97 (0.53–1.75)	1.21 (0.80–1.83)
Southern Europe	0.89 (0.51–1.54)	0.79 (0.37–1.68)	0.85 (0.54–1.32)
Non-European Immigrant	0.63 (0.38–1.04)	**0.50 (0.26–0.95)**	**0.58 (0.39–0.86)**
Compulsory school	1 (ref)	1 (ref)	1 (ref)
Secondary school	**0.76 (0.58–0.99)**	0.83 (0.62–1.11)	**0.79 (0.65–0.96)**
College/university	**0.71 (0.57–0.89)**	**0.56 (0.45–0.69)**	**0.64 (0.55–0.75)**
Employment	**0.68 (0.55–0.84)**	0.85 (0.71–1.03)	**0.86 (0.75–0.99)**

Table 2. Full models for the prevalence of hypertension in immigrant men and women using Swedish-born individuals as reference (presented as odds ratios with 95% confidence intervals).

Analysis Variable	Men OR (95% CI)	Women OR (95% CI)	Both OR (95% CI)
Sex (women)	–	–	**0.71 (0.61–0.83)**
Sweden	1 (ref)	1 (ref)	1 (ref)
Finland	**2.13 (1.34–3.38)**	**1.98 (1.45–2.70)**	**2.02 (1.56–2.61)**
Northwestern Europe	1.14 (0.65–2.01)	0.82 (0.51–1.31)	0.94 (0.66–1.35)
Eastern Europe	1.29 (0.69–2.41)	0.86 (0.47–1.60)	1.08 (0.70–1.66)
Southern Europe	0.89 (0.50–1.58)	1.02 (0.44–2.39)	0.91 (0.57–1.47)
Non-European Immigrant	0.65 (0.37–1.13)	**0.39 (0.19–0.76)**	**0.52 (0.34–0.80)**
Diabetes	**2.18 (1.47–3.22)**	**1.83 (1.18–2.83)**	**2.01 (1.51–2.68)**
Waist 0–87.9 cm	1 (ref)	1 (ref)	1 (ref)
88–91.9 cm	**1.81 (1.33–2.47)**	**1.70 (1.33–2.16)**	**1.68 (1.40–2.03)**
92–102 cm	**2.18 (1.63–2.93)**	**1.90 (1.45–2.48)**	**1.95 (1.62–2.35)**
>102 cm	**3.56 (2.62–4.84)**	**2.23 (1.64–3.05)**	**2.90 (2.36–3.55)**
Never smoked	1.00 (ref)	1.00 (ref)	1.00 (ref)
Daily smokers	0.87 (0.66–1.15)	0.80 (0.63–1.01)	**0.83 (0.69–99)**
Ex-smokers	0.99 (0.79–1.23)	0.94 (0.76–1.15)	0.97 (0.83–1.12)
Regular physical activity	0.90 (0.73–1.10)	**0.76 (0.61–0.93)**	**0.83 (0.72–0.96)**
High alcohol intake (>30 g/d vs 0–30 g/d)	**1.59 (1.22–2.06)**	1.19 (0.80–1.78)	**1.48 (1.20–1.83)**
Compulsory school	1 (ref)	1 (ref)	1 (ref)
Secondary school	0.82 (0.62–1.08)	0.87(0.65–1.16)	0.83 (0.68–1.01)
College/university	**0.71 (0.57–0.89)**	**0.58 (0.47–0.72)**	**0.64 (0.55–0.75)**
Employment	0.92 (0.74–1.15)	0.89 (0.73–1.07)	0.90 (0.78–1.04)

Interpretation of Tables 1 and 2: Small differences are seen between the separate models in men and women and the sex adjusted model of all participants. The non-European immigrant women have a lower prevalence of hypertension, whereas this is not significant in non-European men.

6.3 FACTORS ASSOCIATED WITH UNCONTROLLED HYPERTENSION (II)

In men, a waist circumference above 97 cm (OR= 1.85, CI=1.17–2.92) and no healthcare for financial reasons (OR= 2.71, CI=1.09–6.78) were positively associated. CHD (OR= 0.28, CI=0.17–0.46) and daily intake of fruit (OR= 0.59, CI=0.37–0.93) were negatively associated with uncontrolled blood pressure. In women, three factors remained significantly associated in the optimized multivariate model. A waist circumference above 78 cm was positively associated with uncontrolled hypertension (OR= 1.93, CI=1.09–3.43), and CHD (OR= 0.36, CI=0.18–0.72), and living in an apartment (OR= 0.55, CI=0.35–0.85) was negatively associated with uncontrolled blood pressure.

Four significant (p<0.05) multiplicative interaction terms with gender were found in univariate models of all participants. No healthcare for financial reasons*gender

(OR=0.29, CI=0.10–0.81), indicating that this was associated with uncontrolled hypertension in men but not in women. Daily intake of vegetables * gender (OR= 1.85, CI=1.01–3.93), indicating that there was an association in women but not in men. Weekly intake of sausage or bacon * gender (OR= 0.43, CI=0.24–0.79), indicating a significant association in men but not in women. Finally, living in an apartment * gender (OR= 0.47, CI=0.58–0.86) was associated with uncontrolled blood pressure in women but not in men.

6.4 FACTORS ASSOCIATED WITH NEWLY DIAGNOSED HIGH BLOOD PRESSURE (III)

Both men and women with newly diagnosed high blood pressure often had a large waist circumference, and high fasting glucose and insulin levels. A high HOMA-IR was more common in participants with newly diagnosed high blood pressure both in men and in women. Diabetes was more common in men with newly diagnosed high blood pressure. Subjects with newly diagnosed high blood pressure had lower levels of education. Women with newly diagnosed high blood pressure were less often physically active, while men with newly diagnosed high blood pressure consumed larger amounts of alcohol. Men with newly diagnosed high blood pressure reported a significantly lower intake of fish. Greater waist circumference was the main modifiable risk factor present in both men and women, associated in quintiles 3–5 (≥95 cm) in men and quintiles 4–5 (≥88.5 cm) in women. Diabetes was associated in men (OR=1.57, 95% CI 1.0–2.43). Secondary school was only associated in men (OR=0.73, 95% CI 0.54–0.99). Higher educational level (college/university) was associated in both genders (men OR=0.66, 95%CI 0.52–0.85 and women OR=0.45, 95% CI 0.34–0.59). Regular physical activity was found to be negatively associated in women only (OR=0.77, 95% CI 0.61–0.99), and high alcohol consumption remained associated in men (OR=1.60, 95% CI 1.22–2.09).

6.5 CARDIOVASCULAR RISK FACTORS IN HYPERTENSIVE INDIVIDUALS (II)

In total, 22% of the men and 33% of the women had controlled hypertension (< 140/90 mmHg), see Figure 1. Average blood pressure was 160/97 mmHg and 161/92 mmHg in men and women with uncontrolled blood pressure, respectively.

Blood lipid disturbances were very common, and based on their apolipoprotein ratios about 30% of the individuals with diagnosed hypertension had a high cardiovascular risk. Over 40% of both men and women with diagnosed hypertension had metabolic syndrome.

All men and women with controlled hypertension had antihypertensive therapy. Antihypertensive mono-therapy was more common in both men and women with controlled hypertension.

6.6 BLOOD PRESSURE LEVELS AND FUTURE MORTALITY (IV)

For all blood pressure levels, the HRs were higher for CVD mortality than for all-cause mortality. As more variables were added there was little change, with HRs for blood pressure levels indicating that blood pressure level is an independent predictor of total and cardiovascular mortality. Very high blood pressure (>160/95) was an independent risk factor and remained so for both men and women in all models. In men, other blood pressure levels were non-significant. In contrast, HRs in women showed a gradual increase with higher blood pressure levels. High blood pressure was significant in all models for both all-cause and CVD mortality, while prehypertension was significant for all-cause mortality only. Diabetes had higher HRs than all other variables, but unlike blood pressure levels, the HRs were lower in more adjusted models. Low FPG levels were a significant factor for all-cause mortality in all models in women. Sex adjusted full models for both all-cause and CVD mortality were very similar to the full models presented in men. Men had about a 2 and a 2.5 times higher risk for all-cause and CVD mortality, respectively, compared to women.

6.7 CO-MORBIDITIES AND ANTIHYPERTENSIVE TREATMENT (IV)

Adjusting for healthcare need did not reduce the HRs of the blood pressure levels, indicating that high blood pressure is a risk factor for mortality independent of co-morbidities.

Antihypertensive treatment adjusted for blood pressure level was non-significant in all models in both men and women.

Table 3a. Cox regression models for all-cause mortality in men. All models are adjusted for age (in 5-year intervals).

Men	All-cause mortality			
	Model 1	Model 2	Model 3	Model 4
	HR (CI)	HR (CI)	HR (CI)	HR (CI)
Antihypertensive treatment	1.19 (0.72–1.97)	1.14 (0.68–1.90)	1.00 (0.60–1.69)	1.03 (0.61–1.74)
Very High BP	1.67 (1.21–2.31)	1.72 (1.24–2.38)	1.84 (1.33–2.55)	1.93 (1.38–2.70)
High BP	0.96 (0.69–1.33)	0.95 (0.68–1.32)	1.03 (0.74–1.45)	1.10 (0.78–1.56)
Prehypertension	1.06 (0.76–1.47)	1.08 (0.77–1.50)	1.13 (0.81–1.58)	1.19 (0.85–1.67)
Diabetes		5.69 (2.45–13.23)	3.67 (1.55–8.67)	3.20 (1.32–7.75)
FPG > 7.7 mmol/L		1.79 (0.98–3.29)	1.40 (0.75–2.59)	1.30 (0.67–2.49)
FPG <3.5 mmol/L		2.52 (0.62–10.30)	2.37 (0.58–9.69)	2.22 (0.54–9.09)
FPG 3.5–7.7 mmol/L		1 (reference)	1 (reference)	1 (reference)
Very high healthcare need			2.36 (1.79–3.11)	2.35 (1.76–3.10)
High healthcare need			1.48 (1.09–2.00)	1.46 (1.07–1.97)
Normal healthcare need			1 (reference)	1 (reference)
Unknown healthcare need			1.30 (0.81–2.08)	1.31 (0.82–2.10)
BMI 15–20				1.43 (0.92–2.24)
BMI 20–25				1 (reference)
BMI 25–30				0.87 (0.67–1.11)
BMI 30–40				1.10 (0.69–1.75)

Table 3b. Cox regression models for cardiovascular mortality in men. All models are adjusted for age (in 5-year intervals).

Men	Cardiovascular disease mortality			
	Model 1 HR (CI)	Model 2 HR (CI)	Model 3 HR (CI)	Model 4 HR (CI)
Antihypertensive treatment	1.38 (0.74–2.60)	1.36 (0.71–2.61)	1.29 (0.66–2.49)	1.27 (0.65–2.47)
Very High BP	2.87 (1.72–4.80)	2.91 (1.74–4.87)	3.19 (1.91–5.33)	3.12 (1.84–5.26)
High BP	1.16 (0.67–2.02)	1.11 (0.63–1.94)	1.18 (0.67–2.08)	1.17 (0.66–2.09)
Prehypertension	1.00 (0.55–1.82)	1.00 (0.55–1.83)	1.06 (0.58–1.94)	1.07 (0.58–1.97)
Diabetes		7.67 (2.29–25.68)	5.48 (1.60–18.88)	5.10 (1.41–18.42)
FPG > 7.7 mmol/L		1.44 (0.56–3.68)	1.21 (0.46–3.15)	1.17 (0.42–3.21)
FPG <3.5 mmol/L		*	*	*
FPG 3.5–7.7 mmol/L		1 (reference)	1 (reference)	1.36 (0.61–3.044)
Very high healthcare need			2.38 (1.54–3.67)	1.16 (0.80–1.68)
High healthcare need			2.00 (1.28–3.14)	1.17 (0.58–2.34)
Normal healthcare need			1 (reference)	1 (reference)
Unknown healthcare need			1.46 (0.69–3.11)	1.46 (0.69–3.10)
BMI 15–20				1.36 (0.61–3.04)
BMI 20–25				1 (reference)
BMI 25–30				1.16 (0.80–1.68)
BMI 30–40				1.17 (0.58–2.34)

*Denotes that too few participants were available for statistical analysis.
It is seen that the highest blood pressure level is associated with increased cardiovascular risk independent of all covariate factors in men. Despite many incident cases, no other blood pressure level was significant. Antihypertensive treatment adjusted for blood pressure level was non-significant indicating that hypertension treatment did not lead to side effects that had an influence on mortality. The risk remained after adjustments for healthcare need, which indicates that mortality in hypertension is independent of other concomitant diseases.

Table 4a. Cox regression models for all-cause mortality in women. All models are adjusted for age (in 5-year intervals).

Women	All-cause mortality			
	Model 1	Model 2	Model 3	Model 4
	HR (CI)	HR (CI)	HR (CI)	HR (CI)
Antihypertensive treatment	0.75 (0.46–1.22)	0.62 (0.37–1.04	0.61 (0.36–1.04)	0.63 (0.37–1.06)
Very High BP	2.54 (1.62–3.99)	2.42 (1.53–3.82)	2.34 (1.47–3.72)	2.29 (1.42–3.69)
High BP	1.69 (1.09–2.61)	1.68 (1.09–2.61)	1.57 (1.01–2.44)	1.56 (0.99–2.45)
Prehypertension	1.62 (1.03–2.55)	1.61 (1.02–2.54)	1.67 (1.06–2.64)	1.66 (1.04–2.63)
Diabetes		7.25 (3.33–15.82)	5.33 (2.39–11.90)	5.56 (2.49–12.40)
FPG > 7.7 mmol/L		1.32 (0.41–4.22	1.89 (0.58–6.14)	2.00 (0.61–6.51)
FPG <3.5 mmol/L		3.36 (1.36–8.27)	3.08 (1.25–7.63)	3.10 (1.24–7.71)
FPG 3.5–7.7 mmol/L		1 (reference)	1 (reference)	1 (reference)
Very high healthcare need			2.33 (1.65–3.30)	2.29 (1.61–3.25)
High healthcare need			1.25 (0.86–1.81)	1.21 (0.83–1.76)
Normal healthcare need			1 (reference)	1 (reference)
Unknown healthcare need			1.41 (0.71–2.82)	1.37 (0.68–2.73)
BMI 15–20				1.10 (0.67–1.80)
BMI 20–25				1 (reference)
BMI 25–30				0.91 (0.65–1.27)
BMI 30–40				1.30 (0.82–2.04)

Table 4b. Cox regression models for cardiovascular mortality in women. All models are adjusted for age (in 5-year intervals).

Women	Cardiovascular disease mortality			
	Model 1 HR (CI)	Model 2 HR (CI)	Model 3 HR (CI)	Model 4 HR (CI)
Antihypertensive treatment	0.89 (0.48–1.67)	0.59 (0.29–1.20)	0.58 (0.28–1.23)	0.63 (0.30–1.31)
Very High BP	4.64 (2.05–10.5)	4.20 (1.83–9.66)	4.13 (1.80–9.51)	3.84 (1.62–9.12)
High BP	2.54 (1.12–5.76)	2.63 (1.16–5.98)	2.55 (1.12–5.81)	2.34 (1.01–5.45)
Prehypertension	2.04 (0.84–4.94)	1.96 (0.80–4.80)	2.04 (0.83–5.00)	1.89 (0.76–4.68)
Diabetes		14.9 (5.69–38.91)	11.24 (4.09–30.87)	11.71 (4.29–31.97)
FPG > 7.7 mmol/L		0.89 (0.12–6.60)	1.36 (0.18–10.36)	1.57 (0.20–12.00)
FPG <3.5 mmol/L		4.23 (0.99–18.06)	3.87 (0.90–16.63)	3.37 (0.77–14.77)
FPG 3.5–7.7 mmol/L		1 (reference)	1 (reference)	1 (reference)
Very high healthcare need			2.28 (1.29–4.01)	2.30 (1.30–4.08)
High healthcare need			1.65 (0.92–2.97)	1.64 (0.91–2.97)
Normal healthcare need			1 (reference)	1 (reference)
Unknown healthcare need			1.30 (0.37–4.54)	1.18 (0.33–4.18)
BMI 15–20				0.41 (0.12–1.36)
BMI 20–25				1 (reference)
BMI 25–30				0.68 (0.41–1.15)
BMI 30–40				1.20 (0.63–2.31)

We can see that both high blood pressure and very high blood pressure were associated with increased cardiovascular mortality in women and that they were independent of the covariate factors we adjusted for. Antihypertensive treatment adjusted for blood pressure level was non-significant indicating that the hypertension treatment did not lead to side-effects that had an influence on mortality. The risk remained after adjustments for healthcare need which indicates that mortality in hypertension is independent of other concomitant diseases.

7 DISCUSSION

7.1 MAIN FINDINGS (I–IV)

Findings in this thesis include an alarmingly high prevalence of both known hypertension and newly diagnosed high blood pressure in 60-year-old individuals, see **Figure 1**. The highest prevalence was seen among Finnish immigrants, and this could not be explained by differences in factors that we adjusted for. Furthermore, the subjects with diagnosed hypertension often lacked pharmacological treatment and none of them had a controlled blood pressure. The subjects who did receive antihypertensive treatment were rarely treated aggressively enough, and had poor hypertension control. In addition, subjects with known hypertension often had multiple cardiovascular risk factors and metabolic syndrome. Several factors were independently associated with newly diagnosed high blood pressure. Waist circumference and educational level were important in both men and women, whereas high alcohol intake was associated with newly diagnosed high blood pressure in men and with physical inactivity in women. Gender interactions were found in factors associated with newly diagnosed high blood pressure as well as in factors associated with uncontrolled blood pressure in subjects with diagnosed hypertension. The follow-up study revealed that very high blood pressure (>160/95) was a risk factor for cardiovascular and total mortality in both men and women, and that it was independent of co-morbidities. Lower blood pressure levels were not significant in men, whereas a tendency towards a step-wise increase in risk was seen with higher blood pressure levels in women. We also showed that pharmacologically treated hypertension adjusted for blood pressure level was not a risk factor for mortality. Cardiovascular as well as total mortality were higher among men.

7.2 GENDER DIFFERENCES (I–IV)

The gender differences found in this thesis are important contributions to the previously limited research on hypertension in both men and women [129-132]. The most important factor associated with newly diagnosed high blood pressure in both men and women was large waist circumferences. Waist circumference was also of importance for blood pressure control, so that in order to manage hypertension in the population fighting the obesity epidemic is of importance. This would also limit cardiovascular risk in general as the obesity epidemic is partly responsible for the increasingly common metabolic syndrome and diabetes type 2. High alcohol consumption was associated with newly diagnosed high blood pressure in men, whereas this was not significant in women. However, there were too few women with high alcohol consumption to say with statistical certainty that high alcohol consumption is not associated with newly diagnosed high blood pressure in women. Physical activity was negatively associated with newly diagnosed high blood pressure in women. Waist circumference was strongly associated with newly diagnosed high blood pressure in men, and the best way to reduce waist circumference is exercise. Safe lifestyle advice for preventing high blood pressure is therefore physical activity.

In agreement with our findings, morbidity and mortality among hypertensive individuals has been shown to be higher in men than in women [59]. Men in the 26-year follow-up study had two times the age-adjusted total mortality and two and a half times the age-adjusted cardiovascular mortality compared to women. These data are fairly unique, as many studies with long-term follow-ups come from baseline investigations with men only. Differences were seen in other blood pressure levels between men and women, where the mortality risk seemed to increase gradually with higher blood pressure levels in women, whereas in men this was not as clear cut. However, large pooled epidemiological studies of blood pressure and mortality have shown a gradual relationship between mortality and blood pressure [4].

7.3 FINNISH-BORN IMMIGRANTS (I)

As we have shown, hypertension is more prevalent in men in general and in Finnish-born individuals. We adjusted for many factors, but our finding of a higher prevalence in Finnish immigrants may nevertheless be explained by environmental and psychosocial factors as well as the migration itself. The higher prevalence of hypertension in Finnish immigrants is in agreement with studies comparing the prevalence of hypertension in European countries, and this focuses interest on genetics. Screenings in Finland for polymorphisms in genes coding for ACE [133] (angiotensin converting enzyme), and NO (nitric oxide) synthase [134], have failed to show associations with hypertension. In contrast to these negative findings, a common gene polymorphism in a Finnish population has been associated with endothelial dysfunction and decreased arterial vasodilatation [135]. Preventive action for control of hypertension has, however, been shown to be effective in Finland on both a community and a family level [136, 137]. If a genetic or physiologic explanation for the high prevalence of hypertension in people of Finnish origin were to be found, it would be of value not only in itself. It could also help to explain the mechanisms of hypertension and why different people respond differently to antihypertensive therapy in general. It is known that people of African origin have a salt-sensitive hypertension and low levels of renin, and this explains why they often respond well to diuretics and less well to ACE inhibitors [138, 139]. The high hypertension prevalence in Finnish-born individuals may partly explain the high mortality and cardiovascular morbidity found in several studies in this immigrant group [61, 64, 65]. The tendency towards a lower prevalence of hypertension in non European immigrants is puzzling. However, a high hypertension prevalence has been seen in European countries in studies comparing prevalence in different countries around the world [12, 14].

7.4 BLOOD PRESSURE CONTROL AND ANTIHYPERTENSIVE TREATMENT (II)

Individuals with hypertension rarely had control of their blood pressure. In addition, many other factors that greatly increase the cardiovascular risk were common. Metabolic syndrome for example, was present in nearly half of all participants with diagnosed hypertension. Blood lipid disturbances and tobacco smoking were also

common, making the situation more serious as the recommendation is to assess the global health of each individual [140].

Although lifestyle changes may be helpful, antihypertensive dugs have to be considered as soon as hypertension is diagnosed, since no one in paper II without treatment had a controlled blood pressure. Lifestyle treatment of hypertension includes diets, exercise and reduced salt intake [9, 75, 79]. Although the effects compared to antihypertensive drugs are fairly modest, it is important to remember that some individuals are very sceptical regarding drugs and that there are several side effects of antihypertensive drugs that patients do not directly experience but that may induce diabetes and dyslipidaemia [101, 110]. However, this risk can be reduced by the use of newer antihypertensive drugs and must be considered in relation to the risk of an unsuccessful antihypertensive treatment. In addition to the blood pressure lowering effects of lifestyle changes, a healthier diet such as the DASH-diet (Dietary approach to Stop Hypertension) has been shown to reduce the overall cardiovascular risk and mortality in long-term follow-up studies [80, 81]. Besides the potential lowering of blood pressure, physical activity is important to reduce the overall cardiovascular risk [19]. Vigorous activity is not necessary for benefits; moderate activity has health benefits and is attainable by ordinary people [141]. Daily fruit intake was associated with blood pressure control in men with diagnosed hypertension. This may be explained by the potassium content or soluble fibres: however, it could also be a marker for overall healthy behaviour in men who consume fruit daily.

7.5 ANTIHYPERTENSIVE TREATMENT AND CO-MORBIDITIES (IV)

Another finding that was interesting was that treated hypertension adjusted for blood pressure level was not a risk factor for mortality. Two separate long-term follow-up studies of Swedish men have shown that increased blood glucose, a side effect of antihypertensive therapy, increases the risk of mortality [103, 104], and one would expect higher mortality rates in individuals with antihypertensive therapy. After adjustments for blood pressure level, however, this excess risk was not present in our study. Healthcare need may be regarded as a proxy for co-morbidity, and was adjusted for in our follow-up. Very high blood pressure remained as a risk factor for mortality after these adjustments, and based on this we conclude that hypertension needs to be taken just as seriously in all individuals, even those with severe concomitant diseases needing more attention.

7.6 METHODOLOGICAL CONSIDERATIONS (I–IV)

Cross-sectional studies do not allow any conclusions regarding causality. Follow-up studies adjusted for confounders or randomized controlled trials are needed to determine which factor causes newly diagnosed high blood pressure, for example. When analysing the dramatically high prevalence of hypertension, it is important to bear in mind that we are dealing with epidemiological data and not with clinically diagnosed hypertension. To diagnose hypertension, one needs to measure a high blood pressure on three occasions, whereas we have one measurement, as is the case in most epidemiological studies. This leads to an overestimation of the true prevalence of

hypertension in comparison with what would be found in a study with repeated measures. However, the alternative to measurement on one occasion is self reported hypertension, which would greatly underestimate the prevalence, as high blood pressure is in general asymptomatic. The high prevalence found in this thesis is in agreement with other epidemiological studies showing high prevalences among Europeans [12, 14, 142]. Our finding that high blood pressure levels measured on one occasion proved to be an independent risk factor for cardiovascular and total mortality further justifies this methodology. The cross sectional data came from a baseline investigation of a cohort study performed in 1997–1998. Future studies will reveal if we are diagnosing and treating hypertension better today. Although some of the findings do not reflect the situation today, the poor control of hypertension and the large numbers of individuals with newly diagnosed high blood pressure at that time, have resulted in and continue to result in, serious cardiovascular events, with individual suffering, direct healthcare costs and astronomical indirect costs to society. We also showed that poor control of high blood pressure in the past brings incident cases in years to come (IV). Blood pressure was measured with an automatic device in the cross sectional studies (I–III), and this device requires a different technique than that used with a manual meter (IV). With automatic devices false values may be obtained in individuals with atrial fibrillation.

A strength of the cross-sectional studies (I–III) is that men and women were investigated at the same time, making adjustments for age unnecessary. Blood pressure was measured and not self-reported, rendering more reliable data compared to many other epidemiological studies on the topic. Furthermore, the participants were well characterised and thoroughly investigated, making adjustments for various possible confounding factors possible. The good quality of population registers in Sweden, that allow us to reach the whole population, and the high response rates, assure good representativity. Many previous studies were conducted in either men or women, making our study of both men and women valuable. Finally, with the cross-sectional design, observed associations cannot be interpreted as causal without more evidence.

In the follow-up study of blood pressure levels (IV), some important risk factors, especially for cardiovascular disease and death, were not available, e.g. blood lipid values. The physical examination was performed on only one occasion, which could weaken the associations, as changes in the different factors were not registered. Despite this, many factors apart from blood pressure levels have been found to be predictive for long-term mortality, [29, 32, 127, 143, 144]. The quality of population registers in Sweden which allowed us to reach the whole population and link each individual to The National Cause of Death Register. We had data on both men and women, whereas many other long-term follow-up studies of hypertension only have data on men [103, 104]. The high participation rate of 84% and the long follow-up time of 26 years are strengths. In addition, we had access to many potential confounding factors including healthcare need, which can be used as a proxy for co-morbidities.

7.7 HOW CAN HYPERTENSION AND CARDIOVASCULAR DISEASE BE REDUCED IN SOCIETY?

Given the evolutionary conditions that have rendered the gene pool of humans, the environment in the Western world today is toxic. Food is available everywhere and our

technological achievements have minimized the physical effort needed to manage our daily lives. Our lifestyle, with sedentary activity comprising the main part of the day and with limited physical activity, is probably the driving force of behind the high hypertension prevalence through its effects on waist circumference. Finally, most precooked foods and bread contains too much salt, as does the food served in restaurants.

Overweight is one of the most important risk factors for hypertension [145]. Another important risk factor for hypertension and cardiovascular disease is salt intake [146], which is not given priority as a risk factor in Sweden as is done in countries like Japan, Great Britain and Finland [147]. A reduced salt intake in the population has been proven feasible in these countries through public awareness campaigns, and collaboration between governmental health administration agencies and the food industry [136]. Perhaps any food item containing more than a certain amount of salt should be required to include a governmental warning about the associated health hazard, as is the case with tobacco products today. This may be one of the easier ways of improving health in the population. Reducing salt intake would not only reduce hypertension prevalence and improve hypertension control in society; it would also have the potential to reduce osteoporosis, as salt intake leads to sodium secretion in the urine, which is one of the forces driving calcium secretion [147]. Reductions in salt content in foods may also help to slow down the obesity epidemic, as the associated thirst leads to consumption of soft drinks, juices, beer and other drinks containing excess calories.

Tobacco smoking not only causes cardiovascular disease, it also causes cancer. A ban should be considered. It would potentially be more effective if tried in a larger area like the EU. This would also decrease the risk of smuggling. Until the day cigarettes are banned, we must work with cessation and help for individuals who want to quit. Swedish wet snuff (snus) may be of help for those who are not helped by nicotine replacement and pharmaceuticals.

As hypertension is so common and prevention a definite possibility, society should make it as easy as possible for individuals to modify their lifestyles. Prevention should be life-long and should be accessible to the whole population. Physical activity can be encouraged by constructing walking trails as well as bicycle lanes on streets and roads. Limiting escalator and elevator use to disabled individuals is a more radical approach. Step counters are effective in monitoring physical activity and step contests with counters are becoming popular among employees at offices. These step contests with counters may become annual events.

Grocery stores are designed so that every customer must pass many unnecessary products. Unhealthy foods, such as soft drinks, salty crackers, cookies, potato chips and candy could be sold in certain more remote sections of these. These sections should not automatically be passed every time a customer visits a store.

Awareness campaigns should focus on primary prevention and the risks of hypertension need to be communicated to the public to a greater extent. In these campaigns, factors like weight management, physical exercise and salt restriction can be encouraged [73, 77, 87, 148]. In addition, the advice needs to be gender specific and men and Finnish immigrants should receive more attention because of higher cardiovascular risk and the higher prevalence seen in this thesis.

To achieve better control of hypertension, the individual hypertensive patient needs to be better educated, perhaps in small groups as is popular with type II diabetes. This

would encourage the patient to take more responsibility for his or her health, and potentially achieve a better controlled blood pressure and reduce cardiovascular risk factors in general. This could be combined with a public awareness campaign about cardiovascular risks, the benefits of blood pressure reduction and preventive advice. Electronic blood pressure meters are important in order for individuals to be able to monitor their blood pressure. It would be of interest to study if it is cost-effective to supply older individuals with a free meter. The cost needs to be compared to the cost of screenings. Since most patients with hypertension have no symptoms, screenings are necessary and would still be helpful. Finally, education of primary care physicians has been associated with improvement of the hypertension control rate [82].

Alcohol consumption exceeding 30 g/day can cause hypertension [76], and a primary goal could be to decrease alcohol consumption in as many affected individuals as possible. Physical activity improves many cardiovascular risk factors and is probably more important than other lifestyle changes. A diet rich in vegetables and fruits with low sodium and high potassium, in combination with a low content of saturated fat and dairy products, can be an effective treatment of hypertension ("DASH" (Dietary Approach to Stop Hypertension) diet) [79]. A growing body of evidence indicates that healthy lifestyle factors reduce the risk of cardiovascular diseases. In addition, in studies where a composite healthy lifestyle score is constructed, the preventive effects appear additive [33-38].

Finally, cardiovascular screenings could be performed at certain intervals, as is the case for automobiles in Sweden: today there is legislation stipulating that every automobile older than three years must undergo a yearly check-up. Despite a multiple higher mortality for cardiovascular disease, the population is not checked systematically. This must be considered at least from the age of 45 years for men and 50 for women.

8 CONCLUSIONS

An alarmingly high prevalence of both known hypertension and newly diagnosed high blood pressure was seen in this thesis. The highest prevalence was seen among Finnish immigrants. The subjects with diagnosed hypertension often lack pharmacological treatment, and none of these individuals had a controlled blood pressure. The individuals who do receive antihypertensive treatment have poor hypertension control. Individuals with known hypertension often have multiple cardiovascular risk factors. Waist circumference and educational level were important in both men and women, whereas high alcohol intake was associated with newly diagnosed high blood pressure in men and physical inactivity was associated with newly diagnosed high blood pressure in women. Gender interactions were found in factors associated with newly diagnosed high blood pressure as well as in factors associated with uncontrolled blood pressure in individuals with diagnosed hypertension. Very high blood pressure was a risk factor for cardiovascular and total mortality and this was independent of co-morbidities. Cardiovascular as well as total mortality was higher among men.

As reported in these studies, hypertension was shown to be very common and to be poorly controlled. In Sweden, with socialised medicine and medical care accessible to everyone, opportunities to battle hypertension should be better than in most parts of the world. A healthy lifestyle not only prevents and postpones new-onset hypertension but also diabetes, cardiovascular disease and some cancer types. The benefits of a healthy lifestyle including physical activity, moderate alcohol consumption, normal weight/small waist circumference, daily intake of fruit and vegetables, and non-smoking needs to be disseminated to the population. The environment should also be changed in order to make it less toxic to humans. The gender differences found in our studies, and those found in others, need to be taken into account when planning these preventive actions in society. Morbidity and mortality are higher in men, and the treatment goals need to be gender specific to battle the higher risk in men more effectively. Findings in men cannot be extrapolated to women, and advice to men and women cannot be based on studies adjusted for sex. As shown in this thesis, sex-adjusted models can only be used to find gender interactions, and to show if men or women are more at risk.

It is important to communicate knowledge to the general public about how common hypertension is and the dangers of leaving it uncontrolled in order to motivate individuals to take responsibility for their blood pressure and health in general. In addition to controlling blood pressure, cardiovascular risk factors needs to be managed in individuals with hypertension, as we have shown that most hypertensive individuals have other risk factors in addition to their hypertension. This may prevent premature death, unnecessary suffering and direct healthcare costs.

9 FUTURE RESEARCH

The groups of immigrants among 60-year-old men and women are somewhat different from the immigrants in the total population in Stockholm. Younger immigrants in Sweden have their origins in other countries, so further studies will be needed in the future to see whether the prevalence of hypertension varies in these groups. Furthermore, hypertension and cardiovascular disease in second generation immigrants have not been studied thoroughly. Does the higher risk persist in the next generation? Apart from the high prevalence of hypertension in Finnish-born individuals found in this thesis, the prevalence of hypertension in Finland has been shown to be higher than in other countries [12]. There is evidence of familial aggregation of hypertension in Finland, indicating the possibility of a genetic explanation [149]. To the best of our knowledge, there is no study comparing the response to antihypertensive therapy in Finnish subjects compared to subjects of other origin. If a specific antihypertensive agent were to prove more effective, this could be a clue as to what genetic differences cause hypertension in Finnish people. Based on genetic differences and response to antihypertensive therapy, separate treatment guidelines exist for black people with hypertension [138]. It is possible that other ethnic groups, such as the Finnish may benefit from more specified therapeutic guidelines. A larger database would enable hypertensive research from specific countries.

As clinical trials of antihypertensive drugs are limited to around 5-year follow-ups, epidemiological follow-up studies of antihypertensive treatments are needed. Research regarding the metabolic side effects of antihypertensive therapies and long-term mortality is of particular importance. Studies in this field have the potential to improve antihypertensive drug therapy in the direction of therapies with a favourable metabolic profile.

Many aspects of hypertension that we have studied in this thesis have been shown to differ between men and women. These gender differences are puzzling, and future research on hypertension needs to be gender specific in order to interpret possible explanatory findings.

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SUMMARY IN SWEDISH /
SAMMANFATTNING PÅ SVENSKA

11.1 INTRODUKTION

Högt blodtryck, höga blodfetter, diabetes och rökning räknas som klassiska riskfaktorer för hjärtkärlsjukdom. Det har uppskattats att närmare två miljoner svenskar har högt blodtryck varav ungefär hälften känner till sitt höga blodtryck. Det stora mörkertalet och att blodtrycket ökar med stigande ålder försvårar prevalensbestämningar. Dessutom saknas data på blodtrycksförekomst i de stora invandrargrupperna. Det finns också osäkerhet kring hur bra vi behandlar högt blodtryck och förebygger hjärtkärlsjukdom, hur man ska leva för att inte få högt blodtryck och hur relationen mellan kliniskt relevanta blodtrycksnivåer och framtida död förhåller sig. Vidare saknas ofta könsuppdelade data.

11.2 FRÅGESTÄLLNINGAR

Hur vanligt är diagnostiserat högt blodtryck och hur många har förhöjt blodtryck utan att veta om det? Hur många med diagnostiserat högt blodtryck har ett tryck under målblodtrycket (140/90)? Vilka faktorer påverkar om man kommer nå sitt målblodtryck? Vilka andra riskfaktorer för hjärtkärlsjukdom har personer med högt blodtryck? Vilka faktorer kan kopplas till personer som har förhöjt blodtryck utan att veta om det (referensgrupp personer med normalt blodtryck)? Hur förhåller sig kliniskt relevanta uppmätta blodtrycksnivåer till framtida död?

11.3 METOD

Till studierna användes två populationsbaserade undersökningar från Stockholms län.

Den ena omfattade 4232 män och kvinnor som alla var sextio år vid undersökningstillfället (1997). Deltagarna blev undersökta och besvarade en 40-sidig enkät med frågor om livsstil, arbetsmiljö och hälsa mm. Fokus för undersökningen var hjärtkärlhälsa och materialet nyttjades för tvärsnittsstudier (artikel I–III).

I den andra nyttjades en vårdbehovsundersökning från 1970 med 2578 män och kvinnor som baslinje. Undersökningen omfattar allt från somatiska till psykiatriska och sociala formulär. Individerna följdes som kohort i dödsorsaksregistret i 26 år (artikel IV).

11.4 RESULTAT

Förekomsten av högt blodtryck (nyupptäckt och diagnostiserad) var 62 % hos män och 45 % hos kvinnor. Bland finskfödda hade hela 77 % av männen och 62 % av kvinnorna högt blodtryck och bland icke-européer hade bara 51 % av männen och 36 % av kvinnorna högt blodtryck. Bara 22 % av männen och 33 % av kvinnorna med

diagnostiserat högt blodtryck hade ett blodtryck under 140/90 mm Hg (uppnått målblodtryck). Samtliga som hade uppnått målblodtryck tog antihypertensiva läkemedel. Både män och kvinnor med högt blodtryck hade samtidigt ofta flera kardiovaskulära riskfaktorer såsom höga blodfetter, rökte, hade metabolt syndrom och/eller diabetes. I studien om faktorer som var vanligare bland personer med nyupptäckt högt blodtryck visade sig midjemåttet vara viktigt. Midjemått över 95 cm kunde kopplas till nyupptäckt högt blodtryck hos män, motsvarande midjemått för kvinnor var över 88,5 cm. Hos män var det vanligare med normalt blodtryck bland personer med både gymnasieutbildning och högskoleutbildning medan det hos kvinnor endast var vanligare med normalt blodtryck bland högskoleutbildade. Fysiskt aktiva kvinnor hade ofta normalt blodtryck medan män som hade en hög alkoholkonsumtion ofta hade nyupptäckt högt blodtryck.

I uppföljningsstudien visade det sig att uppmätta blodtryck över 160/95 ledde till en klar överrisk för död bland såväl män som kvinnor. Hos kvinnor sågs en stegvis ökande risk för framtida död med ökande blodtryck. Sambanden var inte lika lättolkade hos män. Blodtrycksbehandling justerat för blodtrycksnivå visade sig inte leda till ökad risk för att dö. Det vid baslinjeundersökningen skattade vårdbehovet visade sig inte påverka sambandet mellan blodtrycksnivå och framtida död.

11.5 SLUTSATSER

Högt blodtryck är mycket vanligt bland sextioåringar och behandlingen är långt ifrån framgångsrik. Dessutom har många av individerna med högt blodtryck också flera andra riskfaktorer för hjärtkärlsjukdom. Detta trots att Sverige borde ha bra förutsättningar att behandla högt blodtryck och andra riskfaktorer jämfört med många andra länder. Olika faktorer kunde kopplas till högt blodtryck hos män och kvinnor. Prevention av högt blodtryck borde därför vara könsspecifik och fokusera på fysisk aktivitet för att minska midjemåttet hos både kvinnor och män. Höga blodtrycksnivåer predicerar framtida död oberoende av samsjuklighet så blodtrycksbehandling förefaller vara lika viktigt hos personer med annan allvarlig sjukdom.

Även om fler med högt blodtryck skulle vara upptäckta och bättre behandlade idag jämfört med när 60-åringarna undersöktes så kommer många av dem som hade högt tryck då att drabbas av stroke och infarkter, onödigt lidande och stora kostnader för samhället som hade kunnat undvikas.

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