High blood pressure - determinants and risks

Implications for treatment and prevention in a primary care setting

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Ineko

To Peter, Erik and Elin

"Superior doctors prevent disease. Mediocre doctors treat the disease before evident. Inferior doctors treat the full-blown disease."

Huang Dee: Nai-Ching (2600 BC).

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ABSTRACT

Aim: The overall aim of this thesis was to study determinants and risks associated with increasing blood pressure categories based on a combination of systolic and diastolic blood pressure ranging from optimal blood pressure to manifest hypertension. Emphasis was placed on the importance of focusing on modifiable lifestyle factors and assessment of global risk. The ultimate aim was to identify targets for treatment and prevention. We set out to: 1) study the prevalence and control of hypertension in a representative Swedish population; 2) investigate the association between global risk (SCORE) and ESH/ESC blood pressure categories; 3) study the extent to which physiological factors and lifestyle factors such as physical activity, smoking and alcohol consumption contribute to higher blood pressure levels; 4) investigate the risk of cardiovascular disease associated with different blood pressure categories.

Methods: A random sample of residents aged 30-74 years in the municipalities of Vara and Skövde, southwestern Sweden, was surveyed for cardiovascular risk factors in 2002-2005, and 2816 individuals were enrolled (76%). Participants provided detailed information about their medical history and current medication, and completed a questionnaire about lifestyle. Blood pressure was categorised according to the 2007 ESH/ESC recommendations based on a combination of systolic and diastolic blood pressure ranging from optimal blood pressure to manifest hypertension. Information about fatal and non-fatal cardiovascular events was collected from national registers from baseline until end of 2011, and global risk was estimated using the Swedish SCORE chart.

Results: In Paper I, the prevalence of hypertension in the age group 30-75 years was 20%. A “rule of thirds” emerged, as 1/3 of the participants were

not previously known, 1/3 were treated but not controlled, and only 1/3 were treated and controlled. The largest proportion of high global risk was seen in subjects with both hypertension and diabetes (men 76%, women 61%), and a major proportion of patients with known hypertension with a blood pressure ≥160/100 mmHg were also at a high global risk (Paper II). However, a large proportion of patients with mild hypertension had a low risk according to SCORE (Paper II). In Paper III, age, insulin resistance, BMI, and CRP showed strong age-adjusted associations with increasing blood pressure categories in both men and women (p-values <0.001). In women, lipids (p<0.001), education (p=0.009), physical activity (p=0.038), and alcohol consumption (p=0.002, inverse association) were also associated with blood pressure levels, whereas the same was not seen in men. In multivariate analyses, age, insulin resistance, BMI (both sexes), and alcohol consumption in females remained significantly associated with blood pressure. In Paper IV, distinct associations between blood pressure and risk of cardiovascular disease morbidity in both sexes were revealed already at levels from 120/80 mm Hg. Compared to those with optimal blood pressure, participants belonging to all other blood pressure categories had an increased cardiovascular risk, and the risks remained statistically significant even after adjustments for both lifestyle and physiological factors, except in the unstable category.

Conclusions: The results of this thesis emphasise that blood pressure is associated with a continuously increased risk of cardiovascular morbidity in men and women, which can be seen already at levels from 120/80 mm Hg. Patients with blood pressure above these levels should thus be identified and advised on lifestyle changes to prevent progression to manifest hypertension as well as future cardiovascular disease. Screening to increase awareness, assessment of global risk, and improvements in the implementation of expert guidelines in clinical practice including pharmacological treatment when indicated, are important steps to achieve this. It is also vital to emphasise population-based prevention, e.g. within the educational system, to also target normotensive individuals.

Keywords: Awareness, blood pressure, cardiovascular disease, cohort study, control, ESH/ESC guidelines, gender differences, hypertension, insulin resistance, lifestyle, mechanisms, physical activity, population survey, prevention, primary care.

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SAMMANFATTNING PÅ SVENSKA

Bakgrund

Hypertoni, d v s högt blodtryck, är en av de viktigaste riskfaktorerna för den totala sjukdomsbördan i världen. Högt blodtryck är förenat med hög förekomst av hjärtkärlsjukdom, såsom slaganfall (stroke), hjärtinfarkt (hjärtattack), hjärtsvikt, och kronisk njursjukdom. Patienters kännedom om sitt höga blodtryck liksom behandlingsresultatet vid hypertoni har i alla tider varit låga. Man vet att individer med högt blodtryck oftast har fler riskfaktorer för hjärt-kärlsjukdom och personer med både hypertoni och diabetes anses ha speciellt hög risk. Därför rekommenderas i generella riktlinjer att patienter med högt blodtryck ska värderas beträffande generell risk, både som stöd för att eventuellt initiera läkemedelsbehandling, och som del i uppföljning av vården.

Riskfaktorer för högt blodtryck är framför allt ålder, övervikt, nedsatt insulinkänslighet och vissa livsstilsfaktorer, såsom hög alkoholkonsumtion, låg fysisk aktivitet och rökning. En ytterligare tänkbar riskfaktor är låggradig inflammation. Eftersom livsstilsfaktorer är starkt kopplade till högt blodtryck är därför också det första steget i blodtrycksbehandling rådgivning beträffande en modifiering av dessa. Vid allvarlig blodtrycksförhöjning påbörjas dock alltid läkemedel direkt och oftast behövs en kombination av åtgärder för att uppnå kontroll.

Syfte

Syftet med denna avhandling var främst att försöka förstå de mekanismer som driver övergången från normalt till högt blodtryck och sedan vidare till hjärtkärlsjukdom, samt att undersöka hur vanligt förekommande olika blodtrycksnivåer är. Vi ville därför studera förekomst, kontroll och utfall av högt blodtryck i en representativ svensk befolkning och även relatera detta till generell riskskattning hos individen. Detta för att i förlängningen förbättra strategier för att ytterligare förebygga följdtillstånd till högt blodtryck, samt för att bättre kunna utvärdera uppnådda behandlingsmål.

Metod

Som del i Skaraborgsprojektet genomgick 2816 individer från Vara och Skövde i åldern 30-74 år (76% deltagarandel) en kartläggning av kardiovaskulära riskfaktorer mellan 2002 och 2005. Deltagarna lämnade detaljerade uppgifter om sin sjukhistoria och pågående medicinering och

fyllde i en enkät om livsstil. Blodtryck mättes två gånger och medelvärdet användes för statistiska beräkningar. Kroppsmått registrerades, blodprover togs, och en sockerbelastning genomfördes. Generell riskskattning gjordes baserat på kön, ålder, blodtryck, kolesterol, rökning och diabetes enligt SCORE. Efter i genomsnitt åtta år togs även information om hjärtkärlsjuklighet och dödlighet fram från det nationella slutenvårdsregistret och dödsorsaksregistret.

Resultat

I första delarbetet bekräftade vi att ålder, en familjehistoria av högt blodtryck, känd diabetes och övervikt var starkt kopplade till förekomst av manifest hypertoni hos båda könen, medan dessa faktorer inte påverkade hur väl blodtryck var kontrollerat hos dem med känd hypertoni. Förekomsten av högt blodtryck var 20% hos både män och kvinnor. Bland patienter med hypertoni var 33% omedvetna om sitt tillstånd, 36 % var medvetna men undermåligt kontrollerade, och 31% medvetna och välkontrollerade.

I det andra delarbetet framkom ett samband mellan en hög riskskattning enligt SCORE och måttlig till svår hypertoni. Dessutom dominerade hög risk enligt SCORE vid förekomst av både hypertoni och diabetes, vilket bekräftar risken av att ha båda tillstånden. Många med mild blodtrycksförhöjning, särskilt kvinnor, hade inte en risknivå som indikerar behov av behandling med läkemedel. På samma sätt särskiljer inte heller en hög risknivå enligt SCORE blodtryckskategorier inom det normala området, trots att vi i fjärde delarbetet visar att risken för hjärtkärlsjukdom är ökad redan vid dessa nivåer.

Det tredje delarbetet visar att ålder, nedsatt insulinkänslighet och övervikt är starkt förknippade med ökande blodtryck hos bägge könen. Hos kvinnor var även måttlig alkoholkonsumtion förknippat med ett lägre blodtryck, medan motsvarande inte sågs hos män.

Slutsatser

De viktigaste resultaten i denna avhandling var den höga förekomsten av hypertoni hos både män och kvinnor, den låga blodtryckskontrollen bland patienter som behandlades för högt blodtryck, den låga medvetenheten om att ha högt blodtryck, och den förhöjda risken för hjärtkärlsjukdom i samband med blodtryck redan inom det normala intervallet. SCORE var ett bra instrument för att identifiera individer med måttligt till svårt högt blodtryck och/eller svår samsjuklighet, men inte känsligt nog för att indikera vilka

individer på en lägre och faktiskt vanligare blodtrycksnivå, som befann sig i riskzonen.

Modifierbara vanligt förekommande livsstilsfaktorer kan vara viktiga mål för att förhindra utvecklingen av manifest hypertoni, särskilt hos kvinnor, och strategier för intervention som är lämpade för implementering i primärvården bör utvecklas. Med tanke på den höga förekomsten av högt normalt blodtryck kan effekten av förebyggande åtgärder vara betydande.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Lindblad U, Ek J, **Eckner J**, Larsson CA, Guangliang S, Råstam L. Prevalence, awareness, treatment and control of hypertension - rule of thirds in The Skaraborg Project. ***Scandinavian Journal of Primary Health Care*** 2012;30:88-94.

II. **Eckner J**, Larsson CA, Råstam L, Lindblad U. Blood pressure and global risk assessment in a Swedish population. ***International Journal of Hypertension*** 2012;2012:835812.

III. **Eckner J**, Bennet L, Råstam L, Lindblad U, Larsson CA. Lifestyle and physiological characteristics in association with blood pressure categories in a Swedish population: a cross-sectional study. (Submitted)

IV. **Eckner J**, Larsson CA, Bennet L, Råstam L, Lindblad U. High normal blood pressure increases cardiovascular risk by three-fold in a Swedish population. (Manuscript)

CONTENT

ABBREVIATIONS

ApoB/ApoA1	Apolipoprotein B/Apolipoprotein A1
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Intervals
CRP	C-reactive protein
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GLM	General Linear Model
HOMA-IR	Homeostasis Model Assessment of insulin resistance
HR	Hazard Ratio
HT	Hypertension
JNC8	The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, the Eight Report
LSM	Life Style Modifications
LTPA	Leisure Time Physical Activity
LVH	Left Ventricular Hypertrophy
OD	Organ Damage
OGTT	Oral Glucose Tolerance Test

OR	Odds Ratio
PWV	Pulse Wave Velocity
RAAS	Renin-Angiotensin-Aldosterone System
SCORE	Systematic COronary Risk Evaluation, Risk score according to the original model
SCORE-DM	Risk score considering Diabetes Mellitus
SCORE-HIGH	10 year risk of cardiovascular death ≥ 5 per cent
SCORE-DM-HIGH	10 year risk of cardiovascular death ≥ 5 per cent considering Diabetes Mellitus
SD	Standard Deviation
VSC	Vara/Skövde Cohort
WHO	World Health Organization

1 INTRODUCTION

Hypertension is one of the most important causes of the total disease burden in the world (1). According to large observational studies, hypertension is thus associated with high incidence of cardiovascular disease, such as stroke, ischemic heart disease, and other vascular diseases (2-5). An increased incidence of cardiovascular disease has in fact been seen in relation to blood pressure levels across the entire blood pressure distribution (6-8), also within the normal blood pressure range (9-11). For half a century, treatment and awareness of high blood pressure has been insufficient, as described by "The rule of halves" (12-14), meaning that only half of those identified with hypertension were aware of their condition, and only half of those aware were treated, and of those treated only half achieved treatment goals. Even though treatment has contributed to a reduction of cardiovascular events, the control of high blood pressure and hypertension can still be improved (15).

1.1 Development of hypertension

The risk of becoming hypertensive in later life is considerable, as studies from almost all high-income countries have shown that blood pressure rises with increasing age (16, 17). The incidence of hypertension is likely to vary depending on the initial blood pressure (18) and the intra-individual variation of blood pressure measurements (19, 20).

Although there are subjects in whom the hypertension can be traced to an underlying disease, i.e. secondary hypertension, those cases are rare and most hypertensive cases have primary hypertension (21). Primary hypertension stems from interaction between multiple genetic and environmental factors, involving complex pathogenetic mechanisms (22). Hypertension has long been recognised to cluster within families in cross-sectional studies (23, 24), and a positive family history of hypertension doubles the prevalence of hypertension (25). More recent studies in twins (26, 27) have concluded that approximately 60% of the family association of blood pressure is explained by shared genes and approximately 40 % by shared environment. Thus, even though genetics might account for the largest impact, there is still a major influence of lifestyle and environmental factors (28-30), which are potentially preventable.

Hypertension may cause structural changes in blood vessels and in the heart, and induce macrovascular complications, such as ischemic heart disease and

heart failure (28, 31, 32). These conditions develop due to the interplay between high blood pressure and metabolic disorders, such as in the metabolic syndrome, and are also influenced by genetics (21) and lifestyle (33). Insulin resistance with the activation of the renin-angiotensin-aldosterone system (RAAS) and inflammation represent common mechanisms in these conditions (34, 35). RAAS is important for the regulation of salt-water balance in the body and contributes to blood pressure regulation in several ways (36). The endothelium in peripheral vessels is another key factor, as endothelial dysfunction with reduced production of nitric oxide (NO) will affect vasodilation, insulin sensitivity, platelet adhesion, and thrombus formation (37). The sympathetic nervous system is also believed to play a major role in initiating primary hypertension (38).

1.2 Lifestyle factors

Moderate alcohol consumption is known to reduce cardiovascular mortality (39) and also seems to have a beneficial effect on blood pressure, at least in women (40). Previous studies have identified biological mechanisms that would explain the beneficial effect of alcohol on blood pressure, such as anti-inflammatory effects (41) and positive changes in lipid metabolism (42-44), which support a causative effect. However, an excessive intake raises blood pressure and causes other problems (45). In the World Health Organisation Global Burden of Disease 2000 Comparative Risk Analysis study (46), 16% of all hypertensive disease was attributed to the consumption of alcohol.

Associations between body mass index (BMI) and blood pressure are generally acknowledged (47, 48) and have been found to be almost linear (49). Some studies suggest that weight gain may account for 65-75 % of the incidence of human essential hypertension (50). Insulin resistance and diabetes are also serious risk factors for hypertension, mainly through the blood pressure increasing effect of elevated concentrations of serum insulin (51, 52). Insulin resistance or diabetes often occurs together with obesity (general or abdominal), dyslipidemia, and high blood pressure in what is usually known as the metabolic syndrome (53), and some also consider proinflamatory and prothrombotic states as part of the syndrome (54). In recent years the syndrome has been the subject of some debate, although it is generally accepted that it constitutes an increased cardiovascular risk (55, 56).

The evidence for a protective effect of physical activity with regard to development of hypertension (57-60) and CVD (33) is well established; however, most people in industrialised societies are unfortunately becoming

less physically active in their daily lives (61). Physical activity not only acts directly on blood pressure (59), but also indirectly through its beneficial influence on body weight and insulin resistance (62, 63), thus making it an important factor to consider.

Previous results regarding the effect of smoking on blood pressure are highly diverse (64-66), and the lower blood pressure seen in some studies (64) in smokers compared to non-smokers is not fully understood. However, residual confounding has been proposed, e.g. with regard to body weight, as smokers are often thinner than non-smokers (48, 67). However, longitudinal studies show that long-term smoking in fact increases blood pressure and thus constitutes a serious risk factor for future hypertension (66).

It is well established that the experience of perceived stress is accompanied by an increase in blood pressure, which is a completely normal physiological adaptation (68). Animal studies show that chronic stress induces also a permanent blood pressure increase, and some behaviour-based approaches to stress management, such as meditation, yoga and muscular relaxation, have shown moderate decreases in elevated blood pressure (69).

1.3 High normal blood pressure

Incidence rates of hypertension are similar for men and women (70); however, older individuals and those with high normal blood pressure are more likely to progress to hypertension than younger people and those with normal or optimal blood pressure (70, 71). These observations support the recommendation to monitor blood pressure in non-hypertensive individuals regularly (28, 31, 32, 72), and since subjects with high normal blood pressure have an increased risk of CVD, emphasis is placed on the relevance of recognising this condition (9). A meta-analysis of longitudinal studies on blood pressure levels from childhood to adulthood verifies the consistent phenomenon of blood pressure tracking, wherein childhood blood pressure levels are associated with blood pressure levels in later life (73). Additionally, as demonstrated by the Bogalusa Heart Study (74), children with elevated blood pressure are 2-3 times more likely to develop essential hypertension in young adulthood.

1.4 Diagnosis of hypertension

Guidelines for the management of hypertension have existed for over 30 years (75, 76). In 1993 (77), the limit for diagnosis of hypertension was lowered to ≥140/90 mmHg for the first time, and this definition has persisted

since then. In the 1999 guideline from the WHO and the International Society of Hypertension (31), the limit for normal blood pressure was lowered to <130/85 mmHg, and two new categories were introduced; optimal blood pressure (<120/80 mmHg) and high normal blood pressure (130-139/85-89 mmHg). Manifest hypertension was further categorised as grade 1 (140–159 mmHg systolic and/or 90–99 mmHg diastolic), grade 2 (160–179 mmHg systolic and/or 100–109 mmHg diastolic), or grade 3 hypertension (≥180 mmHg systolic and/or ≥110 mmHg diastolic). Since 2003, the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) have published joint guidelines, which most recently have been revised in 2007, 2009 and 2013 (78-80, 28). They further suggest dividing blood pressure in the normal range into the three categories.

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal	<120	and	< 80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

Figure 1. Blood pressure categories according to ESH/ESC guidelines 2007, 2009 and 2013 (79, 80, 28).

1.5 Blood pressure measurements

To reduce misclassification of hypertension, blood pressure should be measured in a standardised fashion (81, 82). Intra-individual variation in blood pressure, rather than a so-called white coat effect (83), is known to cause an overestimation of hypertension, and accordingly repeated readings are recommended (84). The recent ESH/ESC guidelines further recommend (28):

- To allow the patients to sit for 3–5 minutes before beginning blood pressure measurements.
- To take at least two blood pressure measurements in the sitting position, spaced 1–2 min apart.
- Consider the mean of the two blood pressure readings if deemed appropriate.
- To use a standard bladder (12–13 cm wide and 35 cm long), but have a larger and a smaller bladder available for large (arm circumference >32 cm) and thin arms (arm circumference 17-22 cm), respectively.
- To have the cuff at the heart level, whatever the position of the patient.

Furthermore, a quiet, comfortable location at normal room temperature is optimal. Ideally, the patient should not recently have eaten, smoked, exercised, or taken caffeine (29, 82). When adopting the auscultatory method, the phase I (appearance) and V (disappearance) of Korotkoff sounds should be used to identify systolic and diastolic blood pressure, respectively. Provided that the arm is supported at the heart level, sitting and supine blood pressure measurements are considered comparable (82). The observer should be well trained in the techniques of blood pressure measurement and use an accurate and properly maintained device (28, 85).

1.6 Prevalence of hypertension and high blood pressure

The prevalence of hypertension increases significantly with age, and is therefore usually reported by different age groups. Geographical gradients in the prevalence of hypertension exist with respect to European versus American studies (86) and also in studies within Europe (86), where an east-west gradient have been observed. A secular trend of decreasing or unaltered prevalence can be noted in large observational studies (87, 88). In the National Health and Nutrition Examination Survey (NHANES) 1999-2004, the overall age-adjusted prevalence of hypertension was 29% (89) and remained so in 2007-2008 (88). The “Eight Countries” study (86) showed an age- and sex-adjusted prevalence of hypertension of 28% in the North

American countries and 44% in the European countries. Prevalence figures for European countries have varied and have been relatively high, which might be explained by differences in design and age span across studies. The prevalence was 39% in the Czech Republic (90), 31% in Greece (91), whereas in the Netherlands, the prevalence of hypertension was only 23% (15), similar to the 20% in Skaraborg (92). In the Västerbotten Intervention Project (VIP) 1985-1999 in the age-group 25-64 years, the prevalence was 31% (93). Generally among those with hypertension, 60% have mild hypertension (grade I), 30% moderate hypertension, and 10% severe hypertension (grade II and III respectively) (94). If those with a blood pressure in the normal high range would be included, at least another 20% in total would be addressed as potentially at-risk (95, 96).

1.7 Treatment of hypertension and blood pressure goals

Although there are no objections towards treating moderate and severe hypertension to reduce mortality in these levels (29, 30), recent guidelines recommend an assessment of global risk in patients with mild hypertension to select those individuals who would benefit more from pharmacological treatment (28, 72). Still, only a small proportion of patients with hypertension have increased blood pressure as the sole risk factor.

The severity of high blood pressure and the impairment regarding glucose and lipid metabolism are highly correlated (97). Blood pressure and metabolic risk factors additionally potentiate each other, leading to a total cardiovascular risk that is higher than the sum of individual risk factors (47), supporting the metabolic syndrome (53). It is becoming more and more evident that other diseases and cardiovascular risk factors interact with high blood pressure in determining the individual's global risk (28, 98). Those with both hypertension and diabetes have been identified to be at a higher risk of complications (33, 99). To correctly identify the individuals in the highest need of treatment, special risk grading tools have been developed; the first of them was The Framingham Risk Score (100). This was developed based on data obtained from the Framingham Heart Study to estimate the 10-year risk of developing coronary heart disease. Thereafter, many risk score algorithms have been developed in order to better suit the actual settings, and the one most commonly used in Northern Europe is SCORE (Systematic Coronary Risk Evaluation) (101-103). SCORE calculates the 10-year risk of cardiovascular death utilising systolic blood pressure combined with other cardiovascular risk factors (sex, age, cholesterol, smoking), sometimes

including diabetes (SCORE-DM) (79, 103). When this risk is estimated to be at least 5%, pharmacological treatment is generally recommended (102).

Since hypertension-related progression of the development of CVD is often asymptomatic over a long period of time, emphasis has been directed towards the identification of organ damage (OD). It has been argued that the observation of any of the four markers of OD (microalbuminuria, increased pulse wave velocity (PWV), left ventricular hypertrophy (LVH), and carotid plaques) can predict cardiovascular mortality independently of SCORE stratification (104-106), and that the risk increases as the number of damaged organs increases (97).

The ESH/ESC Guidelines (28), in similarity with many other guidelines provided by expert organisations (29, 30, 72), recommend the use of antihypertensive drugs in patients with grade 1 hypertension even in the absence of other risk factors, provided that non-pharmacological treatment has proved unsuccessful. Recent guidelines state that a systolic blood pressure goal <140 mmHg (in the elderly blood pressure between 140 and 150 mmHg) and a diastolic blood pressure target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended (28). This has been greatly discussed in recent years. Whereas the 2007 ESH/ESC Guidelines recommended <130/<80 mmHg in patients with diabetes (79), a careful review of the available evidence (107) has led to a re-appraisal of previous recommendations (80). Thus, in the recent JNC 8, a target goal of <140/<90 mmHg was recommended also in patients with diabetes (30).

1.8 Available recommended drugs

Major trials were published between the late 1960s and the 1980s, showing beneficial effects of blood pressure lowering medication with thiazide, diuretics, or beta-blockers in hypertensive subjects (108-112). In the early 1990s, trials convincingly showing benefits of antihypertensive treatment in elderly subjects were published (113-115). Figure 2 shows examples of studies with an effect of active pharmacological therapy against a placebo-treated control group.

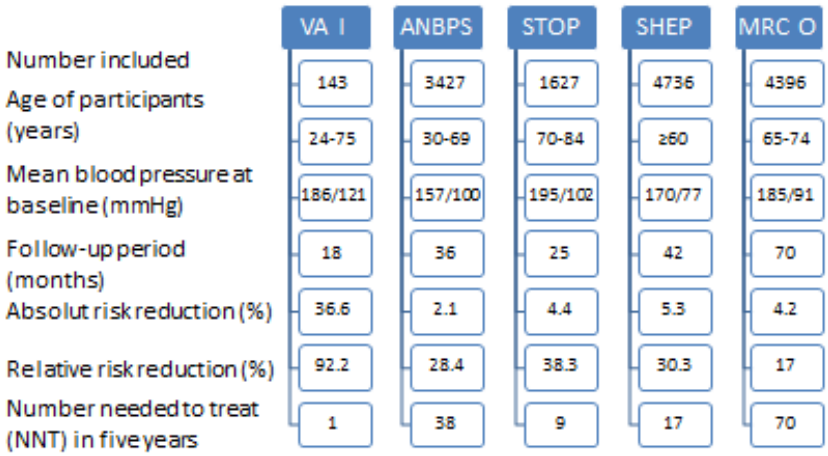

Figure 2. Results from different placebo-controlled trials of pharmacological treatment of hypertension. VA I: Veterans Administration Study I (108). ANBPS: Australian National Blood Pressure Study (110). STOP: Swedish Trial in Old Patients with Hypertension (113). SHEP: Systolic Hypertension in the Elderly Program (114). MRC O: Medical Research Council trial of treatment of hypertension in older (115).

In recent years there have been a large number of randomised trials of antihypertensive therapies other than thiazide, diuretics, or beta-blockers. Most often there are no differences in CVD events between certain therapies, except for subgroups in the study population, such as patients with diabetes (116, 117), and for secondary endpoints, such as heart failure (118). Recent guidelines conclude that the main benefits of antihypertensive treatment are due to lowering of blood pressure per se and are largely independent of the drugs employed (28). Moreover, the largest meta-analyses available do not show clinically relevant differences between classes of blood pressure lowering medications (119-121). Therefore, the current guidelines reconfirm that diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as mono therapy or in some combination (28).

A few trials have examined whether early treatment of prehypertension might prevent or delay the development of subsequent incident hypertension (122-124). With various types of pharmacological regimes, about 30 per cent relative risk reduction in onset of hypertension has been achieved (123). Taken together, the studies have opened the doors for future studies of pharmacological intervention in prehypertension. Moreover, in the TROPHY trial, even after discontinuation of active treatment, a 10% absolute and a 16% relative risk reduction was found in the group previously treated versus the control group (122).

1.9 Non-pharmacological treatment

Lifestyle modification is the cornerstone for the prevention and treatment of hypertension. Lifestyle changes can reduce blood pressure equivalent to drug mono therapy (125), although the major drawback is the low level of adherence over time, which requires special actions to overcome (126). The latest ESH/ESC guideline (28) states that lifestyle measures that are capable of reducing blood pressures are the following: salt restriction, moderation of alcohol consumption, high consumption of vegetables and fruits, weight reduction and regular physical exercise. Lifestyle changes contribute to the control of other cardiovascular risk factors and clinical conditions, and smoking cessation is also of great importance in order to reduce global cardiovascular risk and the further development of high blood pressure (127).

Several studies have shown blood pressure reduction with lifestyle treatments (128-130). The 8-week-long Dietary Approaches to Stop Hypertension (DASH) study (129) reported a -6/-3 mmHg blood pressure decrease with lifestyle modification in patients with prehypertension. In the DASH study, all patients were trained and motivated by experts in specialised study centers, and all meals were prepared in the centres and distributed to the participants. The 6-month-long PREMIER trial (130) showed that a body weight loss by 4-9 kg improved fitness, reduced urine sodium values by 32 mmol per day, and induced blood pressure reduction by a mean of 3.7 mmHg in systolic and 1.7 mmHg in diastolic blood pressure, respectively. In the Gothenburg Primary Preventive Trial (GPPT) (131) and in the Multiple Risk Factor Intervention Trial (MRFIT) (132), where multiple risk factor interventions by drug therapy and non-pharmacological therapy were performed, the group more intensively cared for failed to show a superior improvement as compared to the control group.

2 AIM

2.1 General aim

The overall aim of this thesis was to study determinants and risks associated with increasing blood pressure categories that were based on a combination of systolic and diastolic blood pressure, ranging from optimal blood pressure to manifest hypertension. Emphasis was placed on understanding the importance of focusing on modifiable lifestyle and assessment of global risk. The ultimate aim was to identify targets for treatment and prevention.

2.2 Specific aims

- To study the prevalence and control of hypertension in a representative Swedish population.
- To investigate the association between global risk (SCORE) and the ESH/ESC blood pressure categories.
- To investigate both physiological factors (insulin resistance, obesity, inflammation, lipids) and lifestyle factors (physical activity, smoking, alcohol consumption) in association with the ESH/ESC blood pressure categories.
- To investigate the risk of CVD associated with the ESH/ESC blood pressure categories ranging from optimal blood pressure to manifest hypertension.

3 PATIENTS AND METHODS

3.1 The Skaraborg Project

3.1.1 The Skaraborg Hypertension Project

The Skaraborg Hypertension Project was launched in 1977 in the county of Skaraborg to improve blood pressure control in the population, and to reduce the risk of AMI and acute stroke (133). Special out-patient clinics for hypertension were established in all primary health care settings in the program area, and the project involved guidelines for detection, workup, treatment, and follow-up of hypertension subjects (134).

One of the municipalities included in the project was Skara and at the Skara Health Care Centre, a program similar to that for patients with hypertension was organised for patients with diabetes in the mid 1970´s. This was the only primary health care service available in the area at the time, and in 1986 the care for patients with hypertension and diabetes was combined. All the patients with diabetes or hypertension were seen for annual standardised controls, which included medical history, risk factor control, a standard set of laboratory tests, and re-evaluations of medical treatment.

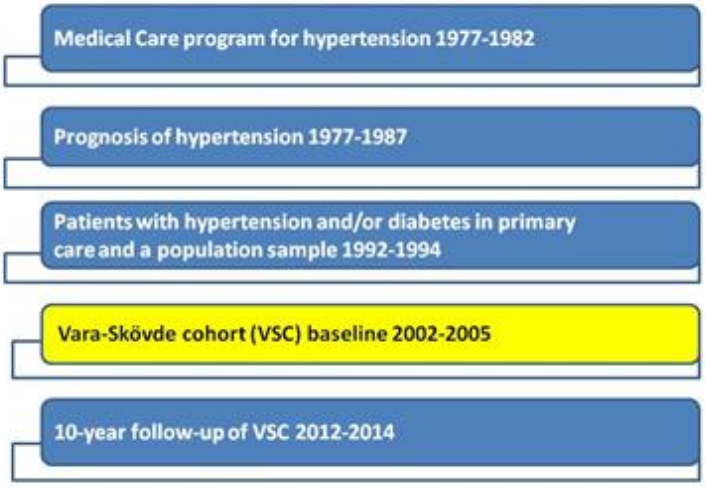

Figure 3. Skaraborg cohorts during 1977-2014.

3.2 Study population Paper I-IV

3.2.1 The Vara-Skövde Cohort

Between 2002 and 2005, two new surveys were conducted in the municipalities of Vara and Skövde. Vara is a small rural municipality with approximately 16 000 inhabitants, where many are farmers. Skövde has 50 000 residents and is the largest town in Skaraborg. Skövde is thus more urbanised than Vara, and has a hospital and a university. Ninety percent of the inhabitants of Skövde are Swedish born, whereas 95% of the inhabitants in Vara are Swedish born.

From the total number of all residents aged 30-74 years in each municipality, a computer-generated random sample from the population census register was selected, stratified by gender and five-year age groups. Although there were no exclusion criteria, an intentional three-fold over-sampling was performed in subjects 30-50 years of age, as compared to subjects over 50 years. Participation was high in both the Vara population (81% participation rate) and the Skövde population (70% participation rate), where 1811 and 1005 subjects, respectively, fulfilled all requirements for participation. The participation requirements comprised visiting the study nurse, completing the questionnaires, and having venous blood samples drawn.

3.3 General Methods

3.3.1 General procedures

After an overnight fast (10h), participants were seen in the morning by the study nurses. The nurses were all specially trained and calibrated in methodological procedures before the surveys began. Participants signed an informed consent form, and venous blood samples were drawn. After collection of the fasting plasma samples, an oral glucose tolerance test was performed in all participants without known history of diabetes, using a 75 g standard glucose load (135). During the two-hour wait for the final blood drawing, participants filled out a detailed questionnaire regarding socioeconomic status and lifestyles, such as smoking habits, alcohol consumption, and physical activity (136).

Approximately two weeks after the first visit, the participants came for a second visit to the nurses. Participants had their blood pressure taken, and they were weighed and had their body height measured. The study nurses

also interviewed them regarding their medical history and ongoing medication, with a special focus on treatment for hypertension and diabetes.

3.3.2 Medical History

The information collected with regard to medical history was established according to predefined criteria. The diagnoses included were acute myocardial infarction, angina pectoris, heart failure, acute stroke, intermittent claudication, diabetes mellitus, and smoking habits.

3.3.3 Physical Examination

After five minutes' rest, with the arm supported by a pillow at heart level, systolic and diastolic (phase V) right brachial arterial pressure was measured twice one minute apart in a supine position using the mean result from the analyses. Tricuff™ for automatic adjustment of cuff size to arm circumference (137) was used, and the blood pressure was recorded to the nearest 2 mmHg. Heart rate was registered simultaneously with blood pressure.

Wearing only light clothing and no shoes, participants were weighed on a calibrated scale to the nearest 0.1 kg and had their body height measured. Waist circumference was measured between the lowest rib margin and iliac crest and hip circumference at the largest circumference between waist and thighs. Height, waist, and hip circumference were recorded to the nearest cm.

3.3.4 Laboratory Examinations

Blood samples were taken in a non-fasting state in insulin-treated patients with diabetes, as fasting tests were considered unsuitable for these patients. For all other participants, tests were performed in the morning after an overnight fast (10 h minimum). Standard laboratory tests were used for serum cholesterol, fasting triglycerides, fasting blood glucose, and HbA1c; however, HbA1c was only analysed in subjects with diabetes, impaired fasting glucose, or impaired glucose tolerance. A modified glucose dehydrogenase method from Hemocue (Hemocue AB, Ängelholm) was used for the analyses of fasting and 2-h blood glucose, and both glucose and HbA1c were analysed by the laboratory at Kärnsjukhuset, Skövde. Immediately after blood sampling, serum samples were frozen to -82°C and analysed later for lipids and C-reactive protein (CRP), at the Department of Clinical Chemistry, Skåne University Hospital, Lund. Serum insulin was also analysed later at the Wallenberg Laboratory (Malmö University Hospital), using an enzyme linked immunosorbent assay (ELISA) with <0.3% cross-reactivity for proinsulin with a kit from DAKO Diagnostics Ltd (138).

3.3.5 Questionnaires

Leisure time physical activity was measured by the previously validated question "How physically active are you during your leisure time?" (139, 140). The question referred to the past year, and the four answer alternatives were: 1) Sedentary leisure time: reading, watching television, stamp collecting, or other sedentary activity; 2) Light leisure time physical activity: walking, cycling, or other physical activity under at least four hours per week; 3) Moderate leisure time physical activity: running, swimming, tennis, aerobics, heavier gardening, or similar physical activity during at least 2 hours a week; 4) Heavy training or competitive sport: heavy training or competitions in running, skiing, swimming, football, etc., which is performed regularly and several times a week.

Alcohol consumption was estimated by questions regarding the number of days during the past 30 days that the subjects had consumed beer, wine, and strong liquor, respectively. Each of these questions was followed by questions regarding how many cans, glasses, and/or bottles that were normally consumed on such days. The total number of grams of alcohol consumed per week was then calculated by multiplying the number of days of alcohol consumption by the number of grams of alcohol contained in the consumed alcoholic beverage.

Smoking habits were assessed by a question comprising current smoking, past smoking (at least one month), and never smoking. In this thesis current smoking was defined as daily smoking (yes/no), as past smokers and never smokers both were considered non-smokers. Educational level was examined by a question with 10 alternative responses reaching from primary school to PhD degree.

3.3.6 Diagnostic procedures

Subjects without an already existing diagnosis of hypertension, who showed a diastolic blood pressure ≥90 mmHg and/or a systolic blood pressure ≥140 mmHg at the initial measurement, were followed up with two additional blood pressure measurements (1-2 weeks between each measurement), which is in accordance with international standards (28, 31). For a new diagnosis of hypertension to be confirmed, the blood pressure had to be ≥90 mmHg for the diastolic pressure, and/or ≥140 mmHg for the systolic blood pressure at three consecutive visits.

Diagnosis of diabetes was confirmed after two fasting plasma glucose values of ≥7.0 mmol L^{-1} (1-2 weeks between measurements), or after one 2-h plasma

glucose value of ≥11.1 mmol L^{-1} in an oral glucose tolerance test (135). Differentiation between type 1 and type 2 diabetes was based on clinical criteria: i.e. age at onset, weight, symptoms at initial stage, tendency of ketosis, treatment, and in some cases C-peptide.

3.3.7 Paper I

The sample was categorised into those with *Normal blood pressure* (i.e., no previous history of hypertension and both systolic and diastolic baseline blood pressure <140/90 mmHg); *Known hypertension, treatment goals not met* (i.e., known hypertension and baseline blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic); *Known hypertension, treatment goals met* (i.e., known hypertension and both systolic and diastolic baseline blood pressure ≤140/90 mmHg); *New screening-detected hypertension* (i.e., no previous history of hypertension and baseline blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic at three consecutive readings).

Age was divided into 5-year age groups, and current smoking was defined as daily smoking (yes/no). Low education was defined as ≤9 years of education. BMI was calculated by the body weight in kilograms divided by the square of the height in meters (kg/m^2), and obesity was defined as BMI ≥30 kg/m^2 and overweight as BMI ≥25 kg/m^2 but <30 kg/m^2 (141).

3.3.8 Paper II–IV

Blood pressure categories

The following blood pressure categories were defined in accordance with the joint guidelines from the ESH/ESC (28): *Optimal* (<120/80 mmHg), *Normal* (120-129/80-84 mmHg), *High normal* (130-139/85-89 mmHg), and *Hypertension* (three consecutive readings (31) of ≥140 systolic and/or ≥90 mmHg diastolic, or when a diagnosis made by a physician was previously documented). If systolic and diastolic blood pressure belonged to different categories, the highest category was chosen. Untreated subjects with a blood pressure of at least 140/90 mmHg were seen again at a second visit within 2 weeks, and if the blood pressure was still ≥140 and/or 90 mm Hg, they were seen a third time within another 2 weeks. Subjects with a high blood pressure at the first study visit who had a normal blood pressure (<140/<90 mm Hg, both systolic and diastolic) at the second or at the third visit were considered to have *Unstable or temporarily high* blood pressure. In all, five blood pressure categories were thus used to describe the distribution of blood pressure.

3.3.9 Paper II

Apart from the categorisation of five blood pressure categories ranging from optimal to manifest hypertension, those with known hypertension were also categorised according to their so-called grade of hypertension in accordance with European guidelines (28). Those categories were *grade 1*: 140-159 mm Hg systolic and/or 90-99 diastolic; *grade 2*: 160-179 systolic and/or 100-109 diastolic; and *grade 3*: ≥180 systolic and/or ≥110 diastolic.

Current smoking was defined as daily smoking (yes/no). Previous CVD was defined as a history of at least one of the following conditions: stroke, myocardial infarction or any other kind of coronary heart disease, angina pectoris, congestive heart failure, or atrial fibrillation.

Risk Score Algorithm

The SCORE model recommended for low-risk countries (101, 103) was used to estimate the 10-year risk of cardiovascular death, accounting for risks based on sex, age, systolic blood pressure, total serum cholesterol, and on current smoking (101, 103). Based on individual values in these variables, all participants were placed in the corresponding score cell, thus to be assigned a risk estimation according to SCORE. The corresponding risk accounting for the risk added by the presence of diabetes was calculated by the multiplication by 2 in men and by 4 in women (79, 103). As suggested in SCORE (101, 103), the global risk was considered as high if the 10-year risk of cardiovascular death ≥5% (SCORE-HIGH), and correspondingly low if <5%. For SCORE-DM, i.e. score with diabetes included, the same procedure was performed, and the result was considered high if the 10-year risk of cardiovascular death ≥5 percent (SCORE-DM-HIGH). Ten per cent of the participants were randomly chosen to have their score manually calculated from the chart and the 10-year mortality risk was accordingly considered high or low. In all participants, the manual calculation yielded the same result as the one based on the algorithm.

3.3.10 Paper III

Level of education was divided into the following three categories: *primary school only (9 years)*, *secondary school*, and *higher education*. Alcohol consumption was measured as grams of alcohol per week. The apolipoprotein B/apolipoprotein A1 ratio (ApoB/ApoA1) was defined as the ratio between apolipoprotein B and apolipoprotein A1. BMI was calculated by the body weight in kilograms divided by the square of the height in meters (kg/m^2). Insulin resistance was estimated based on the Homeostasis Model

Assessment of insulin resistance (HOMA-IR): fasting insulin × fasting blood glucose / 22.5 (138).

3.3.11 Paper IV

The primary endpoint of incident CVD morbidity and mortality, obtained from the National Swedish Hospital Discharge Register and the National Mortality Register (142, 143), included ischaemic heart disease (ICD-10: I21, I22, I23, I25), stroke (ICD-10: I60, I61, I63, I64), percutaneous coronary intervention (PCI), and coronary artery intervention by-pass grafting (CABG). End of follow-up was December 31, 2011.

Level of education was divided into the following three categories: *primary school only (9 years)*, *secondary school*, and *higher education*. Alcohol consumption was measured as grams of alcohol per week. ApoB/ApoA1 was defined as the ratio between apolipoprotein B and apolipoprotein A1. BMI was calculated by the body weight in kilograms divided by the square of the height in meters (kg/m^2). Previous CVD was defined as a history of at least one of the following conditions: stroke, myocardial infarction or any other kind of coronary heart disease, angina pectoris, congestive heart failure, or atrial fibrillation. Insulin resistance was estimated based on the Homeostasis Model Assessment of insulin resistance (HOMA-IR): fasting insulin × fasting blood glucose / 22.5 (138).

3.4 Statistical analyses

3.4.1 Paper I–IV

All proportions of the study population were age-standardised by five-year age groups using the entire Vara population 30–75 years as standard. All statistical tests in this thesis were two-sided, and statistical significance was assumed at $p < 0.05$.

3.4.2 Paper I

All statistical analyses were performed using the SPSS software package for Mac, version 19.0. For comparison between groups in categorical variables, either a chi-square test for bivariate analyses, or multiple binary logistic regression with associations expressed as odds ratios (OR) with 95% confidence intervals (CI) was used. To adjust for possible contextual differences between the municipalities of Vara and Skövde, and for differences in lifestyle between residents in these municipalities, study site was included as a covariate in the analyses together with age.

3.4.3 Paper II

All statistical analyses were performed using the SPSS software package for Windows 19.0. General linear model (GLM), adjusted for differences in age, was used to compare means between groups in continuous variables, and results were given as differences with 95% confidence intervals. Logistic regression was used to estimate associations between categorical variables, and results were presented as ORs with 95% CI. Confounding was accounted for by multivariate analyses adjusting for age and by stratification for sex.

3.4.4 Paper III

SPSS Base System for Windows 21 was used for data analyses. Prevalence rates in the study population were age-standardised by five-year age-groups using the whole Vara population 30-75 years as standard. GLM was used to compare age-adjusted means between groups in continuous variables, and logistic regression analyses were used to compare age-adjusted proportions. For comparisons between blood pressure categories, optimal blood pressure was used as the reference and the results were given as mean differences with 95% CI. Logistic regression was used to analyse associations between categorical variables and blood pressure categories, and the results were presented as ORs with 95% CI. Linear regression was performed to estimate the association between risk factors and blood pressure, using the different blood pressure categories as an approximate continuous variable. Two-way interaction terms were used to explore the interaction between sex and various risk factors in association with high blood pressure. The logarithmic form of HOMA-IR (10-log) was used in all statistical analyses, and subjects with CRP >10 mg/L were excluded from the analyses where CRP was the main independent variable (144). Confounding was accounted for by multivariate analyses and by stratification with regard to age, HOMA-IR, BMI, ApoB/ApoA1, CRP, alcohol, smoking, leisure time physical activity, and education. In the multivariate analyses, all four levels of leisure time physical activity were used, and when dichotomised for stratification and descriptive analyses, the two first categories were considered as low level of physical activity, and the two highest categories as high level of physical activity.

3.4.5 Paper IV

SPSS Base System for Windows 21.0 was used for data analyses. Prevalence rates in the study population were age-standardised by five-year age-groups using the whole Vara population 30-75 years as standard GLM was used to compare age-adjusted means between groups in continuous variables, and logistic regression analyses were used to compare age-adjusted proportions. After controlling for proportionality, hazard ratios (HR) were examined by Cox proportional hazard model and expressed with 95% CI. Potential confounders were age, sex, BMI, HOMA-IR, ApoB/ApoA1, CRP, smoking, alcohol consumption, physical activity, education, and previous CVD. The logarithmic form of HOMA-IR (10-log) was used in all statistical analyses. An interaction term between sex and blood pressure categories in association with CVD morbidity was non-significant ($p_{age\text{-}adj}$=0.833), and men and women were thus combined in the Cox analyses.

4 RESULTS

4.1 Paper I

Prevalence, awareness, treatment, and control of hypertension: Rule of thirds in the Skaraborg Project

4.1.1 Results

Characteristics of the study population (n=2816) are shown in Table 1. The age-standardised prevalence of hypertension overall was 20% (19.9% in men and 20.1% in women) with a steep increase by age (Figure 4). Among patients with hypertension, 33% (n=137) were unaware, 36% (n=149) aware but uncontrolled, and 31% (n=129) aware and controlled, with no statistically significant differences between men and women. Patients with diabetes had a higher awareness (87% vs. 64%, $p<0.001$), but a similar control rate (56% vs. 44%, $p=0.133$), when compared to those without diabetes. In patients aware of their hypertension about one half (46%) had adequately controlled blood pressure at the study visit. Blood pressure levels in aware men with controlled hypertension did not differ significantly from normotensive men, whereas they were significantly higher in the corresponding group of women. In both sexes, general and abdominal obesity were more common, and fasting plasma glucose was higher in all categories with hypertension compared to those with normal blood pressure (Table 2). While traditional determinants of hypertension such as a family history of hypertension, known diabetes, overweight and obesity were all significantly associated with known hypertension, they did not discriminate between those with controlled and uncontrolled hypertension.

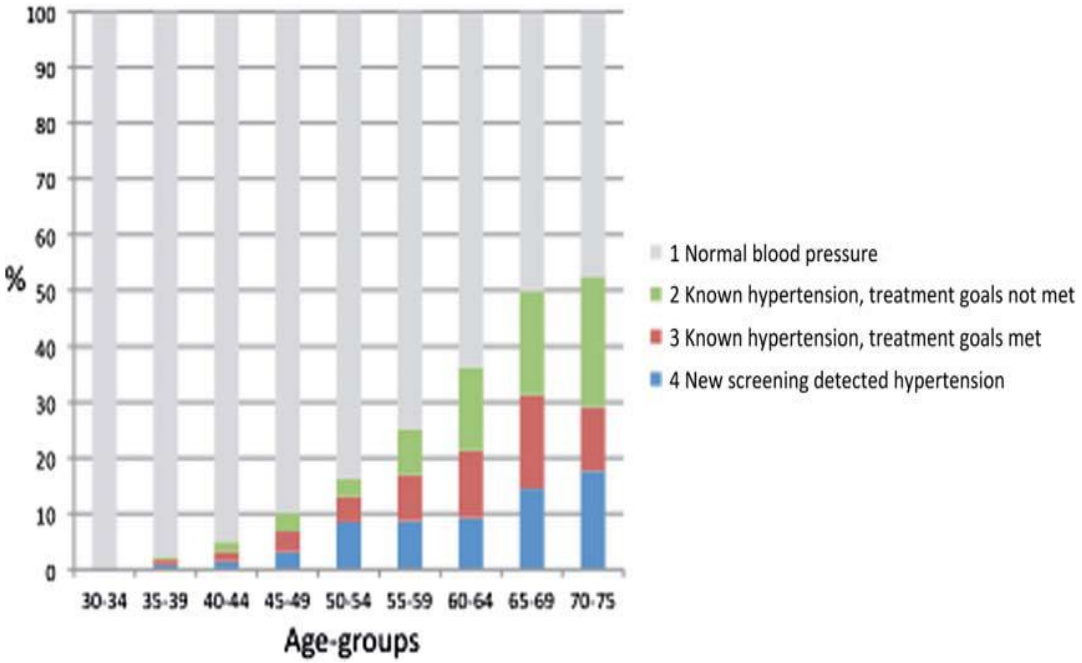

Figure 4. Proportions of normal blood pressure (1), known hypertension, treatment goals not met (2), known hypertension, treatment goals met (3), and new screening detected hypertension (4), respectively: Distribution by five-year age groups in men and women combined in the Vara-Skövde Cohort 2002-2005, Sweden.

Table 1. Study characteristics of men and women participating in the Vara-Skövde cohort 2002-2005, Sweden.

	Men		Women	
	m	**(SD)**	**m**	**(SD)**
	n=1400		*n=1416*	
Age (years)	47.8	(11.8)	47.8	(11.7)
Systolic blood pressure (mmHg)	124	(14.2)	119	(14.2)
Diastolic blood pressure (mmHg)	72	(9.5)	69	(9.6)
Heart rate (beats min^{-1})	63	(8.4)	65	(8.4)
Fasting plasma glucose (mmol L^{-1})	5.6	(1.0)	5.3	(1.1)
HOMA-IR	1.34	0.30	1.18	0.30
Serum cholesterol (mmol L^{-1})	5.3	(1.0)	5.2	(1.0)
ApoB/ApoA1	0.65	(0.15)	0.57	(0.15)
CRP	1.84	(1.9)	2.12	(1.9)
Waist circumference (cm)	95	(11.7)	86	(11.7)
Body mass index (kg m^{-2})	26.9	(4.9)	26.8	(4.5)
	n	**(%)**	**n**	**(%)**
Daily smoking	216	(15)	289	(20)
[a]Known diabetes	51	(4.8)	42	(4.2)
Obesity (BMI ≥30 kg m^{-2})	248	(18.7)	332	(26.2)
[b]Family history of hypertension	559	(39)	652	(47)

[a] Self-reported doctors diagnosis of diabetes (type 1 or type 2).

[b] Self-reported hypertension among first degree family members (siblings and parents).

4.1.2 Discussion

The overall results show that every fifth man and woman aged 30-74 years was found to have hypertension, confirming this condition to be a major public health issue. Although rates of awareness and treatment have increased during recent decades (88), still only about half of those treated for hypertension achieve recommended treatment goals (87, 93). Considering the prevalence of diabetes among patients with hypertension, the rate of controlled hypertension would have been even worse than what we found had we considered accurate blood pressure goals in hypertensive patients with diabetes. It has been argued that the risk score should be accounted for when treatment and control of hypertension are discussed, as mild hypertension at low risk should be treated non-pharmacologically (28, 31, 101, 145). The rate of controlled hypertension may then be better than commonly understood; however, even with the more strict definition of hypertension as used in Skaraborg, the controlled rate is far from acceptable. Our observation of similar controlled rates in hypertensive patients with and without diabetes may be an effect of the physician's recognition of recommendations regarding more intensive blood pressure treatment in diabetes and other risk categories (28, 31). This is consistent with the significantly higher awareness in those with diabetes.

Primary health care does not successfully manage to find, treat, and control individuals with hypertension despite repeated updates of guidelines from expert organisations (146). Although a considerable problem may be low patient compliance with prescribed treatment, the major responsibility should rather be put on the health care and educational systems. Structured care programs for hypertension have previously and recently been found to be effective (133, 147, 148), still, such programs are often not used in primary care today. If physicians and health care clinics would profit economically from reaching targets more often, the situation might change more systematically (149). This also calls for more research and interventions in today's primary care. Still, according to Geoffrey Rose, optimal effect will solely be achieved by combining primary prevention in a population strategy with identification of individuals at high risk to be targeted for individual care (150).

Table 2. Comparison of common cardiovascular disease risk factors between categories of hypertension in men and women using aware controlled hypertension as reference. The Vara-Skövde Cohort 2002-2005, Sweden.

Men	Aware HT controlled *n=66*		Aware HT uncontrolled *n=68*		Unaware HT *n=75*		Normal BP *n=1191*	
	m	(SD)	M	(SD)	m	(SD)	m	(SD)
			Δ	(CI)	Δ	(CI)	Δ	(CI)
Age (years)	59.8	(10.8)	61.2	(9.8)	60.4	(11.0)	45.6	(10.6)
			1.4	(-2.2/5.0)	0.5	(-3.0/4.0)	-14.2	**(-16.8/-11.6)**
Systolic blood pressure (mmHg)	122	(7.5)	148	(12.9)	153	(15.1)	121	(11.6)
			26.0	(**22.3/29.7**)	31.1	(**27.4/34.7**)	-1.0	(-3.8/1.8)
Diastolic blood pressure (mmHg)	71	(8.4)	83	(11.7)	86	(10.7)	71	(8.7)
			11.9	(**8.9/14.9**)	14.9	(**12.0/17.8**)	-0.2	(-2.5/2.1)
Heart rate (beats min^{-1})	62	(9.7)	62	(9.5)	67	(11.8)	63	(8.2)
			-0.2	(-3.1/2.7)	5.0	(**2.2/7.9**)	0.3	(-1.9/2.5)
Fasting plasma glucose (mmol L^{-1})	6.3	(2.2)	5.8	(1.4)	6.0	(1.6)	5.5	(0.9)
			-0.5	**(-0.9/-0.2)**	-0.3	(-0.7/0.02)	-0.8	**(-1.1/-0.6)**
Serum cholesterol (mmol L^{-1})	5.1	(0.8)	5.1	(1.0)	5.4	(1.1)	5.4	(1.0)
			0.4	(-2.9/3.7)	-0.8	(-4.1/2.4)	-3.8	**(-6.4/-1.3)**
Waist circumference (cm)	98	(11.2)	99	(10.5)	97	(7.7)	94	(9.8)
			0.4	(-2.9/3.7)	-0.8	(-4.1/2.4)	-3.8	**(-6.4/-1.3)**
Body mass index (kg m^{-2})	28.4	(4.0)	28.5	(4.1)	27.5	(3.0)	26.7	(3.6)
			0.2	(-1.0/1.4)	-0.8	(-2.0/0.4)	-1.7	(**-2.6/-0.8**)

Women	Aware HT controlled *n=63*		Aware HT uncontrolled *n=81*		Unaware HT *n=62*		Normal BP *n=1210*	
	m	(SD)	M	(SD)	m	(SD)	m	(SD)
			Δ	(CI)	Δ	(CI)	Δ	(CI)
Age (years)	59.5	(10.5)	63.3	(10.2)	60.0	(10.0)	45.5	(10.4)
			3.7	(**0.3/7.2**)	0.4	(-3.2/4.1)	-14.0	(**-16.7/-11.4**)
Systolic blood pressure (mmHg)	121	(8.6)	146	(13.5)	151	(11.8)	116	(13.1)
			25.0	(**21.3/28.8**)	29.5	(**25.5/33.5**)	-5.0	(**-8.0/-2.0**)
Diastolic blood pressure (mmHg)	71	(7.8)	77	(10.4)	81	(15.9)	67	(8.5)
			5.6	(**2.7/8.6**)	10.1	(**7.0/13.2**)	-3.8	(**-6.1/-1.4**)
Heart rate (beats min^{-1})	64	(9.7)	65	(10.3)	69	(8.5)	64	(8.0)
			1.3	(-1.4/4.1)	5.3	(**2.4/8.2**)	0.7	(-1.5/2.9)
Fasting plasma glucose (mmol L^{-1})	6.0	(1.8)	6.3	(2.7)	5.8	(1.9)	5.2	(0.7)
			0.2	(-0.1/0.6)	-0.3	(-0.7/0.1)	-0.8	(**-1.1/-0.5**)
Serum cholesterol (mmol L^{-1})	4.8	(1.0)	4.9	(1.0)	5.6	(1.3)	5.2	(1.1)
			0.04	(-0.3/0.4)	0.8	(**0.4/1.1**)	0.4	(**0.2/0.7**)
Waist circumference (cm)	95	(13.7)	95	(14.4)	93	(14.7)	84	(12.7)
			-0.3	(-4.6/4.0)	-2.2	(-6.8/2.3)	-10.8	(**-14.2/-7.4**)
Body mass index (kg m^{-2})	30.5	(5.4)	30.8	(6.2)	28.9	(5.6)	26.2	(5.0)
			0.4	(-1.3/2.0)	-1.5	(-3.3/0.3)	-4.2	(**-5.6/-2.9**)

4.2 Paper II

Blood pressure and global risk assessment in a Swedish population.

4.2.1 Results

Overall, when men and women were combined, 74% of the subjects had normal blood pressure, 6% had unstable blood pressure, and 20% had hypertension. As seen in Figure 5, the normal optimal blood pressure was the most common blood pressure category in both sexes. The mean SCORE was significantly higher in participants with unstable blood pressure and manifest hypertension than in those with optimal blood pressure in both sexes, regardless of the presence of diabetes (Paper II, Table 2). Thirteen per cent of men and one per cent of women were categorised as high risk (10-year risk of cardiovascular death ≥5%); however, when diabetes was also considered, the corresponding proportions were 14% and 4%. The mean risk scores did not differ between the normal blood pressure categories, regardless of whether diabetes was taken into consideration.

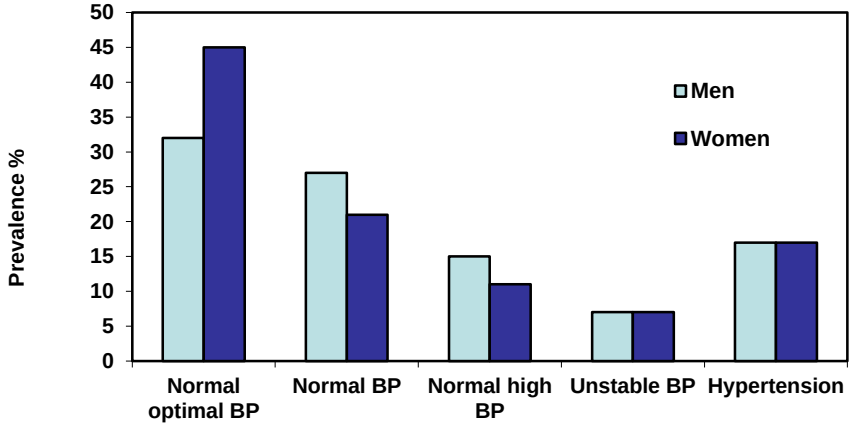

Figure 5: The distribution (%) of blood pressure (BP) categories according to the 2007 ESH/ESC guidelines (79) in men and women. Normal optimal BP: <120/80 mmHg; Normal BP: 120-129/80-84; Normal high BP: 130-139/85-89; Unstable or temporarily high BP: ≥140 and/or ≥90 on one or two reading, but not three; Hypertension: ≥140 and/or ≥90 on three consecutive BP readings, or a documented previous diagnosis made by a physician.

The proportion of subjects defined as high risk in men increased from 2% in the normal blood pressure category to 46% in the hypertension category, and correspondingly from 0% to 7% in women. When diabetes was also taken into consideration, these proportions in men were 3% and 50%, and in women 0% and 19%. In subjects with more severe hypertension, these proportions were considerably higher, i.e. 60% in men and 43% in women with grade 2 hypertension, and 57% and 100% in those with grade 3 hypertension, respectively. In the presence of both hypertension and diabetes, high-risk subjects predominate, i.e. 76% in men and 61% in women (Figure 6). In low-risk subjects, even in the presence of both diabetes and hypertension, age and concentrations of lipids were low. Men and women with high score without hypertension or diabetes were older, had higher concentrations of lipids and were often current smokers.

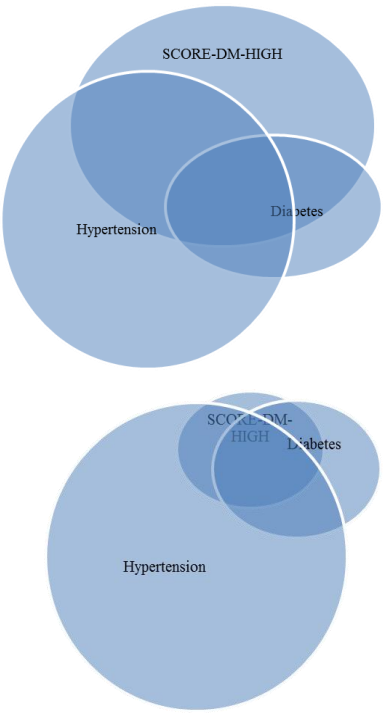

Figure 6: Venn diagrams in men (A) and women (B), showing the overlap between categories of hypertension, diabetes, and a high risk SCORE, respectively, accounting for the risk associated with diabetes.

4.2.2 Discussion

A large proportion of patients with hypertension had a low estimated global risk of CVD according to SCORE. This contradicts previous reports suggesting that SCORE overestimates cardiovascular risk (157). This in turn may partially support our recent findings that only one-half of all subjects treated for manifest hypertension achieve recommended blood pressure goals (15). We may have to accept that some subjects, especially women, are considered adequately cared for, despite not having a blood pressure ≤140/90mmHg. However, in patients with grade 2 or grade 3 hypertension, the estimated mortality risk was considerably higher, thus emphasising the need of more attention for these patients.

Traditional CVD risk factors increased in both men and women the higher the blood pressure category. The accumulation of risk factors among subjects with manifest hypertension and unstable blood pressure was confirmed by the global risk score that significantly differentiated hypertension and unstable blood pressure from all the normal blood pressure categories according to the 2007 European guidelines (79). This pattern was even more pronounced when risk score also took diabetes into consideration. Most subjects with manifest hypertension grade 1 had an estimated 10-year CVD mortality risk <5% and should thus not routinely be prescribed pharmacological treatment at grade 1 hypertension.

The present findings imply that cardiovascular risk estimation using SCORE would yield similar risk increases as those according to 2007 ESH/ESC blood pressure categories and general expert treatment guidelines. These findings support the use of SCORE to evaluate global risk in the assessment of subjects with high blood pressure in clinical practice, and they emphasise the need of non-pharmacological interventions among subjects with high normal blood pressure and among those with hypertension grade 1 with an estimated low global risk (SCORE) (158-160). These questions should be further investigated in longitudinal population-based studies exploring clinical use of SCORE in more detail.

4.3 Paper III

Lifestyle and physiological characteristics in association with blood pressure categories in a Swedish Population: a cross-sectional study.

4.3.1 Results

General characteristics of the male and female study population are shown in Table 3, and sex-specific information on lifestyle, as well as distribution of ESH/ESC blood pressure categories, are shown in Table 4. Levels of HOMA-IR, ApoB/ApoA1, and both systolic and diastolic blood pressure were significantly higher in men than in women. Men also had a considerably higher consumption of beer, spirits, and alcohol in general, whereas wine consumption was similar in men and women (Table 3). More men than women had only 9 years of primary school; however, men were more physically active than women, and fewer of them smoked (Table 3). Age, BMI, and HOMA-IR were higher in the higher blood pressure categories in both sexes. In men, the mean alcohol consumption per week was 74 g in the group with hypertension, compared to 58 in those with optimal blood pressure (p=0.115). In women on the other hand, alcohol consumption was significantly lower (p=0.002) in those with hypertension (15 g/week) compared to those with optimal blood pressure (25 g/week).

In age-adjusted linear regression analyses, age, HOMA-IR, BMI, and CRP showed strong associations with increasing blood pressure in both men and women (p-values<0.005), although the association with regard to HOMA-IR seemed to be prominent in women (data not shown). In women, ApoB/ApoA1 (p<0.001), education (p=0.009), physical activity (p=0.032), and alcohol consumption (p=0.002, inverse association) were also associated with blood pressure levels, whereas this was not observed in men. In the full multivariate model (including age, HOMA-IR, BMI, ApoB/ApoA1, CRP, alcohol, smoking, leisure time physical activity, and education), age, HOMA-IR, and BMI still showed strong associations with increasing blood pressure in both sexes. Among the other factors that came out significant in women in the age-adjusted analyses, only alcohol consumption maintained its statistical significance in the fully adjusted model (p=0.041) (Table 4).

Sex-differences were confirmed by statistically significant two-way interaction terms between sex and HOMA-IR ($p_{age\text{-}adj}$=0.024), and sex and alcohol ($p_{age\text{-}adj}$=0.001), respectively, in association with the blood pressure categories. The interaction with regard to alcohol remained significant in the full model (p=0.022), whereas the interaction with regard to HOMA-IR was independent of all factors apart from BMI ($p_{full\ model}$=0.167).

Table 3. Blood pressure categories and lifestyle in men and women in the Vara-Skövde cohort 2002-2005, Sweden.

	Men		Women		
Characteristics	**n**	**%**	**n**	**%**	**p**
	n=1400		*n=1416*		
Blood pressure categories[1]					
Optimal[2]	557	34	805	46	<0.001
Normal[2]	385	26	230	17	<0.001
High normal[2]	179	13	115	10	<0.001
Unstable[2]	70	6	60	6	0.346
Hypertension[2]	209	20	206	20	0.839
Daily smoking	216	15	289	20	0.001
Diabetes	89	8	69	7	0.088
Low LTPA[3]	820	59	984	71	<0.001
Primary school only	433	38	335	33	<0.001
	m	**q1-q3**	**m**	**q1-q3**	**p**
Alcohol, total, g/week[4]	61	11-77	22	0-31	<0.001
Wine	13	0-14	14	0-19	0.643
Beer	30	3-38	6	0-6	<0.001
Spirits	18	0-15	3	0-0	<0.001

All means are adjusted for age and proportions are age-standardised using the Vara population as standard.

[1] Optimal Blood Pressure: <120/80 mmHg; Normal: 120-129/80-84 mmHg; High normal: 130-139/85-89 mmHg; Unstable: ≥140/90 mmHg on one or two reading(s) but not three; Hypertension: ≥140/≥90 mmHg on three consecutive readings, or a previous diagnosis of hypertension made by a physician.

[2] Differences between men and women in each blood pressure category were calculated using the other categories as reference.

[3] Low LTPA = light leisure time physical activity (exercise, walking and gardening included) less than 4 hours per week.

[4] 12 g alcohol is equivalent to approximately 4 cl of spirits, 1 glass of wine or 1 small beer.

Table 4. Association between risk factors and increasing blood pressure categories in subjects from the Vara-Skövde cohort 2002-2005, Sweden.

	Men			**Women**		
	B *n=1400*	95% CI	P-value	B *n=1416*	95% CI	P-value
Adjusted for age, HOMA-IR, BMI, ApoB/ApoA1, CRP, alcohol consumption, smoking, physical activity, educational level						
Age	0.063	0.057;0.069	<0.001	0.069	0.063;0.075	<0.001
HOMA-IR	0.685	0.418;0.953	<0.001	0.790	0.525;1.056	<0.001
BMI	0.030	0.009;0.052	0.006	0.033	0.019;0.048	<0.001
ApoB/ApoA1	-0.266	-0.674;0.142	0.201	-0.191	-0.595;0.214	0.355
CRP ≤10	0.011	-0.029;0.051	0.586	0.004	-0.032;0.040	0.829
Alcohol	0.000	0.000;0.001	0.257	-0.002	-0.004;0.000	0.041
Smoking	0.021	-0.160;0.201	0.822	0.138	-0.013;0.290	0.073
Physical activity	-0.090	-0.187;0.006	0.066	-0.049	-0.153;0.055	0.354
Educational level	-0.010	-0.102;0.083	0.839	0.012	-0.077;0.100	0.794

Associations analysed with linear regression model using blood pressure as dependent variable. The blood pressure variable contains the following five categories: Optimal Blood Pressure: <120/<80 mmHg; Normal: 120-129/80-84 mmHg; High normal: 130-139/85-89 mmHg; Unstable: ≥140/90 mmHg on one or two reading(s) but not three; Hypertension: ≥140 and/or ≥90 mmHg on three consecutive readings, or a documented diagnosis of hypertension made by a physician.
Analyses with HOMA-IR are based on logarithmic values (10-log).

4.3.2 Discussion

Age, insulin resistance, and overweight were the most important determinants of increased blood pressure and hypertension. The association with regard to HOMA-IR appeared to be stronger in women, which was confirmed in a two-way interaction analysis. However, after adjusting for BMI, or excluding participants with known diabetes, the interaction was no longer statistically significant. Although previous studies that focus on gender differences with regard to the association between insulin resistance and blood pressure are scarce, those that exist seem to indicate a stronger association in men than in women.

Low-grade inflammation (CRP ≤10) was significantly associated with blood pressure categories in both men and women in the age-adjusted analyses; however, in the multivariate analyses all such associations were no longer significant. Whereas several prospective studies have shown an association between CRP and increased risk of cardiovascular events (161, 162), the association between CRP and high blood pressure is not as obvious. Although some studies have found that the association between CRP and high blood pressure is independent of confounders (163), the association found in some studies is no longer significant after multiple adjustments (164).

Lifestyle-related factors

While a significant and independent inverse association between alcohol consumption and increasing blood pressure categories was observed in women, this was not at all seen in men. Although these results are not completely congruent with previous findings, gender differences with regard to alcohol and blood pressure/hypertension have been observed before (40). The association found here between alcohol and blood pressure in women was independent of smoking and leisure time physical activity. However, information on diet was lacking, and diet could potentially have confounded the current results in women. This would especially apply if women who drink alcohol were more likely to also have a healthy diet than men who drink alcohol. The possible confounding from diet in women is in fact supported by the fact that a larger proportion of the total intake of alcohol in women in the present study came from wine, and previous studies have shown that individuals who consume wine are more likely to eat healthy food, such as fruit and vegetables, compared to those who drink beer and spirits (165). These aspects should thus be explored further in future studies, and so should drinking patterns, as consumption of alcohol outside of

mealtimes has been associated with increased risk of hypertension when compared with abstaining or drinking mostly with food (166).

Physical activity has been inversely associated with blood pressure in numerous studies (167). In the age-adjusted analysis in the present study, high level of leisure time physical activity was indeed inversely associated with blood pressure in women, albeit not in men. However, when adjusting for all other factors, high level of leisure time physical activity was not associated with lower blood pressure categories in either gender, probably due to the intimate association between leisure time physical activity and other factors related to blood pressure, such as BMI, insulin resistance, and inflammation.

Differences between men and women in the pathophysiological mechanisms for development of cardiovascular disease have recently received increasing attention (168). However, studies that have also examined lifestyle are fewer and the present study suggests that there might be gender-related differences also with regard to how lifestyle factors are associated with the development of high blood pressure and ultimately cardiovascular disease.

4.4 Paper IV

High normal blood pressure increases cardiovascular risk by three-fold in a Swedish population.

4.4.1 Results

Whereas both systolic and diastolic blood pressure were higher in men than in women (Table 1), optimal blood pressure was more common in women (46%) than in men (34%), and normal and normal high blood pressure more common in men (26% and 13%) than in women (17% and 10%, respectively, both $p<0.001$) (Table 5). However, unstable blood pressure and hypertension were equally frequent in men and women; 6% and 20%, respectively.

In men, 89 CVD events (18 fatal) occurred during the follow-up and 47 events occurred in women (9 fatal). When solely adjusted for age, there was a significantly increased risk of CVD in each of the blood pressure categories vs. the reference category optimal blood pressure (Table 5). In the full multivariate model, however, the association regarding unstable blood pressure became only marginally significant (HR 2.8 (1.0-8.1), $p=0.058$), while all other blood pressure categories remained statistically significant (Table 5). When adjusting for diabetes instead of HOMA-IR, or when excluding subjects with diabetes, the findings remained significant regarding all blood pressure categories, including the unstable group (data not shown).

Table 5. CVD morbidity in association with blood pressure categories in the Vara-Skövde cohort, Sweden, 2002-2005.

		Events of CVD				
	n	**n**	**(%)**	**HR**	**CI**	**p**
Adjusted for age						
Optimal[1]	1362	11	(0.8)	1.0	-	
Normal[1]	615	20	(3.3)	2.4	1.1-5.1	0.022
High normal[1]	294	25	(8.5)	3.6	1.7-7.6	0.001
Unstable[1]	130	12	(9.2)	3.0	1.3-7.1	0.012
Hypertension[1]	415	68	(16.4)	4.5	2.2-9.1	<0.001
Adjusted for age, sex, BMI, HOMA-IR, ApoB/ApoA1, CRP, smoking, alcohol consumption, physical activity, education, and previous CVD						
Optimal[1]				1.0	-	
Normal[1]				2.6	1.1-6.6	0.037
High normal[1]				3.6	1.4-9.0	0.006
Unstable[1]				2.8	1.0-8.1	0.058
Hypertension[1]				3.8	1.5-9.3	0.004

[1] Optimal Blood Pressure: <120/<80 mmHg; Normal: 120-129/80-84 mmHg; High normal: 130-139/85-89 mmHg; Unstable: ≥140/90 mmHg on one or two reading(s) but not three; Hypertension: ≥140 and/or ≥90 mmHg on three consecutive readings, or a documented diagnosis of hypertension made by a physician.

4.4.2 Discussion

In comparison with optimal blood pressure, all other blood pressure categories were associated with an increased independent risk of incident CVD, except for the category represented by unstable blood pressure. However, this category comprised few cases, and as the estimation was still high, with a HR of 2.8 and a 95% CI that was borderline significant, there may be a type 2 error present, or alternatively, there may be some incoherence in that group.

Major strengths of the present study were the fairly large population-based samples of both men and women, the high participation rates, and the accurate blood pressure measurements and strict diagnostic procedures that limit the risk of overestimating the prevalence of new hypertension due to randomly high blood pressure levels (155). Potential weaknesses of the study were the limited power due to few CVD events in this relatively young population, and that pharmacological interventions for CVD risk factors were not accounted for.

These results emphasise that increasing levels of blood pressure are associated with a continuously increased risk of CVD in men and women, and that a significant independent risk increase can be seen already at levels from 120/80 mmHg, even after adjustments for both lifestyle and physiological factors. Patients with blood pressure above these levels should thus be identified and advised on lifestyle changes to prevent progression to manifest hypertension as well as future CVD. Population strategies targeting normotensive individuals should accordingly be improved. These results are, to our knowledge, novel with regard to a European population.

5 GENERAL DISCUSSION

The main findings in this thesis were the high prevalence of manifest hypertension in both men and women, the low blood pressure control among subjects treated for hypertension, the low awareness of having hypertension, and the increased risk of CVD associated with high blood pressure already within the normal range.

5.1 Determinants of hypertension and high blood pressure

In Paper I we confirmed that higher age, family history of hypertension, known diabetes, and overweight and obesity, respectively, were strong determinants of manifest hypertension in both sexes, whereas these factors did not determine the level of blood pressure control. Similarly, in Paper III, age, BMI, and insulin resistance were significantly and independently associated with increasing blood pressure categories in both sexes, confirming the same determinants across the complete blood pressure distribution. Associations between body mass index (BMI) and blood pressure are generally acknowledged (47, 48). Obesity is also strongly associated with insulin resistance, and these two conditions often appear together with high blood pressure in the metabolic syndrome (53). Many consider insulin resistance to be the driving force behind the syndrome (169), and insulin resistance seems to account for a considerable part of the association between obesity and high blood pressure (52). The findings of this thesis confirm that obesity and insulin resistance are indeed strongly linked to elevated blood pressure. However, although high blood pressure, with or without the metabolic syndrome, is often also accompanied by dyslipidemia (53, 170, 171) and inflammation (54, 163), those risk factors were not independently associated with blood pressure categories here (Paper III).

While lifestyle factors did not show any association with blood pressure in men, education, physical activity, and alcohol consumption (inverse) showed significant associations in women when adjusted solely for age (Paper III). Although long-term regular smoking is generally considered a risk factor for increased blood pressure and hypertension (65), short-term smoking has been observed to have a blood pressure lowering effect (172). This, together with the cross-sectional design of Paper III, may have contributed to the lack of an

association found here. Whereas LTPA has been inversely associated with blood pressure in numerous studies (57, 167), the age-adjusted association in women disappeared in the multivariate model (Paper III), probably due to the intimate association between LTPA and other related factors, such as overweight/obesity, insulin resistance, and inflammation (173, 174).

The only lifestyle factor that remained statistically significant in a full multivariate model in women was alcohol consumption, and greater benefits in women from alcohol have been indicated before, even though the results are not completely conclusive (40, 175, 176). On the other hand, residual confounding may have contributed to the findings, as consumption of wine that predominated in women (Paper III) tends to cluster with physical activity, healthy eating, and education (177, 178). Although differences between men and women in the pathophysiological mechanisms for development of cardiovascular disease have recently received increasing attention (168), studies that also examine lifestyle are fewer. However, the present thesis suggests that there might be differences between men and women also with regard to how lifestyle factors are associated with high blood pressure and ultimately with cardiovascular disease. Thus, more focus should perhaps be placed on gender-related differences with regard to modification of lifestyle factors, including alcohol consumption. In conclusion, these findings are in accordance with previous literature, and with suggested mechanisms for the development of high blood pressure.

5.2 Global risk

In Paper II we reported a significant association between a high risk SCORE and stage II-III hypertension. Moreover, when both hypertension and diabetes were present, high-risk SCORE predominated, which confirms the hazard of having both conditions. However, many study subjects with stage 1 hypertension, especially women, did not reach a SCORE that indicates the need of pharmacological treatment. Similarly, SCORE did not differentiate between blood pressure categories within the normal range of blood pressure (Paper II), whereas Paper IV showed that the risk of incident CVD associated with both normal and high normal blood pressure was still considerable. Thus, SCORE may be a good instrument for identifying high-risk subjects with more severe hypertension and/or severe comorbidity, but may not be sensitive enough to indicate which individuals at a lower and actually more common blood pressure level that are at risk. A continuous risk increase across blood pressure level categories (Paper IV) remained in a multivariate model, adding to the arguments against SCORE as an efficient risk-grading

tool at these blood pressure levels (179, 180). Additional risk stratification could come from assessment of target organ damage (OD) (28, 104-106), or further comorbidity (47); however, these risk markers were not specifically addressed in Paper I-IV.

5.3 Blood pressure control in subjects with hypertension

Wilber and Barrow invented the expression "Rule of Halves" in 1972 when describing their epidemiological findings of high blood pressure (12). While only one half of those identified with hypertension were previously aware of it, only one half of those aware were treated, and among those treated, one half were considered well treated (14). Whereas the prevalence and awareness have increased over the years in western countries (88, 181, 182), still only about one half have achieved treatment goals, thus in accordance with the Rule of Halves (92, 93). However, considering that the diagnostic criteria have been successively lowered during this time, approximately step by step corresponding to the thresholds for grade 1-3 hypertension, one must conclude that the control of hypertension indeed has improved (88, 156). Applying the diagnostic criteria for stage 1-3 hypertension, respectively, to those with known hypertension in the Vara-Skövde cohort, the corresponding proportions were 36%, 13%, and 5%. Accordingly, 46% were within the normal range, thus illustrating the great progress that has been achieved in the control of hypertension.

Still, every second patient with hypertension failed to meet treatment goals with regard to blood pressure levels, and our findings indicated a high estimated global risk and incidence of CVD (Paper II and IV). Although the number of events in our study population was too low to draw any conclusions with regard to details concerning the prognosis for specific subgroups, expert guidelines are quite clear on their recommendations, and further improvements need to be achieved to implement guidelines into practice (28). Whereas the indications for pharmacological treatment are consistent concerning hypertension grade 2-3, they are less convincing for mild hypertension as at grade 1. Still, in spite of the low global risk in subjects with grade 1 hypertension (Paper II), there was an increased risk of CVD in all blood pressure categories above optimal (Paper IV), which may strengthen the justification of pharmacological treatment also in those with grade 1 hypertension (183).

5.4 High normal blood pressure

The importance of regarding blood pressure as a continuous variable has been demonstrated in several epidemiological studies (184, 98). Consequently, guidelines during recent years have discussed the term "prehypertension" (32); however, arguments against the term have been the broad blood pressure range within 120-139/80-89 mmHg. There has also been evidence that individuals with levels of 120-129/80-84 mmHg are different from those with levels of 130-139/85-89 mmHg (185, 186), and accordingly, the latest ESH/ESC guidelines (28) define both a normal category (120-129/80-84 mmHg) and a high normal category (130-139/85-89 mmHg). In our studies we thus complied with those guidelines and indeed showed that not only hypertension, but also blood pressure in the higher normal levels, were associated with increased levels of several risk factors (Paper II and III) and with cardiovascular risk (Paper IV).

5.5 Strategies of prevention and future implications for primary care

The findings in this thesis indicate the importance of considering the complete blood pressure distribution, which enables a focus on both high-risk and population-based aspects. The high risk factor levels and the high CVD risk shown here in subjects with hypertension clearly highlight the relevance of a high-risk strategy directed towards clinical practice where patients with hypertension are cared for. Such a strategy could include measures for opportunistic screening to identify new cases of hypertension and individuals at high risk and in need of non-pharmacological advice. Special efforts should be put into improved achievements of recommended target goals according to expert guidelines (28), as today's primary health care does not successfully manage to identify, treat, and control patients with hypertension (Paper I). The fact that patients with grade 2 or grade 3 hypertension had a considerably higher estimated mortality risk (Paper II), emphasises the need of more attention towards these patients, especially considering that subjects with hypertension in general had a high CVD risk (Paper IV). Still, as Geoffrey Rose was the first to highlight in his landmark article (150), a high-risk strategy is not necessarily the most effective way of reducing burden of disease in a population. As individuals with high risk are often greatly out-numbered by those with a more moderate risk, aiming at reducing a small relative risk in a higher number of individuals might consequently prevent a higher absolute number of events than the opposite; i.e. reducing a high relative risk in fewer individuals. Thus, the current findings of moderately,

but yet significantly, increased risk factor levels and risk also in subjects with normal blood pressure support traditional advice concerning nutrition, weight-control, and physical activity that should be promoted at the population level, e.g. within the educational system (187). As stressed many times before, a combination of high risk and population strategies is most preferable.

Thus, strategies for preventive efforts directed towards those with normal and high normal blood pressure should also be developed within primary care, e.g. brief interventions targeting common modifiable lifestyle factors. It is important not only to detect those with high normal blood pressure and metabolic abnormalities, but also to have something to offer to support lifestyle changes. Our studies support early lifestyle interventions that could be developed in primary care.

In summary, the present thesis highlights major issues that should be dealt with both on a primary health care level and at a community level. Considering the high prevalence of high normal blood pressure, the effect of prevention may be substantial. Associations between several lifestyle factors and blood pressure categories in women (Paper III), further emphasise the need of focusing on lifestyle modifications in the higher normal blood pressure ranges to prevent development of manifest hypertension and CVD, and that gender-related differences might need to be taken into account.

5.6 Methodological considerations

This thesis was based on a large population-based sample with a high participation rate. High participation rates combined with random sampling enhance the representativeness of the study sample. However, a minor selection bias is possible, as non-participants tend to have different characteristics and generally have a higher burden of cardiovascular comorbidity (151).

One limitation in studies I-III was the cross-sectional design that prohibits any inferences regarding causality. Moreover, information on lifestyle and demographic and socioeconomic data was gathered by self-reported questionnaires administered by the study nurses, thus possibly introducing some information bias (188). Furthermore, insulin sensitivity was measured by HOMA-IR (189), while the gold standard for assessment of insulin sensitivity is the glucose clamp technique (190). Still, this technique is not applicable for large epidemiological studies, and the HOMA-IR algorithm is well validated (191) and has been frequently used in previous studies (192, 193). Another limitation of this study was the limited number of cardiovascular events due to the generally young study population with an overall good health, and the secular trend of a strong decrease in CVD incidence over several decades (194, 195).

Most previous studies have considered hypertension as a dichotomous variable (48, 163, 171) or have examined either solely systolic or solely diastolic blood pressure (196), even though more recent studies have emphasised both systolic and diastolic blood pressure with regard to the predictive effect for CVD (197, 198). Thus, a major strength of the present study is that in contrast to most previous studies, both systolic and diastolic blood pressure were taken into account by using categories of blood pressure instead of focussing solely on either systolic pressure or diastolic blood pressure. Furthermore, the complete distribution of blood pressures was taken into account, from normal optimal to manifest hypertension. The repeated measurements of blood pressure in potentially new cases before a new diagnosis of manifest hypertension was made also limit the misclassification between hypertension and normal blood pressure. Defining those with a high blood pressure at one or two visits, but not consistently high over three consecutive readings, as having a temporarily high or an unstable blood pressure, might further reduce the misclassification between hypertension and normotension. The use of the entire range of blood pressure allows for a more accurate interpretation for preventive strategies both in the clinical setting and in the population.

5.7 Future studies

The stepwise increase in cardiovascular risk with increasing blood pressure categories emphasises screening with regular blood pressure measurement as an important method for identifying early manifestations of high blood pressure and CVD risk before clinical disease is evident. These questions should be further investigated in longitudinal population-based studies. The present findings also highlight the need of lifestyle interventions among subjects with high normal blood pressure and among those with hypertension having a low risk SCORE. However, although controversial, future studies need to investigate whether also pharmacological treatment is indicated in some individuals with high normal blood pressure (considering the increased CVD risk in those subjects in Paper IV), and if it is still motivated in all hypertensive subjects with low global risk (158-160). Future studies should also investigate how SCORE and other risk grading tools affect the prediction of CVD risk in the different blood pressure categories, to see whether these tools may help identify individuals in special need of pharmacological intervention.

The inverse association between blood pressure and consumption of alcohol seen solely in women needs further investigation. These results have implications both for clinical practice and preventive strategies. Furthermore, previous studies have identified biological mechanisms that would explain the beneficial effect of alcohol on blood pressure, such as anti-inflammatory effects (41) and positive changes in lipid metabolism (42-44), which supports a causative effect. On the other hand, mediating effects from those variables were not seen in the present study (as the result remained when CRP and ApoB/ApoA1 were entered into the model), and it also remains unclear why the association was only seen in women. Further attempts to reveal remaining confounding will be of crucial importance for the implementations of these findings. These aspects should thus be further explored in future studies. Moreover, as also seen elsewhere (199), women in our study generally drank less alcohol than men, and drank wine to a considerably higher degree than beer and spirits (Paper III). Wine drinking has previously been associated with a better diet (165), and lifestyle factors in general, including alcohol consumption, are also known to cluster (177, 200). Such a cluster of lifestyle-related factors will not show in a multivariate analysis where independent effects are the focus. Thus, future studies should perhaps perform a principal component analysis as a complement to also reveal clusters of risk factors associated with alcohol consumption.

6 CONCLUSIONS

6.1 General conclusion

Hypertension is a common condition; however, both awareness and control need to be improved. Likewise, high normal blood pressure is equally common and also accompanied by an increased risk of CVD. The current results have implications for population-based efforts to prevent progress to manifest hypertension and to reduce the global CVD risk, to perform screening to increase awareness, and to improve implementation of expert guidelines in clinical practice to improve blood pressure control. There are thus implications for both clinical practice and for public health strategies.

6.2 Specific conclusions

1. The prevalence of hypertension was 20% in both men and women with a steep increase in relation to age. A large proportion of subjects with hypertension are still unaware of their condition, or aware although having a blood pressure that exceeds the recommended targets. Strong associations were found with traditional risk factors for hypertension; however, all these factors, including type 2 diabetes, failed to distinguish between controlled and uncontrolled hypertension.
2. A large proportion of patients with hypertension had a low risk SCORE. In patients with grade 2 or grade 3 hypertension the estimated mortality risk was considerably higher, emphasising the need for more attention regarding these conditions.
3. Age, insulin resistance, and overweight were strongly associated with increasing blood pressure levels in both men and women. In women, alcohol consumption was also independently associated with lower blood pressure, which needs to be explored further in future studies.
4. A stepwise increase was observed in CVD risk with increasing blood pressure levels. Individuals with high normal blood pressure should be identified and advised on lifestyle changes to decrease global risk and to prevent progression to manifest hypertension.
5. Population-based strategies targeting normotensive individuals should be improved.

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