Medizinische Fakultät
der
Universität Duisburg-Essen

Aus dem Institut für
Medizinische Informatik, Biometrie und Epidemiologie

Blood Pressure Distribution in the German Population

INAUGURAL-DISSERTATION

Zur

Erlangung des Doktorgrades der
Naturwissenschaften in der Medizin
durch die Medizinische Fakultät
der Universität Duisburg-Essen

Vorgelegt von
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2012

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Tag der mündlichen Prüfung: 26. April 2012

Previous conference presentations and manuscripts from this work

Manuscripts

Balijepalli C, Lösch C, Bramlage P, Erbel R, Jöckel. K-H, Moebus S. Percentile distribution of blood pressure readings in 35,683 men and women aged 18 to 99 years. Submitted to “Clinical Research in Cardiology” April. 2012.

Conference abstracts

C Balijepalli, S Moebus, C Lösch, A Scherag, KH Jöckel. Blood pressure distribution according to age and sex in the German Metabolic and Cardiovascular Risk Study with 35869 participants. German Society for Medical Informatics, Biometry and Epidemiology 55th annual conference , 5-9 September 2010, Mannheim, Germany. Abstract number: 114

C Balijepalli, S Moebus, C Lösch, A Scherag, KH Jöckel. Blood pressure distribution according to age in a study population of 35,869 participants aging 18 to 99 years. German society for Epidemiology 5th annual conference, 21-25 September 2010, Berlin, Germany. Abstract number: 216

C Balijepalli, C Lösch, S Moebus. In Germany fifty percent of male primary care patients aged 18 to 99 years presented with elevated blood pressures in the prehypertensive state: The German Metabolic and Cardiovascular Risk Study (GEMCAS). International Conference on Prehypertension and Cardiometabolic Syndrome , 24-27 February 2011, Vienna, Austria.

C Balijepalli, C Lösch, S Moebus. Prevalences of Elevated Blood Pressure and the Age Related Shift of Blood Pressure in German Adult Primary Care Patients: The German Metabolic and Cardiovascular Risk Study. Nutrition, Physical Activity and Metabolism / Cardiovascular Disease Epidemiology and Prevention 2011 Scientific Sessions, March 22-25, 2011, Atlanta, USA. Abstract number: P340

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Chapter 1

Introduction

1.1 Physiology of blood pressure

The cardiac events that occur from the beginning of one heartbeat to the next one are called as cardiac cycle. It consists of systole, a phase in which heart contracts to eject the blood. The systole is followed by a phase called as diastole during which the heart tends to relax and fills itself up (Guyton and Hall 2006).

The circulatory system is categorised into 'systemic circulation' which is otherwise called as peripheral or greater circulation, it supplies to all the tissues of the body except the lungs, which are supplied by the pulmonary circulation. Arteries are the vessels that carry the blood away from the heart under high pressure and therefore arterial walls are stronger, where the blood flow will be rapid (Guyton and Hall 2006).

Blood pressure - definition

Blood pressure "means the force exerted by blood against any unit area of the vessel wall" (Guyton & Hall 2006, p. 166), it is generally measured in millimetres of mercury (mmHg) for example a 100 mmHg of blood pressure means, the force exerted by this blood would be sufficient to push a column of mercury up to a level of 100 mm. As the heart pumps the blood directly into the aorta in a pulsatile manner, the arterial pressure in the aorta varies between 120 mmHg during the systole and 80 mmHg during a diastole. During the systemic

circulation, the pressure of blood falls progressively, before the blood enters the heart through venae cavae its pressure is 0 mmHg. In general the arterial pressure is controlled by either local tissue perfusion control or control of cardiac output (Guyton and Hall 2006).

Each blood vessel, be it an artery or a vein has the capability to distend, but as the walls of arteries are stronger and less elastic, they distend less, and the veins distend almost 8 times as much as the arteries. The distensibility of the vessels serves as an important function, in which it allows the blood to flow through the tissues in both cardiac systole and diastole (Guyton and Hall 2006).

Systolic and diastolic blood pressures

The blood pressure at the height of each pulse is called as the systolic blood pressure (SBP). In a normal young adult its value is usually 120 mmHg. The blood pressure at the lowest point of the pulse is called as diastolic blood pressure (DBP) and in normal young adults it is about 80 mmHg. The difference between SBP and DBP is called as pulse pressure (PP) (Guyton and Hall 2006,).

Regulation of Blood pressure

The flow of blood through the system is represented by the blood pressure, and hence when the rate of blood flow is regulated, blood pressure will also be regulated. The blood flow control to any tissue could happen in two ways,

a) acute control and b) long term control. Acute control is achieved as a quick response to constriction of the arterioles and metarterioles. Long term control occurs due to slow changes in the flow over a period of time due to the tissue needs (Guyton and Hall 2006).

The autonomic nervous system (CNS) plays a crucial role in the regulation of blood flow and thus helps in the short term regulation the blood pressure. The

baroreceptors are extremely quick in buffering blood pressure changes (Hall JE. 1999). The most important nervous mechanisms by which arterial pressure is controlled is the barorecptor reflex, this reflex is elicited by the baroreceptors present on the walls of large arteries. In case of sudden increased pressure, the baroreceptors are stretched and they transmit the signals to the central nervous system, which replies through a 'feedback' signal through the autonomous nervous system leading to a fall in the arterial pressure (Guyton and Hall 2006).

Although nervous control of arterial pressure is one important mechanism to control ischemia due to decreased blood flow, the CNS response to decreased arterial pressure can only be observed in pressures that are below 60 mmHg, and maximum CNS response can be elicited if the pressure falls to as low as 15-20 mmHg, during which perfusion to the brain might be minimal and close to being lethal. If cerebral ischemia persists due to a low blood pressure, the neuronal cells will suffer metabolically and within 3 to 10 minutes they might as well become inactive, and when the ischemia still continues at the same rate, the neuronal cells might die within 20 to 60 minutes (Guyton and Hall 2006).

Long term control of blood pressure is maintained using different physiological mechanisms like the Renal-Body fluid feedback: The balance between the intake and output of fluids in the body determines the extracellular fluid volume and the extracellular fluid volume in turn maintains the blood pressure. The renin-angiotensin-aldosterone system and the pressure natriuresis mechanisms help in regulating the renal excretion of salt and water (Hall JE. 1999).

Humoral regulation of the circulation is an important mechanism to regulate blood flow with the help of substances released into the body, either from glands or from local tissues. These substances are classified into

1. Vasoconstrictors – substances that constrict the blood vessels thereby increase the blood pressure. Examples: Norepinephrine, epinephrine, vasopressin, angiotensin and endothelin.
2. Vasodilators – substances that dilate the blood vessels, there by decrease the blood pressure. Examples: Bradykinin, serotonin, histamine and prostaglandins.

The central nervous system (CNS) also plays a crucial role in the regulation of blood flow and thus regulates the blood pressure. The capabilities of the nervous system for the control of arterial pressure are rapid and usually short term. The most important nervous mechanisms by which arterial pressure is controlled is the barorecptor reflex, this reflex is elicited by the baroreceptors present on the walls of large arteries. In case of sudden increased pressure, the baroreceptors are stretched and they transmit the signals to the central nervous system, which replies through a ‘feedback’ signal through the autonomous nervous system leading to a fall in the arterial pressure (Guyton and Hall 2006).

1.2 Blood pressure and age

Changes in the cardiovascular function with aging was studied from as early as 1809 and various theories have been put forward to explain the physiological responses of cardiovascular system with aging (Nichols et al. 1985).

Increase in the systolic and diastolic blood pressure with age has been consistently demonstrated by the results obtained from the well-known

Framingham Heart Study and other studies (Rodriguez et al. 1994, Kannel 2000, Vasan et al. 2001). The age-related rise of blood pressure has primarily been studied and discussed with respect to hypertension and risk for cardiovascular diseases (CVD). In a report by Franklin and Weber (1994) the 'vascular overload' concept to assess the hypertensive cardiovascular risk was discussed. They argued that hypertensive cardiovascular risk is related to three circulatory abnormalities, increased arteriolar resistance, increased large artery stiffness, and early reflection of pulse waves. These three mechanisms together were referred as 'vascular overload'. Increased arteriolar resistance is associated with increased systolic, diastolic and mean arterial pressures, even in the younger subjects. According to Franklin and Weber (1994) with advancing age a rise in the arterial stiffness occurs. Increased large artery stiffness is associated with increased systolic pressure and also a simultaneous decrease in the diastolic pressure. An inelastic or stiff aorta due to aging leads to a diminished reservoir effect at the end of the cardiac systole, thereby it contributes to diminished diastolic pressure. Young to middle aged hypertensive subjects have a combination of increased arteriolar resistance and increased arterial stiffness which contributes to more rise in systolic pressure compared to diastole with age. As the age advances there is a large rise in the arterial stiffness and a varied arteriolar resistance, this contributes to the isolated systolic or systolic and diastolic hypertension. Also aging and hypertension lead to increase pulse wave velocity which in turn leads to early pulse wave reflection. This increased arterial stiffness combined with early wave reflection result in an increased systolic blood pressure and a decrease in diastolic blood pressure, especially in the elderly subjects (Franklin and Weber 1994).

Whelton (1994) found in most surveys, that SBP tends to rise progressively throughout childhood, adolescence and adulthood to reach an average value of 140 mmHg. Although the DBP also rises with age, the rate is not as steep as for the SBP. This leads to widening of pulse pressure and more common isolated systolic pressure (Whelton 1994).

1.3 Impact of systolic and diastolic blood pressure on CVD

With regard to the prognostic and therapeutic importance of the SBP and DBP for CVD a debate over many centuries has been carried out. For example, researchers in the eighteenth and the early nineteenth centuries associated the 'increased arterial pulse tension' with hypertensive cardiac and renal sequelae like 'dropsy' and 'nephritis'. In 1874 Fred Mahomed noticed that in subjects with albuminuria, high tension in the arterial system coexisted. In the 10th edition of Osler's classic medical textbook in 1925, normal BP was considered to be 120-130 mmHg and 130-150 mmHg if the age is over 50 years. In 1927 Cecil's classic American textbook of medicine stated that systolic pressures of over 250 mmHg are quite common and emphasised the importance of diastolic pressure increases for the diagnostic as well as prognostic purposes. The same text book in the sixth edition in 1943 emphasised on the importance of mean arterial pressure along with the diastolic pressure (Rutan et al. 1989).

Historically, elevated systolic blood pressure was always considered to be an inevitable outcome that occurs due to arterial stiffening especially in the elderly. When it comes to hypertension, its severity was defined previously with the level of diastolic blood pressure until the Framingham Heart study that started in 1948. The results of Framingham study repeatedly showed that systolic blood pressure

was a better marker for cardiovascular disease than diastolic blood pressure especially middle and older age subjects (Kannel 1999).

Prospective studies like the Chicago stroke study (Shekelle et al. 1974), and a study by Rabkin and coworkers. (1978) also showed that a stronger association of SBP than DBP was found for the risk of stroke (Shekelle et al. 1974, Rabkin et al. 1978). Studies like the Western Collaborative Group Study and a Canadian study showed that SBP was found to be a stronger predictor of CHD than mean arterial pressure (MAP) and DBP especially in the subjects who were under 50 years of age (Rosenman et al. 1976, Rabkin et al. 1978). Other prospective studies like the Honolulu Heart Program and the Whitehall Study showed that SBP was more strongly related to the CHD mortality than DBP (Yano et al. 1983, Lichtenstein et al. 1985). A meta-analysis by Staessen et al. (2000) found that a 10 mmHg rise in systolic hypertension is correlated with a 10% increase in all fatal and nonfatal cardiovascular complications (Staessen et al. 2000). Another meta-analysis by He and Whelton (1999) showed that the association between SBP and CHD, stroke and end-stage renal disease was continuous, graded and independent. It also showed that the association of SBP with these outcomes is stronger than that of DBP (He and Whelton 1999).

Interestingly a study that was conducted by Franklin et al. (2001), using the Framingham data with the subjects free of CHD and aged between 20 and 79 years showed that, with increasing age, there was a gradual shift from DBP to SBP and then to PP as predictors of CHD risk. In patients who were younger than 50 years of age, DBP was the strongest predictor for CHD. In the age group of 50 to 59 years all the three BP components (SBP, DBP and PP) were comparable predictors of CHD and in subjects aged above 60 years, DBP was negatively

related to CHD risk and PP became superior to SBP in CHD risk prediction (Franklin et al. 2001).

Domanski et al. (2002) analysed the data from the Multiple Risk Factor Intervention Trial (MRFIT) and compared the relationships of SBP, DBP and PP separately and jointly, with cardiovascular disease related mortality in men. They reported that CVD risk assessment was improved by considering both SBP and DBP not SBP, DBP or PP independently (Domanski et al. 2002).

Franklin and co-workers (2009) showed from the Framingham data that, combining PP with MAP and SBP with DBP produced models that were superior to single blood pressure components for predicting CVD. They also concluded that, combined SBP + DBP, and combined MAP + PP were equally predictive of CVD risk (Franklin et al. 2009)

Although a great amount of research was carried out on blood pressure and CVD risk, uncertainty still exists regarding the relative importance of various components of blood pressure in predicting the CVD risk and controversy still persists about which blood pressure component plays a superior role in predicting CVD.

1.4 Blood pressure level and risk for cardiovascular disease

It is undisputedly established that hypertension is associated with CHD and CVD. The nature of this relationship is well studied. As early as 1969 Kannel et al. from the Framingham Heart Study assessed the relationship between blood pressure and clinical manifestations of CHD with respect to age. They concluded that risk of manifestations of CHD is related to both antecedent systolic and diastolic blood pressure. The risk was also proportional to the level of blood

pressure even at non hypertensive blood pressures levels. Elevated SBP even after the age of 50 years showed a substantial increase in risk of CHD (Kannel et al. 2009).

The relation between blood pressure and CHD manifestations has been consistently proven in studies conducted on both sexes and in people with diverse geographic, cultural and ethnic backgrounds (Whelton 1994). It was also well proven that high blood pressure is a cardiovascular disease risk factor independent of the other risk factors that are associated with CVD (Whelton 1994, Kannel et al. 2009).

Although it is known that the risk of CVD increases with increasing blood pressure there has always been a question about the threshold level of blood pressure above which it is considered as abnormal for the individual. Thus there has been always a need to classify the blood pressure with respect to the level of risk so as to enable the physicians to set up therapeutic goals.

Vasan et al. (2001) investigated from the Framingham cohort study, the association between blood pressure categories at baseline and incidence of cardiovascular disease in Framingham study participants. They concluded that high normal blood pressure (SBP of 130 to 139 mmHg or a DBP of 85 to 89 mmHg) is also associated with an increased risk of cardiovascular disease. Thus, questioning the need to see, if lower high-normal pressure can reduce the risk of CVD (Vasan et al. 2001). The Prospective Studies Collaboration, which had done a meta-analysis with one million adults using 61 prospective studies, concluded that, throughout the middle and old age blood pressure is strongly and directly related to vascular mortality and without any evidence of a threshold down to at least 115/75 mmHg (Lewington et al. 2002). Port et al. (2000) using the

Framingham data challenged the concept that lower blood pressures imply lower risk and using a cut off value of 140 mmHg for all adults. They concluded that, there is an age-dependent and sex-dependent threshold for hypertension (Port et al. 2000).

However, Kannel et al. (2003) in a review stated that, "*there is an overwhelming evidence of a continuous, graded influence of SBP on CVD morbidity and mortality at all ages in both sexes. An optimal BP for avoiding CVD is <140/90 mmHg, and there is no clearly defined critical BP that distinguishes normal from abnormal*" (Kannel et al. 2003, p. 455).

Kshirsagar et al. (2006) analysed the data from the Atherosclerosis Risk in Communities Study and found that "*individuals with prehypertensive levels of blood pressure have an increased risk of developing cardiovascular disease relative to those with optimal levels*" (Kshirsagar et al.2006, p. 133).

Main reason of this long-lasting and controversial debate might be based on the fact that blood pressure is a physiological process and a thus continuous entity. Therefore the construct of a strict threshold to distinguish between normal and abnormal values does not in all cases reflect real physiological processes.

1.5 Risk of progression to hypertension

As it was known that blood pressure progresses with age, studies have been conducted to analyse the progression of normal blood pressure and prehypertension into hypertension.

Leitschuh et al. (1991) analysed the blood pressure data from the Framingham study, and concluded that the individuals who have high normal blood pressure i.e. a DBP of 85-89 mmHg had a 2-3 fold higher probability of

developing hypertension, when compared to the individuals with normal blood pressure (DBP <85 mmHg) (Leitschuh et al. 1991).

Vasan et al. (2001) confirmed from their data that high normal BP and normal BP tend to progress to hypertension over a period of 4 years, this was predominantly found in older adults (Vasan et al. 2001).

Jimenez-Corona et al. (2007) followed 1572 non hypertensive subjects aged between 35 and 64 at baseline for a median period of 5.8 years and found that there was a significant association between BP levels at baseline and hypertension incidence even within the normotensive subjects (Jimenez-Corona et al. 2007).

1.6 Measurement of Blood pressure

The gold standard for the measurement of arterial blood pressure is the direct intra-arterial measurement using a catheter. However, due to the impracticability of this technique for day to day practice and for the majorities of studies indirect methods for blood pressure measurements, mainly the oscillometric and auscultation technique are used. The methodology for the indirect method of blood pressure measurement was first reported in 1896 by Riva-Rocci, an Italian physician. He described the physical principles involved in the measurement of the arterial pressure using a mercury manometer. In 1905 Korotkoff for the first time reported about the measurement of blood pressure using a stethoscope (Booth J 1977). The indirect ausculatory method determines a certain pressure level which is required to collapse the arteries either in the upper arm or the leg using a sphygmomanometer. The cuff of the sphygmomanometer is wrapped around the arm or the leg and inflated to a pressure level above that of

the arterial pressure, which is indicated by the obliteration of the arterial pulse. As the pressure in the cuff is released gradually by deflating the cuff, the pressure at which the arterial pulse waves produces sounds (Korotkoff sounds) that can be heard using a stethoscope is noted this is the systolic blood pressure. As the pressure in the artery drops down further the pulse wave sounds disappear, this pressure is the diastolic blood pressure (Perloff et al. 1993).

The size and dimensions of the bladder and cuff of the sphygmomanometer are important in determining the correct values of blood pressure. The length and width of the bladder and their ratio are important. Acceptable standards of the width of the bladder are 40% of the arm circumference, and for the length of the bladder are 80% of the arm circumference in adults.

Automatic devices measure the blood pressure using oscillometric and auscultatory techniques. The oscillomteric method detects the blood pressure based on the oscillations on the lateral walls of the occluded artery. The oscillations begin at the systolic blood pressure and reach the greatest amplitude at the mean arterial pressure. The diastolic blood pressure is a derivative of SBP and mean arterial pressure (Perloff et al. 1993).

The auscultatory method does not yield exact results, but gives values within 10% of those determined by direct measurement from the arteries (Guyton and Hall 2006). The auscultatory technique using Korotkoff sounds gives slightly lower systolic and slightly higher diastolic blood pressure values when compared to intra-aterial measurements of blood pressure (Jones et al. 2003). The oscillometric method is based on detecting the oscillations on the lateral walls of an occluded artery as the pressure is deflated in the cuff. SBP measurement by these devices is accurate but the DBP may not be. (Perloff et al. 1993)

Although practical, the indirect measurement of blood pressure has its own problems of accuracy. According to Jones and co-workers (Jones et al. 2003) the indirect measurement has accuracy problems for at least 3 reasons:

1. Inherent biological variability
2. The white coat effect
3. Inaccuracies due to suboptimal technique.

1.7 Secular trends of blood pressure

1.7.1 Global trends

Blood pressure as risk factor for CVD was always well studied. However the lion's share of research considers blood pressure in terms of hypertension, assessing prevalence, treatment and control of hypertension in diverse populations.

Studies from different parts of the world examined trends of high blood pressure prevalences. Most studies from the U.S. used data from the different National Health and Nutrition Examination Surveys (NHANES) to examine the trends in the prevalence of hypertension. Burt et al. (1995) described the secular trends of the distribution of blood pressure and prevalence of hypertension in the US adults, using NHANES data from 1960 to 1991. They concluded that "*hypertension prevalence in the United States has declined progressively since 1971 and the distributions of systolic and diastolic pressures have shifted downward during the approximately 30-year period between 1960-1962 and 1988-1991*" (Burt et al. 1995, p. 60). Hajjar and Kotchen (2003) also using the NHANES data described the trends of hypertension prevalence in the US between 1988 and 2000. Contrary to the previous findings, they observed that hypertension

prevalence has increased in the US between 1988 and 2000 (Hajjar and Kotchen 2003).

Hypertension prevalence and secular trends have been extensively studied in the European populations, too. Banegas et al. (1998) studied the distribution of blood pressure among the Spanish population and found that 50% of Spaniards aged between 35 and 64 years were hypertensive and 10% had either isolated systolic or isolated diastolic hypertension (Banegas et al. 1998). Asmar et al. (2001) assessed the prevalences of high blood pressure by using the data of 61,108 French subjects and found that more than a third of men and nearly a quarter of women had high blood pressure (Asmar et al. 2001).

1.7.2 Trends in Germany

There are a number of studies determining the blood pressure in the German population. All of them examined blood pressure readings as a risk factor for CVD, focussing their work on the assessment of the prevalence, treatment and control of hypertension in the German population. None of the German studies reported the distribution of the blood pressure readings.

Hense (2000) examined the trends in the prevalence of hypertension in KORA, a population based study conducted in Augsburg in southern Germany. He concluded that between 1984 and 1994 the prevalence of hypertension in the Augsburg population was relatively constant (Hense 2000). Gasse et al. (2001) analysed blood pressure data from the same study and concluded that the age adjusted prevalence of hypertension between 25 and 64 year old subjects did not change significantly, with 39% of men and 25% of women found to be hypertensive (Gasse et al. 2001).

The German National Health Interview and Examination survey 1998 (BGS) reported that hypertension was prevalent in nearly 30% men and 27% women. The prevalence of hypertension was higher in eastern Germany when compared to the West. When compared to the health surveys conducted in 1991, the hypertension prevalence increased in western Germany, where as it decreased in the east. Just like the findings from other studies in the world, the blood pressure data in the BGS also showed that there is a continuous increase in the SBP with age in both sexes (Thamm 1999).

Chapter 2

Aim and Study Questions

As blood pressure is a continuously distributed feature, prevalence estimates are mostly presented as arithmetic means and dispersion around the mean (range, standard deviation). Only a few single estimates are thus necessary to obtain an overview of the central location of the data and to achieve good predictors of the frequency with which a population will be detected as hypertensive.

Nevertheless, epidemiological information throughout the full range of a distribution within populations (i.e. percentiles and subgroups age groups) may prove helpful in obtaining a more detailed picture of blood pressure distributions. For example, it would be interesting to know whether the full range of the blood pressure distribution differs between the age classes, i.e. with greater differences in the blood pressure range in older age groups compared to the younger ones. Furthermore, it would be interesting to know whether the age-related increase in blood pressure occurs in each part of the distribution, i.e. even in the lowest percentile.

As discussed above, even though there were some studies focussing on the blood pressure in the populations, only few studies worldwide and none in Germany examined the percentile distribution of the blood pressure population-wide. Even more, as to my knowledge, there is no publication evaluating blood pressure readings taking into account age, sex and coexisting cardiovascular risk factors.

Main aim of this thesis was to examine the distribution of blood pressure readings in the German population using data from a large cross sectional study sample of 35,869 women and men aged 18-99 years. In a first analysis step following research questions will be addressed

Part 1:

- How are the percentiles of the systolic and diastolic blood pressure distributed in the German population?
- How are the blood pressure percentiles distributed with respect to age-classes and sex?
- Do the percentile distributions of the systolic and diastolic blood pressure observed in the whole study sample differ in a subpopulation without known cardiovascular risk factors?

Part 2:

In a second step, the observed age effects on blood pressure readings in the cross sectional and patient-based GEMCAS study will be reproduced in an independent study sample, the prospective and population-based Heinz Nixdorf Recall study to answer following question:

- Is the magnitude of the age related effects on blood pressure observed in the cross-sectional GECMAS study sample, comparable to that of an independent study sample of a prospective cohort study?

To answer the study questions, data from the German Metabolic and Cardiovascular Risk Study (GEMCAS) and Heinz Nixdorf Recall study were used. GEMCAS offers an excellent data set including a broad age range of 18 to 99 years and a very large sample size that provides sufficient precision even when stratifying the sample into small age groups, sex or presence or absence of CVD

risk factors. The Heinz Nixdorf Recall study as a prospective, population-based cohort study offers an excellent data base to enable verification of the age effects observed in GEMCAS.

Chapter 3

Material and Methods

3.1 GEMCAS

3.1.1 Study design and participant recruitment

GEMCAS is a cross sectional study conducted in October 2005 for two weeks at 1,511 randomly selected primary care physicians from all over Germany. General practitioners and internists with focus on primary health care were selected by a stratified, randomized sampling method to receive a random distribution across all German regions. Physicians specialized in cardiology and/or diabetes were excluded from the study.

All the subjects who were aged 18 years and above visiting the selected primary care physicians during the days on which the study was conducted, irrespective of the reason for their visit were included in the study. The only reasons for exclusion were conditions that made it impossible or highly problematic for the patient to participate (such as poor German language skills, serious disabilities or diseases), acute emergencies, or pregnancies and breast-feeding within the previous three months.

Ethical approval was granted from the ethics committee of the University Hospital, University Duisburg-Essen, Essen, Germany (Moebus et al. 2006).

3.1.2 Data collection

Data were collected through two types of questionnaires. The medical questionnaire was completed by the participating physician or his/ her assistant. It

furnished all the details about age, reason for attendance, anthropometric measurements, pre-existing clinical conditions, medication intake etc. The patient questionnaire had the relevant information about age, medical history, family anamnesis, lifestyle related and socio-demographic variables used in the study Venous blood samples were collected from all the study subjects and shipped to the central laboratory in Berlin (Labor 28, Berlin, Germany) by an assigned courier service. The samples were analyzed for blood glucose levels, total cholesterol, HDL, LDL, and Triglycerides (Moebus et al. 2006).

3.1.3 Blood pressure measurements

Blood pressure was measured using commonly available equipment in the physician's practice. The blood pressure devices used (manual, automatic, brand name) were reported by the physicians. The readings for blood pressure were obtained after a five minute rest with the participant in a sitting position. Accepted epidemiological standards for blood pressure measurements such as a double measurement with at least two minutes of recovery between measurements (i.e. Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) 2007) were not feasible. However, reported measurements here represent physician practices procedures.

3.1.4 Data Quality assurance

The study was planned and conducted according to the German guidelines for Good Epidemiology Practices (GEP) (Hoffmann et al. 2005). The participating

physicians received no other instructions than the information material that was sent to them. A special monitoring system was designed to minimize systematic errors. The monitoring was done in two ways, telephonic and random on-site visits. Telephone monitoring was done at 50% of the enrolled practices prior to the day of survey to make sure that the participating physicians had correct knowledge of the operation procedures and also had all the relevant material needed for the study in the form of questionnaires, other documents and blood sampling materials. Physicians to be included in the monitoring were selected randomly and stratified into three groups. The interviewers rated the monitored site based on standardized interview. Their performance was rated on a scale ranging from one to six, with six being the worst rating. Furthermore, in about 10% of the participating medical practices random on-site visits were performed during the day of survey. These practices were chosen at random prior to the survey. Additionally, a special emphasis was laid on sites that received a poor rating during the telephonic monitoring and where ever possible these practices were included in the list for the on-site monitoring during the survey day (Moebus et al. 2006).

3.2 Heinz Nixdorf Recall study

3.2.1 Study design and aims

The Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcium and Lifestyle) study, henceforth abbreviated as HNR, is a German population-based prospective cohort study that started in 2000 in the metropolitan Ruhr region including the cities Bochum, Essen and Mülheim/R. Main aims of the HNR study are to study the extent of subclinical coronary atherosclerosis to predict the

risk of myocardial infarction in the general population and to define appropriate methods for identifying high-risk subgroups in the general urban population (Schmermund et al. 2002).

3.2.2 Participant recruitment

A detailed description of the recruitment of the participant was discussed in detail by Stang et al. (2005). Briefly, for the baseline examination study participants were randomly selected from the mandatory registries of residence from the three cities included in the study between December 2000 and August 2003. About 9,484 subjects were invited to participate in the study. A multimode contact approach including an invitational letter, a maximum of two reminder letters and phone calls were used for the recruitment of study subjects (Stang et al. 2005). As the study was aimed at general population very few exclusion criteria were applied to the study: inability or unwillingness to give an informed consent to participate in the study, conditions (medical or other) that preclude follow-up for five years, severe psychiatric disorders or illegal substance abuse and pregnancy (Schmermund et al. 2002).

Overall 4,814 eligible subjects of both sexes, aging 45-75 years could be examined, corresponding to a baseline response of 56%. All participants had provided the informed consent for the study and the study was approved by the local institutional ethics committees. The study also comprised extended quality management procedures and was certified according to DIN ISO 9001:2000.

The follow up has been conducted for a median of 5 years (mean 5.1 ± 0.3 years). Participants have been annually contacted by a mailed questionnaire. Between May 2006 and July 2008 a second medical examination was conducted

in the fifth year of follow up, including 4,157 subjects corresponding to a follow up response of 90.2% (Erbel et al. 2010).

3.2.3 Blood pressure measurements

Blood pressure was recorded using an automated oscillometric blood pressure device (AOD) (Omron HEM-705CP; OMRON Corporation, Hoofdorp, the Netherlands) The AOD displayed blood pressure to the nearest 1 mmHg. Study personnel were certified and regularly trained in measuring blood pressure according to the standards of the World Health Organization (WHO) MONICA blood pressure recording protocol (Stang et al. 2005).

Blood pressure was recorded three times for each subject with a three minute interval in between the measurements. The blood pressure was recorded during a computer assisted personal interview that was automatically interrupted for blood pressure recording. This ensured that subjects had a rest for at least five minutes before their first blood pressure was measured. The first measurement was disregarded as it is typically systematically higher than subsequently serial measurements. Mean SBP and DBP were calculated from the second and third measurements (Stang et al. 2005).

3.2.4 Risk factor assessment

Behavioural risk factors like smoking, nutrition and physical activity, medical family history concerning ischemic heart disease, intake of any medications, and information about socio-demographic variables was obtained using questionnaires and computer assisted interviews. Laboratory parameters have been conducted

immediately at the central laboratory at the University Hospital of Essen (Schmermund et al. 2002).

3.3 Diagnostic conventions

Following diagnostic conventions have been used in all analyses of this thesis.

- Body mass index (BMI): The subjects were classified as normal with a BMI between 18 and 24.99 kg/m^2, overweight 25 and 29.99 kg/m^2, obese 30 kg/m^2 or more.
- Smoking status was defined as never smokers, past smokers (quit of smoking and time since quitting), and current smokers (actual smoking of either cigarettes or other forms of tobacco).
- CVD in GEMCAS was defined as a history of cardiovascular disease reported by the physician, including myocardial infarction or acute coronary syndrome.
- CAD in HNR was defined by self-reports of previous myocardial infarction.
- Diabetes In GEMCAS was defined when the subject had any one of the following: a self-reported history of type 1 or type 2 diabetes or a reported history of type1 or type 2 diabetes by a physician, intake of insulin or oral anti-diabetic medications. In the HNR subjects it was defined when the subjects reported a history of the diagnosis or intake of glucose lowering drugs.

3.4 Statistical Analyses

Of the 35,869 study participants included in GEMCAS, 186 with missing data for blood pressure readings were excluded for the present analysis, leaving a study sample of 35,683 (mean age 51.7±16.1 years, 61.2% women).

Means and their standard deviation and percentiles (5^{th}, 25^{th}, median, 75^{th} and 95^{th}) of SBP and DBP were computed, each stratified by age-groups and sex.

In sensitivity analyses the percentile distribution of blood pressure in "healthy" subjects were studied by excluding (n=24,399) subjects with the following cardiovascular risk factors and diseases: elevated waist circumference (>102 cm in men, >88 cm in women), elevated triglycerides (≥1.7 mmol/L (150 mg/dl)), low high density lipoprotein(HDL) (<1.08 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women), elevated blood glucose (GL, fasting GL ≥ 5.6 mmol/L (100 mg/dl) or non-fasting GL ≥11.1 mmol/L (200 mg/dl)), antihypertensive treatment, presence of diabetes mellitus and history of a CVD.

The characteristics of the GEMCAS subjects were described according to 10 year age groups. Means, medians and quartiles were reported wherever applicable for continuous variables and frequencies were reported for categorical variables.

The characteristics of the subjects of GEMCAS were also stratified according the JNC 7 definition of hypertension (Chobanian et al. 2003) to observe the prevalences of risk factors in different blood pressure classes according to JNC 7.

As the GEMCAS samples had a very wide age range and to allow for an age independent comparison of the study characteristics, a direct age standardisation according to the 2004 standard German population (Statistisches

Jahrbuch für die Bundesrepublik 2006) has been computed for all variables. For this purpose, in a first step the GEMCAS sample was stratified into 5 year age classes (18-30, 31-45, 46-60, 60-75 and >76 years). For all variables means respective frequencies were computed according to these 5 year age-groups. In a second step the age specific rates were (1) multiplied with the proportion of people in the respective age groups in the 2004 standard German population to compute the expected age specific rates in GEMCAS and (2) summed up to get the directly standardized rates. Additionally, 95% confidence intervals (95% CI) for the standardized rates were computed by calculating the variance of the standardized rate/mean and subsequently using the 97.5% quantile of a standard normal distribution to determine the lower and upper confidence bound.

The characteristics of the GEMCAS study sample were compared to the characteristics of the Heinz Nixdorf Recall study population. To make both the studies comparable with respect to age, this analysis included only the GEMCAS subjects who were aged between 45-75 years.

Age and sex specific frequency distribution curves were used to present the blood pressure data for the GEMCAS subjects.

The age effects on blood pressure observed in the cross sectional GEMCAS sample (restricted to the age group 45 to 75 years) were validated with the data of the prospective study of HNR by applying the observed age-effect in GEMCAS (by calculating estimators for the age effect) on baseline blood pressure data in HNR by computing expected blood pressure readings with the GEMCAS estimators and comparing these with the measured blood pressure readings in the 5 year follow up. This has been done for men and women separately as follows:

(a) Comparison of the 5 year and yearly changes of blood pressure readings

(1) For the HNR sample the 5 year cumulative changes of blood pressure readings were calculated by subtracting the individual 5 years follow up (t_1) with the baseline (t_0) readings as follows:

$$\Delta_{SBP} = SBP_{t1} - SBP_{t0}$$
$$\Delta_{DBP} = DBP_{t1} - DBP_{t0}$$

Means of Δ_{SBP} and Δ_{DBP} were computed to estimate the cumulative 5 years mean changes in blood pressure (after 5 years of follow-up).

(2) To obtain the mean yearly changes, the means of Δ_{SBP} and Δ_{DBP} were divided by five.

$$\Delta_{SBP} = SBP_{t1} - SBP_{t0} / 5$$
$$\Delta_{DBP} = DBP_{t1} - DBP_{t0} / 5$$

(b) <u>Observed versus expected blood pressure readings in HNR</u>

(1) Effect estimators (*ß*s) for age on the systolic and diastolic blood pressure in GEMCAS have been computed by crude and multiple linear regression analyses, with age as the predictor and SBP or DBP as the outcome (Table 1). The analysis was done for the whole GEMCAS sample and separately for the subjects who were aged between 45 and 75 years to match with the age group of the HNR subjects. In order to perform an adjusted linear regression analyses following variables have been preselected as covariates: intake of antihypertensive medication, history of CVD, diabetes mellitus, intake of anti-diabetic medication, BMI, and smoking status.

Table 1: Linear regression models

Variable	Crude model	Adjusted model
Dependent	SBP/DBP (mmHg)	SBP/DBP (mmHg)
Independent	Age in years	Age in years
Covariates		CVD history (yes/no) Antihypertensive intake (yes/no) Diabetes (yes/no) Diabetic medication intake (yes/no) BMI in kg/m^2 Smoking (never/past/current smokers) reference: never smokers

The linear regression model has been computed as follows

Crude model: $y = ß_0 + ß_{age} + \mathcal{E}$

Fully adjusted model:

$y= ß_0+ ß_{age}+ ß_{CVD}+ ß_{antihypertensives}+ ß_{diabetes}+ ß_{anti\text{-}diabetic\ intake}+ ß_{BMI} + ß_{smoking} + \mathcal{E}$

Where y denotes the dependent variable (outcome) SBP respective DBP, $ß_0$ the regression coefficient of the intercept, $ß_{age}$ the regression coefficient of the independent variable age (predictor), $ß_{covariate2\text{-}6}$ the regression coefficients of the covariates described in table 1 and $\mathcal{E}$ the error term.

(2) The crude $ß_{age}$ achieved as described in (1) for both men and women, aged 45-75 years, were subsequently applied in the HNR sample to estimate expected blood pressure readings after five years. The $ß_{age}$ values were multiplied by 5 to get an estimated five year increase and added to the observed SBP or DBP readings at baseline. Observed

blood pressure readings are those measured for each HNR subject at baseline (t_0) and 5 year follow up (t_1):

$SBP_{expected}$ after 5 years = Observed SBP_{t0} + (5 x $ß_{age}$)

$DBP_{expected}$ after 5 years = Observed DBP_{t0} + (5 x $ß_{age}$)

As the data were skewed and thus not perfectly normally distributed, the Wilcoxon signed rank test - a nonparametric test - was performed to assess whether the median ranks of expected and observed SBP/ DBP differed. The two sided significance level α has been set at 0.05, assuming differences with a p-value < 0.05 as significant.

However, the significance testing of these differences were the only statistical significance tests computing p-values in this work. Since it is well known that significance tests are sample size driven, even in sub-group analysis the tests of significance will be mostly positive in the GEMCAS study. Instead, 95% confidence intervals were reported to indicate the reliability of an estimate wherever appropriate. Additionally, the work was intended to present the distribution of blood pressure in a purely descriptive form.

Since the effects of age and other covariates differed between men and women substantially, all analyses were done separately for men and women.

All analyses have been carried out using SAS 9.2 version (SAS Institute, Cary, NC, USA).

Chapter 4

Results

4.1 Study characteristics of the GEMCAS subjects

The characteristics of GEMCAS participants according to 10-year age-classes are presented for men in Table 2 and for women in Table 3. GEMCAS included 35,869 subjects, 13,942 men (39%). As expected the prevalence of most risk factors increased with age. However, in both the sexes this increase can be observed only up to the age of 70 years and thereafter the risk factors showed a decreasing trend. Exceptions from this observation are the trend of SBP and blood glucose levels, which showed a continuous increase even up to the oldest age group (81-99 years) and smoking status, which decreases with increasing age. More than 60% of men and women aged >60 years were on antihypertensive therapy. At least 40% of men and women aged >70 years had a history of cardiovascular disease.

The characteristics of the GEMCAS participants according to the JNC 7 blood pressure classes are presented in Table 1 for men and Table 2 for women (Appendix B). Overall, the risk factors except current smoking status showed an increasing prevalence with increasing blood pressure. Age-standardization of the prevalence data also did not change this observation (Table 1 and 2, Appendix B)

4.2 Frequency distribution and mean blood pressure

Figures 1 and 2 depict the frequency distribution curves of the systolic and diastolic blood pressure readings stratified by 10-year age groups in men and

women respectively. Overall the absolute range of the diastolic readings is smaller than the range of the systolic readings. With increasing age, the curves of the systolic blood pressure show a flattening and a shift to the right, equating to higher blood pressure readings (figure 1). The shift to the right was more pronounced in women compared to men. In contrast, the diastolic blood pressure curves show only minimal changes by age in both sexes (figure 2).

The mean BP across different age groups can be seen in the Figure 3. In both sexes the mean SBP and DBP showed a gradual increase with age especially up to 60 years, there after it remained almost constant. Men showed higher mean SBP values than women in the younger and middle age, however in the age group of 61-65 years there was a cross over in the mean SBP curves between men and women. The DBP mean values also showed an increase just similar to SBP in both men and women, reaching maximum values of 84 mmHg in men 50-55 years and 83 mmHg in women who were aged n 61-65 years. In contrast to SBP the mean DBP values showed a sharp decline in the older age groups in both sexes (figure 3).

Table 2: Characteristics of men in GEMCAS according to 10-year age classes

	18-30 years (N=1,354)	31-40 years (N=1,736)	41-50 years (N=2,847)	51-60 years (N=3,249)	61-70 years (N=2,729)	71-80 years (N=1,706)	81-99 years (N=320)
Age (years)							
Mean (±SD)	24.4±3.7	36.1±2.8	45.6±2.8	55.5±2.7	65.8±2.7	74.7±2.7	83.7±3.0
Weight (Kg)							
Mean (±SD)	80.6±15.1	86.9±15.4	88.4±16.0	88.4±14.9	86.6±13.4	82.8±12.3	77.8±11.6
BMI (%)							
18-<25 25 kg/m^2	62.2	38.0	31.1	22.4	19.2	23.4	35.9
25 - < 30 kg/m^2	27.0	42.0	44.1	48.0	51.6	51.7	48.4
≥ 30 kg/m^2	10.8	20.0	24.8	29.6	29.2	24.9	15.6
Waist circumference (cm)							
Mean (± SD)	86.8±12.6	93.9±12.2	98.2±12.9	101.6±12.4	102.7±11.6	102.6±12.9	100.9±10.8
Lipid Profile							
Total Cholesterol **(mg/dl)** Mean(± SD)	174.2±37.2	201.6±39.8	213.2±42.7	208.8±44.4	205.1±39.4	198.5±38.2	193.3±39.5
HDL **(mg/dl)** Mean(± SD)	52.3±11.7	52.7±13.1	53.9±14.7	54.6±14.4	55.6±14.5	55.4±14.4	55.7±16.0
LDL **(mg/dl)** Mean (± SD)	107.4±33.4	128.4±35.9	136.3±37.8	130.8±35.8	129.6±35.7	124.3±34.2	120.6±34.2
Triglycerides **(mg/dl)** Median (Q1; Q3)	108(76;160)	140(95;209)	153(103;231)	155(106;239)	148(105;215)	139(100;194)	126(90;185)
Blood Pressure (BP)							
Systolic BP **(mmHg)** Mean (± SD)	123.8±14.7	126.5±14.7	130.5±16.8	135.1±17.7	139.2±18.6	140.5±19.0	141.7±19.0
Diastolic BP **(mmHg)** Mean (± SD)	77.2±10.0	80.1±9.8	82.6±10.7	83.1±10.2	81.9±10.2	80.3±10.6	79.0±10.7
Blood glucose (mg/dl)							
Mean (± SD)	85.7±17.5	90.9±21.9	97.9±32.0	108.3±41.1	111.1±39.7	113.0±39.8	119.0±47.3

Table 2 (cont.): Characteristics of men in GEMCAS according to 10 year age classes

Risk Factor	18-30 years (N=1,354)	31-40 years (N=1,736)	41-50 years (N=2,847)	51-60 years (N=3,249)	61-70 years (N=2,729)	71-80 years (N=1,706)	81-99 years (N=320)
Smoking status (%)							
Current Smoker	49.3	39.0	37.8	26.6	13.4	9.3	4.5
Past Smoker	13.0	23.4	32.3	44.7	52.4	56.5	63.1
Never Smoker	37.7	37.6	29.9	28.7	34.2	34.2	32.4
Pharmacotherapy (%)							
Anti-diabetic	1.1	2.4	6.4	15.1	20.0	20.1	18.8
Antihypertensive	4.4	11.1	25.1	47.0	65.5	75.0	80.6
Lipid lowering	0.6	3.7	10.2	21.7	31.6	29.3	29.4
Comorbidities (%)							
Cardiovascular diseases	1.0	2.2	8.2	21.1	36.0	50.3	63.9
Diabetes (Self reported)	0.8	3.0	8.6	20.3	26.1	27.5	26.2

Table 3: Characteristics of women in GEMCAS according to 10 year age classes

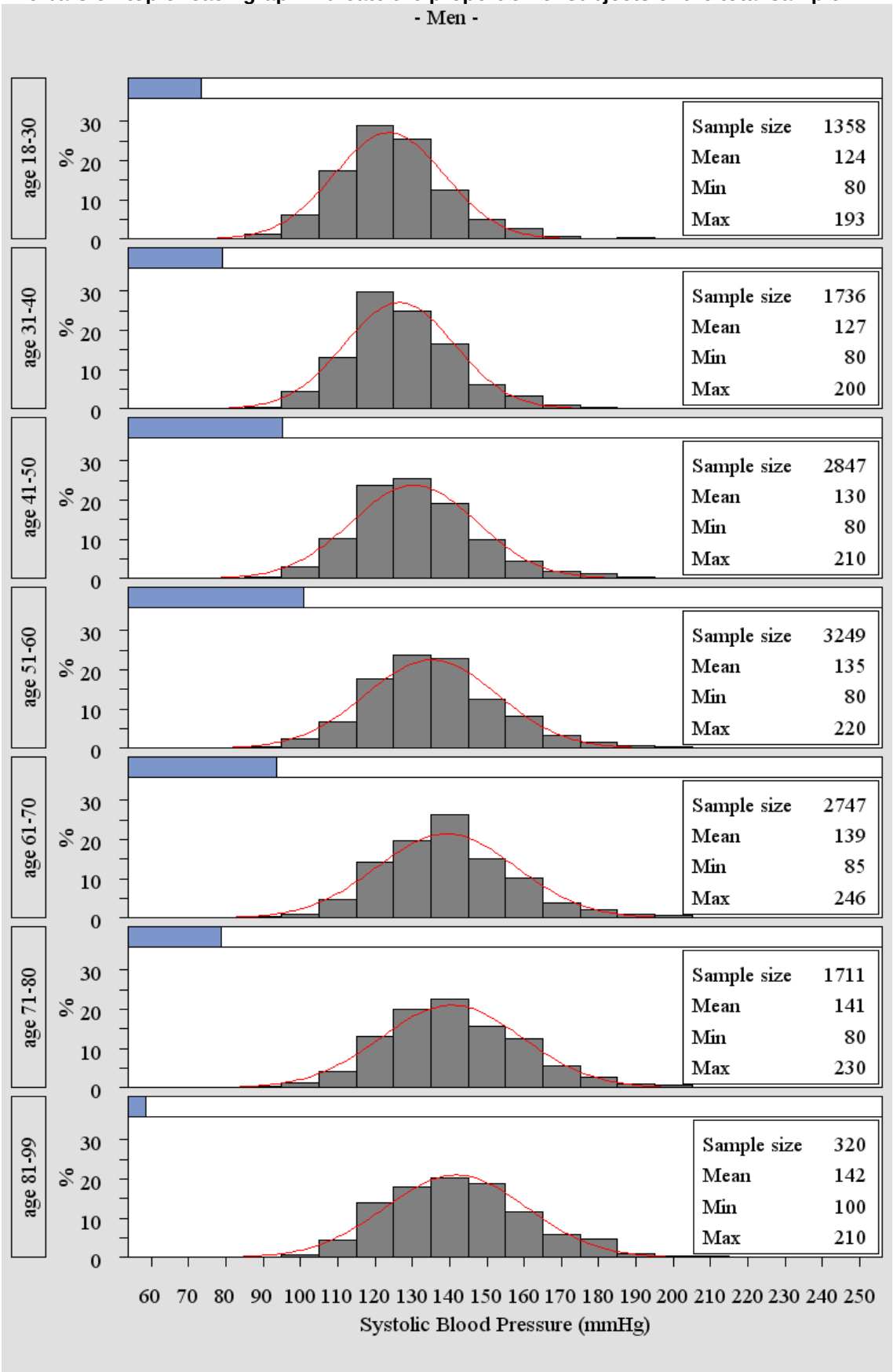
Risk Factor	18-30 years (N=2,641)	31-40 years (N=3,330)	41-50 years (N=4,969)	51-60 years (N=4,677)	61-70 years (N=3,422)	71-80 years (N=2,257)	81-99 years (N=630)
Age (years)							
Mean (±SD)	24.1±3.7	36.2±2.8	45.4±2.9	55.3±2.8	65.7±2.8	75.0±2.8	83.9±3.1
Weight (Kg)							
Mean (±SD)	66.9±15.6	70.6±16.1	71.6±15.8	74.4±15.6	74.9±13.7	72.7±12.5	70.0±11.4
BMI (%)							
≤ 25 kg/m^2	71.9	60.3	52.7	37.2	28.9	27.7	42.5
25 - < 30 kg/m^2	16.7	23.2	27.1	33.7	39.9	41.4	39.6
≥ 30 kg/m^2	11.4	16.5	20.2	29.2	31.2	30.9	17.9
Waist circumference (cm)							
Mean **(**± SD**)**	77.7±12.7	82.0±13.4	84.9±13.9	89.8±14.3	92.5±13.0	93.1±11.9	89.7±11.3
Lipid Profile							
Total Cholesterol **(mg/dl)** Mean(± SD)	182.9±34.1	188.0±33.1	205.4±36.6	222.9±39.9	225.8±41.0	219.7±40.4	218.9±42.2
HDL **(mg/dl)** Mean(± SD)	66.8±16.6	66.7±16.7	67.7±17.3	68.5±18.0	67.3±17.2	65.1±16.6	66.2±17.6
LDL **(mg/dl)** Mean (± SD)	105.8±30.4	111.3±29.8	125.1±34.1	138.6±36.7	141.7±36.5	136.9±36.9	136.0±37.0
Triglycerides **(mg/dl)** Median (Q1; Q3)	95(70;131)	93(68;133)	104(74;150)	124(89;180)	136(100;192)	139(104;193)	135(102;176)
Blood Pressure (BP)							
Systolic BP **(mmHg)** Mean (± SD)	115.5±13.2	118.4±14.5	124.2±16.7	131.9±18.1	138.7±18.7	141.6±19.6	142.2±20.3
Diastolic BP **(mmHg)** Mean (± SD)	73.6±9.5	76.1±10.0	79.0±10.5	81.3±10.3	82.4±10.1	81.2±10.7	79.2±10.7
Blood glucose (mg/dl)							
Mean (± SD)	82.5±13.2	85.7±15.2	90.7±22.7	97.8±30.8	102.6±32.6	107.8±39.1	112.0±41.6

Table 3 (cont.): Characteristics of women in GEMCAS according to 10 year age classes

Risk Factor	18-30 years (N=2,641)	31-40 years (N=3,330)	41-50 years (N=4,969)	51-60 years (N=4,677)	61-70 years (N=3,422)	71-80 years (N=2,257)	81-99 years (N=630)
Smoking status (%)							
Current Smoker	41.0	31.2	31.3	21.6	8.7	5.0	2.2
Past Smoker	14.9	20.5	26.4	25.6	22.7	19.2	15.4
Never Smoker	44.1	48.3	42.3	52.8	68.6	75.8	82.4
Pharmacotherapy (%)							
Anti-diabetic	0.5	1.2	2.7	7.4	13.6	18.0	19.7
Antihypertensive	3.1	7.5	19.8	40.1	60.7	77.0	79.4
Lipid lowering	0.4	1.0	3.3	11.6	23.0	28.1	20.3
Comorbidities (%)							
Cardiovascular diseases	0.7	1.8	3.7	9.1	20.3	39.7	51.9
Diabetes (Self reported)	0.6	2.0	4.2	10.9	18.3	25.9	26.6

Figure 1: Frequency distribution of systolic blood pressure by sex

The bars on top of each graph indicate the proportion of subjects of the total sample



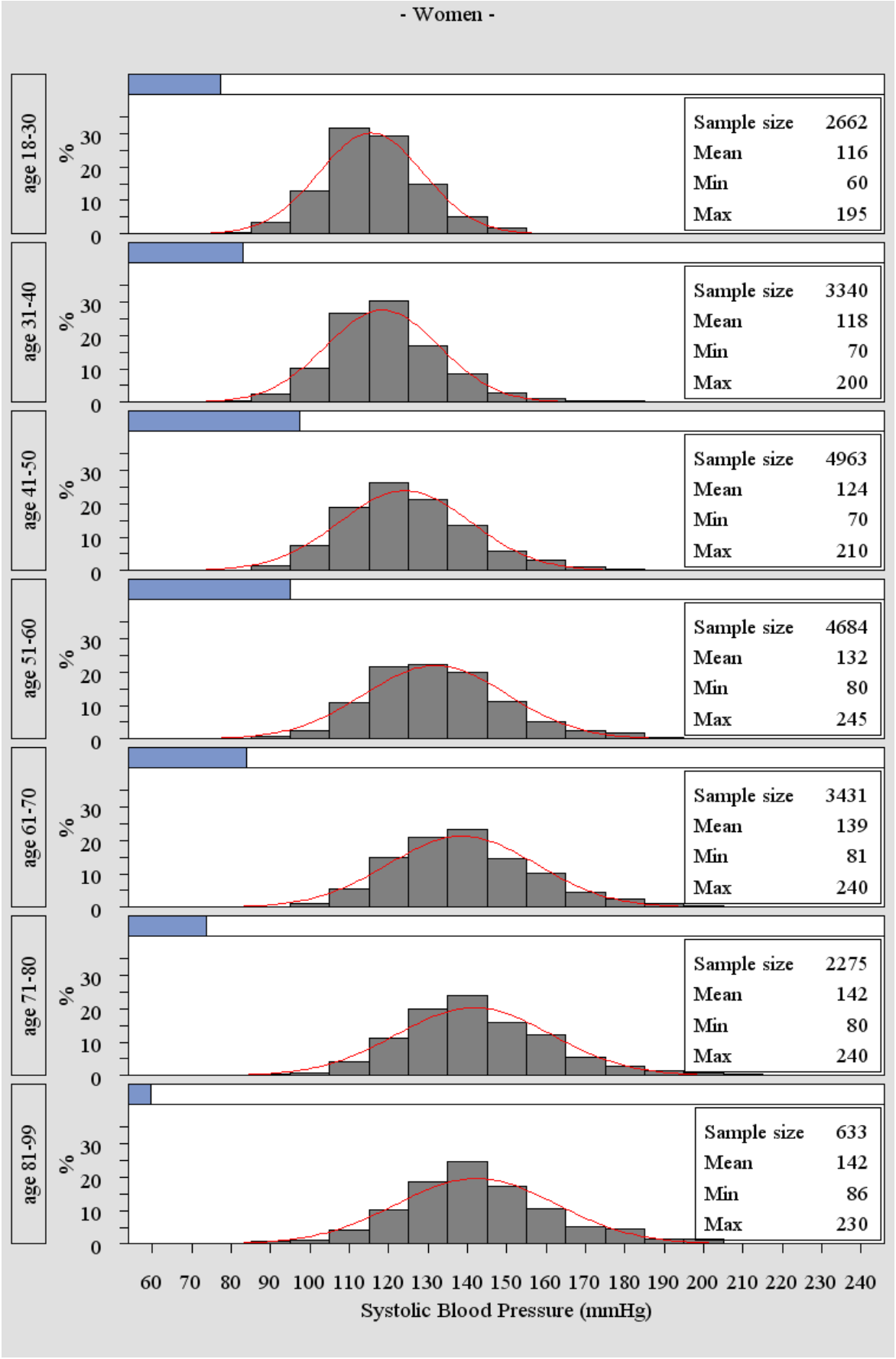
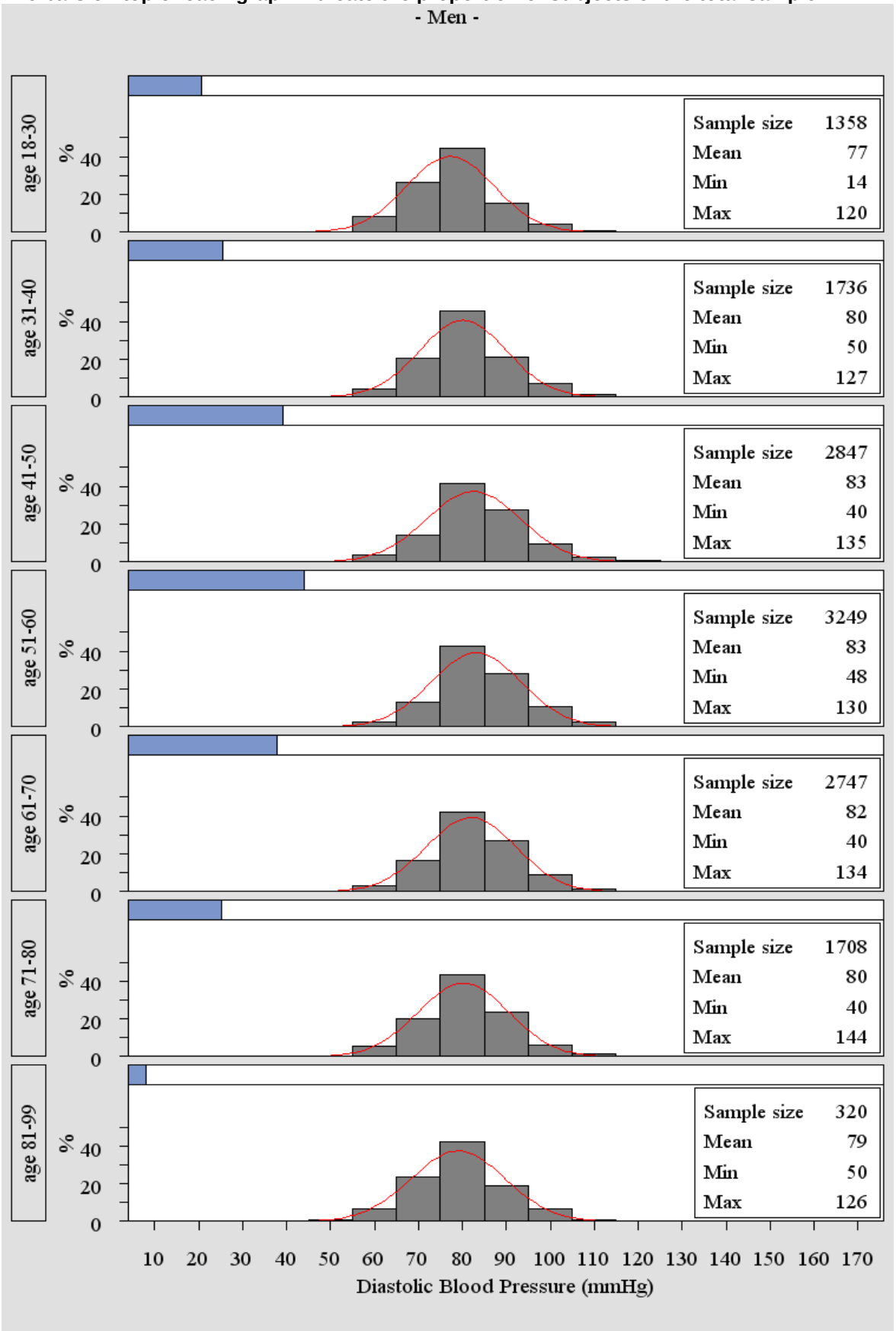

- Women -
age 18-30
Sample size 2662
Mean 116
Min 60
Max 195
age 31-40
Sample size 3340
Mean 118
Min 70
Max 200
age 41-50
Sample size 4963
Mean 124
Min 70
Max 210
age 51-60
Sample size 4684
Mean 132
Min 80
Max 245
age 61-70
Sample size 3431
Mean 139
Min 81
Max 240
age 71-80
Sample size 2275
Mean 142
Min 80
Max 240
age 81-99
Sample size 633
Mean 142
Min 86
Max 230
%
0
10
20
30
60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240
Systolic Blood Pressure (mmHg)

Figure 2: Frequency distribution of diastolic blood pressure by sex

The bars on top of each graph indicate the proportion of subjects of the total sample



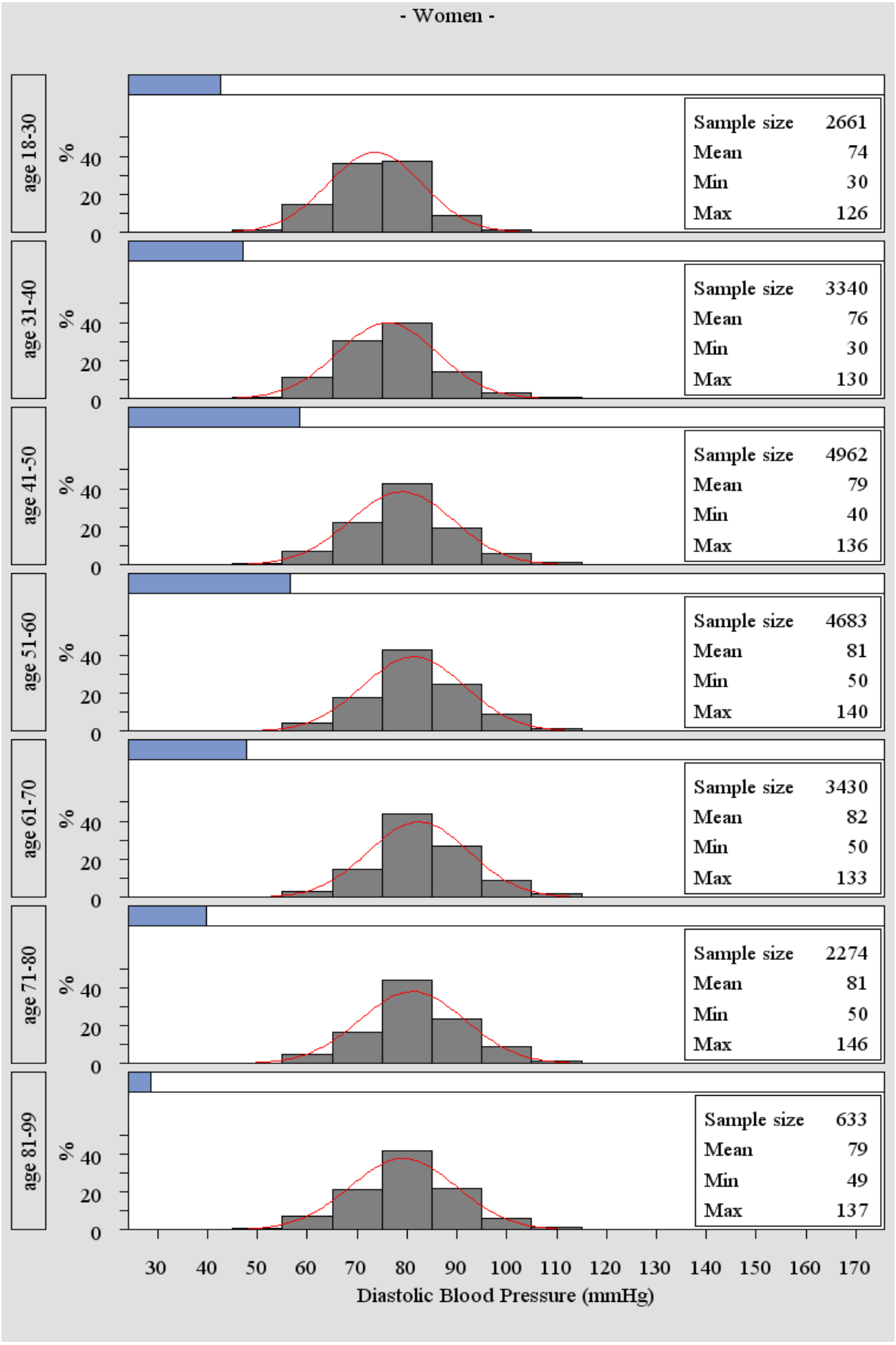
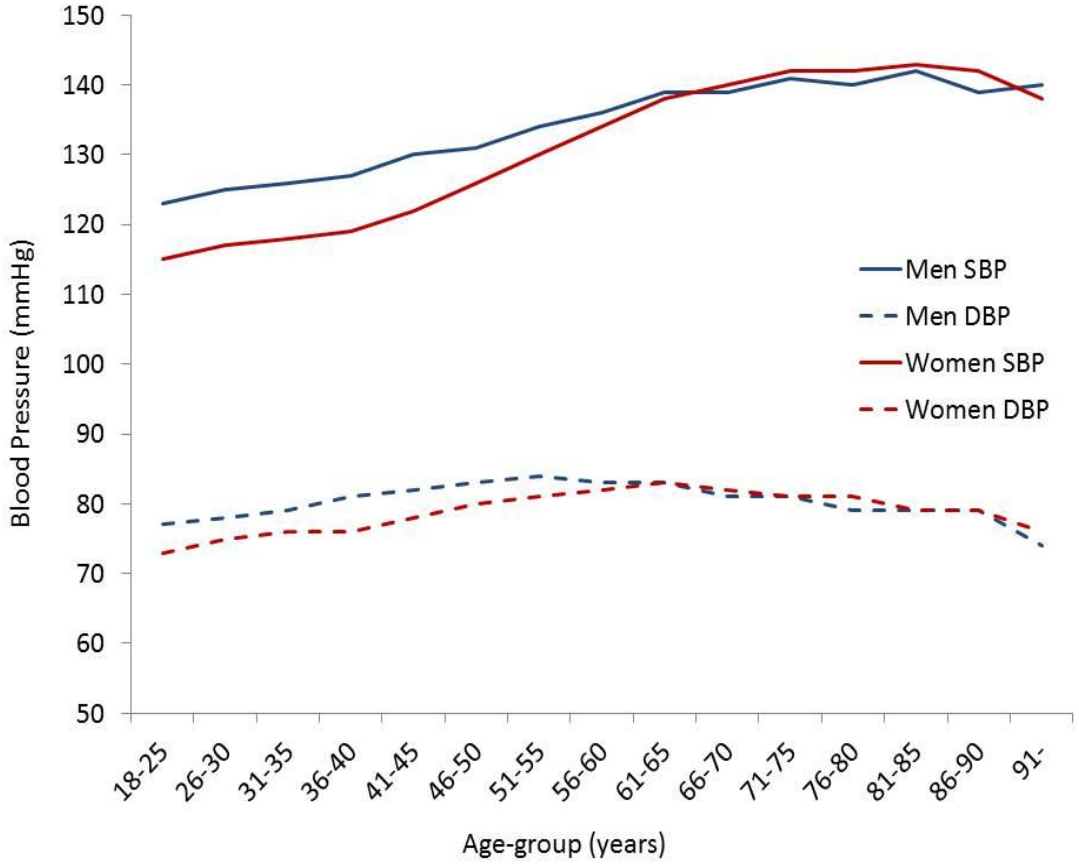

- Women -
age 18-30
Sample size 2661
Mean 74
Min 30
Max 126
age 31-40
Sample size 3340
Mean 76
Min 30
Max 130
age 41-50
Sample size 4962
Mean 79
Min 40
Max 136
age 51-60
Sample size 4683
Mean 81
Min 50
Max 140
age 61-70
Sample size 3430
Mean 82
Min 50
Max 133
age 71-80
Sample size 2274
Mean 81
Min 50
Max 146
age 81-99
Sample size 633
Mean 79
Min 49
Max 137
%
0
20
40
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
Diastolic Blood Pressure (mmHg)

Figure 3: Mean systolic and diastolic blood pressures by age-groups and sex, whole study sample



4.3 Percentile blood pressure distribution

4.3.1 Percentile distribution of systolic blood pressure

The percentile distribution of SBP is depicted in Figure 4. Since the distribution differed between women and men, the distribution for women and men are separately presented here (figure 4). The illustration of the overall distribution – thus not only the mean – can be viewed from two perspectives: (1) possible differences of the blood pressure range between age categories, and (2) course of an age-related increase in blood pressure in each part of the distribution.

(1) The range of systolic blood pressure does not proceed in parallel between the percentile bands; instead, the spread between the 5th and the 95th percentile increases with increasing age: the systolic blood pressure of the youngest women aged 18-25 ranges between 95-136 mmHg (Δ +41 mmHg) and rises to 110-180 mmHg (Δ +70 mmHg) in the older women (81-85 years). Overall, the ratio between the lowest 5th and highest 95th percentile ranges between 1.43 and 1.64 (figure 4). A similar observation can be made in men, with blood pressure readings ranging between 100-150mmHg in the youngest men and 115-180 mmHg in the older age group (figure 4), and ratios ranging between 1.50 in younger (18-25 years) and 1.57 in older men (81-85 years).

(2) What seems striking is that in all percentiles, even the lowest, a gradual increase in blood pressure with increasing age was observed (figure 4). It could be observed from the graph that, all the SBP percentiles showed a shift in their values as the age advanced especially until the 65th year or so. From the age of 66, the shifts in the SBP percentiles were minimal in the successive age groups. In women, the difference in the lowest 5th percentile between younger and older women was around +15mmHg (95–110mmHg) and between 20-32 mmHg in the 25th and 75th percentile, rising to +40 mmHg in the 95th percentile (136-180 mmHg). A similar observation can be made in men, in this case with a more constant increase of +20 mmHg in all percentiles with the exception of young men (+10 mmHg for 5th percentile). Although women had lower SBP values in the younger ages when compared to men, after the age-class 55-60 years the SBP percentiles in both sexes were almost similar.

Lastly, half of all the women in our study sample had by the age of 30 already had to be classified according to their systolic blood pressure at least as

prehypertensive according to JNC VII classification of blood pressure (Chobanian 2003). In men this situation is even more pronounced, with all men, even the youngest age group, having to be classified at least as prehypertensive. In men and women who were over the age class of 66-70 years, half of them had a systolic blood pressure in the hypertensive range.

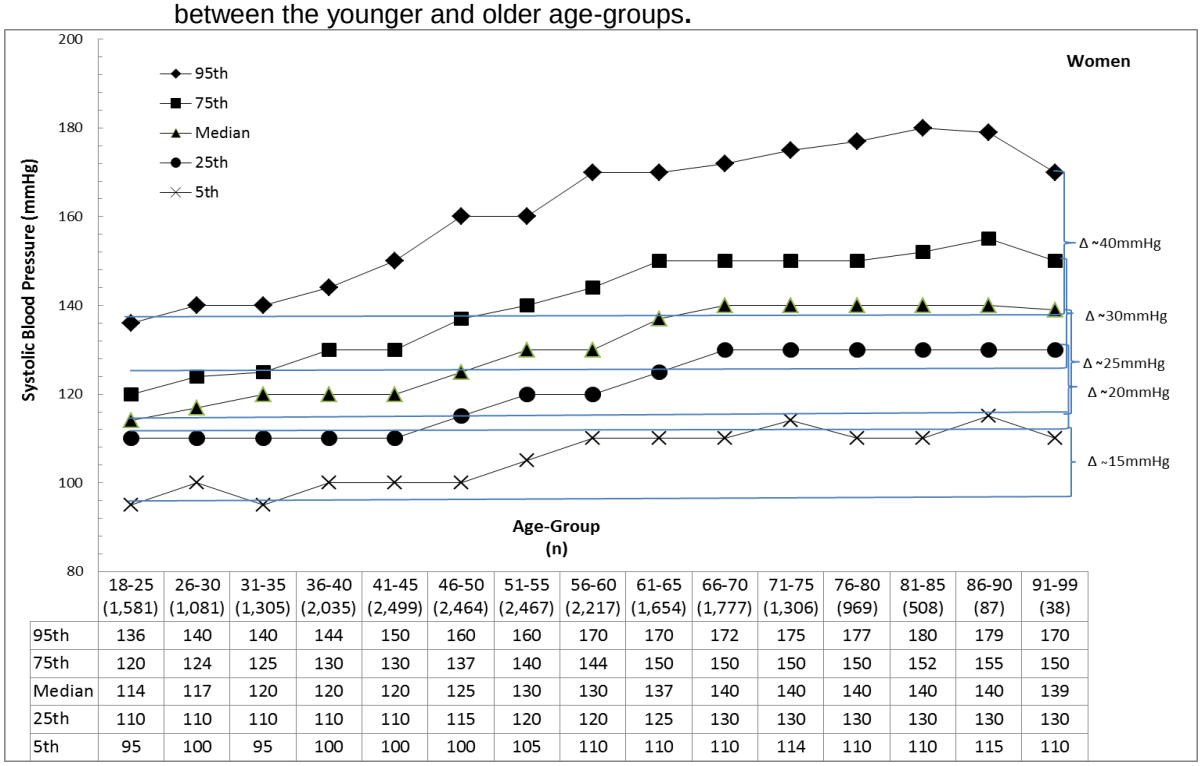
4.3.2 Percentile distribution of diastolic blood pressure

The percentile distribution of SBP is depicted in Figure 5. When compared to the systolic blood pressure, a different picture emerges with regard to the diastolic blood pressure distribution. Overall, in both women and men a slight increase in the diastolic blood pressure can be observed, reaching a plateau between 40 and 60 years and decreasing slightly thereafter (figure 5). However, a detailed analysis of the age course of the different percentiles reveals some notable differences. For instance, in women in the lowest 5th percentile of the blood pressure readings we observed a constant blood pressure of 60 mmHg up to the age of 50 (figure 5). An increase in this percentile of the diastolic blood pressure by 10 mmHg only occurred within a 15-year period (51-65 years). Thereafter, the 5^{th} percentile of diastolic blood pressure decreased again within 10 years to 60 mmHg. A similar course was observed in the 25^{th} percentile. All other percentiles differ in their course by an earlier increase, a more prolonged plateau and a marginal decrease, if any, in the highest age groups. It is striking that the median changed only up to the age of 41-45 years and remained constant at 80 mmHg after that time. This is even more striking in men, where in any age group the median blood pressure was 80 mmHg (figure 5).

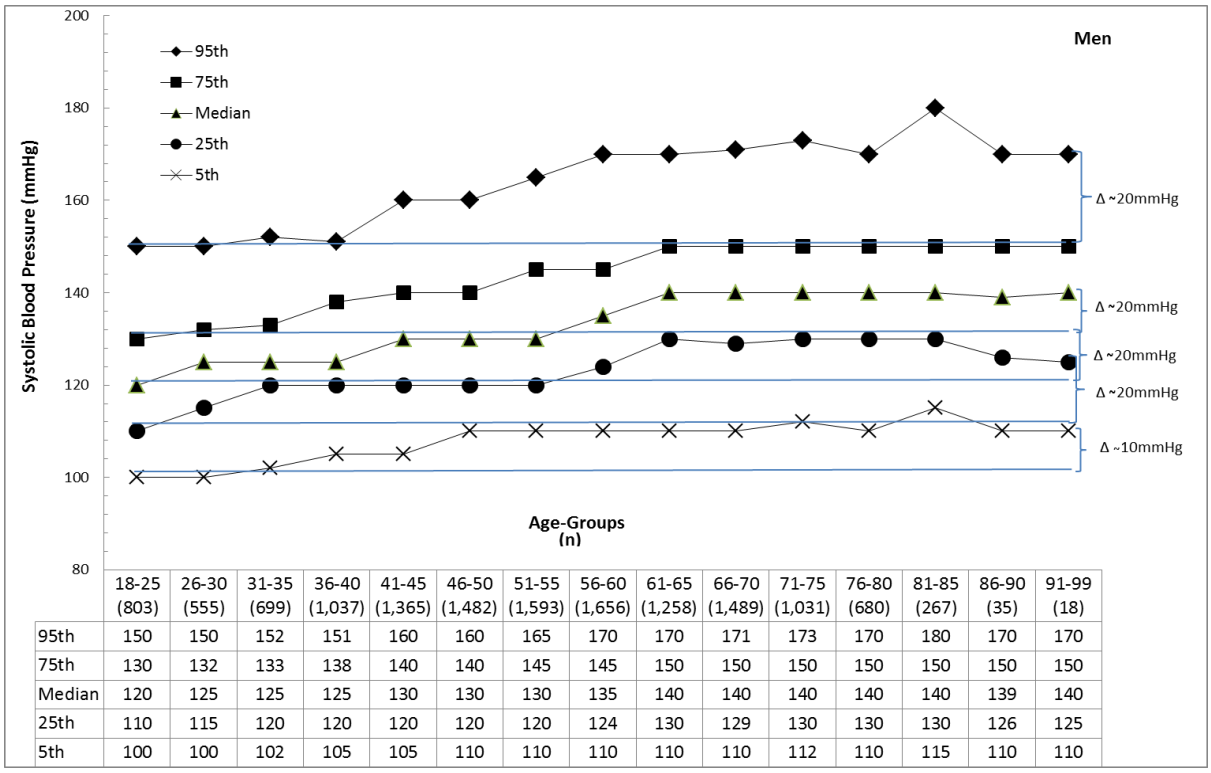
Overall it seems that low diastolic blood pressure readings are associated with greater age-related changes.

Figure 4: Percentile Distribution of systolic blood pressure by Sex and Five Year Age-Groups

The delta indicates the approximate increase of blood pressure in each percentile between the younger and older age-groups**.**

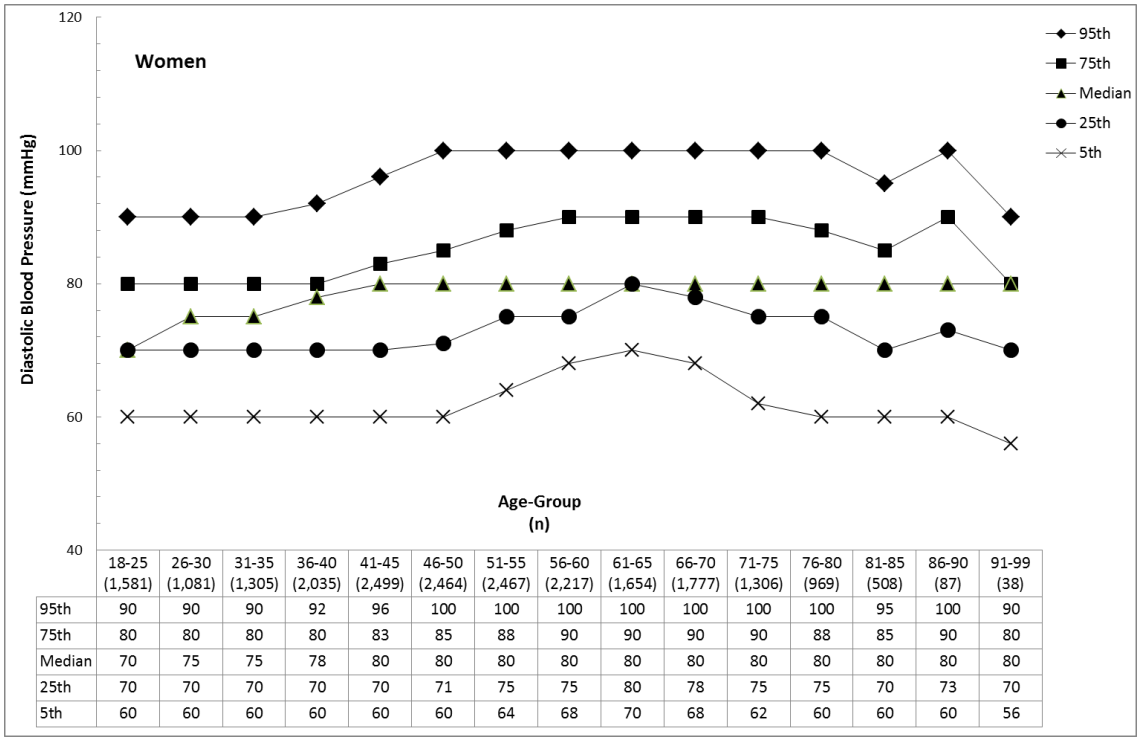


	18-25 (1,581)	26-30 (1,081)	31-35 (1,305)	36-40 (2,035)	41-45 (2,499)	46-50 (2,464)	51-55 (2,467)	56-60 (2,217)	61-65 (1,654)	66-70 (1,777)	71-75 (1,306)	76-80 (969)	81-85 (508)	86-90 (87)	91-99 (38)
95th	136	140	140	144	150	160	160	170	170	172	175	177	180	179	170
75th	120	124	125	130	130	137	140	144	150	150	150	150	152	155	150
Median	114	117	120	120	120	125	130	130	137	140	140	140	140	140	139
25th	110	110	110	110	110	115	120	120	125	130	130	130	130	130	130
5th	95	100	95	100	100	100	105	110	110	110	114	110	110	115	110

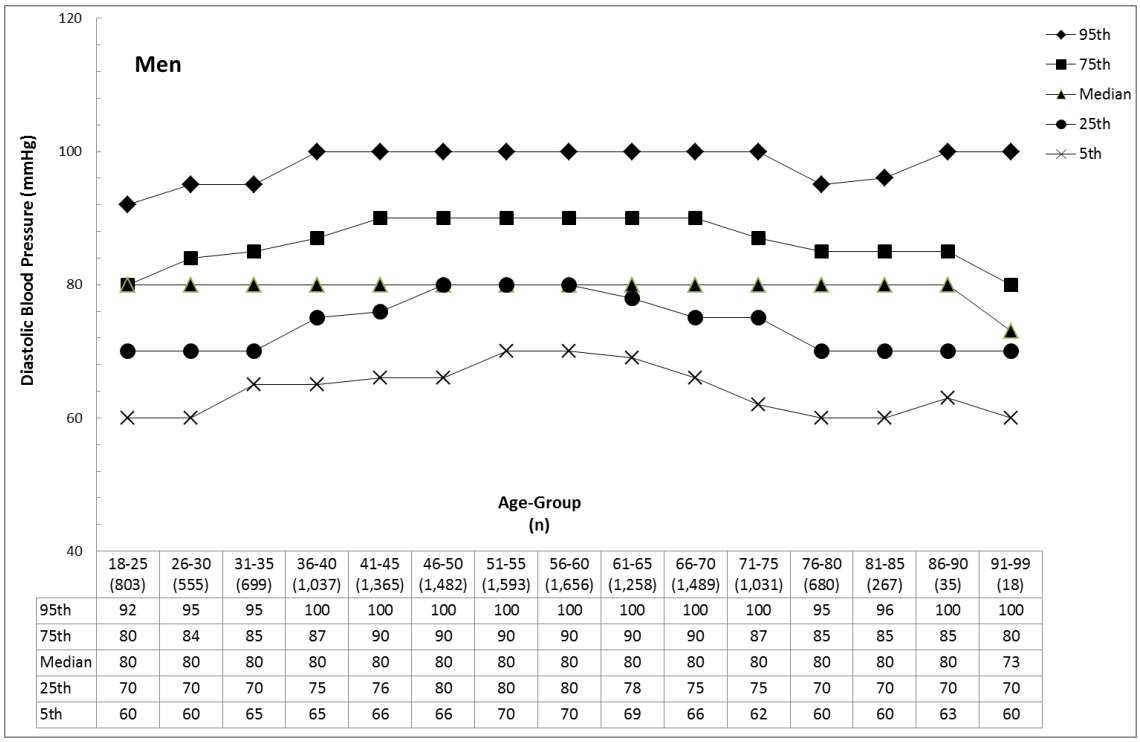


	18-25 (803)	26-30 (555)	31-35 (699)	36-40 (1,037)	41-45 (1,365)	46-50 (1,482)	51-55 (1,593)	56-60 (1,656)	61-65 (1,258)	66-70 (1,489)	71-75 (1,031)	76-80 (680)	81-85 (267)	86-90 (35)	91-99 (18)
95th	150	150	152	151	160	160	165	170	170	171	173	170	180	170	170
75th	130	132	133	138	140	140	145	145	150	150	150	150	150	150	150
Median	120	125	125	125	130	130	130	135	140	140	140	140	140	139	140
25th	110	115	120	120	120	120	120	124	130	129	130	130	130	126	125
5th	100	100	102	105	105	110	110	110	110	110	112	110	115	110	110

Figure 5: Percentile Distribution of the diastolic blood pressure by Sex and Five Year Age-Groups



	18-25 (1,581)	26-30 (1,081)	31-35 (1,305)	36-40 (2,035)	41-45 (2,499)	46-50 (2,464)	51-55 (2,467)	56-60 (2,217)	61-65 (1,654)	66-70 (1,777)	71-75 (1,306)	76-80 (969)	81-85 (508)	86-90 (87)	91-99 (38)
95th	90	90	90	92	96	100	100	100	100	100	100	100	95	100	90
75th	80	80	80	80	83	85	88	90	90	90	90	88	85	90	80
Median	70	75	75	78	80	80	80	80	80	80	80	80	80	80	80
25th	70	70	70	70	70	71	75	75	80	78	75	75	70	73	70
5th	60	60	60	60	60	60	64	68	70	68	62	60	60	60	56



	18-25 (803)	26-30 (555)	31-35 (699)	36-40 (1,037)	41-45 (1,365)	46-50 (1,482)	51-55 (1,593)	56-60 (1,656)	61-65 (1,258)	66-70 (1,489)	71-75 (1,031)	76-80 (680)	81-85 (267)	86-90 (35)	91-99 (18)
95th	92	95	95	100	100	100	100	100	100	100	100	95	96	100	100
75th	80	84	85	87	90	90	90	90	90	90	87	85	85	85	80
Median	80	80	80	80	80	80	80	80	80	80	80	80	80	80	73
25th	70	70	70	75	76	80	80	80	78	75	75	70	70	70	70
5th	60	60	65	65	66	66	70	70	69	66	62	60	60	63	60

4.3.3 Sensitivity Analyses

Sensitivity analyses were performed to test whether antihypertensive medication and CVD risk factors alter the observations of the blood pressure distribution described above.

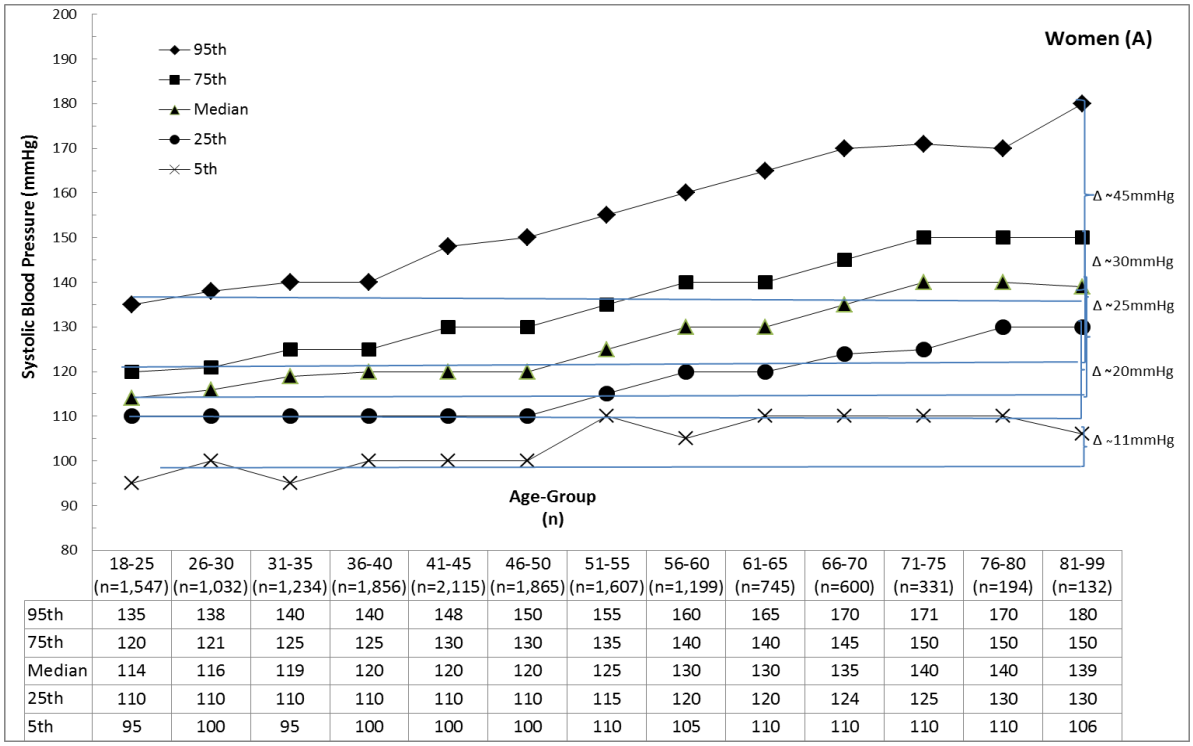
Overall, the systolic blood pressure distributions of the subgroups were similar to the full study sample, i.e. we observed increasing systolic blood pressure measurements by age in each percentile in both sexes (Figure 6 a-d). However, the absolute differences varied. For example, in men we observed a maximum increase of +20 mmHg in the systolic blood pressure between younger and older age-groups in the lowest percentile. This can be observed even in the subsample with no antihypertensive intake and CVD risk factors (figure 6 c-d), which is twice as high as in the study sample as a whole. All other percentiles in men showed an increase of +20 mmHg even in the absence of CVD risk factors and antihypertensive intake (figure 6c-d). In women, the maximum increase in systolic blood pressure was rather higher in all percentiles compared to men, with nearly 45 and 55 mmHg rise in the 95^{th} percentiles (figure 6a-b). Although there was not much of an age related shift of SBP percentiles in the younger ages (< 45 years), there is an obvious shift in the middle and old ages, especially between 46 and 85 years in both the sexes.

As expected, the absolute systolic blood pressure measurements were lower in the “healthy” subgroup of participants with no CVD and no CVD risk factors compared to those with CVD and CVD risk factors. However, women in the lowest percentile (5th) had very similar absolute readings (90-110 mmHg) independent of their risk factor status (figure 4, figure. 6a-b).

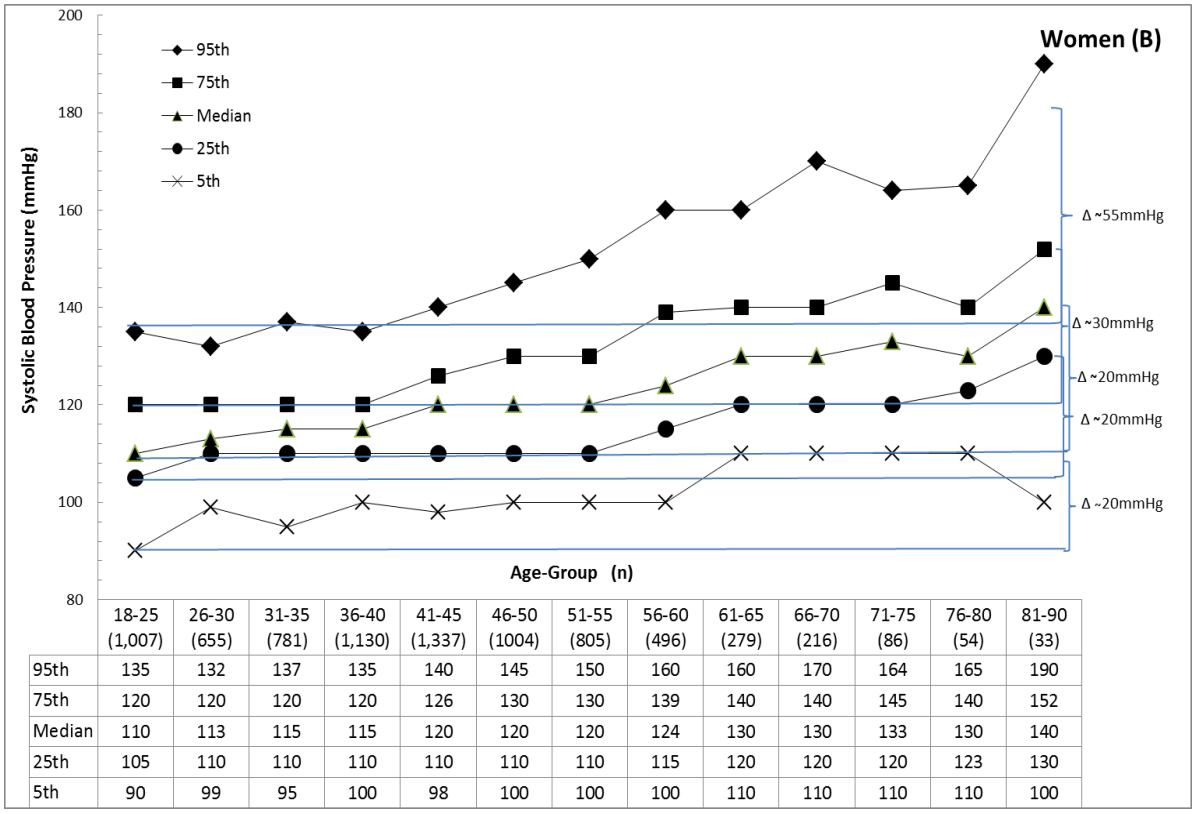
With regard to the diastolic blood pressure, the sensitivity analysis did not alter the observations described above of the study sample as a whole, with the exception that in women the observed increase in the lower percentile began later (>51 years in women of the full study sample, >56 years without antihypertensive medication, >61 years without CVD and CVD risk factors). However, it may be worth noting that (a) compared to the full study sample, the diastolic blood pressure measurements in women were only slightly higher and in men almost identical to or in some cases even lower than those in the subgroup of participants without intake of antihypertensive medication (figure 7a-d); and (b) especially in men the median of all age groups was almost exactly 80 mmHg independent of the kind of risk group.

Figure 6: Percentile Distribution of the systolic blood pressure by five year age-groups and sex; (A) Women without antihypertensive intake, (B) Women without antihypertensive intake and no CVD risk factors.

The delta indicates the approximate increase of blood pressure in each percentile between the younger and older age groups

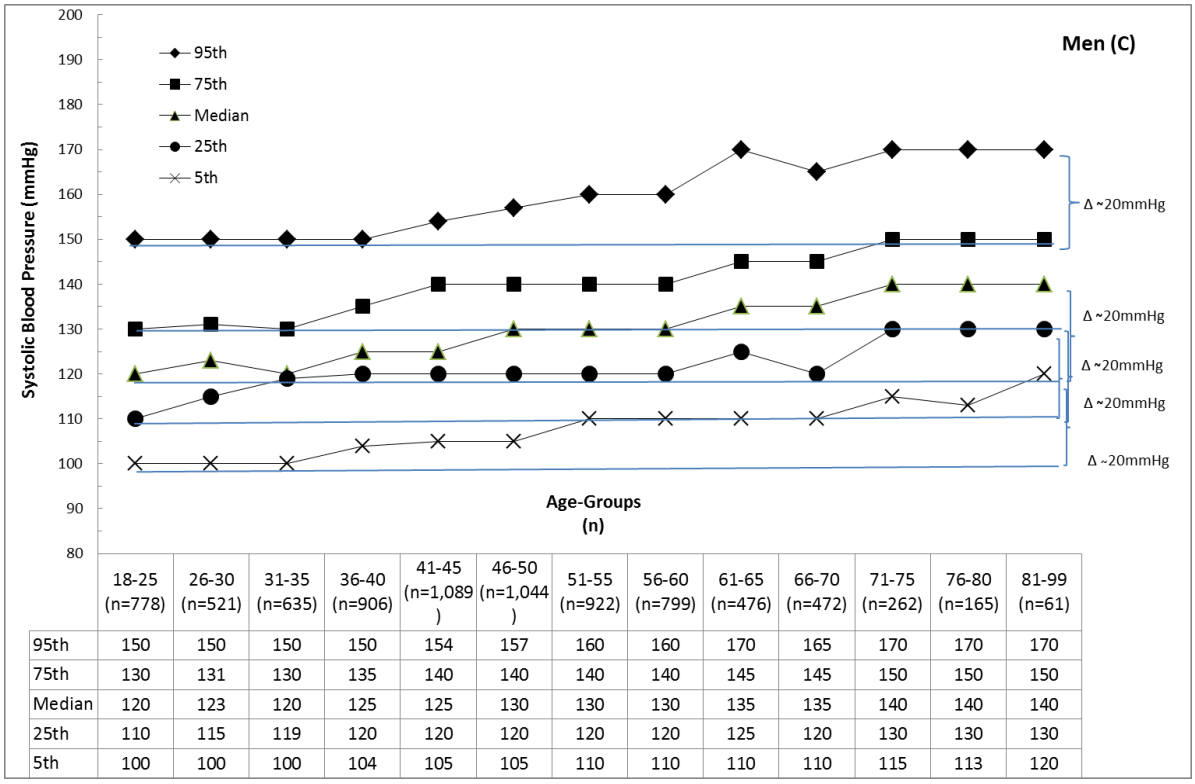


	18-25 (n=1,547)	26-30 (n=1,032)	31-35 (n=1,234)	36-40 (n=1,856)	41-45 (n=2,115)	46-50 (n=1,865)	51-55 (n=1,607)	56-60 (n=1,199)	61-65 (n=745)	66-70 (n=600)	71-75 (n=331)	76-80 (n=194)	81-99 (n=132)
95th	135	138	140	140	148	150	155	160	165	170	171	170	180
75th	120	121	125	125	130	130	135	140	140	145	150	150	150
Median	114	116	119	120	120	120	125	130	130	135	140	140	139
25th	110	110	110	110	110	110	115	120	120	124	125	130	130
5th	95	100	95	100	100	100	110	105	110	110	110	110	106

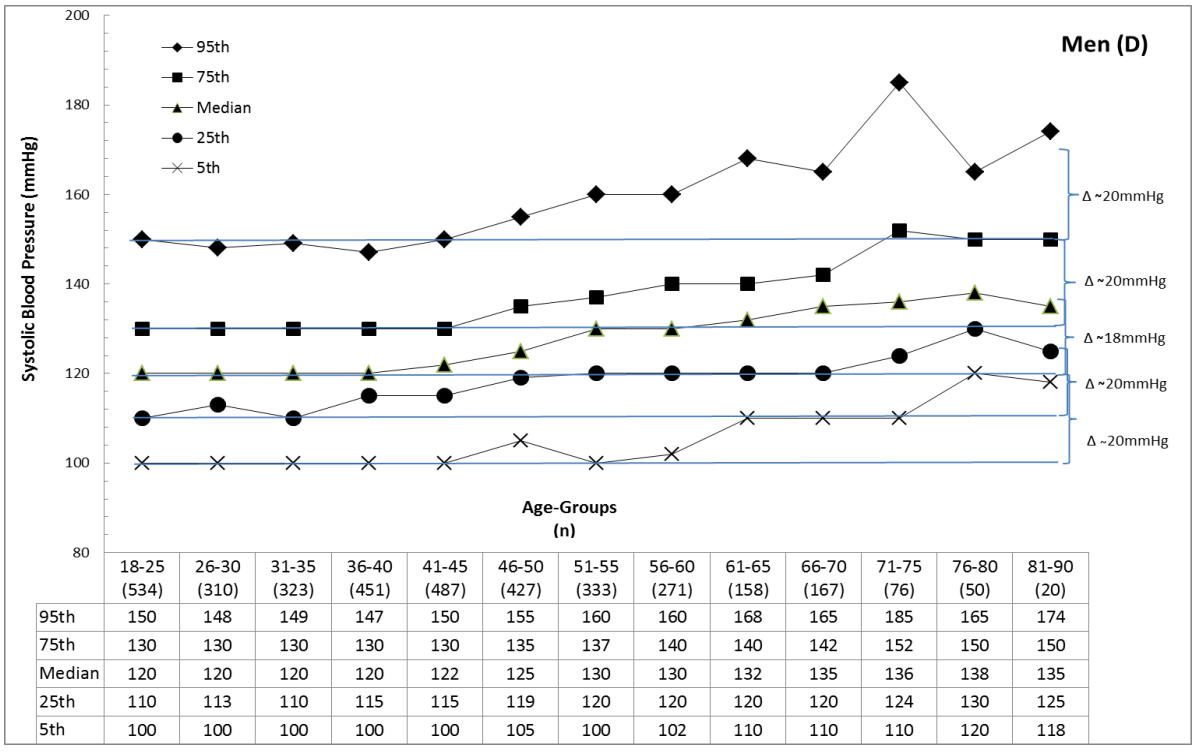


	18-25 (1,007)	26-30 (655)	31-35 (781)	36-40 (1,130)	41-45 (1,337)	46-50 (1004)	51-55 (805)	56-60 (496)	61-65 (279)	66-70 (216)	71-75 (86)	76-80 (54)	81-90 (33)
95th	135	132	137	135	140	145	150	160	160	170	164	165	190
75th	120	120	120	120	126	130	130	139	140	140	145	140	152
Median	110	113	115	115	120	120	120	124	130	130	133	130	140
25th	105	110	110	110	110	110	110	115	120	120	120	123	130
5th	90	99	95	100	98	100	100	100	110	110	110	110	100

Figure 6: Percentile Distribution of the systolic blood pressure by five year age-groups and sex; (C) Men without antihypertensive intake, (D) Men without antihypertensive intake and no CVD risk factors.
The delta indicates the approximate increase of blood pressure in each percentile between the younger and older age groups

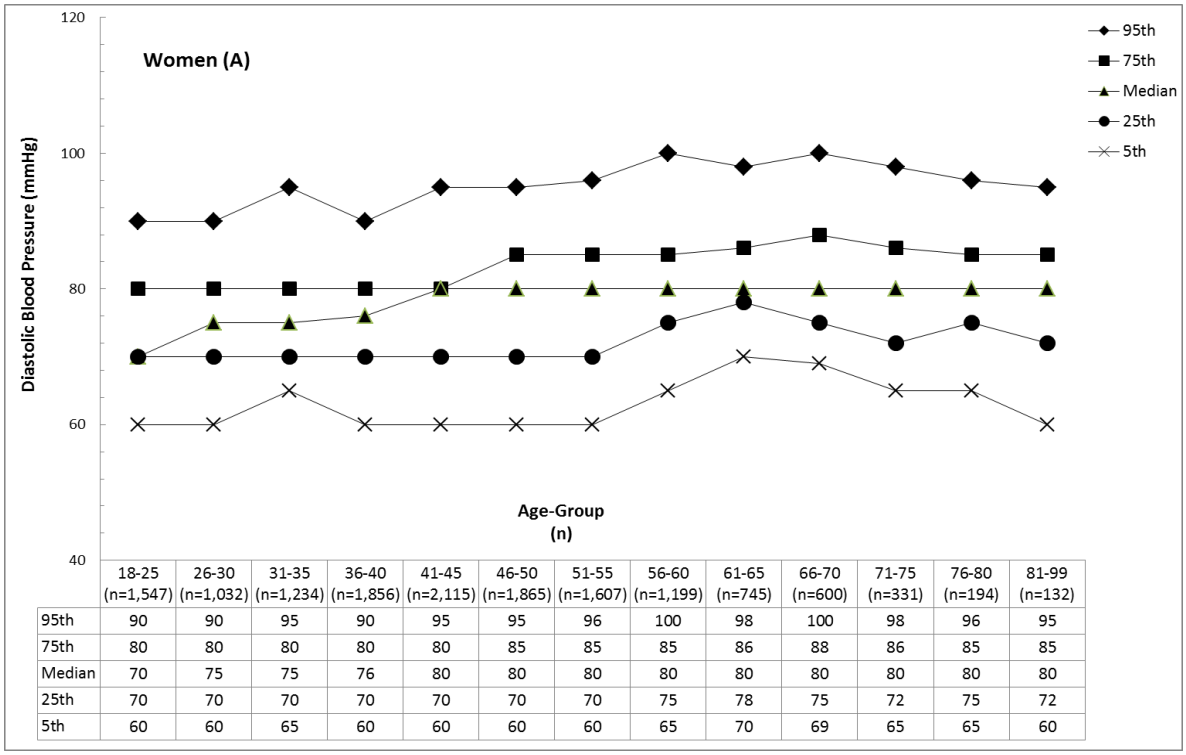


	18-25 (n=778)	26-30 (n=521)	31-35 (n=635)	36-40 (n=906)	41-45 (n=1,089)	46-50 (n=1,044)	51-55 (n=922)	56-60 (n=799)	61-65 (n=476)	66-70 (n=472)	71-75 (n=262)	76-80 (n=165)	81-99 (n=61)
95th	150	150	150	150	154	157	160	160	170	165	170	170	170
75th	130	131	130	135	140	140	140	140	145	145	150	150	150
Median	120	123	120	125	125	130	130	130	135	135	140	140	140
25th	110	115	119	120	120	120	120	120	125	120	130	130	130
5th	100	100	100	104	105	105	110	110	110	110	115	113	120

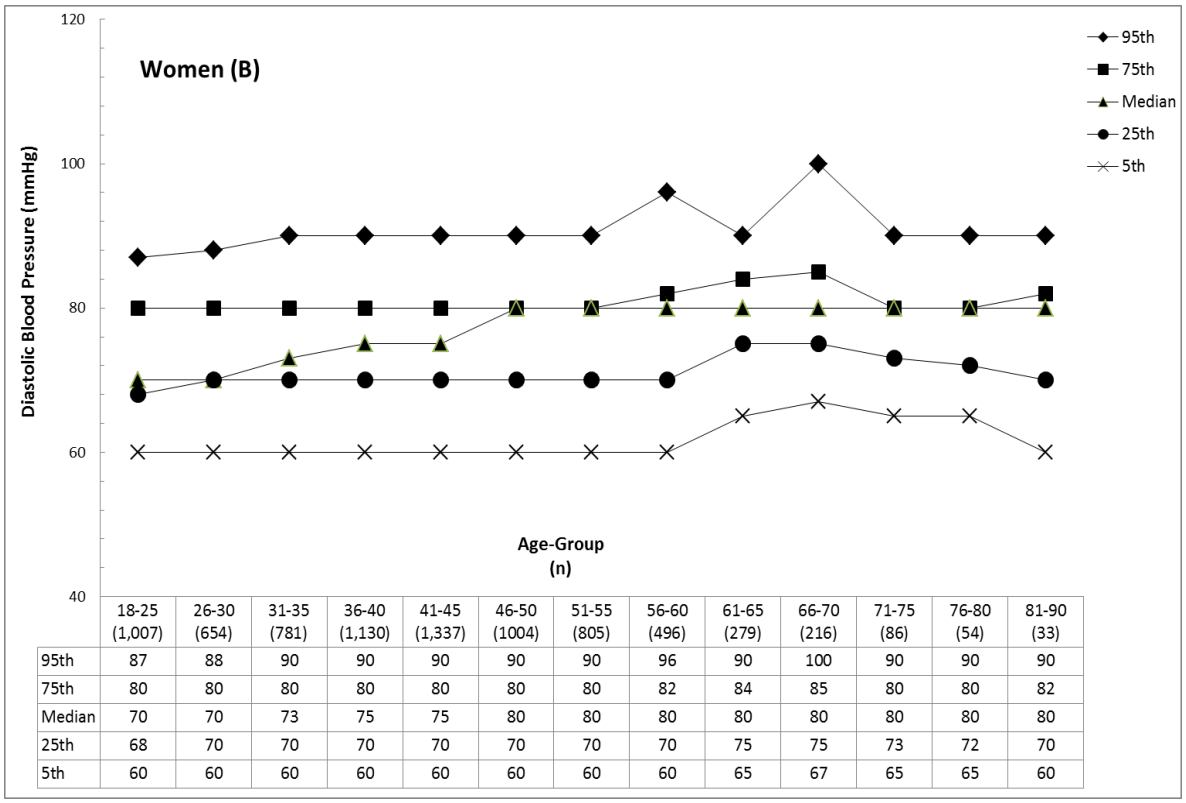


	18-25 (534)	26-30 (310)	31-35 (323)	36-40 (451)	41-45 (487)	46-50 (427)	51-55 (333)	56-60 (271)	61-65 (158)	66-70 (167)	71-75 (76)	76-80 (50)	81-90 (20)
95th	150	148	149	147	150	155	160	160	168	165	185	165	174
75th	130	130	130	130	130	135	137	140	140	142	152	150	150
Median	120	120	120	120	122	125	130	130	132	135	136	138	135
25th	110	113	110	115	115	119	120	120	120	120	124	130	125
5th	100	100	100	100	100	105	100	102	110	110	110	120	118

Figure 7: Percentile Distribution of the diastolic blood pressure by five year age-groups and sex; (A) Women without antihypertensive intake, (B) Women without antihypertensive intake and no CVD risk factors

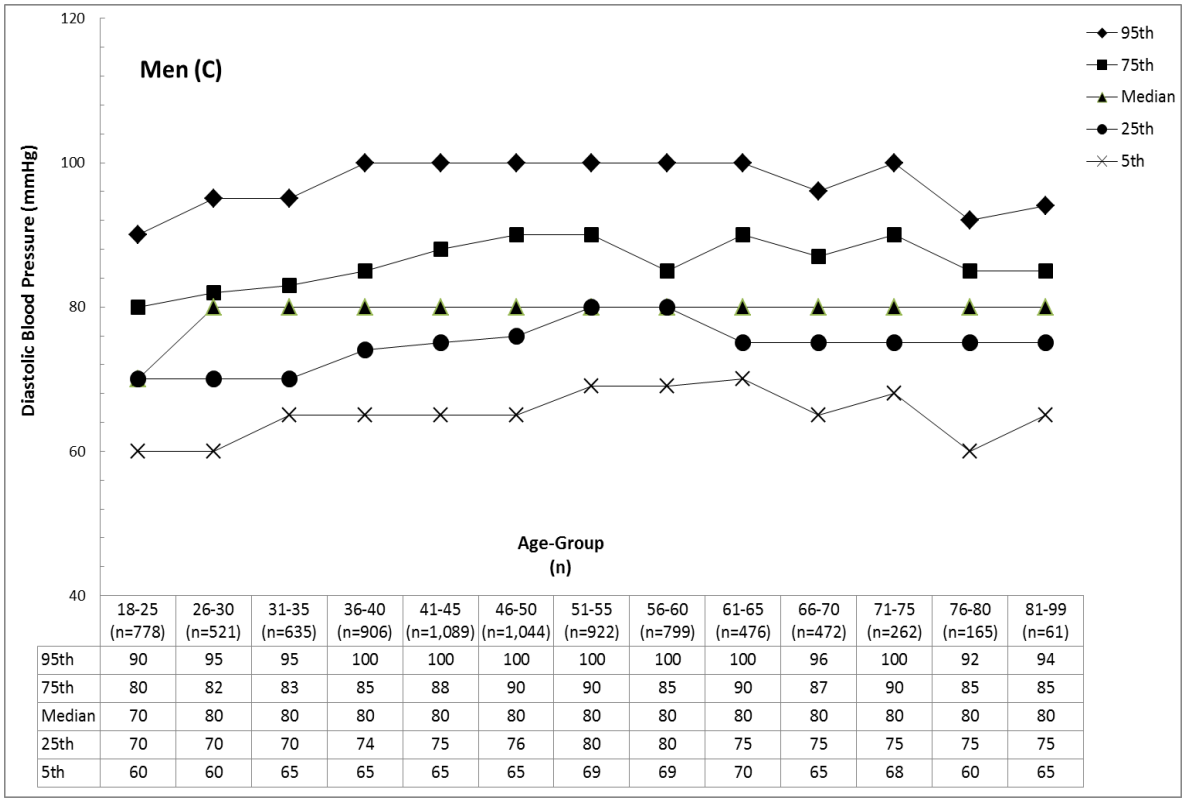


	18-25 (n=1,547)	26-30 (n=1,032)	31-35 (n=1,234)	36-40 (n=1,856)	41-45 (n=2,115)	46-50 (n=1,865)	51-55 (n=1,607)	56-60 (n=1,199)	61-65 (n=745)	66-70 (n=600)	71-75 (n=331)	76-80 (n=194)	81-99 (n=132)
95th	90	90	95	90	95	95	96	100	98	100	98	96	95
75th	80	80	80	80	80	85	85	85	86	88	86	85	85
Median	70	75	75	76	80	80	80	80	80	80	80	80	80
25th	70	70	70	70	70	70	70	75	78	75	72	75	72
5th	60	60	65	60	60	60	60	65	70	69	65	65	60

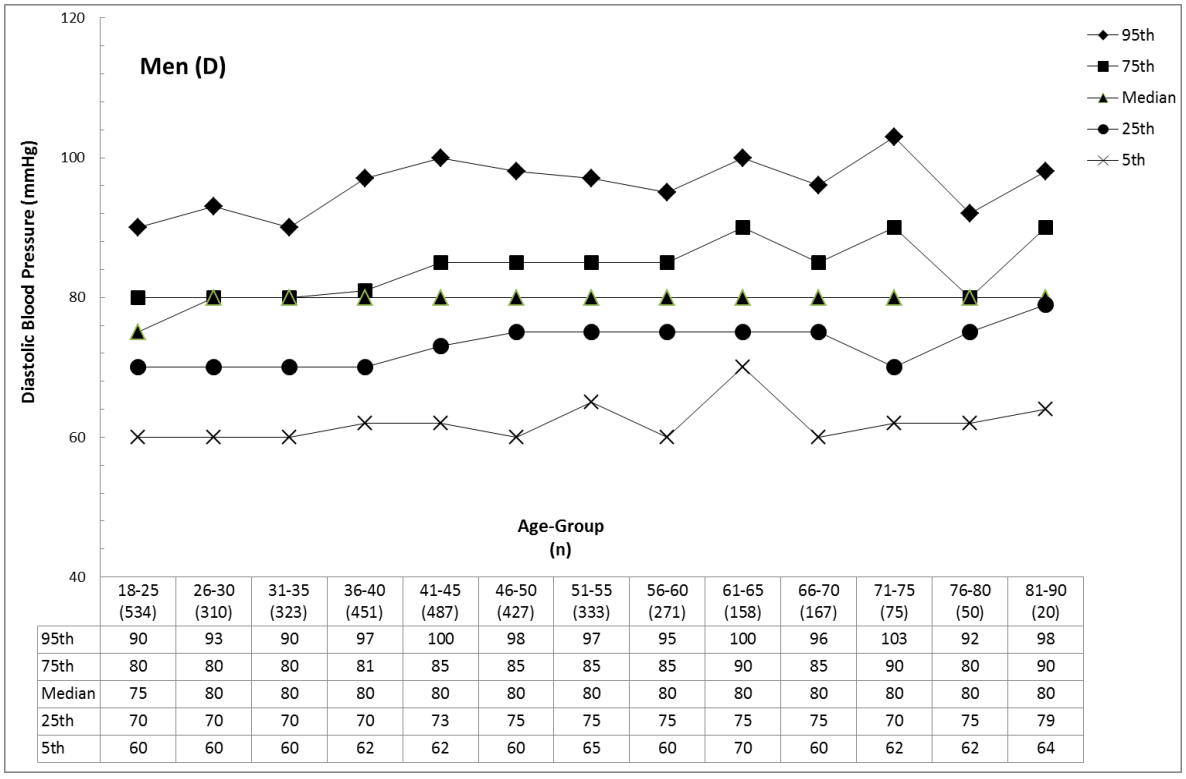


	18-25 (1,007)	26-30 (654)	31-35 (781)	36-40 (1,130)	41-45 (1,337)	46-50 (1004)	51-55 (805)	56-60 (496)	61-65 (279)	66-70 (216)	71-75 (86)	76-80 (54)	81-90 (33)
95th	87	88	90	90	90	90	90	96	90	100	90	90	90
75th	80	80	80	80	80	80	80	82	84	85	80	80	82
Median	70	70	73	75	75	80	80	80	80	80	80	80	80
25th	68	70	70	70	70	70	70	70	75	75	73	72	70
5th	60	60	60	60	60	60	60	60	65	67	65	65	60

Figure 7: Percentile Distribution of the diastolic blood pressure by five year age-groups and sex; (C) Men without antihypertensive intake, (D) Men without antihypertensive intake and no CVD risk factors.



	18-25 (n=778)	26-30 (n=521)	31-35 (n=635)	36-40 (n=906)	41-45 (n=1,089)	46-50 (n=1,044)	51-55 (n=922)	56-60 (n=799)	61-65 (n=476)	66-70 (n=472)	71-75 (n=262)	76-80 (n=165)	81-99 (n=61)
95th	90	95	95	100	100	100	100	100	100	96	100	92	94
75th	80	82	83	85	88	90	90	85	90	87	90	85	85
Median	70	80	80	80	80	80	80	80	80	80	80	80	80
25th	70	70	70	74	75	76	80	80	75	75	75	75	75
5th	60	60	65	65	65	65	69	69	70	65	68	60	65



	18-25 (534)	26-30 (310)	31-35 (323)	36-40 (451)	41-45 (487)	46-50 (427)	51-55 (333)	56-60 (271)	61-65 (158)	66-70 (167)	71-75 (75)	76-80 (50)	81-90 (20)
95th	90	93	90	97	100	98	97	95	100	96	103	92	98
75th	80	80	80	81	85	85	85	85	90	85	90	80	90
Median	75	80	80	80	80	80	80	80	80	80	80	80	80
25th	70	70	70	70	73	75	75	75	75	75	70	75	79
5th	60	60	60	62	62	60	65	60	70	60	62	62	64

4.4 Validation of the observed age effects

4.4.1 Study characteristics of GEMCAS and Heinz Nixdorf Recall study subjects

A comparison of the study populations of the Heinz Nixdorf Recall study and the GEMCAS subsample restricted to participants aged 45-75 years is presented in Table 4. Men of the HNR sample were slightly more often overweight (54%) or obese (26.6%) compared to men of the GEMCAS subsample (48.9% resp. 28.6%). In women it was the opposite with 65.6% women in HNR being either overweight or obese compared to 67.6% women in GEMCAS. However, the mean WC for both men and women were higher in the GEMCAS subsample than in the HNR subjects. Overall, the GEMCAS subsample in both sexes had a better lipid profile compared to the HNR with lower means for total cholesterol, LDL, and higher means for HDL. Men in HNR had a higher mean SBP and DBP (138.0 mmHg, 83.9 mmHg) compared to the GEMCAS subsample (136.3 mmHg, 82.4 mmHg), In spite of a higher proportion of women in GEMCAS taking antihypertensive therapy compared to HNR women (45.6 % in GEMCAS, 38.4% in HNR) the mean SBP and DBP (133.4 mmHg and 81.2 mmHg) of GEMCAS women compared to the HNR women (128.4 mmHg and 79.0 mmHg). The mean blood glucose concentration was higher in HNR subjects compared to the GEMCAS subsample: 6.4 mmol/L in HNR and. 6.0 mmol/l in GEMCAS for men and 6.0 mmol/l in HNR and 5.5 mmol/l in GEMCAS for women. The anti-diabetic medication intake of HNR subjects was nearly half that of the GEMCAS sub sample. Nearly 7.3% men and 4.6% women from HNR were taking anti-diabetic medications compared to 15.7% men and 9.3% women from the GEMCAS sub sample. Men and women from the HNR cohort smoked more when compared to

the GEMCAS subsample. About 46.3% men in HNR and 22.7 % men in GEMCAS, 23.1% women in HNR and 18.8% women in GEMCAS smoked at the time of the study. The intake of antihypertensive and lipid lowering medications was also higher in GEMCAS subsample men (52.4% and 23.9% respectively) and women (45.6% and 15.0 % respectively) compared to the men (37.9% and 15.1% respectively) and women (34.8% and 11.3% respectively) in the HNR cohort. As expected from a patient based sample out of primary care practices compared to a population based sample, Men (26.6% in GEMCAS and 10.9% in HNR) and women (14 % in GEMCAS and 2.8% in HNR) in the GEMCAS subsample reported more of a history of CVD compared to HNR cohort.

Table 4. Comparison of GEMCAS and Heinz Nixdorf Recall (HNR) study subjects by sex, both aged 45-75 years

	MEN		WOMEN	
	GEMCAS (n=8,774)	**HNR (n=2,395)**	**GEMCAS (n=12,325)**	**HNR (n=2,419)**
Age (years) Mean (±SD)	59.1± 8.6	59.7± 7.8	58.2± 8.7	59.6± 7.8
BMI				
≤ 25 kg/m^2	22.5	19.4	36.4	34.4
25 - < 30 kg/m^2	48.9	54.0	39.0	37.2
≥ 30 kg/m^2	28.6	26.6	28.6	28.4
Waist circumference (cm) Mean (± SD)	101.6± 12.2	100.3± 10.8	90.1± 13.9	88.5± 12.9
Lipid Profile				
Total Cholesterol (mmol/l) Mean (± SD)	5.4 ± 1.1	5.8 ± 0.99	5.7 ± 1.0	6.0 ± 1.02
HDL (mmol/l) Mean (± SD)	1.4 ± 0.38	1.3 ± 0.37	1.8 ± 0.45	1.7 ± 0.44
LDL (mmol/l) Mean (± SD)	3.4 ± 0.94	3.8 ± 0.92	3.5 ± 0.94	3.8 ± 0.95
Triglycerides (mmol/l) median (Q1; Q3)	1.7 (1.2;2.6)	1.6 (1.1;2.3)	1.7 (1.0;2.0)	1.3 (1.0;1.8)
Blood Pressure (BP)				
Systolic BP (mmHg) Mean (± SD)	136.3 ± 18.3	138.0 ± 19.5	133.4± 18.9	128.4 ± 21.1
Diastolic BP (mmHg) Mean (± SD)	82.4 ± 10.3	83.9 ± 10.6	81.2 ± 10.4	79.0 ± 10.6
Fasting Blood glucose (mmol/l) Mean (± SD)	6.0 ± 2.21	6.4 ± 1.75	5.5 ± 1.75	6.0 ± 1.34
Smoking status (%)				
Current Smoker	22.7	46.3	18.8	23.1
Past Smoker	46.2	25.7	24.7	21.2
Never Smoker	31.1	28.0	56.5	55.7
Pharmacotherapy (%)				
Anti-diabetic	15.7	7.3	9.3	4.6
Antihypertensive	52.4	37.9	45.6	34.8
Lipid lowering	23.9	15.1	15.0	11.3
Comorbidities (%)				
Cardiovascular disease	26.6	-	14.0	-
Diabetes (self reported)	20.9	9.8	13.0	6.7
Coronary artery disease	-	10.9	-	2.8

- data not obtained

4.4.2 Linear regression analyses

The effects of age upon blood pressures for the GEMCAS subjects are presented in Table 5. In a first crude model linear regression was computed using systolic blood pressure or diastolic blood pressure as outcome and age as the predictor.

Age showed an effect on SBP in both sexes, and women had a higher effect of age on SBP with a ß value of 0.555 compared to men with a ß value of 0.355. After adjusting for antihypertensive medication, history of CVD, diabetes, smoking and BMI, the effect of age on SBP was still observable and also higher in women compared to men with ß values of 0.402 and 0.267 for women and men respectively.

Age showed an effect also on the DBP in both sexes, and women had a higher effect of age on DBP with a ß value of 0.154 compared to men with a ß value of 0.04 after adjustment for the above mentioned risk factors the effect of age upon DBP still persisted, even after adjustment women showed higher effects of age upon DBP compared to men, with ß values of 0.104 and 0.019 respectively for women and men (Table 5).

In subgroup analyses the same models as above were used, but the analyses was restricted the age group of 45 - 75 years.

Compared to the whole sample, the age effect on SBP was slightly higher for both men and women in the subgroup. Similar to the whole sample, the age effects on SBP were higher in women compared to men in the crude model with ß values of 0.651 and .0.385 for women and men respectively. After adjustment, the age effect in women markedly decreased, but was still higher compared to the age effect on SBP in men with ß values of 0.489, and 0.319 for women and men.

With regard to men and women aged between 45 and 75 years, contrasting effects of age were observed upon the DBP. In men, the diastolic blood pressure decreased with age (ß= -0.085), the decreasing effect remained even after adjustment (ß= -0.102). Whereas in women, a positive effect of age on DBP was observed (ß=0.096), which was still observable even after adjustment (ß=0.0420) (Table 5).

Table 5. Effect of age upon blood pressure for the GEMCAS subjects.

	Whole sample				Subjects aged 45-75 years			
	Men		Women		Men		Women	
	ß (SE)	P >t	ß (SE)	P >t	ß (SE)	P >t	ß (SE)	P >t
SBP								
Unadjusted								
Age	0.355 (0.009)	<0.0001	0.555 (0.007)	<0.0001	0.385 (0.022)	<0.0001	0.651 (0.019)	<0.0001
Adjusted*								
Age	0.267 (0.011)	<0.0001	0.402 (0.009)	<0.0001	0.319 (0.024)	<0.0001	0.489 (0.021)	<0.0001
DBP								
Unadjusted								
Age	0.040 (0.006)	<0.0001	0.154 (0.004)	<0.0001	-0.085 (0.013)	<0.0001	0.096 (0.010)	<0.0001
Adjusted*								
Age	0.019 (0.006)	0.005	0.104 (0.005)	<0.0001	-0.102 (0.015)	<0.0001	0.0420 (0.013)	0.008

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; ß**,** effect estimator for age; SE, Standard Error; P >t, P Value;

*Adjusted for: antihypertensive medication, CVD history, diabetes, anti-diabetic medication, smoking, BMI

4.4.3 Five year differences of blood pressure values in Heinz Nixdorf Recall subjects

The blood pressure differences for HNR subjects between baseline (t_0) and five year follow-up (t_1) are presented in Table 6. The cumulative mean difference of the systolic blood pressure (Δ SBP_{t1-t0}) was higher in women (+2.87 mmHg) compared to men (+0.51 mmHg). The cumulative mean DBP (Δ DBP_{t1-t0}) declined more in men (-3.21mmHg) compared to women (-1.52 mmHg) between baseline and 5-year follow up.

In a sub-group analysis of "healthy" study participants – excluding participants (93% of the whole sample) with diabetes, CAD, overweight, intake of antihypertensive and/or anti-diabetic medications, a history of smoking or current smokers – the difference of the systolic BP between follow-up and baseline was even higher in both women and men (ΔSBP_{t1-t0}: +6.65 mmHg, respective +2.08 mmHg) compared to the whole study sample. With regard to the diastolic blood pressure the cumulative mean DBP in this very specific "healthy" group declined in men by -2.0 mmHg, which is similar to the whole study sample, but increased in women by +0.52 mmHg, which is an opposite trend compared to the whole study sample of women.

4.4.4 Expected versus observed blood pressure readings in the Heinz Nixdorf Recall Study

The expected and observed means of blood pressure readings in HNR subjects are presented in Table 7. Despite the different study characteristics of both GEMCAS and Heinz Nixdorf Recall, the expected and observed blood

pressures readings were surprisingly alike, with only slightly higher observed than expected blood pressures in both sexes and irrespective of the risk factor status. In women the difference was only 0.9 mmHg (131.3 mmHg resp. 130.4 mmHg), which was despite the high sample size not significant. In men the expected and observed values differed by 1.8 mmHg (139.7 mmHg to 137.9 mmHg).

The difference between expected and observed was higher with regard to the DBP. Here in men differences of 2.9 mmHg (83.7 mmHg to 80.8 mmHg), and in women 2.1 mmHg (79.5 mmHg to 77.4 mmHg) were observed.

Table 6. Mean BP differences in HNR study subjects between baseline and 5-year follow up, by sex

	Complete HNR cohort (N=4,814)		HNR Sub-sample* (N=310)	
	Men [mmHg]	Women [mmHg]	Men [mmHg]	Women [mmHg]
Δ SBP_{t1-t0} (mean ± SD)				
Cumulative (5 years)	0.51 (±19.30)	2.87 (±19.52)	2.10 (±11.98)	6.65 (±16.27)
Yearly (year)	0.10 (±3.86)	0.57 (±3.90)	0.42 (±2.40)	1.33 (±3.25)
Δ DBP_{t1-t0} (mean ± SD)				
In 5 years	-3.21 (±11.07)	-1.52 (±10.46)	-2.00 (±8.69)	0.51 (±8.78)
Yearly (year)	-0.64 (±2.21)	-0.34 (±2.09)	-0.40 (±1.74)	0.10 (±1.76)

*No CAD history, no diabetes, no smoking history, normal BMI, no intake of antihypertensive and anti-diabetic medications

Table 7: Expected and observed blood pressures HNR

	Men (N= 2,384)			**Women (N=2,415)**		
	Expected	**Observed**	**P value**	**Expected**	**Observed**	**P value**
Mean (± SD) SBP (mmHg)	139.7 (±19.5)	137.9 (±19.2)	-	131.3(±20.8)	130.4 (±19.9)	-
Mean (± SD) DBP (mmHg)	83.7 (±10.6)	80.8 (±10.8)	-	79.5 (±10.3)	77.4 (±10.0)	-
Median SBP (mmHg)	138.4	137.0	0.038	128.8	128.5	0.988
Median DBP (mmHg)	83.1	80.0	<0.0001	79.0	77.0	<0.0001

- Not computed

Chapter 5

Discussion

This work was aimed (a) to analyse the distribution of the systolic and diastolic blood pressure in a German healthcare population with regard to age, sex and cardiovascular risk factors, and (b) to examine if age related effects on blood pressure observed in a cross-sectional study could be reproduced in an independent longitudinal study.

This study provides for the first time, detailed descriptive estimates of the distribution of the systolic and diastolic blood pressure for both sexes and for a wide age range of age, taking into account individuals with and without CVD and CVD risk factors. The application of percentiles rather than one single measure of location - e.g. the arithmetic mean - combines aspects of ordered data and cumulative frequencies. Together with the large sample size of 35,869 participants of GEMCAS, it was possible to perform a percentile distribution for men and women at the age of 18 to 99 years and to learn more about the full range of blood pressure variation, especially in the borderline range.

In the first section of the discussion (5.1) key findings of the study will be summarized. In the following sections (5.2) the mean blood pressure readings will be discussed, followed by a detailed discussion of percentile distribution of blood pressure (5.3) and sensitivity analyses (5.4). Section (5.5) discusses the validation of the effects of age. The discussion chapter closes with an overview of strengths and limitation of the work (5.6) followed by the conclusion (5.7).

5.1 Key findings

In both sexes the mean systolic and diastolic blood pressure showed the well-known gradual increase with age especially up to the age of 60 years, followed by a flattened course of the systolic and an almost constant course of the diastolic blood pressure.

A consistent increase of the systolic blood pressure with age was not only restricted to the mean blood pressure readings, but could also be observed in all percentiles examined. Even in the lowest percentile (5^{th}) a gradual increase from the age-group <25 to >80 years of about 10 mmHg in men, in all other percentile groups an increase of 20 mmHg. Accordingly, as women exhibit lower blood pressures in younger and cross men in middle age their increases form the youngest to the higher age-groups ranged from 15 mmHg (5^{th}) to 40 mmHg (95^{th}).

Furthermore, the ranges between the 5^{th} and 95^{th} SBP percentiles in the youngest and the oldest age groups varied considerably in both sexes and did not proceed in parallel with age. The range of the 5^{th} - 95^{th} SBP percentile was 100-150 mmHg in the youngest age group and 115-180 mmHg in the oldest age group in men. Whereas in women, the ranges were 95-136 mmHg and 110-180 mmHg for the youngest and the oldest age groups.

In men without any antihypertensive therapy, an increase of 20 mmHg of the SBP between the youngest and the oldest age groups was observed. In women an increase of at least 20 mmHg could be observed in all percentiles between the youngest and the oldest age groups. Except in the 5^{th} percentile a lower increase was observed (11 mmHg). A similar increase between the youngest and the oldest age groups was observed in a subpopulation of “healthy” subjects without any history of CVD and/or any CVD risk factors: all percentiles

showed an increase of at least 15 mmHg of SBP in men, in women the increase was at least 25 mmHg in all the percentiles except the 5th percentile (10 mmHg).

The DBP percentiles showed a different picture when compared to the SBP, as the age related differences in the percentiles were minimal irrespective of the occurrence of cardiovascular risk factors. Overall it seemed that low diastolic blood pressure readings are associated with greater age-related changes.

The age related changes in the blood pressure observed in the cross sectional data from the GEMCAS sample could also be observed in the longitudinal Heinz Nixdorf Recall study. Although the rise in blood pressures with respect to age was slightly different in both studies, a definite age related shift was observed in both the samples and this age related shift was independent of the occurrence of cardiovascular risk factors.

Overall an increase of the SBP of 0.10 mmHg/year in men and 0.57 mmHg/year in women could be observed in the Heinz Nixdorf Recall study after five years during the follow up examination. In the sub-sample of subjects without CVD risk factors the increases were 0.42 mmHg/year and 1.33 mmHg/year for men and women respectively.

In the HNR study cohort, the mean expected SBP (calculated by data of the GEMCAS sample) was only slightly higher than the mean observed SBP in both men (1.8 mmHg) and women (0.9 mmHg). The expected mean DBP was higher than the observed mean DBP in both sexes.

Thus our data suggest that an age-related increase in systolic blood pressure occurs independently of known associated factors for elevated blood pressure as part of an age-relating process.

5.2 Age related changes in blood pressure

The effects of age upon blood pressure were studied extensively both in cross- sectional studies (Joffres et al. 1992, Plans 1993, Burt et al. 1995, Banegas 1998, Thamm 1999) and longitudinal studies (Harlan et al. 1962, Landahl et al. 1986, Pearson et al. 1997). Age related changes in blood pressure when studied, showed that the blood pressure differences between men and women were most obvious in young, middle ages, but in the later ages the differences narrowed down (Whelton 1994). GEMCAS study results with respect to mean blood pressure in different age classes in Germany were almost in concordance to a previous nationwide German study conducted in 1998 (Thamm 1999). Both studies showed that the mean SBP and DBP values in men were clearly higher than women in young and middle ages but the values did not differ much after 60 years of age. A similar trend for mean SBP was also observed in other studies (Joffres et al. 1992, Plans et al. 1993, Asmar et al. 2001, Primatesta et al. 2001, Azizi et al. 2002,).

The SBP in women crossed the SBP level in men around the age of 60 years which is well in line to other studies (Plans et al. 1993, Azizi et al. 2002, Wilkins et al. 2010). This cross-over and thus higher blood pressures in women compared to men are probably due to the fact that men with higher blood pressure values have a higher mortality rate than women especially in the older ages. This is a major problem when data from cross-sectional studies are analysed. This selective survival of men with lower blood pressure and higher mortality of men with higher blood pressure might lead to a less proportional representation of men in the cross-sectional surveys and thereby might lead to underestimation of the effect of age on systolic and diastolic blood pressure. Although, the selective

survivorship has been the most widely postulated concept with cross-sectional studies, this concept has been challenged by Franklin et al. 1997. In their analyses of the blood pressure data from the Framingham study they found that, even when all deceased participants and patients with non-fatal myocardial infarction or congestive heart failure were removed from their study sample, the late decline of the diastolic blood pressure was still present (Franklin et al. 1997).

5.3 Percentile distribution of blood pressure

Many studies in the past examined the blood pressure distribution in different populations across the world (Joffres et al. 1992, Plans et al. 1993, Wolf et al. 1997, Banegas et al. 1998, Thamm 1999, Asmar et al. 2001, Wolf-Maier et al. 2003, Wang, Wang 2004, Choi et al. 2006, Yadav et al. 2008, Erem et al. 2009, Wilkins et al. 2010). However, very few studies analyzed the percentile distribution of blood pressure in the population and even less with respect to age, sex and cardiovascular risk factors (Acheson 1973, Pobee et al. 1977, Lim et al. 2000, Azizi et al. 2002, Wright et al. 2011).

A study from Acheson (1973) described the distribution of the systolic and diastolic blood pressure in a nationwide sample of 6,546 subjects of the two largest racial groups in the United States, aged 18-79 years. As in our study, the data of this survey showed the same age-related increase in the systolic blood pressure even in the 5th percentile. Compared to our study sample, the absolute readings and age-related increases in the blood pressure readings were considerably higher (as expected especially in the higher blood pressure ranges), the latter ranging from 16 mmHg in the 5th percentile to 73 mmHg in the 95th percentile in women (men: 10-57 mmHg); In GEMCAS we found (taking into

account the maximum age of 79 years): 15-41 mmHg in women; 10-20 mmHg in men, cf. figure 4). However, this survey was conducted more than 50 years ago. Recent NHANES data representing the period 2001-2008 and including 19,921 participants reported much lower blood pressure readings (Wright et al. 2011). They reported an age-related increase in blood pressure readings ranging from 13 mmHg in the 5th percentile to 53 mmHg in the 95th percentile in women, in men this was only 2 mmHg in the 5th percentile and 31 mmHg in the 95th percentile. With the exception of the low increase in men in the 5th percentile, these recent data are in line with the observation made in GEMCAS study (Wright et al. 2011).

. The increase of SBP with respect to age in the study of Acheson was comparatively higher than in GEMCAS, especially observable in the higher percentiles. Acheson reported that half of all men had a SBP of at least 120 mmHg by the age of 18 years. This means to say that under the current guidelines for definition of hypertension, at least half of the men were prehypertensive by the age of 18 years, which is similar to men in the GEMCAS study.

Pobee et al. (1977) in their study observed the blood pressure distribution in Ghanaian population, comprising 1,670 subjects who were 16 years and older. Similar to GEMCAS they also found that in most of the age groups of their study population the mean blood pressure was higher than the median value. They additionally reported an age related increase of SBP in women of at least 20 mmHg between the youngest (15-24 years) and the oldest age groups (>75 years). Whereas in men a considerable age related SBP increase was observed only in the 75th and 95th percentiles between the youngest and the oldest age groups (Pobee et al. 1977). Although the study results from Pobee et al. were comparable to GEMCAS, they were not similar with respect to increase in SBP

percentiles. However, a set of important differences between both studies might explain these differences: Pobee and co-workers used a mean of three blood pressure measurements, whereas in GEMCAS it was only a single measurement, also the various ethnicities, the much younger study population (<45 years) and the noticeable lower sample size in the Ghanaian might all play an important role.

In another study conducted by Lim et al. (2000) from a Malaysian sample of 9,656 subjects aged 30 years and above, there was a clear increase of SBP percentiles with respect to age. In women they reported an increase of at least a 20 mmHg of SBP from the youngest (30-34 years) to the oldest (>70 years) in all the percentiles (5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th}). These increases of 20 mmHg they observed in men for the 50^{th}, 75^{th} and 95^{th} percentiles, too (Lim et al. 2000). Although this study used two measurements for the assessment of blood pressure, their results are well in concordance with the results of GEMCAS women.

The age related increase of DBP percentiles was comparable to all studies citied here, especially in studies with high sample sizes. Pobee et al. 1977 and Lim et al. 2000 reported an only small age related shift of DBP, the median DBP across youngest to oldest age groups differed by less than 5 mmHg (Pobee et al. 1977, Lim et al. 2000). In GEMCAS the median DBP value was almost constant for men and differed by 10 mmHg between younger and older age groups in women.

5.4 Sensitivity analyses

Azizi et al. (2002) described the distribution of blood pressure in Iranian population from the Tehran Lipid and Glucose study. They analysed blood

pressure data from 7,825 participants aged between 20-69 years, not taking any antihypertensive medications. An age-related increase (age group 20-29 to 60-69 years) in systolic blood pressure in both sexes can be abstracted from the tables by Azizi et al (Azizi et al. 2002). This increase ranges from 15 mmHg in the 5th percentile to 44 mmHg in the 95th percentile in women. This is well in line with the GEMCAS data of 15-35 mmHg (cf. figure 6a) taking into account the subgroup of participants without antihypertensive treatment and the age range of the study group of Azizi et al. (at most 69 years). In men, the respective data in the Azizi et al. study were 8-39 mmHg; in GEMCAS sample the age-related increase was lower, especially in the highest percentile (10-15 mmHg).

Azizi et al. observed that the DBP percentiles (5th, 25th, 50th, and 75th) did not differ by more than 5 mmHg across the age groups in both the sexes (Azizi et al. 2002). The age related increases in DBP observed in the GEMCAS sub-sample of subjects with no antihypertensive medications intake, differed slightly with the increases in DBP percentiles observed by Azizi et al. In the GEMCAS sub-sample men showed a difference of at least 10 mmHg across ages in 5th, 25th, 75th, and 95th percentiles, whereas women showed a difference of at least 10 mmHg in the 50th, 75th, and 95th percentiles.

5.5 Validation of the effects of age

In cross-sectional studies that investigated the effects of age upon blood pressure, although it is well established that age has an effect on blood pressure, the limitation of the study design does not allow to draw conclusions about causality that, the observed effects are due to age alone. The effects of age upon

blood pressure observed in cross-sectional studies might be due to a) Selective survivorship or b) Birth cohort effects.

Selective survivorship (shifting the blood pressure readings downwards) is a widely postulated concept within cross-sectional studies. To overcome these limitations of the cross-sectional study, the observed age-effect in GEMCAS (by calculating estimators for the age effect) was validated by applying on baseline blood pressure data in HNR to compute expected blood pressure readings in the HNR subjects. These expected blood pressure readings were then compared with the measured blood pressure readings in the 5 year follow up examination. To my knowledge there is no study that validated the effects of age observed in a cross-sectional data set with an independent longitudinal study, and this work is the first to do so. In men the expected SBP was only 1.8 mmHg higher compared to the measured SBP. In women this difference was even lower with 0.9 mmHg, and despite the high sample size it was non-significant. The slight differences in the age related effects in both the GEMCAS and Heinz Nixdorf Recall study sample could be possibly due to the risk factor profiles of the subjects. GEMCAS being a patient based sample is expected to have subjects with higher risk factors and receive more pharmacotherapy, which could influence the progression of blood pressure with age. BMI and weight gain are considered to be some of the important risk factors for the progression of blood pressure (Vasan et al. 2001). GEMCAS subjects were more obese than the HNR subjects (cf. Table 4). Also well known risk factors for increasing blood pressure like physical activity, smoking habits, diet with high salt intake and family history of hypertension, could be reasons for a difference in the blood pressure progression in both the study samples.

Thus from this analyses it could be shown that, although with slight differences, the age effect upon blood pressure observed in the cross-sectional study GEMCAS was reproducible in an independent , HNR longitudinal study for men and women aged from 45 to 75 years.

5.6 Strengths and Limitations of the work

The strengths of this work include the nationwide approach, the large sample size and the extensive quality assurance concept of the GEMCAS study. The large study size allows a comprehensive description of the full range of the blood pressure distribution and provides sufficient precision even when stratifying the sample into small age groups, sex, or presence or absence of risk factors. A notable advantage of the GEMCAS study is the broad age range, which includes very old individuals even over the age of ninety. The reliability of the GEMCAS data is also a strength for this work. Although the GEMCAS study is a patient based sample it has been successfully used as a population control for other clinical studies (Kahl et al. 2010, Kahl et al. 2011). A further strength of this work is the comparison and validation of the GEMCAS finding with data of the well-known prospective Heinz Nixdorf Recall Study. As to my knowledge, there is no study that validated the effects of age observed in a cross-sectional study in an independent longitudinal data and this work is the first of its kind. Since special cardiology practices were excluded from the study, there is a possibility that very high blood pressure readings may have been underreported. However, the blood pressure readings in GEMCAS are comparable to those of the German National Health Interview and Examination Survey from 1998 (Thamm 1999). The study characteristics of this primary health care sample are comparable to other German

population-based samples and to the German federal statistical data with regard to anthropometric measures, smoking status, marital status, schooling and unemployment rate (i.e. GEMCAS: 10.2%, Germany October 2005: 10.4%). This high conformance might be explained by the fact that 92% of adults in Germany consult a general practitioner at least once a year (Kohler et al. 2004).

Several aspects must be considered with regard to the blood pressure measurements. (1) Blood pressure measurements were conducted with automated and manual blood pressure devices, whichever was available at the participating physician's practice. As has been shown in other studies (Coe et al. 2002, Stang et al. 2006) and replicated in GEMCAS study, automated devices systematically measure higher blood pressure values than manual devices. In GEMCAS, the mean systolic and diastolic blood pressures differed between manual and automated devices by +5 mmHg and +2 mmHg in men (and +3 mmHg and +1 mmHg respectively in women). By way of comparison, in the study by Stang et al. (2006) the difference was reported to be 7.0 mmHg in men and 1.1 mmHg in women for the systolic blood pressure, and 3.4 mmHg and 1.9 mmHg respectively for the diastolic blood pressure. However, over 70% of the sample had been measured with manual devices, and no evidence was found in GEMCAS that manual and automated devices were systematically distributed between the participating practices (i.e. automated devices in practices with a higher proportion of participants with high blood pressure readings). (2) GEMCAS results are based on one blood pressure measurement. The recommended double measurements with at least two minutes of recovery between measurements could not be accomplished in this real-life setting. Thus GEMCAS blood pressure readings are likely to be overestimated. However, the pattern of the overall distribution of both

systolic and diastolic blood pressure should not have been fundamentally influenced by this procedure. Furthermore, previous studies documented that accurate group means could be obtained with single readings. This is particularly true when the single blood pressure measurement is taken under appropriate conditions (Wolf-Maier et al. 2003). (3) As this was a cross-sectional study, the observed age-related courses of the blood pressure readings are influenced by possible selective survivorship (shifting the blood pressure readings downwards). Although selective survivorship is a widely postulated concept within cross-sectional studies, it has been challenged particularly in relation to the diastolic blood pressure decline in older age by Franklin and co-workers (1997) who reported a late decline in diastolic blood pressure even after removing the deceased participants and subjects with non-fatal myocardial infarction or congestive heart failure from the study. (4) Birth cohort effects may have influenced the course of the blood pressure readings as well. The wide age-range of GEMCAS sample encompasses a number of birth cohorts (1906 – 1987) with different social and environmental conditions and lifestyles, resulting in different blood pressure readings. Therefore the observed age course in GEMCAS sample might be due to intergenerational effects. However, i tried to observe for any possible birth cohort or healthy survivor effect by applying the age-effect estimated in GEMCAS in an independent longitudinal and population-based cohort HNR and were able to reproduce the age effects observed in GEMCAS in the independent longitudinal population based cohort.

5.7 Conclusions

This study showed an age-related increase in the systolic blood pressure readings in all percentiles in both men and women, independent of the intake of antihypertensive medication, and/or presence of CVD or CVD risk factors. These data thus suggest that an age-related increase in the systolic blood pressure is independent of known associated risk factors for elevated blood pressure. This is the first study to provide detailed information on the population distribution of blood pressure readings relating to both sexes, very old individuals and CVD risk factors. One benefit of this study is that it may serve as a resource for planning future biomedical and epidemiological studies in which blood pressure plays a key role. The detailed descriptive statistics and especially the dispersion measures may help during sample size calculation and power analysis. Furthermore, these data are useful for public health issues in planning the extent of necessary prevention strategies tailored to affected age groups and both sexes to control progression into hypertension among people with normal blood pressure.

6. Summary

Many epidemiological studies have addressed various aspects of blood pressure, ranging from descriptions of normal blood pressure distributions in different populations to the influence of age and other factors on blood pressure. However studies consider blood pressure in terms of hypertension, assessing prevalence, treatment and control of hypertension in diverse populations. Very few studies are available dealing with the distribution of blood pressure values in population as percentiles, none of which is from Europe and none of which addresses a wide age range, sex and coexisting cardiovascular risk factors.

Therefore, main aim of this thesis was to examine in detail the distribution of blood pressure of a large cross sectional study sample of 35,869 women and men aged 18-99 years. The second aim was to validate the observed age-effects in the cross-sectional German Metabolic and Cardiovascular Risk Study, in the independent, longitudinal and population-based Heinz Nixdorf Recall study, using baseline and 5 year follow up data of 4,157 men and women, aged 45-75 years.

This study showed an age-related increase of the systolic blood pressure in all percentiles in both men and women, independent of the intake of antihypertensive medication, and/or presence of Cardiovascular Disease (CVD) or CVD risk factors. This is the first study to provide detailed information on the population distribution of blood pressure readings relating to both sexes, very old individuals and CVD risk factors. Furthermore, the age related increase observed in the systolic blood pressure in the cross sectional study could be confirmed for men and women, aged 45-75 years in the independent, longitudinal Heinz Nixdorf Recall study.

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List of Tables and Figures

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Abbreviations

AOD	Automated Oscillometric Device
BGS	Bundesgesundheitssurvey
BMI	Body Mass Index
CHD	Coronary Heart Disease
CNS	Central Nervous System
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EBCT	Electron Beam Computerized Tomography
ESH	European Society of Hypertension
ESC	European Society of Cardiology
GEMCAS	German Metabolic and Cardiovascular Risk Study
GEP	Good Epidemiology Practices
JNC 7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
HDL	High Density Lipoprotein
HNR	Heinz Nixdorf Recall Study
LDL	Low Density Lipoprotein
MAP	Mean Arterial Pressure
PP	Pulse Pressure
RECALL	Risk Factors, Evaluation of Coronary Calcium and Lifestyle
SBP	Systolic Blood Pressure
RZS	Random Zero Sphygmomanometer

Appendix

Tables

Table 1: Comparison of characteristics of GEMCAS subjects according to blood pressure in men (crude and age-standardized)

	Normal Blood Pressure n=1,555		**Prehypertension** n=6,042		**Stage I Hypertension** n=4,397		**Stage II Hypertension** n=1,880	
	Crude	Standardized	Crude	Standardized	Crude	Standardized	Crude	Standardized
Blood Pressure (BP)								
SBP (mmHg) mean ± SE	107.7± 0.2	107.7± 0.3	125.1 ± 0.09	124.9 ± 0.2	141.6 ± 0.1	140.7 ± 0.3	163.8 ± 0.4	160.6 ± 0.5
DBP (mmHg) mean ± SE	67.9 ± 0.2	67.9 ± 0.3	78.0 ± 0.07	77.9 ± 0.2	85.1± 0.1	85.7 ± 0.3	94.9 ± 0.3	96.9 ± 0.4
Weight (kg) mean ±SE	79.5± 0.3	79.5± 0.4	84.9± 0.2	84.5± 0.3	88.4± 0.2	89± 0.4	90.5± 0.4	92.6± 0.5
BMI								
≤ 25 kg/m^2	53.5	52.4	33.3	36.6	21.8	25.9	16.4	18.3
25 - < 30 kg/m^2	34.5	35.1	46.5	44.7	48.0	45.1	46.8	43.4
≥ 30 kg/m^2	12.0	12.5	20.2	18.7	30.1	29.0	36.8	38.3
WC (cm) mean ± SD	91.7± 0.3	92.2±0.4	97.0± 0.2	95.8±0.3	101.6± 0.2	99.6±0.3	104.0± 0.3	103.0± 0.5
Lipid Profile								
TC (mmol/l) mean ± SE	5.0 ± 0.03	5.0 ± 0.02	5.2 ± 0.01	5.1 ± 0.01	5.4 ± 0.02	5.3 ± 0.02	5.4 ± 0.02	5.4 ± 0.02
HDL (mmol/l) mean ± SE	1.4 ± 0.01	1.4 ± 0.01	1.4 ± 0.00	1.4 ± 0.01	1.4 ± 0.01	1.4 ± 0.01	1.4 ± 0.01	1.4 ± 0.01
LDL (mmol/l) mean ± SE	3.1 ± 0.02	3.1 ± 0.02	3.3 ± 0.01	3.1 ± 0.01	3.4 ± 0.01	3.3 ± 0.01	3.4 ± 0.02	3.4 ± 0.02
TG (mmol/l) median (IQR)	1.3 (0.9; 2.0)	-	1.6 (1.1; 2.3)	-	1.7 (1.2; 2.6)	-	1.8 (1.2; 2.8)	-
Geometric mean ± SE	1.4(0.01)	1.4(0.01)	1.6(0.01)	1.6(0.01)	1.8(0.01)	1.8(0.01)	1.9(0.01)	1.9(0.01)
Blood glucose (mmol/l) mean ± SE	5.2 ± 0.04	5.2 ± 0.03	5.5 ± 0.02	5.4 ± 0.02	6.0 ± 0.03	5.7 ± 0.03	6.3 ± 0.06	5.7 ± 0.04
Pharmacotherapy (%)								
Anti-diabetic	7.0	7.5	9.5	8.2	14.9	10.6	17.8	12.6
Anti-hypertensive	24.2	26.6	34.1	30.1	50.0	37.7	62.1	45.2
Lipid lowering	14.2	15.3	17.0	14.7	19.4	13.7	22.0	14.2

Table 1 (cont.): Comparison of characteristics of GEMCAS subjects according to blood pressure in men (crude and age-standardized)

	Normal Blood Pressure		Prehypertension		Stage I Hypertension		Stage II Hypertension	
	n=1,555		n=6,042		n=4,397		n=1,880	
	Crude	Standardized	Crude	Standardized	Crude	Standardized	Crude	Standardized
Smoking status (%)								
Current Smoker	37.3	35.8	28.9	31.3	24.4	30.6	21.8	29.5
Past Smoker	29.5	30.9	37.5	34.3	43.8	36.1	46.4	38.0
Never Smoker	33.1	33.3	33.7	34.4	31.8	33.3	31.8	32.5
Comorbidities (%)								
Cardiovascular disease	17.9	20.0	18.9	16.5	24.4	16.7	27.1	16.9
Diabetes	9.3	9.9	13.3	11.5	20.6	14.8	24.1	16.6

Legend: Normal blood pressure (SBP< 120 and DBP< 80 mmHg); Prehypertension (SBP 120-139 or DBP 80-89 mmHg); Stage I Hypertension (SBP 140-159 or DBP 90-99 mmHg) ; Stage II Hypertension (SBP ≥160 or DBP≥ 100 mmHg); SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; SD, standard deviation; SE, standard error; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TG, triglycerides; IQR, interquartile range

Table 2: Comparison of characteristics of GEMCAS subjects according to blood pressure in women (crude and age-standardized)

	Normal Blood Pressure n=4,781		**Prehypertension** n=9.417		**Stage I Hypertension** n=5,352		**Stage II Hypertension** n=2,262	
	Crude	Standardized	Crude	Standardized	Crude	Standardized	Crude	Standardized
Blood Pressure (BP)								
SBP (mmHg) mean ± SE	106.4 ± 0.1	107.0 ± 0.2	123.7 ± 0.1	123.9 ± 0.2	141.3 ± 0.1	139.8 ± 0.3	164.8 ± 0.3	161.6 ± 0.5
DBP (mmHg) mean ± SE	67.6 ± 0.1	67.5 ± 0.2	77.9 ± 0.1	77.6 ± 0.2	85.2 ± 0.1	85.8 ± 0.2	94.8 ± 0.3	96.6 ± 0.4
Weight (kg) mean ±SE	64.7± 0.2	66.1± 0.3	71.5± 0.2	71.1± 0.3	76.6± 0.2	76.7± 0.4	78.3± 0.4	81.0± 0.6
BMI								
≤ 25 kg/m^2	72.2	64.0	48.0	48.7	29.2	33.7	24.1	25.7
25 - < 30 kg/m^2	20.6	26.7	31.4	31.2	35.8	33.0	35.3	31.8
≥ 30 kg/m^2	7.1	8.9	20.6	20.1	35.1	33.3	40.7	42.5
WC (cm) mean ± SD	78.2± 0.2	80.9± 0.3	85.9± 0.1	85.8± 0.3	92.7± 0.2	91.2± 0.3	94.8± 0.3	94.2± 0.5
Lipid Profile								
TC (mmol/l) mean ± SE	5.0 ± 0.01	5.2 ± 0.01	5.4 ± 0.01	5.4 ± 0.01	5.6 ± 0.01	5.4 ± 0.01	5.8 ± 0.02	5.5 ± 0.01
HDL (mmol/l) mean ± SE	1.8 ± 0.01	1.8 ± 0.01	1.8 ± 0.01	1.8 ± 0.01	1.7 ± 0.01	1.7 ± 0.01	1.7 ± 0.01	1.7 ± 0.01
LDL (mmol/l) mean ± SE	3.0 ± 0.01	3.1 ± 0.01	3.3 ± 0.01	3.3 ± 0.01	3.5 ± 0.01	3.4 ± 0.01	3.6 ±0.02	3.4 ± 0.02
TG (mmol/l) median (IQR)	1.0 (0.8; 1.5)	-	1.3 (0.9; 1.8)	-	1.5 (1.1;2.2)	-	1.6 (1.1;2.2)	-
Geometric mean ± SE	1.1±0.01	1.2± 0.01	1.3± 0.01	1.3± 0.01	1.5± 0.01	1.5± 0.01	1.6± 0.01	1.6± 0.01
Blood glucose (mmol/l) mean ± SE	4.8 ± 0.01	5.0 ± 0.02	5.1 ± 0.01	5.2 ± 0.02	5.6 ± 0.03	5.2 ± 0.02	5.9 ± 0.05	5.6 ± 0.03
Pharmacotherapy (%)								
Anti-diabetic	2.1	4.6	5.4	5.9	11.2	8.4	14.3	9.3
Anti-hypertensive	11.1	24.9	28.7	30.9	51.9	41.5	64.6	48.2
Lipid lowering	4.0	9.5	9.1	10.0	16.2	11.9	16.6	10.5

Table 2 (cont.): Comparison of characteristics of GEMCAS subjects according to blood pressure in women (crude and age-standardized)

	Normal Blood Pressure		Prehypertension		Stage I Hypertension		Stage II Hypertension	
	n=1,555		n=6,042		n=4,397		n=1,880	
	Crude	Standardized	Crude	Standardized	Crude	Standardized	Crude	Standardized
Smoking status (%)								
Current Smoker	32.0	25.3	24.5	23.4	17.8	21.9	14.2	20.3
Past Smoker	21.2	21.1	23.0	22.0	22.5	21.5	21.3	20.1
Never Smoker	46.8	53.5	52.5	54.5	59.7	56.7	64.6	59.6
Comorbidities (%)								
Cardiovascular disease	5.0	14.8	10.0	12.4	17.2	13.6	21.4	14.9
Diabetes	3.2	7.8	7.8	8.7	16.1	12.3	19.9	14.1

Legend: Normal blood pressure (SBP< 120 and DBP< 80 mmHg); Prehypertension (SBP 120-139 or DBP 80-89 mmHg); Stage I Hypertension (SBP 140-159 or DBP 90-99 mmHg) ; Stage II Hypertension (SBP ≥160 or DBP≥ 100 mmHg); SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; SD, standard deviation; SE, standard error; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TG, triglycerides; IQR, interquartile range

Acknowledgment

I would like to take this opportunity to thank all those who helped me for the successful completion of my dissertation. Firstly, I owe my deepest and sincere gratitude to Prof. Dr. Susanne Moebus, my supervisor for this work, for her incessant support and encouragement throughout my PhD studies. It was an excellent opportunity to work with her. It really made me realize my mistakes at work, gave me a chance to learn and improve upon.

I would like to thank Prof. Dr. Karl-Heinz Jöckel for providing me the intellectual support when needed. I also would like to thank Dr. Christian Lösch and Dr. Andre Scherag the statisticians for their expert opinions during my consultations with them. I would also like thank Prof. Dr. Raimund Erbel for his intellectual inputs for the work.

I would like to thank all the colleagues and fellow PhD students for a great working atmosphere and also for providing the platform to present and discuss the work at our meetings.

I would like to thank my family, who were really supportive during stressful times.

Finally, I would like to thank Prof. Ralf Reintjes, who introduced me to the field of epidemiology and also helped me to start my career with Prof. Dr. Susanne Moebus.

Curriculum Vitae

For reasons of data protection, the Curriculum Vitae is not included in the online version of the dissertation.