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The 10 - year risk of incident hypertension across blood pressure categories in a population based cohort study in southwestern Sweden

Degree Project in Medicine

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Abstract

Objective. To explore the determinants of incident hypertension, and especially the impact of baseline blood pressure category, in a representative Swedish population during 10 years follow-up.

Design and method. A population based cohort study with sex ratio 1:1 and mean age 47. Blood pressures were measured and categorized according to ESH guidelines with optimal blood pressure <120/80 mmHg, normal 120-129/80-84 mmHg, high normal 130-139/85-89 mmHg, and unstable ≥140 systolic and/or ≥90 mmHg diastolic at one or two visits. Hypertension was defined as ongoing treatment or readings of ≥140 and/or ≥ 90 mmHg at three consecutive visits. Subjects with hypertension at baseline were excluded. Data were analyzed with multiple binary logistics regression.

Results. At baseline, blood pressure was optimal in 633 subjects (56.1%), normal in 292 (25.9%), high normal in 141 (12.5 %) and unstable in 63 (5.6%). Within the optimal blood pressure group 18 (2.8%) converted to hypertension during follow up. Corresponding numbers for subjects with normal, high normal and unstable blood pressure were 58 (19.9%), 56 (39.7%) and 47 (74.6%) respectively. Normal, high normal and unstable baseline blood pressure were all associated with an increased risk of development to manifest hypertension compared to optimal blood pressure, with odds ratios (OR) and 95% CI of 5.4 (2.9-9.9), 12.5 (6.3-24.8) and 87.5 (33.1-231.4), respectively, independent of age and other main cardiovascular risk factors. The progression to hypertension was also independently predicted by age, BMI and family history of hypertension, with OR 1.03 (1.00-1.05), 1.12 (1.05-1.19) and 2.59 (1.59-4.23), respectively.

Conclusions. Subjects with high normal or unstable blood pressure should be identified in clinical practice and evaluated for global risk accounting for family history of hypertension. Thereupon personalized advice on lifestyle modification should be given, as early prevention of cardiovascular disease.

Keywords: Incident hypertension, high normal blood pressure, prehypertension, cohort, population survey.

Populärvetenskaplig sammanfattning på svenska

Högt blodtryck, eller hypertoni, är vanligt förekommande och ökar risken att drabbas av hjärt- och kärlsjukdomar så som t.ex. hjärtinfarkt och stroke. Orsakerna till högt blodtryck är inte helt klarlagda men forskning har visat att det hänger nära samman med övervikt och typ 2 diabetes samt även med livshållning - brist på motion, frukt- och grönsaksfattig kost och högt saltintag samt att det i viss mån också är ärftligt. Även om högt blodtryck blir betydligt vanligare med åldern finns anledning att misstänka att utvecklingen som leder dit tar sin början redan i relativt unga år.

I denna studie har vi försökt att ytterligare kartlägga orsakerna bakom högt blodtryck genom att i 10 år följa en stor grupp individer i åldrarna 30-74 år från Vara och Skövde kommun. Vid studiens början undersöktes deltagarna, lämnade blodprover samt information om sitt hälsotillstånd, psykiska mående och sina levnadsvanor. Deltagarnas blodtryck mättes också och delades in i fem kategorier, närmare bestämt optimalt (<120/80 mmHg), normalt (120-134/80-84 mmHg), högt normalt (135-139/85-89 mmHg), högt blodtryck (≥140/90 mmHg) samt instabilt blodtryck (blodtryck som växlade mellan högt och normalt mellan olika mättillfällen). De som hade högt blodtryck redan vid studiens start, eller medicinerade mot detta, uteslöts. Efter 10 år genomgick deltagarna samma procedurer igen. Vi noterade vilka som drabbats av högt blodtryck och jämförde detta med övriga uppgifter vi hade om individerna. Vi såg att bland de som haft högt normalt eller instabilt blodtryck från början var det betydligt fler som utvecklat hypertoni än i gruppen med ursprungligt optimalt tryck. Detta gällde även oberoende ålder inom grupperna och andra faktorer som anses kunna påverka blodtrycket. Äldre individer, överviktiga och personer med släktingar (föräldrar eller syskon) med högt blodtryck var också överrepresenterade i gruppen som utvecklat högt blodtryck. Även rökning sågs ha ett samband med höjning av blodtrycket.

Vi har genom denna studie med stor statistisk säkerhet fastslagit att personer med ett blodtryck som ligger högt i det normala intervallet löper en markant ökad risk att på sikt drabbas av högt blodtryck jämfört med de som har optimalt blodtryck. Ärftlighet för hypertoni är också av stor betydelse för denna risk. I framtiden kan dessa resultat vara till hjälp i utvecklingen av bedömningsmallar för läkare på vårdcentral, tänkta som stöd i vården av patienter som ännu inte har högt blodtryck men som riskerar att få det. Genom att sätta in lämplig insatser, så som livsstilsförändringar i tid han man chans att bromsa utveckling mot högt blodtryck och på så vis minska risken för alvarliga, potentiellt dödliga följdsjukdomar i hjärta och kärl.

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1. Background

Introduction

Hypertension is a common condition, strongly associated with cardiovascular mortality and morbidity [1, 2]. In fact, since 2010 it has been established also as the leading cause behind the world's global burden of disease. The mechanisms behind essential hypertension are complex and based on interactions between multiple biological and behavioral factors [3]. Age, insulin resistance and overweight are known to be strong predictors [4], and so is genetic predisposition [3]. Nevertheless lifestyle aspects such as physical inactivity, smoking, low intake of fruits and vegetables and high alcohol consumption have also been associated with the progression of hypertension [5-8]. The prevalence of hypertension increases with age [9], but earlier longitudinal studies also show that blood pressure levels late in life can be traced back to levels earlier in life, even in childhood [10]. In a similar fashion it has been shown that subjects with high blood pressure within the normal range, with a *high normal* blood pressure, are at increased risk of developing hypertension compared to subjects of normal or optimal blood pressure [11]. The connection between hypertension and cardiovascular disease (CVD) is well established, but increased prevalence of CVD has actually been seen in relation to blood pressure levels across the entire blood pressure distribution, also within the normal range [12]. These observations support the recommendation to monitor blood pressure in non-hypertensive individuals regularly [13], as well as indicate an important field of study. Over recent decades awareness concerning hypertension and its preliminary stages, determinants and risks, has increased [14]. Nevertheless medical, economic and human costs related to

hypertension are still enormous [15], forcefully justifying further research on the determinants of hypertension and subsequent trials on new potential preventive strategies.

Definition of hypertension

Guidelines for the management of hypertension have existed for over 30 years even if the definition of the condition has altered [13, 16, 17]. In 1993 however, the limit for diagnosis of hypertension was lowered to 140/90 mmHg [17] and in late 1990s two new blood pressure categories were introduced by the Word Health Organization and the International Society of Hypertension [18], namely, optimal blood pressure and high normal blood pressure. At the same time hypertension was further categorized into grade I, grade II, and grade III. These categories, as well as the hypertension limit, have essentially remained unchanged to this date and were once again presented among the joint guidelines of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) in 2013, see Table 1.1.

Table 1.1. Blood pressure categories according to ESH/ESC guidelines 2013.

Category	Systolic (mmHg)		Diastolic (mmHg)
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

When a subject's systolic and diastolic blood pressures fall into different categories, the higher category should apply.

Development of hypertension

In 5-10 % of hypertensive subjects there is an identifiable underlying disease causing the blood pressure elevation [19], such as primary aldosteronism, renal artery stenosis or obstructive sleep apnea, the condition therefore referred to as *secondary hypertension*. The vast majority of hypertension cases though, is attributed to *primary* or *essential hypertension*, the cause of which is complex, and subject of research.

The association between overweight and hypertension is generally acknowledged and an almost linear relation has been established between BMI and blood pressure [20]. Some studies suggests that weight gain may account for 64-78 % of human essential hypertension [21], making it an invaluable risk factor to consider, especially since the epidemic of obesity is steadily growing nearly all across the world [20]. Closely related to overweight is the so called *metabolic syndrome*, besides overweight, and especially of abdominal type, including high blood pressure, atherogenic dyslipidemia (i.a. high serum levels of LDL and triglycerides and low serum levels of HDL), insulin resistance with glucose intolerance, as well as proinflammatory and prothrombotic states [20]. A further development of the impaired glucose metabolism and insulin resistance in the metabolic syndrome, could lead to frank type 2 diabetes [20]. Even if it in recent years has been subject of some debate, the clinical relevance of the metabolic syndrome concept is usually acknowledged [13].The abnormalities included in the syndrome are generally believed not only to correlate, but also to potentiate each other [4], leading to cardiovascular risk higher than the sum of risks associated with the individual factors. Several pathophysiologic mechanism combine to create these interactions, some of them yet not fully understood and [20]. There are hemodynamic changes occurring in relation to obesity and metabolic syndrome believed to start out from endothelial dysfunction, impaired vasodilation and microvascular recruitment (the ability of small vessel beds to react

with vasodilation on increased flow in large vascular beds). These effects are at least in part mediated by insulin, through its attenuating effect on endothelial release of nitric oxide, a potent vasodilator, and also promoting vascular hypertrophy based on its progrowth effects as a hormone. Later, such small vessel effects may translate into stiffness in large arterial conduits, with both hypertensive and arteriosclerotic consequences. Visceral adipose tissue hormones such as Leptin has also gained a lot of attention in recent years [20], believed to be one of the most important signals in regulation of energy homeostasis. Some earlier studies have found plasma norepinephrine levels to be elevated in obese persons, a possible explanation being the norepinephrine and epinephrine releasing effect of leptin trough stimulus of ventral hypothalamus [20]. Elevated adrenergic tone contributes to endothelial dysfunction [20] as well as decreased arterial responsiveness to vasodilation, with overall increased vascular tone and hypertension as a consequence. The enhanced adrenergic tone also causes activation of the renin-angiotensin-aldosterone system (RAAS), increasing renal sodium retention and peripheral resistance, thereby contributing to hypertension. Elevated levels of the angiotensin II hormone is also believed to affect insulin signaling pathways [20], although precise mechanism has not been clearly defined. Several trials tough [20], have shown fewer cases of new-onset diabetes when angiotensin receptor blockers or angiotensin-converting enzyme inhibitors are used in hypertensive patients. High circulating insulin levels in turn, also exert sodium retentive effects. It is well established that inflammation is an important mechanism behind the development of atherosclerosis [22], but in recent years it has also been posed that oxidative stress, and the consequent inflammatory response, play an important role in association with obesity and is an underlying factor also in insulin resistance and the metabolic syndrome as a whole [22].

It is undisputed that lifestyle aspects also are effecting the risk of developing hypertension [13]. The protective effect of physical activity regarding both hypertension and CVD is well

established [5], acting directly on blood pressure but also indirect trough weight reduction and improved insulin sensitivity [23]. Moderate alcohol consumption has in many population based studies shown a protective effect in relation to multiple cardiovascular outcomes, including cardiovascular death [24]. These findings however, are according to some, rather the result of underestimated bidirectional confounding than a causality [6]. Extensive alcohol consumption, in any case, raises blood pressure [25] and in the World Health Organization Global Burden of Disease Comparative Risk Analysis study from 2000, 16 % of all hypertension should be attributed to alcohol consumption [6]. Regarding the relationship between hypertension and smoking results differ [7]. The lower blood pressures seen in smokers in some studies, compared to non-smokers could at least in part be attributed to residual confounding with body weight whereas smokers are generally thinner than non-smokers [26]. Longitudinal studies, however, shows that long-term smoking in fact increases blood pressure and constitutes a risk factor for hypertension [7]. High sodium intake has a well-documented blood pressure elevating effect, and a high habitual salt intake is one of the quantitatively important, preventable factors causing unfavorable population-wide blood pressure patterns [27]. The hypertensive effect of liquorice is well known [28], but the size of this effect differs greatly between individuals, which at least partially can be attributed to a certain genetic mutation.

Psychological stress has been suggested as an underlying cause of hypertension, and has also been implicated as a part in the pathogenesis of the metabolic syndrome [29]. The principal hypothesis is that chronic stress-induced activation of the two interacting effector systems, the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, and the consequent release of catecholamines and cortisol, could lead to cardiovascular adjustments and an increased risk of hypertension. This theory has found support both in animal and human studies [29]. It has furthermore been posed [29] that psychosocial factors interplay with

certain genetic variants, making some individuals more vulnerable to these effects than others. Behavior-based approaches, such as meditation, muscle relaxation and yoga have shown to have some, although moderate, decreasing effect on blood pressure [30].

Hypertension has since long been recognized to cluster within families [13]. Heritability has been estimated to vary between 35% and 50% in different studies [13], and a positive family history of hypertension has been suggested to double the risk, independently of overweight [31]. The genetic component of essential hypertension is not arising from a single gene, but rather from a wide range of different combinations [13]. Several genome-wide association studies and their meta-analyses have identified a total 16 genetic locus associated with blood pressure regulation, and 29 genetic variants correlated with hypertension [32].

Recommended blood pressure measurements

To reduce misclassification of hypertension, blood pressure should be measured in a standardized fashion [33]. Intra-individual variation in blood pressure, as well as the somewhat disputed "white coat effect" [13] is known to cause over estimation of hypertension, and accordingly repeated readings are recommended [34]. The recent ESH/ESC guidelines further recommend:

* To allow the patient to sit for 3-5 minutes before beginning blood pressure measurements
* To take at least two blood pressure measurements, spaced 1-2 min apart, and if deemed appropriate, take the mean of the two blood pressure readings
* To use a standard bladder (12-13 cm wide and 35 cm long), but have a larger and smaller bladder available for large arms (circumference >32 cm) and thin arms (circumference 17-22cm), respectively (alternatively use a self-adjusting bladder)

* To have the cuff at heart level, whatever the position of the patient

Furthermore, a quiet, comfortable location for the patient in a room of normal room temperature, is optimal. Ideally the patient should not recently have eaten, smoked, exercised, or taken caffeine [33]. When using the auscultatory method, the phase I (appearance) and V (disappearance) of the Korotkoff sounds should be used to identify systolic and diastolic blood pressure, respectively. A semiautomatic oscillometric devise may equivalently be used instead [13]. Provided that the arm is supported at heart level, measurements from sitting and supine position are considered comparable [33]. The examiner should be well trained in the techniques of blood pressure measurement and use accurate and properly maintained devices, checked periodically through calibration [13]. Out-of-office blood pressures, at home or by 24-hour ambulatory measurements, is an option when for example episodic hypertension is suspected.

Prevalence

Hypertension is equally common in men and women and is increasing with age [35]. The prevalence appear to differ across the world, tough there are limited comparable data available. Reported figures differ between European countries [13] as well as across the world. The European average in hypertension prevalence has been estimated to 44 % as compared to 28 % in North America [36], the cause of the extensive difference not being fully understood. Since 1980 though, there has been a slight decrease in average blood pressures in the western world [14]. In low-income countries, however, an inverse trend is seen, with evaluations of recent publications [37] showing a 30 % prevalence of hypertension in the adult (30–60 years of age) population in sub-Saharan Africa, poorly acknowledged and

controlled. According to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) [35] 1.8 million, or 27 %, of the Swedish adult population (age 20+) are subjects to hypertension, and by the age of 65 the prevalence has raised to more than 50 %. In an earlier study on the Vara-Skövde cohort (age range 30-74), the hypertension prevalence was found to be 20 % [38]. Among Swedish subjects with hypertension 60 % have mild hypertension (grade I), 30 % moderate (grade II) while 10 % are suffering from severe hypertension (grade III). Earlier studies [39, 40] estimates the number of subjects of *high normal* blood pressure to about 20 % in the grown up population.

Cardiovascular risk and prevention

There are risk grading tools developed to correctly identify patients in need of treatment. The most commonly used in Northern Europe today is SCORE (Systematic Coronary Risk Evaluation) [41]. SCORE calculates the 10-year risk of cardiovascular death using systolic blood pressure combined with sex, age, serum cholesterol and smoking. In presence of diabetes, the calculated cardiovascular risk is believed to be tripled in men, and fivefold higher in women. Estimated risk at 5 % or higher, it is considered high and pharmacological treatment is generally recommended [42].

It's an undisputed fact that treatment reduces mortality in subjects of moderate and severe hypertension, while treatment of mild hypertension, treatment goals and approach to certain subgroups have been subjects to never-ending reconsiderations [13]. Previous ESH guidelines, from 2007, in similarity with many other expert guidelines, set blood pressure treatment goals to <140/90 mmHg for the general population, and <130/80 mmHg for patients with diabetes [42]. ESH:s most recent guidelines, tough, states that systolic blood pressure under 140 mmHg (in the elderly between 140 and 150 mmHg) and diastolic blood pressure

under 90 mmHg is always recommended, except in patients with diabetes in whom diastolic blood pressure should not exceed 85 mmHg [13]. This was the result of a careful review of available evidence. In stage I and II of hypertension furthermore, it is advisable to try life style modification before the initiation of drug treatment, while in stage III recommendations are to start pharmacological treatment immediately, together with lifestyle changes, in order to effectively reduce cardiovascular risk [13].

Even though improvements have been made [14], hypertension is still largely undertreated, not only in low income countries but also, still, in the western world and according to observations, especially in Europe [37]. Earlier European studies have led to the formulation of "the rule of halves" [43] stating that among all subjects with hypertension, only half of them are aware of their condition, and among those aware, half are treated and among those treated only half are reaching the treatment goals. Earlier analysis of the Vara-Skövde cohort indicated 64 % of hypertensive subjects being aware, and among those about half were well controlled [38], indicating progress but still plenty of room for improvement.

Treatment: pharmacological and non-pharmacological

Lifestyle modification is considered a cornerstone in prevention and treatment of hypertension [13]. Actually, lifestyle changes have proven to potentially reduce blood pressure equivalently to drug mono therapy, with its major drawback being low level of adherence over time. Most recent ESH guidelines [13] states the following as lifestyle measures able to lower blood pressure: weight reduction, regular physical exercise, salt restriction, moderation of alcohol consumption and high consumption of fruits and vegetables. Regarding pharmacological treatment international guidelines conclude [13] that the main benefits of antihypertensive treatment are due to the lowering of blood pressure per se and is largely independent of the

drugs employed. Large meta-analyses show no clinically relevant difference between the common classes of blood pressure lowering medications, with exceptions made for certain patient's subgroups, such as diabetics and subjects of heart failure [13].

High normal blood pressure

"Arterial pressure is a quantity and its adverse effects are related numerically to it. The dividing line (between normal blood pressure and hypertension) is nothing more than an artifact."

Sir George Pickering, 1968 [44]

As is obvious from the above quote the thought of the possible clinical relevance of blood pressures below the level of defined hypertension have crossed the minds of researchers for a long time. Actually already in 1939 Robinson and Brucer [39] defined blood pressures in the range of 120–139/80–89 mmHg as prehypertensive, after having observed that many hypertensives originated from this part of the blood pressure range and that these individuals had about double the mortality of people with blood pressures less than 120/80 mmHg. This last observation seems to have remained true in subsequent studies even if the figures vary. Results from a recent meta-analysis [44] of data from 61 prospective studies demonstrate that blood pressure in the general population down to a level of 115/75 mmHg, is related to elevated incidence of ischemic heart disease mortality, stroke mortality, and mortality from other vascular causes. Referring to such findings, some experts claim that the term

prehypertensive should more properly be applied to blood pressures of 120–139/80–89 mm Hg. This interval is then usually further divided into stage 1 prehypertension 120-129/80-84, and stage 2 prehypertension, 130–139/85–89 mm Hg, equivalent to the ESH-definitions of strict normal and high normal blood pressure respectively.

An earlier Swedish population-based survey found the prevalence of high normal blood pressure to be 27% in the study population consisting of young middle-aged men in southern Sweden [40]. Previous analyses of the Vara-Skövde cohort showed 12 % high normotensives at baseline [45], quite similar to figures reported from North America of 14 % in the grown-up population [39]. As mentioned earlier, subjects of high normal blood pressure, in addition to running an elevated CVD risk, are more likely to develop overt hypertension [11]. Meta-analysis of longitudinal studies across the entire life span has shown that even elevated childhood blood pressure is associated with high blood pressure later in life [10], suggesting that the progress towards hypertension starts very early.

Estimates of the exact conversion rate vary. Among the above-mentioned middle-aged men in southern Sweden, 24 % converted to hypertension within 3 years and 46 % of the original number of subjects with high normal blood pressure had converted after 6 years [40]. In the American TROPHY study, 52 % converted within 4 years [39]. Framingham heart study, the famous cohort started in 1948, concluded that after 26 years as many as 75 % of the subjects with high normal blood pressure at baseline had converted to hypertension [11]. To conclude, despite the fact that unanimous data is lacking, it is clear that subjects with high normal blood pressure are at a significantly elevated risk of developing hypertension, and it seems that at least every second of them within 5-10 years do.

It has also been shown [39] that subjects of high normal blood pressure, compared to those of optimal blood pressure, are more likely to be overweight, insulin resistant, exhibit dyslipidemia and show high levels of inflammatory cytokines and to display endothelial

dysfunction. Most patients of high normal blood pressure have at least one other major cardiovascular risk factor [39]. Meta-analysis of several cohort studies estimates the risk of clinical cardiovascular disease in subjects of high normal blood pressure to be doubled compared to subjects with optimal blood pressure, and this is independent of the progression to hypertension [39].

Being a subject of ongoing trials and discussion, high normal blood pressure should according to international guidelines [13, 46] be treated solely with life style modification, since benefits of pharmacological treatment have failed to clearly show. What has been seen is that a few years' administration of antihypertensive agents to individuals with high normal blood pressure can delay transition to hypertension [47], but how far this benefit goes, whether it can also delay cardiovascular events and be cost effective, remains to be proven [13]. The benefits of lifestyle intervention on subjects of high normal blood pressure have, in the relatively small extent to which it is investigated, shown efficacious for preventing or delaying hypertension and for reducing cardiovascular morbidity and mortality in affected subjects [39, 48].

Essential hypertension acts as both cause and effect in a complex etiologic machinery, starting from cardiovascular alterations [44], in many cases probably initiated already at young age [40]. Subjects of high normal blood pressure, especially in younger population strata, constitute a highly interesting group, still poorly studied, potentially holding a large part of the key to the public health issue of hypertension. In order to take the next significant step in better prevention of hypertension and cardiovascular disease, we need to fill out the gap by more detailed data on the prevalence of high normal blood pressure, characteristics of the affected group and its longitudinal outcomes, which is what this study is addressing.

2. Aim

General aim

To investigate the development of hypertension in a relatively young, representative Swedish population over a decade, as a part in better understanding the determinants of hypertension. The overall aim is to provide necessary knowledge for future development of better preventive strategies that can help reducing cardiovascular morbidity and mortality.

Specific aim

- Determine the proportion of subjects with optimal, normal, high normal and unstable baseline blood pressure that has converted to hypertension, respectively, during the follow-up time.
- Investigate which factors are associated with conversion to hypertension and which are associated with an overall progression in blood pressure category, with special focus on determining the impact of baseline blood pressure.

3. Methods

Subjects

In 2002-2005 the baseline survey was conducted in the municipalities of Vara and Skövde, resembling the starting point of "the Vara-Skövde cohort". From the population census register of the two municipalities, a computer-generated random sample was drawn in the age interval of 30-74 years, stratified by gender and five-year age groups. A three-fold over-

sampling was performed in subjects 30-50 years of age, as compared to subject over 50 years in order to obtain the relatively young population required to meet the aims of the study. Requirements for participation were providing written consent for participation, undergo physical examination, completing the questionnaires and having venous blood samples drawn. Except from fail in meeting any of these conditions there were no exclusion criterions. The subjects were called in the order in which they had been randomly selected. The final cohort consisted of 2816 subjects, 1811 from Vara and 1005 from Skövde, representing a participation rate of 81 % and 70 %, respectively, with respect to the number invited.

In 2012-2014 subjects were summoned to a follow-up survey in the same order as for the baseline survey. Due to the complex and costly study protocol only the first 1954 individuals were invited. Among those 490 declined participation, 85 were deceased, 35 had moved from the region and 17 were unable to participate due to other reasons, leaving 1327 (68 % of the subjects invited to follow-up) participating in the second survey. Among those 198 had been diagnosed with hypertension at baseline or earlier and were therefore excluded from the present part of the study, leaving 1129 subjects finally included in the analysis. Fig 3.1 shows an overview of the Vara-Skövde cohort and study design.

Data collection

At both surveys participants were seen at least at two occasions (extra visits were conducted if blood pressure or fasting glucose exceeded normal) the first in the morning after a 10 h fast and the second about two weeks later for blood pressure measurements. The visits followed the same procedures at both surveys, described below, and was conducted by trained study nurses.

Blood pressure measurement. The procedure was carried out according to expert guidelines [13] as follows. After five minutes rest, blood pressure was measured in the right brachial artery, two times, one minute apart, with the subjects in a supine position with the cuff in heart position supported by a pillow. TricuffTM was used for automatic adjustment of cuff size to arm circumference and reading was done at the closest 2 mmHg. Heart rate was registered simultaneously with blood pressure.

Blood pressure classification. If treatment against hypertension had been initiated during follow-up time hypertension was considered regardless of actual blood pressure. If else, when the observed blood pressure was at least 140 mmHg systolic and 90 mm Hg diastolic (one or both), the subject was seen again and if blood pressure still exceeded normal, a third time with 1-2 weeks between the visits. Following this procedure three consecutive high reading was required for a new diagnosis of hypertension at both surveys. Blood pressure was further categorized according to European and American expert guidelines into optimal, normal, high normal blood pressure, and manifest hypertension, respectively, (Table 1.1). If systolic and diastolic blood pressures were falling in different categories the higher was applied. An *unstable* blood pressure category was further added, covering subjects with high readings on one or two visits but not on three.

Diabetes. New diagnosis of diabetes mellitus was confirmed after two fasting plasma glucose values of ≥ 7.0 mmol/L, or one 2-h plasma glucose value of ≥ 11.1 mmol/L in an oral glucose tolerance test. [BD 83] Differentiation between type 1 and type 2 diabetes was based on clinical criteria, i.e. age at onset, body weight, symptoms at initial stage, tendency of ketosis, treatment and in some cases C-peptide.

Body measurements. Body weight was measured with participants shoeless, wearing light clothing, on a calibrated scale to the nearest 0.1 kg. Body height was measured without shoes to the nearest cm. Waist circumference was measured between the lowest rib margin and iliac

crest and hip circumference at the largest circumference between waist and thighs. Waist-hip ratio was defined as the waist circumference divided by the hip circumference. Body mass index (BMI) was calculated by the body weight in kg divided by the square of the height in meters (kg/m2).

Laboratory examination. Venous blood samples were drawn in the morning after an overnight fast (10 h minimum, patients with insulin-treated diabetes excepted, since fast was considered unsuitable for them). Serum cholesterol, triglycerides, blood glucose, serum insulin, c-reactive protein (CRP) and creatinine were analyzed according to standard procedures, previously described in detail [49]. Oral glucose tolerance test was performed through intake of a 75 g standard glucose load, with the final blood sample for glucose level analysis was drawn after two hours. Insulin resistance was estimated based on the Homeostasis Model Assessment of insulin resistance (HOMA-ir): fasting insulin × fasting blood glucose / 22.5.

Medical history. Study nurses collected information on medical history and current medication according to predefined criteria from the subjects at both surveys, including occurrence of previous acute myocardial infarction, acute stroke and diabetes mellitus, as well as family history of hypertension among first-degree relatives.

Questioners. Participants filled out validated lifestyle questioners, as well as questionnaires regarding psychosocial health, stress and quality of life.

Questions, answer alternatives and variable dichotomization of the questioner derived variables used in this project (name of variable used in tables in italics):

- "How physically active are you during your leisure time? The question is referred to the last year. 1) Sedentary leisure time: reading, watching television, stamp collecting or other sedentary activity; 2) Light leisure time physical activity: walking, cycling, or similar physical activity at least four hours per week; 3) Moderate leisure time physical activity:

running, swimming, tennis, aerobic, heavier gardening, or similar activity during at least 2 hours per week; 4) Heavy training or competitive sport in running, skiing, swimming, football, etc., performed regularly and several times a week". *Leisure time physical activity* (LTPA) was dichotomized into low LTPA (1+2) and active LTPA (3+4).

- "How would you describe your current state of health in general? 1) Very good 2) Good 3) Fairly good 4) Poor 5) Very poor". *Self-rated health* was dichotomized into Good self-rated health (1+2) and poorer self-rated health (3+4+5).
- "Do you think your efforts are important for maintaining good health? 1) Yes I think my own efforts are very important 2) Yes, I think my own efforts are of some importance 3) No, I don't think my own efforts are of any importance". *Self-efficacy* was dichotomized into "I think my own efforts are of great importance" (1) and "I think my own efforts are of less importance" (2+3).
- "Do you get *enough sleep at night* to feel rested? 1) Yes, generally 2) Not often enough 3) No, never or almost never". Self-reported feeling of being rested after sleep *(thoroughly rested after sleep*) was dichotomized into "Yes, most of the time" (1) and "Not often enough" (2+3).
- "Do you feel stressed in your everyday life? 1) Yes, a lot of the time 2) Yes, sometimes 3) No, never". Self-reported degree of stress in everyday life (*everyday stress*) was dichotomized into "Yes" (1) and "No, seldom" (2+3).
- Current smoking was defined as daily smoking (yes/no).
- Alcohol consumption was assessed by questions concerning the number of days during the past 30 days during which the subject had consumed beer, wine and strong liquor, respectively, followed by the question of how many glasses, cans and/or bottles that were normally consumed on such days. Based on this information the quantity of alcohol in grams consumed per week was calculated.

Statistical methods

All statistical analyses were performed using the SPSS software package for Windows, version 24.0. Standard methods were used for descriptive statistics. Results were expressed in terms of mean and standard deviation (SD) for al continuous variables except for those appearing to have a skew distribution, namely triglycerides, HOMA-ir, CRP and amount of consumed alcohol, for which median and interquartile range (P_{25} - P_{75}) were used. All statistical tests were two sided, and statistical significance was assumed at $p<0.05$. For comparison between groups multiple logistic regression was used with associations expressed as odds ratios (OR) with 95 % confidence intervals (CI). Two different analyses were performed with the outcome "hypertension or no hypertension at follow-up" and progression or regression/stagnation with respect to blood pressure category during the follow-up time". To adjust for possible contextual differences between municipalities of Vara and Skövde, and for differences in lifestyle between residents in the two regions, study site was included as a covariate in the analysis, and so was also time between baseline and follow-up visit (8-12 years). To further account for possible confounding the following variables were introduced as covariates in a stepwise fashion (to avoid over adjustment): sex, age, BMI, low-density lipoprotein (LDL), CRP, estimated glomerular filtration rate (eGFR), weekly alcohol consumption, smoking status, degree of LTPA, previous CVD events, family history of hypertension and blood pressure category at baseline. All the variables used in the multiple binary logistic regression model were recorded at the baseline survey, except for information on family history, taken from follow-up. To investigate possible sex-differences stratification for sex was performed and interaction terms including sex were tested. To compare the impacts of the predicting variables the Wald chi-square value for *each* variable of statistically

significant contribution in the multiple logistic regression model ($p<0.05$ required) was divided by the sum of the Wald chi-square values of *all* the significantly contributing variables. These fractions were used in Figure 5.5 and 5.6.

The relationship between OR and risk ratio (RR) is mathematically described as: $RR=OR/(1-p0+(p0\times OR))$ [50], where p0 is the baseline risk (in this case probability of subjects of optimal BP to develop hypertension during follow-up). When $p0\leq 0.1$ OR and RR are usually considered approximately equal [50]. $P0\leq 0.1$ can be assumed in this case.

4. Ethics

Since this project evolves personal data obedience of The Personal Data Act (Personuppgiftslagen, PuL) was required as well as subjects' informed consent. The ethical board at the University of Gothenburg has approved the use of the Vara-Skövde cohort for all parts of this project. All participants have given informed signed consent before being enrolled in the study.

5. Results

Characteristics of the population with respect to sex, age, anthropometric and metabolic data and life style factors at baseline are presented in Table 5.1. Among the 1129 participating subjects 633 (56.1%) had optimal blood pressure, 292 (25.9%) had normal blood pressure, 141 (12.5%) had high normal blood pressure and 63 (5.6 %) had unstable blood pressure at the baseline survey, see Fig 5.1. Fig 5.2 shows blood pressure category distribution at the follow-up survey. We observed 179 (15.9 %) incident cases of hypertension during follow-up. Of those with optimal blood pressure at baseline, 18 (2.8 %) converted to hypertension. Corresponding numbers for subjects with normal and unstable blood pressure were 58 (19.9%) and 47 (74.6 %) respectively. Among subjects with high normal blood pressure at baseline, 29 (20.6 %) remained in the high normal category while 31 (22.0 %) and 11 (7.8 %) regressed to the normal and optimal group, respectively, 14 (9.9 %) transferred into the unstable group and 56 (39.7 %) progressed to hypertension, see Fig 5.3. Characteristics of the study population for each blood pressure category group at follow-up is presented in Table 5.2. Age, BMI, WHR, fastening plasma glucose, HOMA-ir and CRP increased with category from optimal to normal, high normal and in many cases throughout unstable and are highest in subjects with hypertension. History of CVD and family history of hypertension is also observed as increasing with category.

The mean difference in blood pressure was an increase of 5.6 mmHg (SD 11.6), systolic, and 2.9 mmHg (SD 9.4), diastolic. 44.5 % of the subjects remained stable between baseline and follow-up with respect to blood pressure category while 46.1 % progressed into higher categories, and the rest, 9.4 %, showed decrease in category. Regression or stagnation versus progression within each baseline blood pressure category are shown in Fig 5.4 and indicates unstable blood pressure category members to be at the highest risk for progression. The

transitions between categories can be viewed in detail in Table 5.3. The different number of steps change in respect to blood pressure category taken between baseline and follow-up by the entire population as well as within each baseline blood pressure category is displayed in Table 5.4.

Both normal, high normal and unstable baseline blood pressure were associated with an increased odds for development to manifest hypertension compared to optimal blood pressure, with odds ratios (OR (95% CI)) of 5.4 (CI 2.9-9.9), 12.5 (CI 6.3-25) and 87.5 (CI 33-231), respectively, independent of sex, age, municipality, time to follow up, BMI, serum levels of LDL and CRP, eGFR, amount alcohol consumed per week, current smoking status, degree of leisure time physical activity, experience of previous cardiovascular disease events and family history of hypertension. A trend test showed that the OR for incident hypertension per unit increase of baseline blood pressure category was 3.8 (CI 2.9-5.0). The progression to hypertension was also independently predicted by age, BMI and family history of hypertension with OR 1.03 (1.00-1.05), 1.12 (1.05-1.19) and 2.59 (1.59-4.23), respectively. Smoking did not show a significant association on the conversion to hypertension but presented with OR 1.53 (0.83-2.80). (See Table 5.5 and Fig 5.5.)

Progress of blood pressure category was, when adjusting for the same variables as in the previous analysis, independently predicted by age, BMI and family history of hypertension with OR of 1.03 (1.02-1.05), 1.06 (1.02-1.10) and 1.69 (1.28-2.23) respectively. Furthermore, current smoking versus current non-smoking predicted category progress with OR 1.72 (1.16-2.56). (See Table 5.6 and Fig 5.6.)

Stratification for sex reviled no essential sex-differences, and when adjusting for age no significant interactions between sex and each of the other factors included in the multivariable analysis were found.

6. Discussion

This 10 years long observational study showed that subjects of normal, high normal and unstable blood pressure were at a stepwise increasing risk of developing hypertension compared to subjects of optimal blood pressure, independent of age and other main cardiovascular risk factors. The conversion rate was substantial in all three baseline categories but more so in the high normal category and especially in the unstable. Blood pressure category at baseline was the by far strongest predictor of development to manifest hypertension, but of significant impact were also, in descending order, family history of hypertension, overweight and age. These findings are essentially in accordance with previous studies [11, 40, 51, 52]. ORs obtained in this analysis were generally higher than values obtained in other studies, despite equal or higher hypertension conversion rates seen in the other studies, and fairly comparable populations with respect to age and comorbidity. A plausible explanation is the fact that several of these [11, 40] have used normal blood pressure (BP <130/85 mmHg) as a reference, therefore naturally a higher baseline risk of hypertension development. In one of the studies [52], which is a new cohort within the Framingham study, OR figures are more similar to ours but still smaller, probably because of the fact that though they have used optimal category as a reference, they still saw substantially higher conversion rate for this category than we did in the corresponding group. Unstable blood pressure at the baseline survey was associated with the highest risk of development of hypertension and the vast majority in this category were converting. Possibilities to compare this result with previously obtained are limited due to the fact that the definition of unstable blood pressure is not generally acknowledged. The question emerging is whether the condition of a blood pressure shifting between normal and hypertensive values resembles another significant step on the road towards hypertension, as our data indicate. In a forthcoming analyze this group

should be more carefully studied, starting from available data, determining blood pressure range of these individuals. The association of ageing and overweight to the development of hypertension is well established [4]. Hypertension is also known to cluster within families, still the family history variable is not seldom left out in studies [11, 40, 52]. Our finding, that family history was strongly associated with development of hypertension, therefore serves as an important reminder of the clinical implications of theoretical heritability.

The results concerning overall progression in blood pressure category were considered a secondary aim, but were nevertheless interesting. Variables showing significant impact on outcome were age, BMI, smoking and family history of hypertension, with age and family history accounting for 1/3 of the significant associations each with last 1/3 being equally distributed between BMI and smoking. Baseline blood pressure was notably not significantly associated with progress in blood pressure category, resembling a counter-intuitive contrast to the progression proportions displayed in Figure 5.4. We believe though that this is a less cogent finding and an effect of lower categories inability to lower even more, especially in the optimal category where category regress is not possible. Age showed a comparatively strong association with blood pressure category progression compared with development of hypertension, a possible interpretation being that age, as well known, is important for the initiation and progression of structural changes leading to hypertension but after reaching a certain increase in the level of blood pressure, possibly already at young age, you have entered an unstoppable train, taking no heed of chronological age. The strong association of smoking to blood pressure category progression constitutes an interesting finding since previous results concerning the effects of smoking on blood pressure differ [26]. In a cross-sectional study on factory employees in Israel [26] smokers, despite of careful attention to possible confounders, were found to have in average lower blood pressure than both non-smokers and ex-smokers. A 14 years longitudinal study conducted on Japanese workers at a

steel company [7] though, showed an increased risk of incident hypertension over time among smokers, compared to non-smokers, consistent with or results. The fact that smoking was significantly associated with progression in blood pressure category, made it reasonable to expect that it would also show significant effect on the conversion to hypertension, which was not the case. ORs for smoking are very similar in both analyses though, leading us to believe that the mentioned lack of significance could be a matter of power, owing to the fact that the group of individuals progressing in respect to blood pressure category is substantially larger than the group converting to hypertension (521 compared to 179). Reversed causation can nor yet be ruled out, since smoking individuals diagnosed with hypertension during follow-up time might have followed advice to quit smoking cessation upon diagnosis, therefore being underrepresented among incident hypertension cases. Previous smoking was not taken into account, something that should be done in future analysis of available data.

The aim of this study was to determine the conversion rate and calculated risk for incident hypertension in different blood pressure categories in a relatively young Swedish population sample. The results are in accordance with previous studies and confirm the fact that also a mild blood pressure elevation, also in middle age, constitutes a serious risk factor for future hypertension. We also pose a new question concerning the significance of occasional hypertensive blood pressure readings, as our results indicate that “one time is no time”, as the Swedish expression goes, might not be entirely true for blood pressures. Home – or ambulatory blood pressure measurements is an option to consider in those cases and clinical follow-up is advisable. CVD-risk grading tools, such as SCORE [41], are important instruments for cardiovascular disease- and death-risk calculation and can serve as support in approaching question of treatment initiation. We believe however, that in order to make prevention of cardiovascular disease more effective, use of early prevention of hypertension is essential. Results obtained from this study can be instantly implemented into clinical practice

of primary care, in a cost-effective manner, through doctors including our findings in their choice of questions to the patients and in their risk analysis, thereby better assessing the risk of hypertension development and the need of lifestyle interventions in these patients. In the larger forthcoming picture our results can actually open up for the development of hypertension-risk grading tools, taking both systolic and diastolic baseline blood pressure, age, BMI and family history of hypertension into account, thereby presumably assessing risk for hypertension with greater precision. Future studies should focus on developing such tools, as well as more precisely evaluate the benefits and optimal design of life style interventions for subjects with normal, high normal or unstable blood pressure, with respect both to medical effects, quality of life and economic efficiency.

Methodological considerations. Major strengths of this study is its fairly large population-based sample, with high participation rate, including both men and women in relatively young age forming a suiting sample for the studying of earlier stages of hypertension development. Additional strengths include the strict procedures according to which blood pressures were measured and other diagnostic procedures were carried through, the former limiting the risks of overestimating of blood pressures due to randomly high values as is the risk when new diagnosis of hypertension is based on only one measurement. There were also very few exclusion criteria, and at follow-up the baseline protocol was also very closely followed. Limitations of this study include the well-known risk for inaccuracy regarding self-reported information. Furthermore the study did not take into account diet and especially not salt consumption, an important factor in hypertension etiology and a potential confounder. More information on socioeconomic aspects could also have been valuable in the analysis as well as an extended analysis of smoking habits taking at least previous smoking into account. Lastly, there were no non-participation analysis performed on subjects declining participation in baseline survey or dropping out for the follow-up. Despite a high participation rate such

analysis would have provided better control for confounding due to the possibility of certain features being over represented in the participating population as compared to the non-participating population.

7. Conclusions

Baseline blood pressure category has a major impact on the risk of developing hypertension. Subjects with high normal or unstable blood pressure should be identified in clinical practice and evaluated both for global cardiovascular risk and for the risk of progression to manifest hypertension, also accounting for family history of hypertension. Preventive strategies should include individualized advice on life style modification, all to avoid or postpone the development of hypertension, thereby reducing the risk of cardiovascular disease and postpone death.

8. Figures

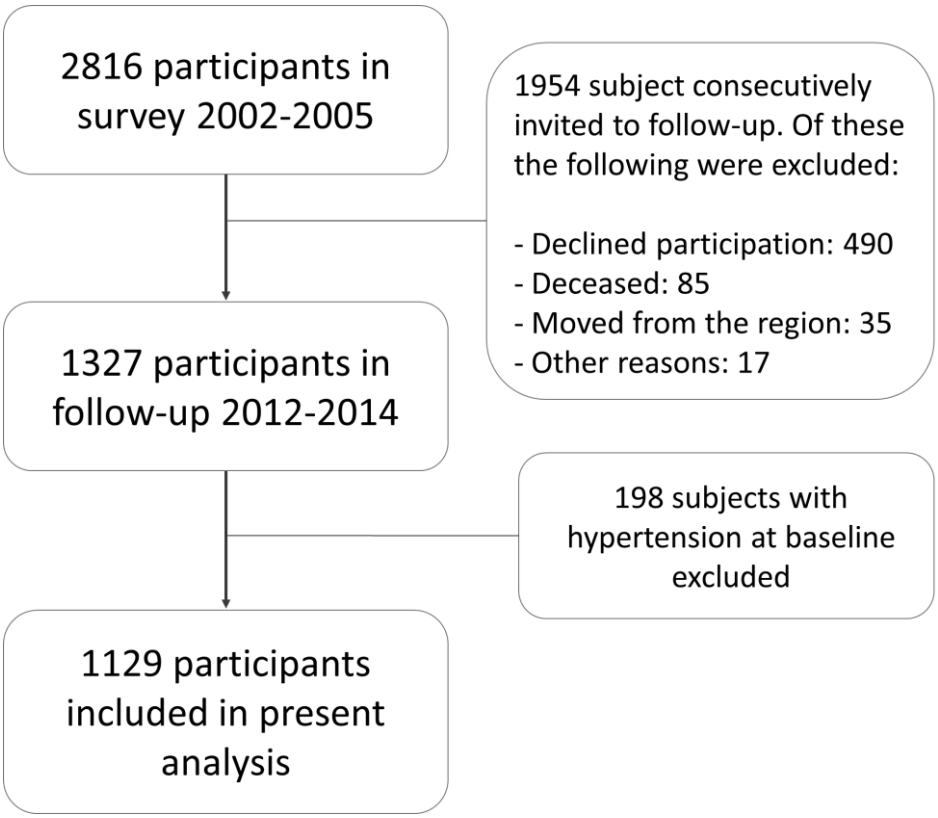

Figure 3.1. Overview of the Vara – Skövde cohort: study design and follow-up.

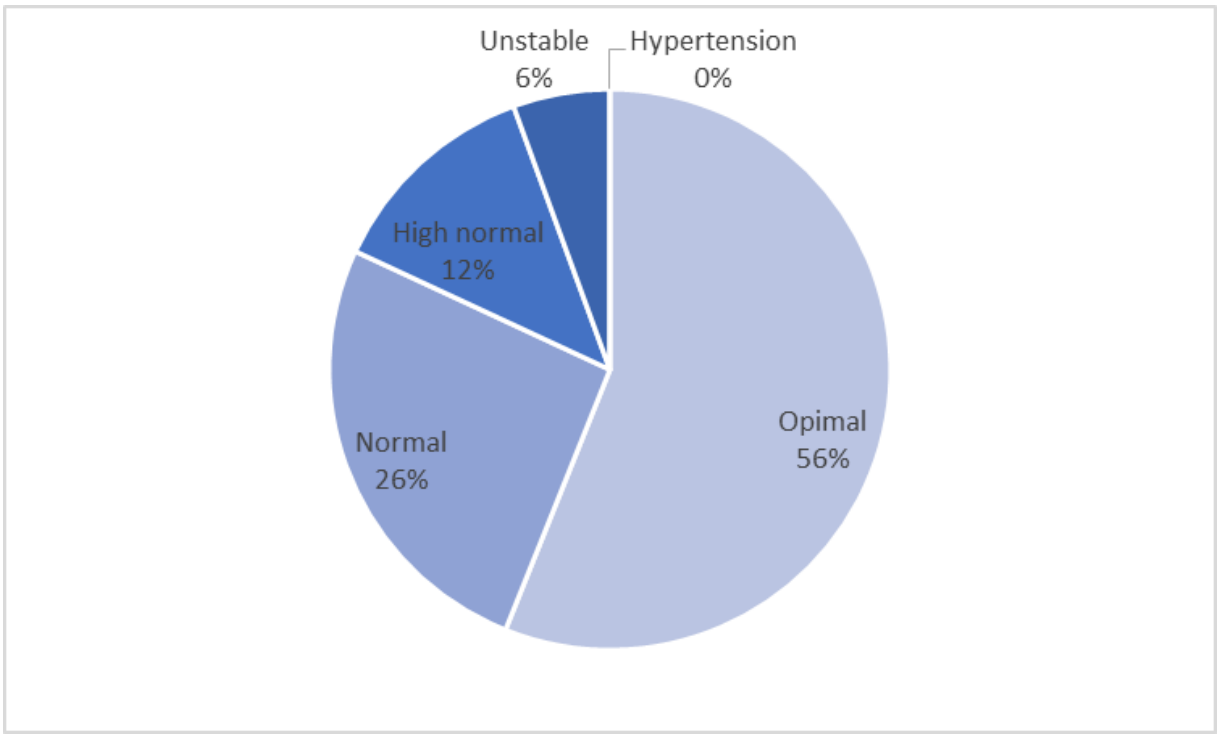

Figure 5.1. Distribution of blood pressure categories in the study population at baseline.

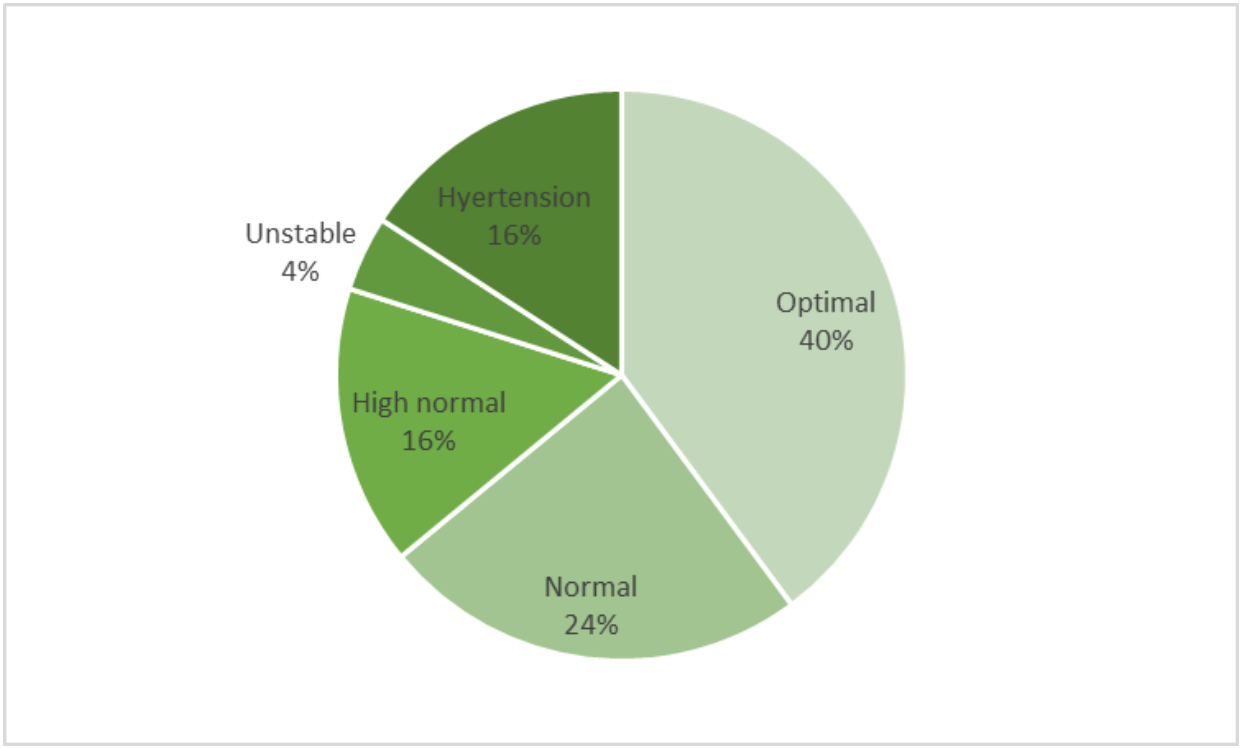

Figure 5.2. Distribution of blood pressure categories in the study population at follow-up.

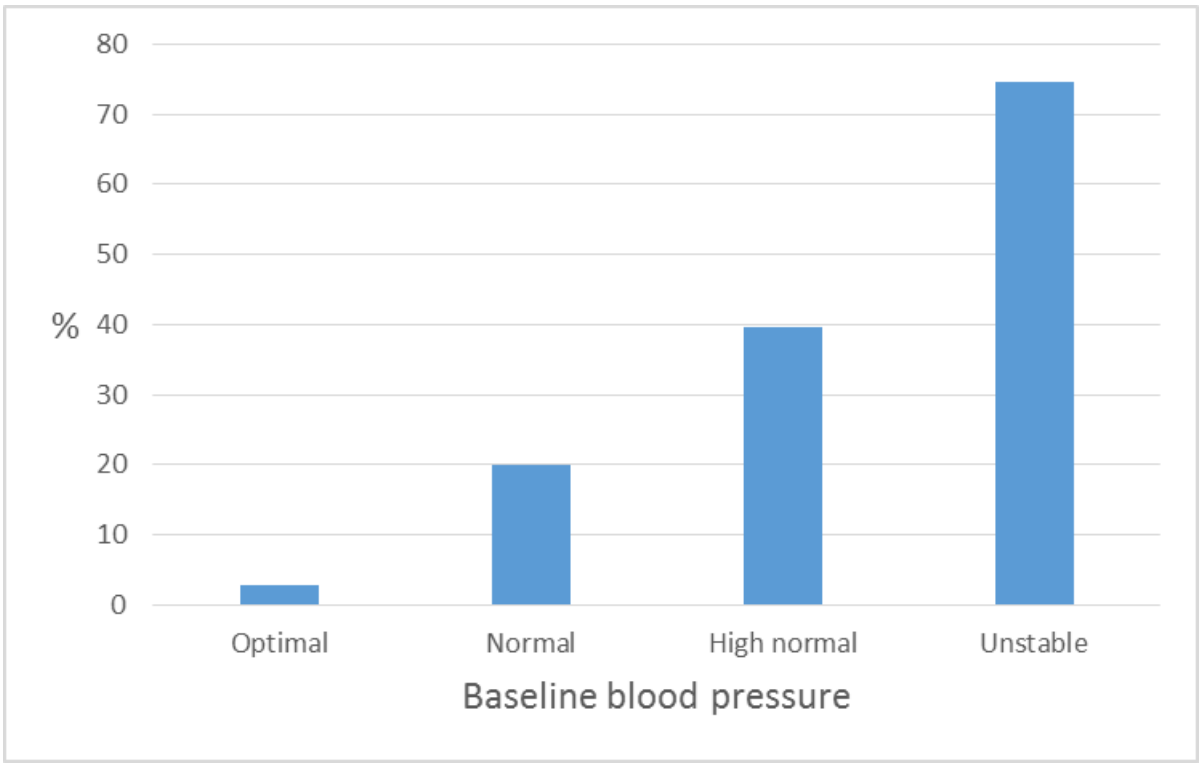

Figure 5.3. Proportion developing hypertension during follow-up time within each baseline blood pressure category.

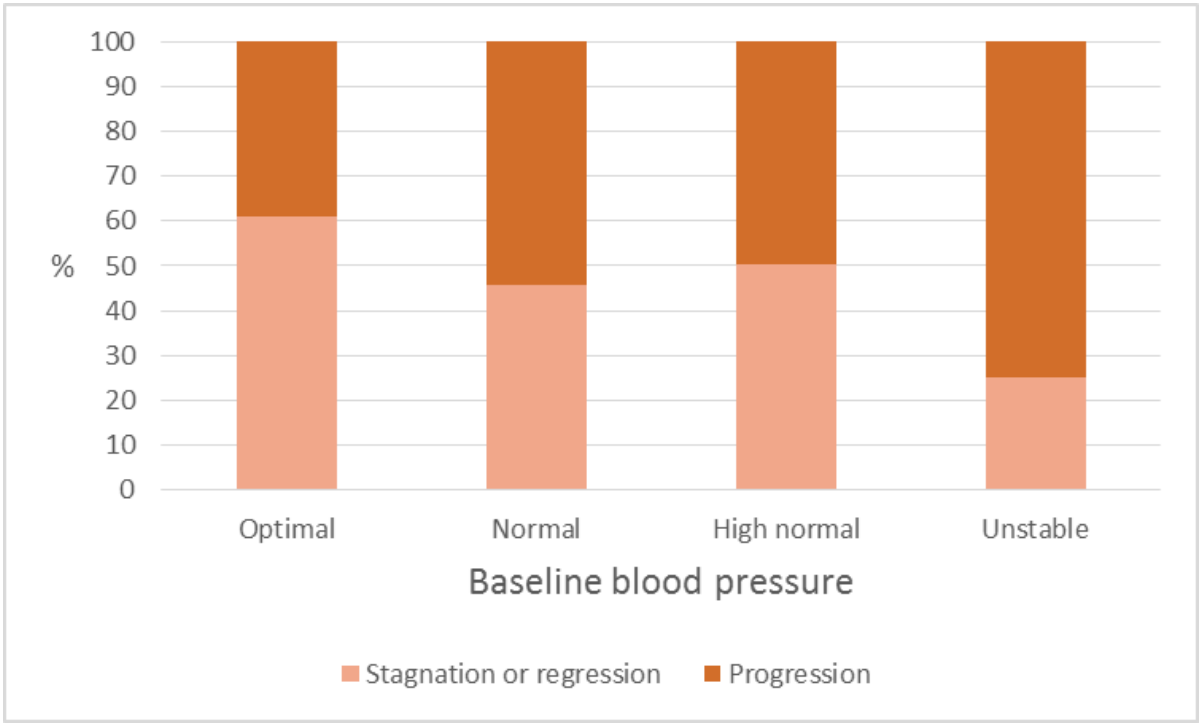

Figure 5.4. Regression or stagnation versus progression during follow-up time within each baseline blood pressure category.

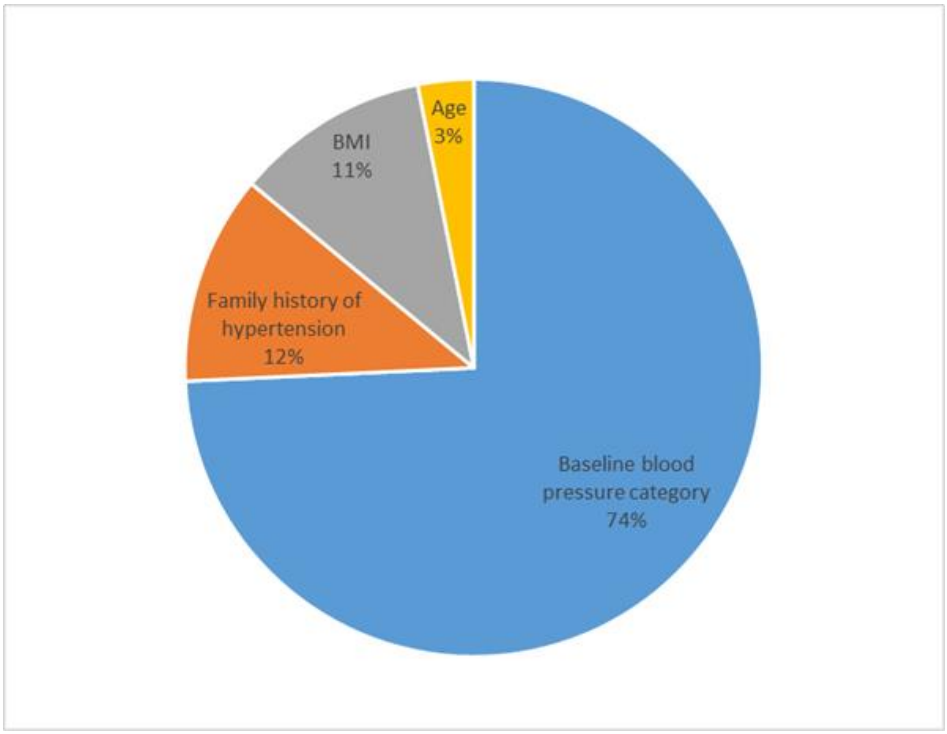

Figure 5.5. Main determinants of hypertension conversion over 10 years (based on Wald chi-square values for the individual factors).

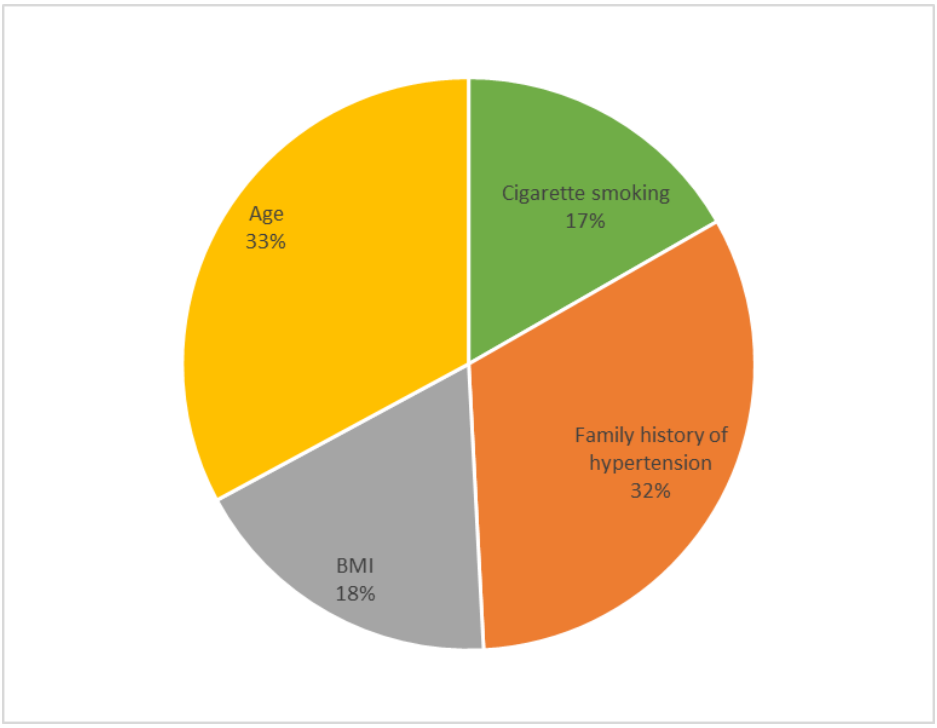

Figure 5.6. Main determinants of blood pressure category progression over 10 years (based on Wald chi-square for the individual factors).

9. Tables

Table 5.1. Study characteristics of the population at the baseline survey.

	N=1129 (100 %)	
	Mean	**SD**
Age (yers)	47.1	10.8
BMI (kg/m^2)	26.2	3.8
WHR	0.9	0.1
Heart rate (beats/min)	63	8
eGFR (mL/min)	86.5	14.5
Fasting plasma glucose (mmol/L)	5.3	0.7
LDL-cholesterol (mmol/L)	3.2	0.9
HDL-cholesterol (mmol/L)	1.3	0.3
	Median	$\mathbf{P_{25} - P_{75}}$
Triglycerides (mmol/L)	1.05	0.77-1.45
HOMA-ir $(mmol * mU/L^2)$	1.14	0.77-1.73
CRP (mg/L)	1.18	0.67-2.31
Alchohol (g/week)	25.2	8.2-61.7
	Number	**%**
Sex (men)	555	49.2
Diabetes mellitus II (affected)	27	2.4
Smoking (current daily smokers)	158	14
Leisure-time physical activity (active level)	381	33.7
Self-rated health (good)	269	23.9
Self-efficacy (high)	891	78.9
Everyday stress (affirmative)	189	16.7
Thoroughly rested after sleep (affirmative)	705	62.4
Family history of hypertension (affected)	518	45.9
Experienced CVD episodes (affected)	14	1.2

Abbreviations: *BMI – body mass index, WHR – waist hip ratio, eGFR – estimated glomerular filtration rate, LDL – low-density lipoprotein, HDL – high-density lipoprotein, HOMA-ir – homeostatic model assessment of insulin resistance, CRP – c-reactive protein, CVD – cardiovascular disease, SD – standard deviation, % – percent of total.*

Table 5.2. Study characteristics for each blood pressure category-defined group at follow-up survey.

	Blood pressure category at follow-up											
	All		Optimal		Normal		High normal		Unstable		Hypertension	
	N=1129 (100%)		N=450 (39.9%)		N=273 (24.2%)		N=179 (15.9%)		N=48 (4.3%)		N=179 (15.9%)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	47.1	0.3	42.9	0.4	46.2	0.6	50.4	0.8	52.3	1.3	54.0	0.8
BMI (kg/m^2)	27.0	0.1	25.9	0.2	27.2	0.2	27.5	0.3	26.8	0.7	28.6	0.3
WHR	0.91	<0.01	0.88	<0.01	0.92	0.01	0.93	0.01	0.94	0.01	0.94	0.01
Heart rate (beats/min)	64.6	0.3	62.7	0.4	65.0	0.6	66.6	0.7	65.4	1.3	66.2	0.7
eGFR (mL/min)	80.8	13.7	79.9	12.3	82.5	14.6	81.3	13.7	79.5	13.2	80.3	15.4
Fasting plasma glucose (mmol/L)	5.6	<0.1	5.4	<0.1	5.6	0.1	5.7	0.1	5.8	0.1	5.9	0.1
LDL-cholesterol (mmol/L)	3.5	<0.1	3.4	<0.1	3.6	0.1	3.7	0.1	3.9	0.1	3.4	0.1
HDL-cholesterol (mmol/L)	1.5	<0.1	1.5	<0.1	1.5	<0.1	1.5	<0.1	1.6	0.1	1.4	<0.1
	Median	$P_{25} - P_{75}$	**Median**	$P_{25} - P_{75}$	**Median**	$P_{25} - P_{75}$	**Median**	$P_{25} - P_{75}$	**Median**	$P_{25} - P_{75}$	**Median**	$P_{25} - P_{75}$
Triglycerides (mmol/L)	1.03	0.78-1.38	0.93	0.71-1.23	1.03	0.82-1.4	1.16	0.84-1.45	1.17	0.86-1.53	1.21	0.9-1.6
Homa-ir ($mmol * mU/L^2$)	1.83	1.29-2.78	1.51	1.11-2.26	1.86	1.37-2.66	2.07	1.47-3.41	1.93	1.42-3.13	2.41	1.62-3.44
CRP (mg/L)	1.31	0.68-2.59	1.04	0.3-1.94	1.22	0.67-2.63	1.6	0.85-2.99	1.37	0.72-3.01	1.95	1.06-3.31
Alchohol (g/week)	29.4	7.5-63.8	28.4	7.6-58.5	33.8	11.2-70.4	31.9	6.3-68.9	29.8	0-80.6	25.4	3.8-61.5
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Sex (men)	555	49.2	182	40.4	151	55.3	100	55.9	23	47.9	99	55.3
Diabetes mellitus II (affected)	48	4.3	7	1.6	8	2.9	6	3.4	2	4.2	25	14.0
Smoking (current daily smokers)	122	10.8	48	10.7	33	12.1	15	8.4	5	10.4	21	11.7
Leisure-time physical activity (active level)	435	38.5	208	46.2	96	35.1	59	32.9	19	39.6	53	29.6
Self-rated health (good)	838	74.2	358	79.5	207	75.8	129	72.0	35	73.0	109	60.9
Self-efficacy (high)	915	81.0	391	86.9	214	78.4	147	82.1	34	70.8	129	72.1
Everyday stress (affirmative)	129	11.4	68	15.1	35	12.8	12	6.7	1	2.1	13	7.3
Thoroughly rested after sleep (affirmative)	816	72.3	326	72.4	199	72.9	131	73.2	38	79.2	122	68.2
Family history of hypertension (affected)	518	45.9	185	41.1	121	44.3	84	46.9	24	50.0	104	58.1
Experienced CVD episodes (affected)	47	4.2	8	1.8	6	2.2	6	3.4	2	4.2	25	14.0

Abbreviations: *BMI – body mass index, WHR – waist hip ratio, eGFR – estimated glomerular filtration rate, LDL – low-density lipoprotein, HDL – high-density lipoprotein, HOMA-ir – homeostatic model assessment of insulin resistance, CRP – c-reactive protein, CVD – cardiovascular disease. SD – standard deviation, N – number, % - percent of total within each blood pressure category.*

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Table 5.3. Transition between categories between baseline and follow-up.

Baseline category	Category at follow-up					
	Optimal	Normal	High normal	Unstable	Hypertensive	Row total
Optimal	387 (61.1)	156 (24.6)	64 (10.1)	8 (1.3)	18 (2.8)	633 (100)
Normal	52 (17.8)	82 (28.1)	78 (26.7)	22 (7.5)	58 (19.9)	292 (100)
High normal	11 (7.8)	31 (22.0)	29 (20.6)	14 (9.9)	56 (39.7)	141 (100)
Unstable	0 (0)	4 (6.3)	8 (12.7)	4 (6.3)	47 (74.6)	63 (100)
Column total	450 (39.9)	273 (24.2)	179 (15.9)	48 (4.3)	179 (15.9)	1129 (100)

Number of subjects and (row percentage).

Table 5.4. Change in levels for blood pressure categories between baseline and follow-up in different baseline blood pressure categories.

Baseline category	Transition in categorical steps							
	-3	-2	-1	0	1	2	3	4
Optimal				387 (61.1)	156 (24.6)	64 (10.1)	8 (1.3)	18 (2.8)
Normla			52 (17.8)	82 (28.1)	78 (26.7)	22 (7.5)	58 (19.9)	
High normal		11 (7.8)	31 (22.0)	29 (20.6)	14 (9.9)	56 (39.7)		
Unstable	0 (0)	4 (6.3)	8 (12.7)	4 (6.3)	47 (74.6)			
All	0 (0)	15 (1.3)	91 (8.1)	502 (44.5)	295 (26.1)	142 (12.6)	66 (5.8)	18 (1.6)

Number of subjects and (row percentage).

Table 5.5. Odds ratios (OR) for converting to manifest hypertension during follow-up.

	OR	95 % CI	p-value
Sex*	1.13	0.70-1.82	0.617
Age	**1.03**	**1.0-1.05**	**0.049**
District*	10.8	0.15-772	0.274
Time to follow up	0.49	0.11-2.18	0.347
BMI	**1.12**	**1.05-1.19**	**<0.001**
LDL	0.96	0.73-1.25	0.738
CRP	1.01	0.97-1.06	0.601
eGFR	1.01	0.99-1.02	0.314
Alcohol	1.00	0.99-1.00	0.252
Smoking*	1.53	0.83-2.80	0.173
Leisure time physical activity*	1.15	0.70-1.89	0.588
Undergone CVD*	5.13	0.98-26.9	0.053
Family history of hypertension*	**2.59**	**1.59-4.23**	**<0.001**
Blood pressure category at baseline*:			
Optimal	1		
Normal	**5.40**	**2.93-9.94**	**<0.001**
High normal	**12.5**	**6.28-24.8**	**<0.001**
Unstable	**87.5**	**33.1-231**	**<0.001**

Multivariable analysis where each variable has been considered under adjustment for all the others. Extra bold type indicates significance p<0.05.
Asterix indicates that the variable has been considered as categorical using the following as reference: sex - woman, district - Skövde, smoking - no, physical activity - active LTP, undergone CVD - no, family history of hypertension - no, blood pressure category at baseline - optimal.

Table 5.6. Odds ratios for progression in blood pressure category during follow-up.

	OR	95 % CI	p-value
Sex*	1.28	0.96-1.71	0.097
Age	**1.03**	**1.01-1.05**	**<0.001**
District*	1.10	0.10-11.8	0.937
Time to follow up	1.06	0.46-2.43	0.890
BMI	**1.05**	**1.02-1.10**	**0.006**
LDL	0.99	0.84-1.18	0.927
CRP	1.03	0.99-1.07	0.201
eGFR	1.01	1.00-1.02	0.121
Alcohol	1.00	0.998-1.00	0.972
Smoking*	**1.69**	**1.14-2.51**	**0.008**
Leisure time physical activity*	1.00	0.75-1.33	0.996
Undergone CVD*	5.54	0.66-46.3	0.114
Family history of hypertension*	**1.69**	**1.28-2.23**	**<0.001**
Blood pressure category at baseline	1.07	0.90-1.27	0.472

Multivariable analysis where each variable has been considered under adjustment for all the others.
Extra bold type indicates significance p<0.05.
Asterix indicates that the variable has been considered as categorical using the following as reference: sex - woman, district - Skövde, smoking - no, physical activity - active LTP, undergone CVD - no, family history of hypertension - no, blood pressure category at baseline – optimal

10. Acknowledgements

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11. References

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