

# Trends in Population Blood Pressure and Determinant Factors for Population Blood Pressure

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## Papers

1. Andersen UO, Henriksen JH, Jensen G. Sources of measurement variation in blood pressure in large-scale epidemiological surveys with follow-up. *Blood Pressure* 2002;11:357-65
2. Andersen UO, Jensen G and the CCHS group. Decreasing population blood pressure: 15 years of follow-up in the Copenhagen City Heart study. *Blood Pressure* 2004; 13: 176-82
3. Andersen UO, Jensen G and the CCHS group. Decreasing population blood pressure is not mediated by changes in habitual physical activity. Results from 15 years of follow-up. *Blood Pressure* 2007; 16: 28-35.
4. Andersen UO, Jensen GB. Trends and determinant factors for population blood pressure in a large population study with 25 years of follow-up. Results from the Copenhagen City Heart Study. *Eur J Cardiovasc Prev Rehabil.* 2010 Dec;17(6):655-9.
5. Andersen UO, Jensen GB. Trends and patient-related factors in hypertension control in a population study with 25 years of follow-up. Results from the Copenhagen City Heart Study. *J Hypertens* 2010; 19(3):182-7.

6. Andersen UO, Marott JL, Jensen GB. Decreasing systolic blood pressure and declining mortality rates in an untreated population: results from the Copenhagen City Heart Study. *Eur J Cardiovasc Prev Rehabil.* 2011 Apr;18(2):248-53. Epub 2011 Feb 11.
7. Andersen UO, Jensen GB. Population blood pressure and low to moderate alcohol intake in an untreated population followed over 20 years. Copenhagen City heart study. *Eur J Intern Med.* 2011 Oct;22(5):514-7. Epub 2011 Feb 18.
8. Andersen UO, Jensen GB. Gender difference and economic gradients in the secular trend of population SBP. Results from the Copenhagen City Heart Study *Eur J Intern Med.* 24 (2013), pp. 568-572 DOI 10.1016/j.ejim.2013.05.005

## Abbreviations

PBP: Population blood pressure  
SBP: Systolic blood pressure  
DBP: Diastolic blood pressure  
BMI: Body mass index  
CVD: Cardiovascular disease  
CCHS: The Copenhagen City Heart Study  
ANOVA: One-way analysis of variance  
SD: Standard deviation  
SE: Standard error

## Introduction to a SBP trend study

Ischemic heart disease is a multifactorial disease. The most important and known risk factors are age, smoking, high blood pressure, dyslipidemia, obesity, sedentary life style and diabetes. Ischemic heart disease is not as dangerous as it was before. Mortality rate has declined<sup>1</sup> and nearly 200000 Danes live with chronic ischemic heart disease. Improvements in treatment substitute one part of the explanation for the declining mortality rate. The medicine is now very effective and there is an effective invasive treatment. Beneficial changes in all risk factors (except obesity and diabetes) constitute the other part of the explanation.

All risk factors for ischemic heart disease have been evaluated in repeated cross-sectional analyses<sup>2</sup>. Population blood pressure has also been investigated in multiple cross-sectional analyses and SBP mean value is decreasing in Denmark and in most of the western countries (see page 23). If we want to go a step further and prevent high population blood pressure and hypertension in a population, we have to follow both trends and the factors that determine trend in population blood pressure. It is important to identify both beneficial and deleterious factors; they are both targets in preventive strategies. Therefore the two main topics for this thesis<sup>3-10</sup> are trends in population blood pressure during 25 years and the factors that determine trends.

### Population blood pressure and secular trend in PBP

PBP is the average or typical BP contributed to by all individuals in a population. PBP represent a time-dependent population characteristic, typical of a population at a given time but different from one population to another (much in the same way that e.g. the typical population height may be different in populations and may change over time<sup>11</sup>. Globally, population systolic BP (SBP) is one of the leading risk-factors for death<sup>12-14</sup> and one of the most significant factors for myocardial infarction and stroke<sup>13</sup>. Worldwide 54% of stroke and 47% of ischaemic heart disease were attributable to high blood pressure<sup>16</sup>.

When measuring BP in a population, most subjects are healthy in general and with respect to BP. A minority will present low BPs, and a significant proportion will present high BPs. Some of the hypertensives receive treatment, but most hypertensives are not treated and may be unaware of their condition. The individuals with SBP <140 mmHg are at a small individual risk for BP attributable diseases, but when they are studied as populations, their individual risks add up and overtake the sum of risks from the hypertensives.

Secular trend is a concept in time series analysis that refers to the basic tendency of a series to grow or decline over a period of time. By exploring secular trends in SBP and the possible underlying biology and conditions, beneficial processes may be identified and strengthened or deleterious risk factors identified and eliminated in the population, as argued by Rose<sup>17</sup>. Therefore, secular trends in PBP in the untreated population and the identification of determinant factors for PBP are important in prevention of high blood pressure and associated diseases. Secular trends in PBP in the treated population and determinant factors in treated SBP are important when analyzing the management of hypertensive patients.

### The Copenhagen City Heart Study

The Copenhagen City Heart Study is a longitudinal epidemiological study in a sample of subjects of both genders aged 20 and above, randomly selected from the civil register of people living in a defined area of Copenhagen. Thus the study population is a cohort with the common characteristic that they live in a region of Copenhagen. The subjects were invited to four examinations carried out from 1976 through 1978, from 1981 through 1983, from 1992 through 1994, and from 2001 through 2004, respectively (Figure 1). CCHS invited five hundred, 3000 and 1040 younger subjects to participate as new entrants in surveys 2, 3 and 4, respectively. Total response rates were 74%, 70%, 61% and 50%. The sex distribution was the same in the four surveys. Data from the first

three surveys were analysed in the first papers<sup>3-5</sup>. Data from the last three

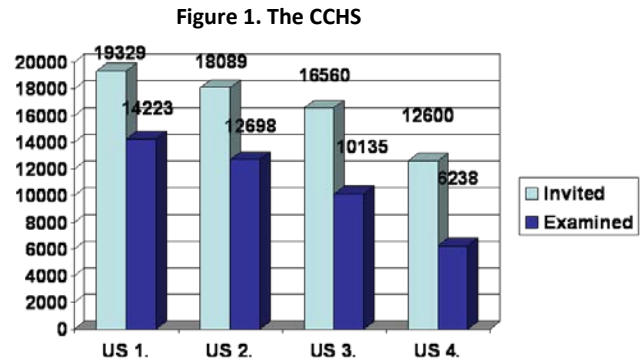


Figure 1. The Copenhagen City Heart Study consists of four surveys. This graph shows the number of invited and examined subjects in each of the surveys.

surveys were analysed in one of the papers<sup>9</sup>. The remaining papers were based on all surveys. Details of the selection procedure, a description of the eligible non-participants, the complete examination program, and information on the subjects have been presented elsewhere<sup>18-20</sup>.

The study population was followed over 25 years with 1-4 measurements on each subject. The CCHS was approved by the Regional Ethical Committee for Medical Research in Copenhagen.

In paper 4 and the forthcoming papers, the population was subdivided into two groups. The untreated population consists of subjects who answered “no” to the question “Are you treated for hypertension?” The treated subjects are subjects who at least once answered “yes” to the same question. The last untreated values in the treated hypertensive subjects are analysed as pre-treatment values. The subdivision may give rise to selection bias when studying the untreated population: The fraction of treated subjects increased survey by survey and the increasing fraction of subjects with high SBP leaving the untreated group may result in a decreasing SBP in the remaining untreated population. Therefore the possibility of selection bias was evaluated carefully when analysing results. Selection biases are discussed further on page 27 and 40. The division of the population into an untreated population and a treated population is, however, obligatory when performing mixed linear analysis: individuals who are treated on the outcome parameter cannot be evaluated together with untreated individuals. The two populations have different linear trends and different determinant factors. The assumption on linearity cannot be accepted in a mixed population of treated and non-treated individuals.

### BP measurements

WHO guidelines, as recommended by Rose and Blackburn<sup>20</sup> were observed. BP was measured once under highly standardised circumstances that were unchanged in every detail throughout the surveys. Specially trained

technicians using a London School of Hygiene sphygmomanometer<sup>21</sup> measured BP once on the non-dominant arm after a 5-min rest with the subject in the sitting position. The LSH sphygmomanometer is designed to eliminate observer bias, in particular with regard to digit preference<sup>21</sup>. The cuff is standardised according to arm circumference<sup>22-23</sup>. The fall of the mercury column was set to 2 mm/sec. During this time the Korotkoff sounds were measured through a stethoscope placed over the brachial artery. The first Korotkoff sound signified SBP. The fifth Korotkoff sound (the sounds disappear) signified DBP.

Epidemiological studies that measure a large number of BPs can handle the BP variability in two ways: The single BP measurement strategy was suggested by Rose and Blackburn<sup>18</sup> as a feasible method for large-scale population studies. The result from a single measurement of BP is called a casual BP. Casual BP has been used in several epidemiological studies<sup>24-26</sup> and it is a very reliable predictor of hypertension, stroke and CVD<sup>24-26</sup>. Another approach is to measure two or three BPs and calculate the mean value<sup>27-29</sup>. The reliability of casual BPs for reflecting BP status and predicting cardiovascular sequelae of hypertension was examined in the Framingham cohort of 5209 men and women followed for 18 years. They observed that BPs were more variable in persons with high levels. They concluded that although a single casual measurement does not afford a precise characterization for an individual, it was found to be highly predictive of future cardiovascular disease. A series of BP measurements (averaged) improved the predictability somewhat, but this seemed to be fully explicable by the greater stability of an average of several measurements as against a single measurement<sup>30</sup>.

In this study the value “casual SBP $\geq$ 140 mmHg” was used as a cut-off value between high and low SBP and between success and failure in hypertension treatment.

### Possible BP measurement errors

The careful methodology is one of the strengths of the CCHS. The technicians were instructed in the same way in all four surveys and the equipment was unchanged. Every effort was made to eliminate systematic variations and diminish random variation. Systematic variations are potentially serious, as the bias they cause may lead to invalid conclusions. Random variations, on the other hand, reduce precision.

The topic, “measurement error”, has been dealt with in several international reports on BP measurement<sup>31,32</sup>. Any possible systematic variation (day-time variation, seasonal variation, variations due to meteorological variation, observer variation, subject variation, variation due to faulty equipment and non-responder bias) has been thoroughly investigated in the first paper<sup>3</sup>. There were day-time variations in SBP and DBP but they disappeared after adjustments for age. The age-related differences were ascribed to the phenomenon that younger subjects preferred examinations in the morning or after work. The elderly, however, attended the study in the mid-day hours. There was a trend towards lower SBP and DBP during summer and a trend towards higher BP when cold outside. Seasonal variations were of minor importance in the CCHS, because measurements were taken in all seasons.

There were differences in mean BP in the subsamples of each observer. However, these differences disappeared after adjustments for differences of seasons, because the observers worked at different times of the year. There is a learning effect: After 100

measurements of BP the observers’ subsamples converged towards a common mean. Some of the observers participated in more than one survey.

A risk of introducing systematic bias occurs when not all individuals in the sample are examined. Non-responder bias was carefully evaluated at baseline<sup>33</sup>. It has been reported that the non-responder group in survey 1 differed significantly from the examined population in respect to morbidity, mortality, socio-economic status, age and gender<sup>33</sup>. In the following surveys there was a drop-out problem: a group of individuals that missed one, two or three surveys. There was also a group of individuals, who died and there was a missing value problem. The mixed effect analysis is able to handle missing values. An alternative to the inclusion of subjects with missing values or missing examinations is the use of analyses that discard the incomplete cases. These analyses create large biases with poor confidence coverage.

Figure 2

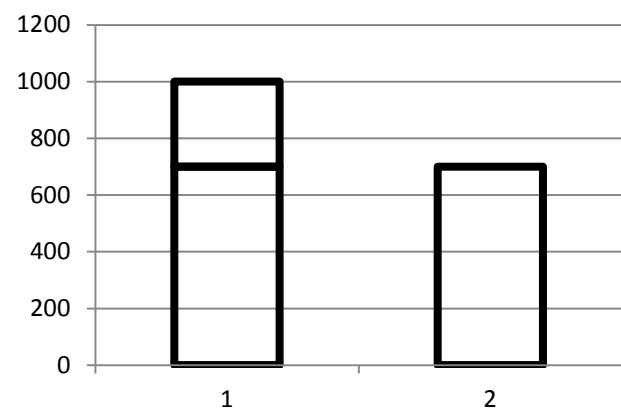


Figure 2. An example that shows how non-responder bias was calculated: In survey 1 1000 cases were examined. 700 also completed examination in survey 2 whereas 300 were non-responders in survey 2. The mean values and frequencies from survey 1 were evaluated between the 700 responders and the 300 non-responders. Any significant difference may support the assumption that non-responder bias interfere with the calculation of trends.

The evaluation of non-responder bias was based on the results from the last attended survey (Figure 2). In the last attended survey SBP and other variables in the group of non-responders, drop outs and deceased were compared to similar variables in the group of subjects attending both surveys. Mean values and frequencies were included in the comparison. In these analyses there were significantly more smoking women in the non-responder group in survey 3 and more smoking men in the non-responder group in survey 4 than in the relevant responder population. There was no non-responder bias in respect to BPs and no other non-responder bias.

Can the results be explained by the phenomenon ‘Regression toward the mean’? This question is relevant when there is more than one measurement on the same individual. Regression toward the mean is the phenomenon that if a variable is extreme on its first measurement, it will tend to be closer to the average on a second measurement, and if it is extreme on a second measurement, will tend to have been closer to the average on the first measurement. Thus the phenomenon implies a correlation between the repeated measures. Correlation is very well handled in the mixed linear analysis (see page 17).

## Statistics

CCHS is a longitudinal study that involves repeated, time-ordered observations for each individual (Figure 3). Such designs are uniquely suited to studying changes of an outcome parameter and determining the explanatory variables most associated with any change.

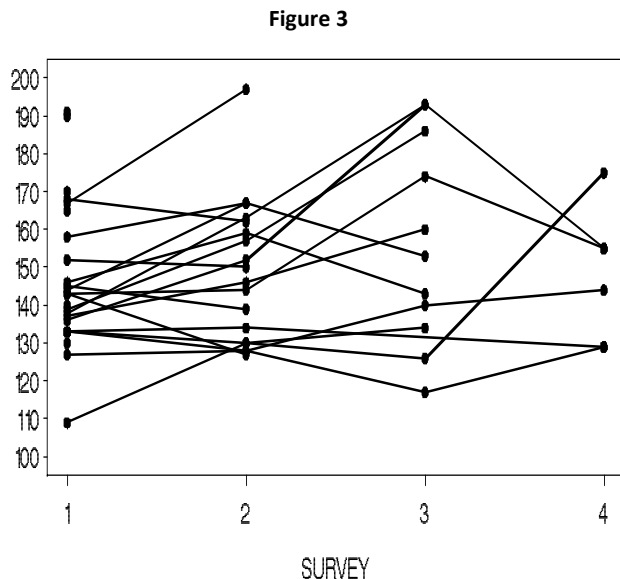


Figure 3. Repeated, time-ordered observations of SBP in 30 subjects followed from survey 1 to survey 4.

The most frequently used longitudinal approaches, repeated cross-sectional analysis, multivariate repeated measures, and pre- and post-test differences have restrictive assumptions and unrealistic data requirements<sup>34</sup>. Some of these methods were used in paper 2 and 3. A more flexible approach in analysing repeated-measures longitudinal design is the use of mixed linear models. The advantages of a mixed linear model are

- It describes and tracks each individual's BP curve and its relationship with covariates.
- It is not restricted by unrealistic assumptions.
- It solves the commonly observed problems of missing data.
- It does not require fixed time intervals
- It provides a more precise estimation. Firstly, there are several measurements to confirm the association between SBP and one of the factors. Secondly, the random part of the mixed linear model minimizes the chance that the incidence of confounding (particularly unknown confounding) variables will differ between surveys.

Linear mixed effects models for repeated measures data formalize the idea that an individual's pattern of responses is likely to depend on many characteristics of that individual, including some that are

## Box 1

The primary assumptions underlying the analyses performed by Proc Mixed are as follows:

- The data are normally distributed (Gaussian).
- The means (expected values) of the data are linear in terms of a certain set of parameters.
- The variances and covariances of the data are in terms of a different set of parameters, and they exhibit a structure matching one of those available in Proc Mixed.

Citation from reference 35

unobserved. These unobserved variables are then included in the model as random effects. The essential feature of the model is that correlation amongst the repeated measurements on the same unit arises from the shared, unobserved variables. Therefore the analysis of secular trend in SBP was performed by mixed analysis<sup>35,36</sup> with age, gender, cardiovascular risk factors, household income and family structure as variables. The adequacy of models in a stepwise selection procedure was tested by means of a residual likelihood ratio test. SBP was log-transformed to satisfy the assumption on normality. The final model was determined by a restricted/residual likelihood ratio test. Model diagnostics were used to check if the final model captured all systematic effects in the data and fulfilled all other model assumptions.

This is the first report on trends in SBP by means of the random effect model. Thus, no comparison can be performed to similar studies in other countries. Instead the results are compared to cross-sectional studies. The random effect model has been used by several investigators. Two examples are: 1: An investigation of weight gain in late adolescence on variables in bone structure<sup>37</sup> and 2: An investigation of signal intensity on doubling the contrast dose in MR-mammography<sup>38</sup>. These studies are very different but they all involve several measurements on the same subject in order to describe a change by time.

Figure 4 and 5

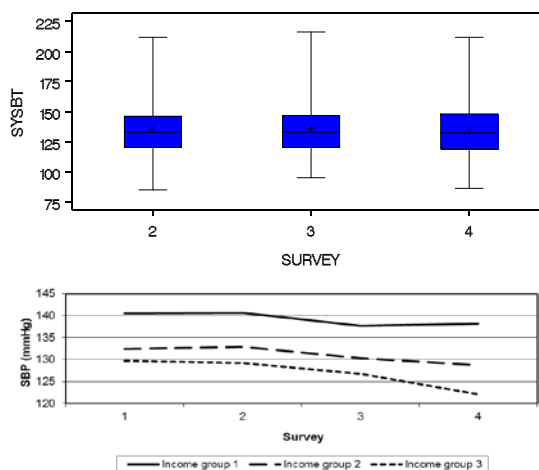


Figure 4 and 5. These two figures illustrate the difference between several cross-sectional analyses (left) and a trend analysis (right). The cross-sectional analyses produce the mean values and the risk factors most associated to the mean values. The inference test decides whether the risk-factor adjusted mean values are significantly different. The trend analysis produces trend lines and the determinant factors most associated with trends. The inference test determines whether the trend lines are significantly different.

Differences between multiple cross-sectional surveys and longitudinal analyses are illustrated in figure 4 and 5. The figures show the trend lines for risk-factor adjusted SBP for each subgroup (Figure 5). The inference test determines whether the trend curves are significantly different from each other. The p-values for the inference tests are given in the legends to the figures.

The secular changes in SBP may, theoretically, occur in different ways: Groups with different explanatory variables may differ according to set-off points at baseline, by slopes or both (Figures 6-8).

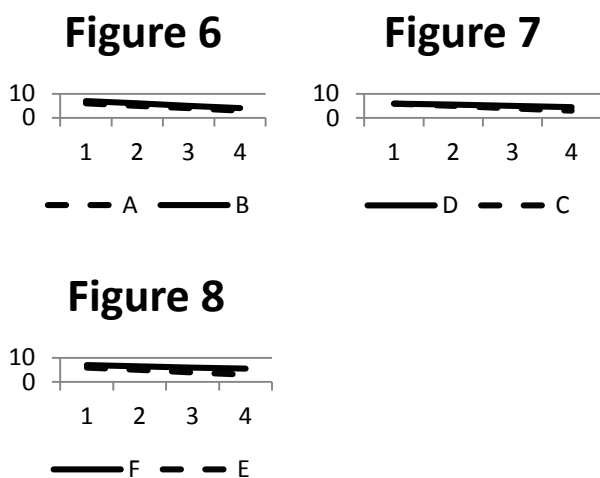


Figure 6-8. These three graphs illustrate, that changes in SBP may theoretically occur in three ways: 1. The set-off point for one group (A) is lower than the other group (B). 2. The two groups share the set-off point at baseline but slopes are different (Group C and D). 3. Both set-off point at baseline and slopes are different (Group E and F).

It is worth noting that all tables on baseline characteristics were based on the population in survey 1, but more individuals joined the study in the following surveys giving rise to a larger total number of examined individuals.

In paper 2 and 3 cross-sectional analyses of risk-factor adjusted SBP by categories were performed by multivariate analysis with age, gender, BMI, smoking and other possible significant factors as variables. SBP was log-transformed to satisfy the assumption of normality. The adequacy of models in a stepwise selection procedure was tested by means of a residual likelihood ratio test. The final model was determined by a restricted/residual likelihood ratio test.

Chi-square analyses were performed to test differences in frequencies.

One of the papers dealt with survival analyses<sup>8</sup>. The multivariate survival analyses are based on Cox's proportional hazards model using 'proc tphreg'. The covariates in the final model are selected by means of the log-likelihood method.

All statistical models were checked by relevant model diagnostics and the covariates were log-transformed if appropriate. The statistical analyses in the three first papers were performed using the statistical package SPSS. 9.0. 1998. Chicago IL, SPSS Inc. All analyses in the last five papers were performed with SAS software (SAS System for Windows, release 9.1, SAS Institute Inc, Cary, NC). Values of  $p < 0.05$  in two-sided tests were considered significant.

### Characteristics in the PBP distribution Figure 9 and 10

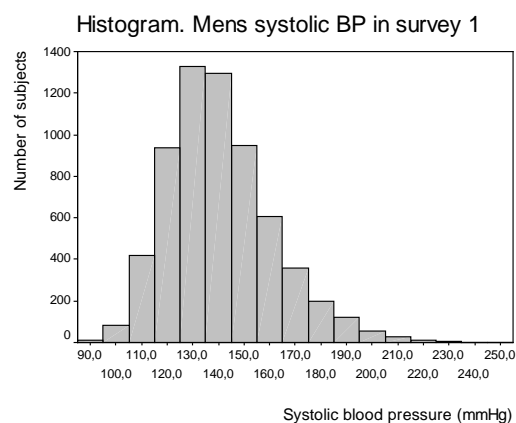
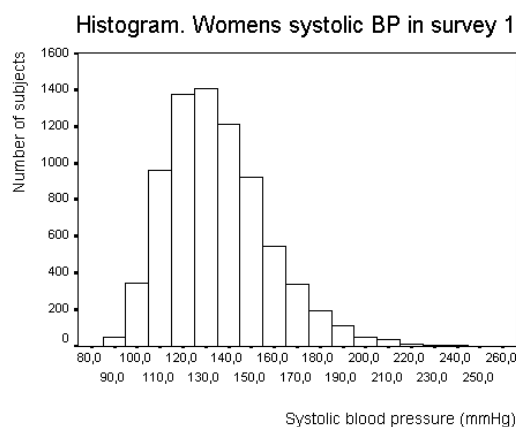


Figure 9 and 10. Histograms that show the distribution of systolic BP in the population in survey 1. Women are to the left and men to the right. Both histograms show skewness to the right.

Two results from the descriptive statistical analyses are important when analysing results in the trend analyses. Firstly, the SBP distribution in the population is skewed to the right (Figure 9 and 10). After log-transformation of SBP the assumption of normality is accepted in model diagnostics. Secondly, the progression of systolic BP by age follows an almost linear curve whereas diastolic BP increases and reaches a plateau. Hereafter DBP declines (Figure 11). The hemodynamic pattern is described by others as well and is consistent with the introduction of large artery stiffness by increasing age<sup>39</sup>.

It will be shown that DBP is not easily fitted into a linear regression model. The two phases in the age-DBP association may be part of the explanation (Page 36).

**Figure 11. Progression of SBP and DBP by age**

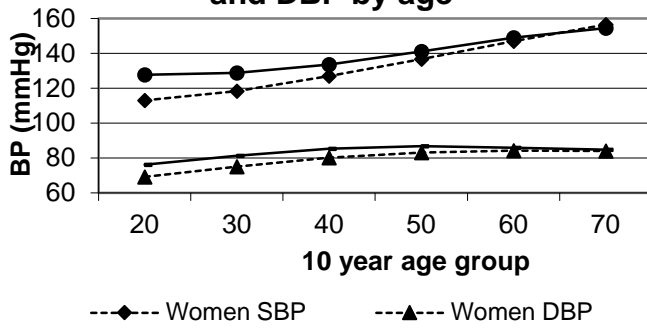


Figure 11. The association between age and un-adjusted SBP/DBP in both men and women. The graph is the result of a cross-sectional analyses of mean values in 10 year age groups.

**The untreated population**

Trend in SBP

The result of the trend analysis was an increase in age- and risk factor-adjusted SBP between survey 1 and survey 2 ( $p < 0.0001$ )<sup>4,6,40</sup>. Hereafter SBP decreased significantly (Figure 12). The trend analysis in the CCHS study population is in line with decreasing mean SBP in several cross-sectional analyses from other western countries<sup>28,29,41-47</sup>. However, some authors report a stable SBP<sup>48,49</sup> or an increasing SBP<sup>50</sup>.

**Figure 12. Trend in untreated**

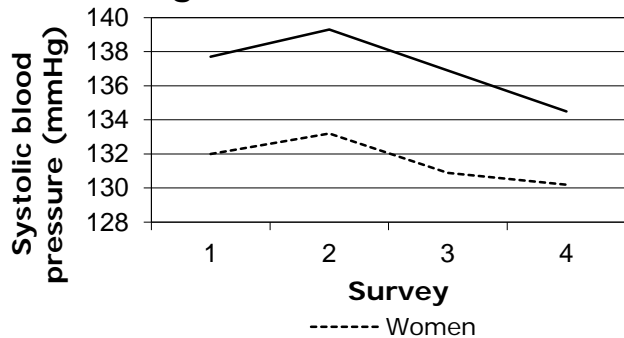


Figure 12. Gender-differentiated trend curves for untreated risk-factor adjusted SBP ( $p < 0.0001$ ). Risk-factor adjusted SBP increased between survey 1 and survey 2. Hereafter it decreased. The net result is a 2.2 mmHg decrease in female SBP and a 3.2 mmHg decrease in male SBP over 25 years.

Significant factors for untreated SBP

In the trend analyses six factors were identified as significant factors for trend in SBP: gender, age, BMI, the interaction age/gender, the interaction age/survey and household income.

**1. Age**

It is very well known that in the western countries SBP increases by increasing age. The present results show that i.e. SBP trend for 60 years old individuals have higher value than trend for 30 years old individuals. It has been observed that some primitive societies with a lifestyle, that is very different from western lifestyle; have low population SBP throughout their lifetime<sup>51</sup>. Thus, the association between age and SBP in western societies may represent the total sum of common life style factors that in a synergistic or additive way affect trend in SBP throughout a lifetime.

**2. Gender**

Men have higher SBP than women and their trend in SBP have higher values than the female trend in SBP. Both trend curves are decreasing (Figure 9).

**Figure 13. Impact of BMI on untreated SBP**

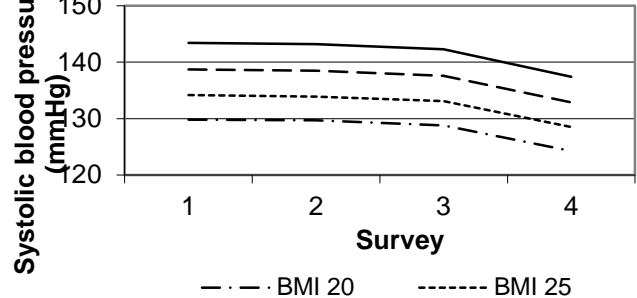


Figure 10. Untreated risk-factor adjusted SBP is positively associated with BMI ( $p < 0.0001$ ).

**3. BMI**

Similar to the positive association between SBP and BMI in cross-sectional analyses, trend in SBP is positively associated with BMI and the trend lines were parallel (Figure 13). The parallel trend lines indicate that trend in SBP in i.e. individuals with BMI=25 kg/m<sup>2</sup> share the same slope as individuals with BMI=35 kg/m<sup>2</sup> only the trend lines were parallel displaced. The link between BP and obesity may be one or more of the hormones secreted by the adipose tissue<sup>52,53</sup>.

**4. Interaction between age and gender**

The fourth factor is an interaction between age and gender<sup>54</sup>. According to this interaction the gender difference in SBP trend is large in young adults but diminishes and disappears at age 70 years (Figure 14). This result is in line with results from cross-sectional studies both in CCHS (Figure 11) and in other western societies<sup>54</sup>.

**Figure 14. The age/gender interaction**

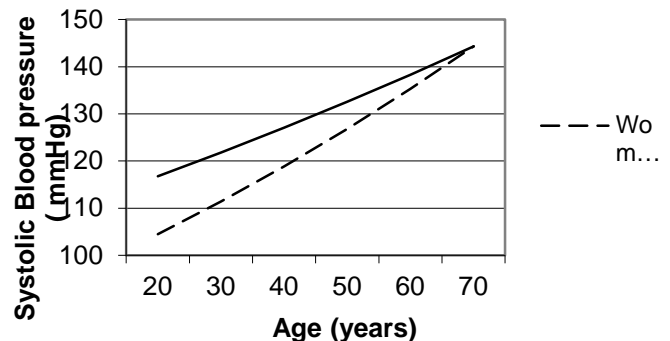


Figure 14. The interaction between age and gender ( $p < 0.0001$ ). The gender difference in multivariate adjusted SBP is large in young adults and diminishes with age. At age=70 years there are no age differences in untreated SBP.

**5. Interaction between survey and age**

The next significant factor was the interaction between survey and age. According to the survey/age interaction the SBP-decrease was not evenly distributed over the population. A marked decreasing SBP trend was seen when comparing SBP in the 20-years old cohort in survey 1 with SBP in the 20-years old cohort in survey 4 (Figure 15). At the age '40 years', the decrease was less, and at the age '60 years' there was only a minor decrease that may also be explained by a previously mentioned selection bias because more and more of the 50-60-years old or older subjects started treatment and leave the non-treated group. The mean age of this subgroup is 64 years<sup>6</sup>. Therefore, selection bias was not a valid explanation for the SBP decrease in the younger cohorts but may be a relevant explanation for changes in the generations that are over 50-60 years of age.

**Figure 15. The age/survey interaction**

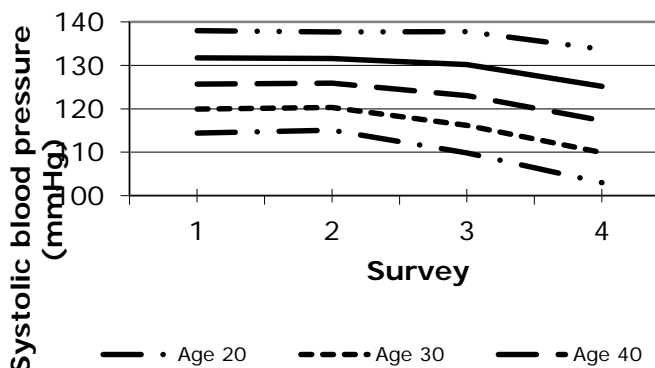


Figure 15. The age/survey interaction ( $p=0.029$ ). The SBP-decrease is not distributed evenly in the population. The difference between untreated SBP in the 20-years old subjects in survey 1 and the 20-years old subjects in survey 4 is very large compared to the difference between the cohorts of 60-years old subjects.

Thus the observed trend in SBP was partly explained by the introduction of new age-cohorts with lower SBP into the study population. It has only been described in CCHS. Consequently, an important factor for the changing PBP lies in the prenatal life, childhood or adolescence. The exact nature of this factor is not known. It may be changes in diet or better housing and living conditions for mothers and children. The SBP differences between the generation that was 20 years old in 1976 and the generation aged 20 years in 2001 is about 10 mmHg. According to the nomograms<sup>15</sup> the 2001 generation will have a 50% less risk for stroke and 35% less risk for ischemic heart disease provided that they maintain SBP differences throughout lifetime.

#### 6. Household income

Income factors and other socioeconomic factors may explain variations in population SBP in the same way as socioeconomic factors explain differences in CVD and other diseases<sup>55</sup>. Social inequality is traditionally investigated by using one or more of the following three socioeconomic indicators: Household income, education and social strata by job classes. Each of them has advantages and disadvantages and some authors recommend to use more than one indicator<sup>56,57</sup>.

Unlike cross-sectional studies, longitudinal studies distinguish short-term phenomena from long-term phenomena. Longitudinal studies are therefore suited for studying the effect of changing income. Many cross-sectional studies combine the effects of income and education as a measure of social position. However,

the amount of years spent in school has the same level throughout a lifetime and therefore education level may be treated either as a long-term phenomenon or as an unobserved variable that is included in the random part of the model. In this report education was treated as an unobserved variable in the random part of the model.

Household income increased in the observation period. Therefore three groups were constructed. The groups were comparable in relative size in each of the surveys. The low-income group comprised about 30% of the individuals in a survey. The next group comprised about 50% of the population and the high-income group consisted of almost 20% of the population in a survey. Income factors play a role in determining risk factor adjusted population SBP independently from the known risk factors but only among women. High-income women had low SBP and a more beneficial secular trend in SBP than women with lower income (Figure 16). In survey 4 there were six levels of income allowing a

**Figure 16. Household income and SBP among untreated women**

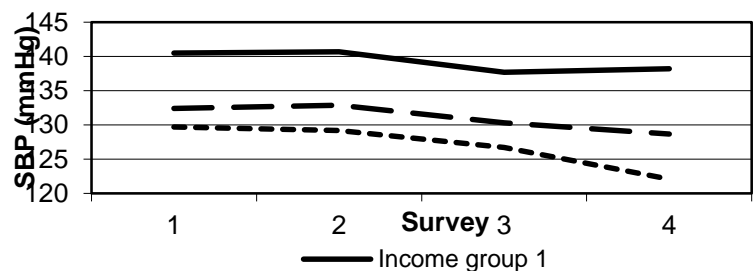


Figure 16. Trend in age- and BMI-adjusted SBP in untreated women subdivided into three income groups. The graph represents a post-hoc analysis of the significant variable 'income group' ( $p=0.005$ ). In addition there is a significant diversion (interaction) between the three groups indicating that there are different secular trend curves for each income group: income group 1 experienced only minimal change in SBP during the observation period whereas income group 2 and 3 experienced a large decrease in SBP during 25 years ( $p$  for the interaction 'income group/survey'  $<0.0001$ ).

stepwise evaluation of income in a multivariate cross-sectional analysis. It was concluded in the cross-sectional analysis that every small increment of income was associated with a lower SBP. Thus, trend in the national population BP is determined by population mean age, BMI and gender but the estimate is more precise when adding the distribution of income in the society as a determinant factor. Denmark has a very low Gini coefficient (0.29) indicating that the income differences in the society are relatively small. More equal societies tend to be healthier. Therefore, it is surprising to find both social inequality in SBP and a tendency towards aggravating the differences across social strata.

A high-risk index (modified version of the risk index in the European Hypertension Guidelines<sup>58</sup> was used as an indicator of unhealthy life style and men were in majority in the high-risk group (60%). The low-income groups both among men and women had more high-risk individuals than the high-income groups. Thus, a part of the observed difference in relation to gender and income group may be explained by unhealthy life style among men. Unhealthy life style may also explain some of the SBP differences between high-income women and low-income women. However, the job situation is different in the two genders and in the different income groups. Therefore, competing risk factors, i.e. job strain<sup>59</sup> among high-income may also explain a part of the gender differences and the social differences. The economic gradient in SBP trend may mirror an increasing wealth in the country, an unequal distribution of income with time or that a healthy lifestyle

has become trendy in the high-income women. The social inequality in SBP indicates that improvements in population health are not achieved by continued economic growth in the society. The society has to address social needs and improve the social environment. One topic that may help to address social needs is to analyse the differences (apart from income) that exist between high-income women and low income women.

#### Non-significant factors for untreated SBP

It is important to identify both significant and non-significant factors for trend in PBP because factors may be part of a pattern of mechanisms that leads to different trend curves in two groups. Two non-significant risk-factors need special attention because they participate in hypertension aetiology and physicians recommend relevant actions to be taken by hypertensives. The first risk factor is physical activity<sup>5</sup>. The subjects were asked about their habitual physical exercise, and based on the answers, the population was subdivided into four physical activity groups: Group 1: sedentary subjects or less than 2 h of light activity. Group 2: subjects with less than 4 h of light physical activity in the leisure time. Group 3: light physical activity in more than 4 h per week or more strenuous activity for 2–4 h per week. Group 4: More than 4 h of strenuous activity per week. A decreasing heart rate is associated to increasing number of activity group. An inverse association between resting HR and the levels of activity signifies that the questionnaire was a powerful tool to subdivide the population into 4 discrete activity levels. The majority of the population was either sedentary or preferred low daily activity. Thus, a total of more than 70% do not follow the recommendations for an active life style<sup>60</sup>. There was no change in the pattern of activity<sup>61</sup>. This result is consistent with other population studies from western countries<sup>62</sup>. Recently some authors from Canada reported a weakly positive trend in physical activity<sup>63</sup>. The positive trend has not yet been observed in the CCHS population. There was no association between physical activity and risk-factor adjusted SBP<sup>5</sup>. In hypertension trials, hard physical activity had a BP-lowering effect<sup>64–67</sup> and it has been proposed that physical activity prevents hypertension<sup>68</sup>. However, the activity level in the population in general is fairly low and the subdivision into four activity levels is too crude to monitor any subtle changes. Non-significance may be a result of the distribution in the pattern of physical activity, because all epidemiological methods assume heterogeneity of exposure in the population. Thus, the possible effect of habitual physical activity may be underestimated. This is not a statement saying that sedentary lifestyle is acceptable in preventive medicine. In fact, physical activity carries a great potential to improve population health<sup>61,69</sup>. The study on physical activity was carried out without the random effect analysis. The results from the study on physical activity and SBP were later re-investigated by means of the random effect model (not published). The second investigation on the role of physical activity in population SBP concluded that physical activity was not a determinant factor for trend in SBP.

The second non-significant risk-factor that needs special attention is habitual alcohol intake. In univariate analyses, SBP correlates with alcohol intake<sup>70–73</sup>. Hypertension is common among alcoholics<sup>72,73</sup>, and several studies observed a positive effect on BP of alcohol reduction. The observations of BP in alcoholics led to investigations of the effect of alcohol in the much larger part of the population with a low or moderate alcohol intake.

**Figure 17. Habitual alcohol intake and untreated SBP**

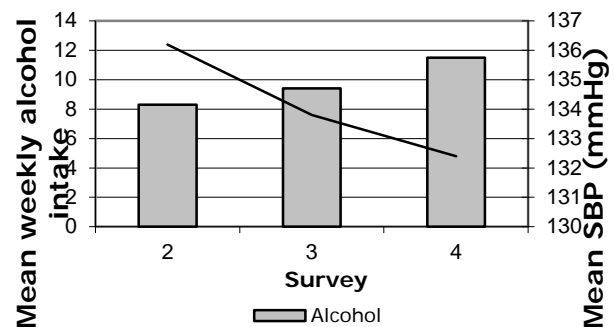


Figure 17. This graph shows the increasing population alcohol intake ( $p < 0.0001$ ) and the decreasing risk-factor adjusted trend in SBP ( $p < 0.0001$ ) from survey 2 to survey 4.

Alcohol intake is not a stable lifetime characteristic. Throughout a lifetime, people may start drinking or stop drinking. They may increase or decrease their intake due to alterations in social life, health, family life or economy<sup>74,76</sup>. If alcohol intake is a true determinant, then population BP will change with changing alcohol intake. The alcohol question in the questionnaire changed between survey 1 and 2 and therefore the analysis is based on the results from survey 2–4. The CCHS population consists mainly of subjects that increase alcohol intake moderately over 20 years, and PBP did not increase with increasing alcohol intake. On the contrary, trend in population SBP decreased (Figure 17). It has been proposed that the association between alcohol and BP is not linear<sup>77,78</sup>. According to the non-linear principle, a small or moderate alcohol intake is without impact on SBP whereas alcoholism is associated with hypertension<sup>71,79</sup>. The non-significance of a low to moderate alcohol intake on trend in SBP in the CCHS population is in line with the non-linear theory from cross-sectional studies. It is also in line with results from a comparison of geographically separated populations<sup>80</sup>.

#### Factors that are not investigated

The investigation of determinant factors and their contributions to trends in BP is restricted to the variables examined in the CCHS. There are several relevant factors that cannot be investigated in CCHS. Four of them are especially interesting in relation to blood pressure:

- 1: Further attention should be drawn to diet factors including the effect of the DASH diet<sup>81,82</sup>.
- 2: The salt intake is also important for systolic BP, and modest reductions of salt intake may influence population BP and incidence of cardiovascular disease<sup>83,84</sup>.
- 3: Genetic factors<sup>85,86</sup>. Blood pressure is the phenotype of a complex impact of environmental influences on the expression of a number of genes. The genetic contribution to hypertension is not evaluated in this report.
- 4: Low birth weight has been evaluated as a risk factor for high blood pressure and hypertension in adulthood. The discussion is interesting because birth weight is increasing in Denmark<sup>87</sup>. However, there is no agreement yet: some find a negative association between birth weight and adult SBP<sup>88</sup> and some find a positive association<sup>89</sup>. Birth weight is closely related to maternal health and other factors may act as confounders in the relationship between SBP and birth weight<sup>90</sup>. Childhood factors have been investigated in a Danish path-analysis that concluded that increases in body



size prior to age 11 years are less harmful to adult blood pressure than increases after this age<sup>91</sup>.

#### Trend and determinant factors for untreated DBP

DBP increased to a peak value (83.2 mmHg) in survey 3. Hereafter DBP decreased to 80.2 mmHg (Figure 18). Age, gender and all the life-style factors mentioned in connection with SBP were tested as determinant factors in the analysis of DBP, but they were non-significant.

When analysing DBP the statistical package accept the statistical model in all model diagnostics but the results call for careful consideration. Trend in population diastolic blood pressure (DBP) is best described by a curvilinear regression curve (Figure 18) and the relation between age and SBP is also curvilinear. The association between age and SBP reflects two phases: In the first phase DBP increases parallel to SBP. In the second phase population DBP decreases while SBP continues to rise. Population DBP is therefore

**Figure 18. Trend in untreated DBP**

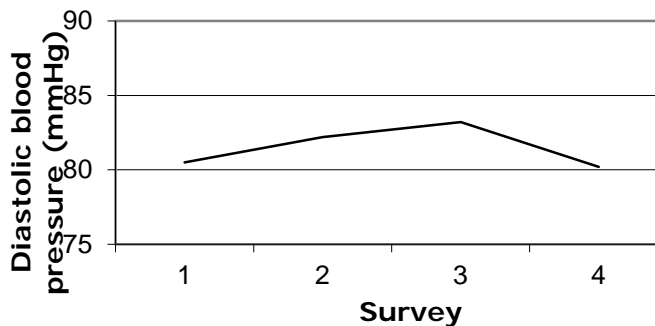


Figure 18. Risk-factor adjusted untreated DBP increases significantly from survey 1 to survey 3. Hereafter DBP decreases. The net result is a 0.3 mmHg decrease in DBP ( $p=0.03$ ).

probably not suited for analysis in linear regression models (See page 22).

Conclusion for the analysis of SBP and determinant factors in the untreated population: Trend in SBP is decreasing when analysed over 25 years. The conditions and biology that drive trend in SBP are: age, gender, BMI, the interaction sex x age, the interaction age x survey and household income. The interaction age x survey refers to the condition that younger individuals join the survey with a lower SBP than the previous generations of young people. Thus, two groups experienced great decreases in SBP: young generations and well-off women. The other determinant factors play their role on all individuals of all ages.

#### **Mortality and untreated PBP**

Population SBP is one of several determinant factors for a population's morbidity and mortality. Therefore, it is interesting to investigate the consequences of the decreasing trend in SBP on all-cause mortality<sup>8</sup>. The study on mortality aimed to answer three questions:

1. Was SBP a covariate for death in all age groups
2. Did trend for all-cause mortality change and was the change different in different age groups.
3. Did the risk of mortality for a given value of SBP change?

Risk of all-cause death in the CCHS population declined consistently with risk of all-cause death in Denmark<sup>92</sup>. Improvements in life-expectancy have also been reported in other western countries<sup>12</sup>. The leading risk-factor for all-cause mortality in Denmark is cardiovascular disease (CVD). From 1975 to 1990 cardiovascular mortality decreased from 500 per 100 000 men to 400 per 100 000 men and from 200 per 100 000 to 150 per 100 000 women<sup>93</sup>. A similar trend was observed in other European countries<sup>12</sup>.

The recent decline in coronary heart disease mortality is explained by primary and secondary risk prevention as well as treatment effects<sup>49,94-97</sup>. There are reports on improvements in cholesterol, BP and smoking in several countries<sup>42,48</sup>. However, the beneficial effects of these changes are somewhat offset by an increasing number of diabetics, obese and sedentary subjects. SBP decreased by 2 – 3 mmHg in 25 years<sup>5</sup>. Theoretically a decrease of this size equals a 7-10 % decrease in coronary mortality and a 10-15 % decrease in stroke<sup>14,15</sup>. A decrease in all-cause mortality is also to be anticipated<sup>12,98</sup>. So a seemingly minor change in population SBP has a huge impact on population life expectancy.

Cox proportional-hazard regression analyses were performed after subdividing the populations into 10-years age groups. In all age-groups the following factors were significantly associated with all-cause mortality: age, gender, smoking status, systolic BP, diabetes and physical exercise. In addition, cholesterol and BMI were predictors in the age group 60-69 years and in the age group 70-79 years. Thus, SBP is a significant predictor of all-cause death in all age groups<sup>8</sup>.

The result from the study on mortality show that consistently with the Gubbio study<sup>99</sup>, the CCHS population experienced decreasing all-cause mortality<sup>8</sup>. The SBP decrease is not evenly distributed throughout the population. The cohorts of young and middle-aged gained a larger SBP decrease than the elderly and old<sup>7</sup>. The very young part of a population has a low 15-years mortality risk, and they die mainly of injuries<sup>98</sup>. The number of young subjects in the CCHS population is too low to evaluate any trend in mortality. However, the young/middle-aged part of the population experienced a decreasing SBP followed by a decrease in all-cause mortality. The elderly and old part of the population experienced a somewhat decreasing SBP that was partly explained by selection bias (page 9). The elderly and old part of the population did not experience a mortality risk reduction.

These results may indicate an association of decreasing SBP and declining mortality risk in age-specific cohorts of the population, which points to a role of SBP in age-cohort differentiated improvements in life expectancy.

The trend in mortality risk is not explained by a changing risk associated to SBP. The results of the survival analysis showed that a given risk-factor adjusted SBP-value, for instance 150 mmHg, is associated to the same level of risk in survey 1 as in survey 3. Thus a high SBP is as dangerous as it always was, and prevention of high BP and hypertension is still very important. Consequently, the results from the survival study underline the importance of the observed SBP changes.

### The treated population

Hypertension control is evaluated by the frequency of treated individuals, by treatment success and by the trend in treated SBP. The European Hypertension guidelines recommend starting pharmacological treatment after an evaluation of individual risk<sup>58</sup>.

**Figure 19. Percent treated**

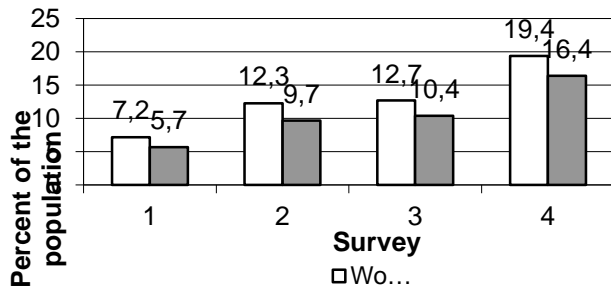


Figure 19. The proportion of treated subjects increased survey by survey. More women than men are treated for hypertension.

In survey 1 6.5% of the total population took antihypertensive medicine. 25 years later, 18.1% of the total population took antihypertensive medicine (Figure 19) ( $p < 0.0001$ ). However, many are still untreated. Figure 20 shows that nearly half of the study population were hypertensive (SBP > 139 mmHg and/or treatment for hypertension). The trend towards an increasing number of treated hypertensives has been reported in other western countries as well<sup>100-104</sup>.

**Figure 20**

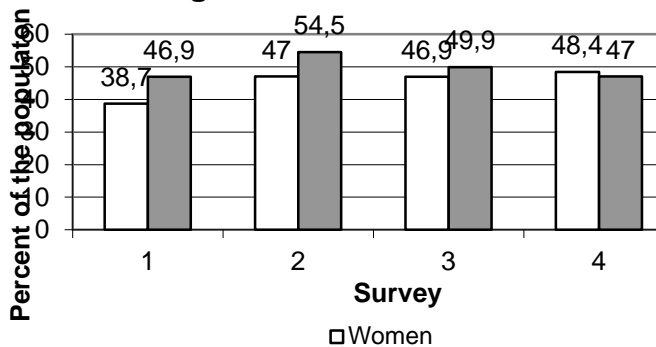


Figure 20. Crude data showing the percentage of subjects with SBP > 139 and/or treated subjects.

The value of SBP<sub>treated</sub> is used as an indicator for hypertension control in the treated population. Hypertension control is a collection of topics that includes guidelines, available medicine, physicians attitude towards hypertension treatment, systematic control, patient awareness and patient compliance. Age-adjusted SBP<sub>treated</sub> was 157.9 mmHg (SE: 1.00) in survey 1 and decreased to 148.7 mmHg (SE: 1.00) in survey 4 ( $p < 0.0001$ ) (Figure 21). The frequencies of hypertension control increased from 21% in survey 1 to 26% in survey 4 ( $p = 0.0002$ ). The frequency of well-controlled hypertensives was low compared to most of the reported frequencies in Denmark and in other western countries<sup>25,27,58,100,101,104-110</sup>. One explanation for that may be that CCHS

focused on general health when addressing the patients whereas several of the other studies intended to investigate blood pressures and hypertension control and thereby indirectly reminding the patients to take their antihypertensive medication in a period up to the examination.

**Figure 21. Trend in treated SBP**

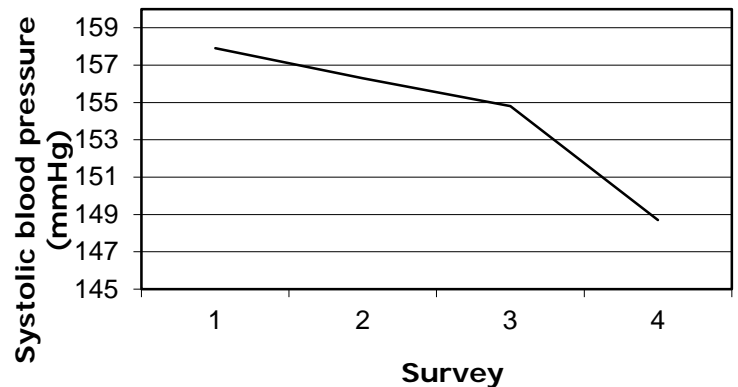


Figure 21. In 25 years, risk-factor adjusted SBP<sub>treated</sub> decreased by 9.2 mmHg ( $p < 0.0001$ ).

### Pre-treatment SBP

Before accepting the decreasing treated SBP as a result of improvements in therapy, a possible change in start-to-treat practice has to be evaluated. If practice changed towards starting medication at a lower SBP, then the value of SBP in the treated population would decrease. Therefore pre-treatment SBP was investigated as an indicator for start-to-treat practice. It was evaluated in an analysis of SBP in patients that started antihypertensive therapy in the next survey. The result was a stable pre-treatment SBP. Risk-factor adjusted pre-treatment PBP was 148.2 (SE 1.00)/90.0 (SE 0.24) mmHg and did not change significantly in the observation period. The mean age was 64 years. The observed threshold values reflected general practitioners self-reported hypertension treatment practice very well<sup>111,112</sup>. Some details are worth noting concerning pre-treatment SBP. Men, elderly or obese subjects are taken later into treatment than women, young and non-obese subjects.

Two persons interact in the start-to-treat practice: the patient and the physician. We know from reports on GPs' practice that women, obese and elderly visit their GP more often than men, non-obese and young persons<sup>112-117</sup>. Patients who visit their GP frequently are more likely to have their BP measured and to start antihypertensive therapy<sup>114</sup>. The added sum of knowledge from the start-to-treat values and the frequencies of visits to GPs may give indirect evidence of physicians' reluctance to start treatment in the elderly and in the obese and of men's reluctance to visit their physician, thereby delaying the first measurement of BP.

### Determinant factors for treated SBP

In addition to the analysis of pre-treatment SBP, several potential determinant factors have been evaluated in the longitudinal model for trend in treated SBP. Two factors (age and the diagnosis of myocardial infarction) contributed significantly to treated SBP.

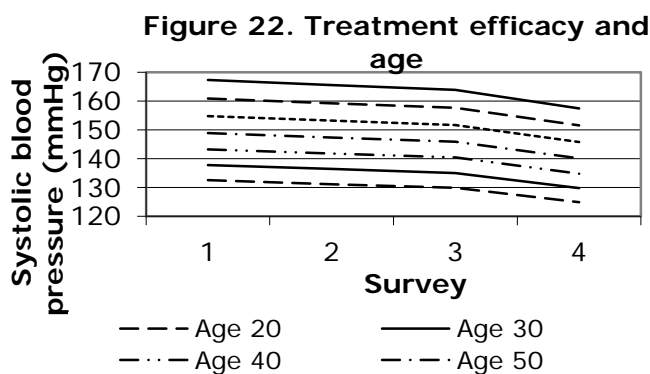


Figure 22. Individuals of all ages gained an improvement in treatment. Hypertension treatment is most effective in patients of younger age. The graph represents estimates from a post-hoc analysis.

In comparison with younger patients, elderly patients are treated poorly (Figure 22). In survey 4, SBP in the 80 years old hypertensives was 157.4 mmHg (SE: 1.00) whereas SBP in 40 years old hypertensives was 134.8 mmHg (SE: 1.00). In survey 4, the corresponding rates of effective treatments were 44.8% in the group of 40-49 years old hypertensives and 18.2% in the group of 80-89 years old patients ( $p=0.001$ ).

The tendency towards poor control of the elderly is reported in all other hypertension control studies<sup>118,119</sup>. It may be the remnants of the “100 + age” rule that was previously standard in hypertension control. European guidelines now recommend treatment to target goal also to the elderly<sup>58</sup>. It may be argued that it is difficult or impossible to treat old hypertensives with a high number of risk factors. However, treatment of elderly is possible and beneficial<sup>120</sup>.

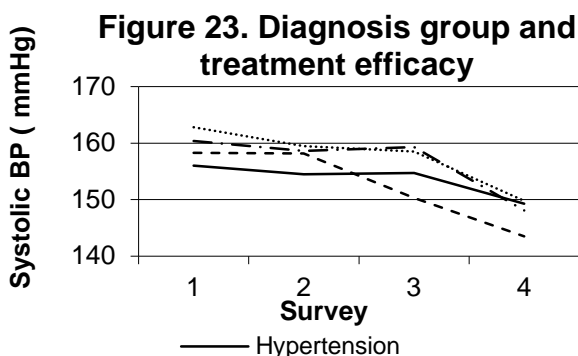


Figure 23. Treatment efficacy is significantly better in the group of post-MI patients in comparison with stroke-patients, post-MI- and stroke-patients or patients without these diagnoses. Results from a post-hoc analysis of the diagnosis effect in the treated population.

The second determinant factor for effective antihypertensive treatment was the variable ‘diagnosis’. ‘Diagnosis’ includes four possible diagnoses: myocardial infarction, stroke, both, or none of the two diagnoses among the treated hypertensives (Figure 23). The diagnoses of myocardial infarction and stroke were taken from the National Patient Registry. A diagnosis of myocardial infarction required the presence of at least two of the following criteria: characteristic chest pain, elevated cardiac enzymes, or electrocardiographic changes indicative of myocardial infarction. The degree of agreement between the diagnosis myocardial infarction and information from the medical records was investi-

gated and validated<sup>121</sup>. Therefore the cases of myocardial infarction were not re-evaluated. The stroke events, however, needed a re-evaluation. An experienced neurologist reviewed all potential cases of intracerebral vascular disease. Possible ischemic stroke events were validated using the WHO definition of stroke: an acute disturbance of focal or global cerebral function with symptoms lasting > 24 hours or leading to death with presumably no other cause than of vascular origin. To distinguish between infarction, intracerebral haemorrhages and subarachnoid haemorrhages, either a CT or an MRI scan, autopsy, spinal fluid examination, or surgical description was necessary.

Age-adjusted SBP did not differ significantly between the diagnosis groups at baseline. However, group 2 (myocardial infarction) showed a different slope in SBP over time as compared to the three other diagnosis groups. In survey 4 group 2 had a significantly lower age-adjusted SBP. In survey 4 the corresponding rates of effective treatments were 37.5% for diagnosis group 2 compared to 24.7% for diagnosis group 1 ( $p=0.003$ ). It has been observed by others that ischemic heart patients are better treated than other hypertensives<sup>114,118</sup>. This can not be explained by an increasing number of surviving heart failure patients. An efficient treatment for heart failure was established in the late 1990’s, and before that time-point the mortality was very high among heart failure patients. A possible explanation is that cardiologists differed from other physicians in their approach to hypertensive patients by offering a new element in treatment. The nature of the new element is not known. It may be the rehabilitation clinics that were introduced in the 1990’s in addition to invasive treatment. The rehabilitation clinics offer the hypertensives a systematic control during a limited time after a myocardial infarction<sup>122,123</sup>. A similar systematic control is not accessible to stroke patients, and it is not provided by all general practitioners<sup>123</sup>.

#### Non-significant factors

There is a pattern of significant and non-significant factors that characterise trend in hypertension treatment practice. A very large number of potential determinant factors were evaluated in a stepwise selection procedure, but they did not contribute significantly to the longitudinal data structure: gender, alcohol intake, smoking, plasma-cholesterol, marital status, family structure and BMI. A metabolic index was defined as one or more of the following: diabetes, BMI > 27.0, cholesterol > 5.0 mmol/l and treated hypertension. Diabetes and the metabolic index were without importance for trend in treatment success. Level of income and level of school education were not relevant factors for trend in antihypertensive treatment efficacy. This information may indicate that medicine costs and level of information are of minor importance in hypertension treatment.

#### Factors that are not investigated

In addition to the above mentioned patient-related factors, there are a number of non-patient-related factors that determine whether an antihypertensive strategy is successful or not. The physician’s role is important<sup>119,124</sup>. The selection of antihypertensive drugs is important in respect to effective BP lowering, side-effects, and problems in multi-drug regimes. An important factor is the production of new antihypertensive agents. The ACE-inhibitors and calcium antagonists were introduced in the 1990’s and several other effective antihypertensive agents came hereafter. Thus, the observation period is characterised with a shift from only weak antihypertensive agents available to a variety of weak and potent antihypertensive agents on the pharmaceutical market. There is now an electronic registry of prescriptions. It has

been available for almost 10 years and therefore interesting but at present not in CCHS longitudinal studies. The health care policy in the country and the system that manages hypertensives<sup>122</sup> are important as well. These factors cannot be investigated in the CCHS.

#### Treated DBP

Treated DBP was stable. Except for gender differences, there was no other determinant factor for treated DBP.

### **Perspectives**

The results from this thesis may be incorporated in population health strategies. The result that show decreasing population SBP and the result that young people start adult life with SBP lower than the preceding generations of young people are very important because they may tell the story that hypertension epidemic in present time may disappear and leave only the hypertensives suffering from hypertension based on genetic factors. Age and gender are non-modifiable factors but obesity is a modifiable factor. An obesity epidemic may threaten the beneficial trend in population SBP. The gap between low-income and high income women in the country is characterised with a gap in SBP and – more importantly – with a difference in trend lines that foretells that the gap in SBP will increase by time. Only the well-off women will increase their health by continuing economic growth. If the society wants increased population health (and lower budget for hospitals and nursing homes), it has to change social environment and secure a healthy life style for all citizens. Treated SBP decreased 9 mmHg and was 148 mmHg in the last survey. The decrease mirrors the increasing selection of antihypertensive medicine very well. But the analysis of patient-related factors revealed that a large selection of effective medicine is not enough. Daily hypertension treatment practice present serious weaknesses: Few are treated; only 26 % of the treated subjects are treated effectively. Elderly are treated ineffectively and there are treatment differences between hypertensives with different concomitant diseases.

### **Summary**

Strategies to reduce the burden of blood pressure attributable diseases require knowledge of secular trend in PBP and its determinants. The issues were investigated in the Copenhagen City Heart Study. The design of CCHS is a repeated measures study. Such designs are uniquely suited to studying changes of an outcome and what risk factors may be associated with that outcome. Repeated measures studies are very well suited for trend analysis by using mixed effect analyses. SBP decreased about 2 mmHg in 25 years. The risk factors age, gender and BMI was found valid as determinant factors for secular trends in SBP. In addition, the following factors were identified: household income and the interactions 'gender\*age' and 'survey\*age'. The interaction 'gender\*age' stated that the difference between SBP in the two genders was great in the young individuals and diminished by age. The interaction 'survey\*age' stated that SBP in the young individuals decreased more with survey than SBP in the older individuals. Thus, the 20 years old subjects in survey 2, 3 and 4 have lower SBP than the 20 years old subjects in preceding surveys. The slopes were less steep in higher ages. In the group of elderly and old subjects the trend is partly explained by treatment bias because more and more subjects leave the untreated group and start treatment. The factor 'household income' was significant only in the female population and stated that high-income women had lower SBP and a more

beneficial secular trend in SBP than low-income women. Marital status, self-reported physical exercise and alcohol intake were not significant factors. A number of factors, that are interesting in relation to SBP, were not included in the CCHS and therefore not investigated. Among them are salt intake, childhood factors, genetic factors and the DASH diet.

A survival study was performed to investigate the mortality rate in relation to SBP changes during the observation period. A Cox regression analysis was used in this study. The survival study demonstrated that SBP was a significant variable in survival models for all age groups. There was a decrease in mortality rate in young to middle-aged individuals. The mortality rate that is associated with a particular value of SBP did not change. Thus, it was concluded that SBP was as dangerous as it has always been and that the reduction in mortality rate was most pronounced in the age classes that also experienced the greatest reduction in blood pressure.

During the observation period the number of treated individuals in the population increased from 6.5 % to 18.1 %. About 50 % of the population was hypertensive (SBP $\geq$ 140 mmHg or treated with antihypertensive medication).

The value of SBP<sub>treated</sub> was used as an indicator for hypertension control in the treated population. Hypertension control is a collection of topics that includes guidelines, available medicine, physicians attitude towards hypertension treatment, systematic control, patient awareness and patient compliance. The analysis of trends in SPB in treated hypertensives showed that SBP<sub>treated</sub> decreased 9.2 mmHg in 25 years. The result may be ascribed to improvements in treatment but may also be caused by a change in start-to-treat practice: If hypertensives start treatment at an increasingly lower SBP<sub>threshold</sub> then SBP<sub>treated</sub> will decrease without improvements in treatment. Therefore the start-to-treat practice was evaluated by SBP<sub>threshold</sub>. A change in SBP<sub>threshold</sub> was not observed. Thus, the 9.2 mmHg decrease in SBP<sub>treated</sub> may represent improvements in treatment. 'Age' was a significant factor for SBP<sub>treated</sub>. This result demonstrated that elderly and old individuals were treated less successful than young and middle-aged individuals.

Subjects diagnosed with ischemic heart disease constitute a group with a more advantageous slope than subjects with other diagnoses (stroke, IHD in combination with stroke, and hypertension alone).

Self-reported physical exercise, gender, alcohol intake, household income and family structure were not significant as variables in the decreasing SBP among treated hypertensives.

Thus, the papers in this thesis described SBP trends in the untreated and in the treated part of a population. Different patient-related factors were identified as determinant factors for trends in the two groups. The determinant factors are the explanatory variables most associated with trends in SBP. The determinant factors were different for the two groups (except for age).

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