Prognostic interactions between cardiovascular risk factors

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1.
Vishram JKK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Broda G, Palmieri L, Giampaoli S, Donfrancesco C, Kee F, Mancia G, Cesana G, Kuulasmaa K, Sans S, Olsen MH, On behalf of the MORGAM Project. Impact of age on the importance of systolic and diastolic blood pressures for stroke risk. The Monica, Risk Genetics, Archiving, and Monograph (MORGAM) Project. Hypertension. 2012;60:1117-1123.

2.
Vishram JKK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Broda G, Palmieri L, Giampaoli S, Donfrancesco C, Kee F, Mancia G, Cesana G, Kuulasmaa K, Salomaa V, Sans S, Ferrieres J, Tamosiunas A, Söderberg S, McElduff P, Arveiler D, Pajak A, Olsen MH, On behalf of the MORGAM Project. Do other cardiovascular risk factors influence the impact of age on the association between blood pressure and mortality? The MORGAM Project. J Hypertens. 2014;32(5):1025-1033.

3.
Vishram JKK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Palmieri L, Giampaoli S, Donfrancesco C, Kee F, Mancia G, Cesana G, Kuulasmaa K, Salomaa V, Sans S, Ferrieres J, Dallongeville J, Söderberg S, Arveiler D, Wagner A, Tunstall-Pedoe H, Olsen MH. Impact of age and gender on the prevalence of the metabolic syndrome and its components and risk of cardiovascular morbidity and mortality in Europeans. The MORGAM Project. (Submitted to journal)

INTRODUCTION

Despite declining trends in mortality from cardiovascular disease (CVD) in several areas of the world including most countries of Europe [1,2], CVD still remains the leading cause of death worldwide [3]. Furthermore, although the Framingham study already established the concept of cardiovascular risk factors in the early 1960s [4], and was rapidly followed by other major population based studies [5-9], risk factor control is still poor. Apart from age and male gender (non-modifiable risk factors), the major cardiovascular risk factors cigarette smoking, elevated blood pressure (BP) and total cholesterol, and a high body mass index (BMI) are all modifiable, and have been the target of public-health campaigns for many decades now.

These primary prevention strategies have increased our awareness of the cardiovascular risk factors and have led to important risk factor modifications on a population level through life style changes. However, better targeted and more individualized prevention has been inadequate due to difficulties in estimating cardiovascular risk in individuals and reaching especially optimal BP control.

Hypertension affects almost 30% of the world´s population [3], with a 60% higher prevalence in Europe compared with the United States and Canada [10], and hypertension is the cause of 7.6 million premature deaths [11]. Despite the availability of effective BP lowering treatment [12], BP control is still described by the traditional “rule of halves” [13], which states that only half of all hypertensive patients are diagnosed, only half of these receive treatment, and only half of these obtain optimal control.

Furthermore, since Reaven in 1988 [14] established the clinical importance of the clustering of the metabolic disorders dysglycemia, central adiposity, hypertension and dyslipidemia (low levels of high density lipoprotein cholesterol (HDL-C) and high levels of triglycerides), known as the metabolic syndrome (MetS), many studies [15-31] have shown that participants with MetS are at a higher risk of developing CVD. However, in recent years the clinical relevance of MetS in assessing risk for developing CVD has been questioned since studies [20,32-45] have stated that MetS is no single disease entity and no better than its individual components in identifying individuals at high risk of CVD. This critical appraisal of MetS as a prognostic marker of CVD risk comes at a time when the prevalence of MetS has increased dramatically, with approximately one-fourth of the adult population in Europe carrying this syndrome [46].

In an attempt to improve estimation of cardiovascular risk and optimize risk factor control, a deeper understanding is needed of the interplay between cardiovascular risk factors. We need to investigate prognostic interactions between the cardiovascular

risk factors: how the prognostic importance of one independent variable varies depending upon the other independent variable for a specific outcome [47]. This deeper understanding might lead the way for future studies dealing with improved identification of high risk subjects and better risk factor control through simplified diagnostic methods. Williams et al [48] have for example proposed that in patients with hypertension older than 50 years it is only necessary to measure systolic BP (SBP) due to stiffening of the large arteries. However, maybe the age, at which SBP becomes more important than diastolic BP (DBP) is lowered in individuals with more cardiovascular risk factors present? A clearer picture of the prognostic shift from DBP to SBP can perhaps be found by looking at the influence of cardiovascular risk factors on the prognostic interactions between age and DBP, and age and SBP, respectively. Furthermore, before the possible final burial of MetS as a prognostic marker, it is important to clarify whether prognostic interactions exist between age / gender and MetS and its individual components, respectively, which could perhaps justify the use of MetS.

The investigation of the above mentioned prognostic interactions between the cardiovascular risk factors form the basis of the present PhD thesis.

BACKGROUND

CARDIOVASCULAR RISK FACTORS

The Framingham study, launched in the late 1940s, was the first study to establish the concept of cardiovascular risk factors [4]. This study found that the three risk factors most strongly related to coronary risk were cigarette smoking, BP, and total cholesterol. While diabetes mellitus (DM) was found to be less common, obesity and exercise were less consistent. Soon after, the Seven Countries study [5] examined the large variation in death rates from coronary heart disease (CHD) in different countries, and found that total cholesterol varied significantly across populations, while BP was of some significance, and obesity, physical exercise, and cigarette smoking, accounted for only little of the variation. In the early 1980s the first protocols of the MONItoring of trends and determinants in CArdiovascular disease (MONICA) Project [6,7] were established, with the objective to measure trends in cardiovascular morbidity and mortality and to assess the extent to which these trends were related to changes in known risk factors in different countries. The MONICA Project used risk-factor scores, consisting of daily cigarette-smoking status, SBP, total cholesterol, and BMI, to summarize the combined effect in individual participants in determining their estimated coronary risk. Consistent with the Framingham study, it was found that smoking, BP, and total cholesterol, contributed heavily to the score, while the contribution of BMI was smaller, particularly in women [49-52]. The follow-up of cohorts examined in the MONICA risk factor surveys and other studies using the same standardized MONICA survey procedures for data collection lead to the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project [8,9], a multinational collaborative study exploring the relationships between the development of CVDs, their classic and genetic risk factors and biomarkers. The MORGAM Project is used in the present thesis and further details are found in the materials and methods section (4.1 the MORGAM Project).

From these previous studies it is evident that elevated BP is a common and powerful contributor to CVD, and more recent analyses [3,53] have established it as the leading risk factor for mortality worldwide.

BLOOD PRESSURE

Definition and classification of hypertension

Unchanged from previous guidelines, the new 2013 ESH (European Society of Hypertension) / ESC (European Society of Cardiology) guidelines define hypertension as BP level exceeding 140 mmHg SBP and / or 90 mmHg DBP, and classify it according to mild (grade 1), moderate (grade 2) and severe (grade 3), or isolated systolic (table 1) [54].

Higher levels of BP, even within the non-hypertensive range, impose increased rates of CVD [55], and thus indicate a continuous graded relationship between BP and the risk of CVD. The level of BP, along with the risk of the patient, are both considered prior to the initiation of antihypertensive drug treatment. A few differences between previous and current ESH / ESC guidelines with regard to the initiation of antihypertensive drug treatment in those individuals classified with high normal BP or grade 1 hypertension need mentioning.

Table 1: ESH / ESC definitions and classification of office BP levels (mmHg)

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

The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the range indicated. Modified from Mancia et al [54].

Whereas in previous guidelines, it was recommended to start antihypertensive drug treatment in high-risk (DM) or very high-risk (CVD or chronic kidney disease) patients with high normal BP (130-139 / 85-89 mmHg) due to an increased risk in these patients of developing hypertension and/or cardiovascular events, the current guidelines suggest only lifestyle changes in these patients, since the evidence, in favour of this early antihypertensive drug intervention, is limited [54]. Furthermore, for grade 1 hypertension (140-159 / 90-99 mmHg), the current guidelines take into consideration the age factor, and recommend a higher threshold of 160 mmHg in SBP for initiation of antihypertensive drug treatment in elderly patients primarily below 80 years aiming at a SBP below 150 mmHg. In addition, due to lack of evidence in favour of drug treatment in young individuals with isolated systolic hypertension, it is only recommended that these individuals should be followed closely with lifestyle interventions. In contrast, isolated elevation of DBP should be reduced to < 90 mmHg in these young individuals due to a strong relationship between elevated DBP and total as well as cardiovascular mortality [54].

A shift in emphasis from DBP to SBP as the most important risk factor

Despite being the most frequent treatable cardiovascular risk factor, uncertainties still remain about which BP measure, SBP or DBP, is the most important risk factor for a given cardiovascular event. The evolution of attitudes has shifted from an emphasis on DBP as the most important BP component and the primary target of antihypertensive therapy, to SBP [12,48,55-66,73-81]. For

instance, in the first report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC I), published in 1977, DBP was used as the basis for diagnosis and treatment of hypertension, while in 1993 the Fifth Report (JNC V) defined hypertension as an elevation of SBP and / or DBP [56,57].

Some of the earliest studies acknowledging SBP as an important risk factor for CVD showed that the clinical concept of normal SBP corresponding to a value of 100 plus the subject´s age was incorrect. They also found that mortality rates increased more steeply in relation to SBP than DBP [58]. In the Framingham Heart Study, for participants with systolic hypertension (SBP > 160 mmHg), the accompanying DBP was only weakly related to risk of CVD, whereas in those with diastolic hypertension, the risk of such events was strongly influenced by the associated SBP. Furthermore, among subjects with DBP below 95 mmHg, cardiovascular event rates increased steeply with SBP at all ages [55]. In the 1990s the results of the Systolic Hypertension in the Elderly Program (SHEP) and SYSTolic hypertension in Europe (SYST-EUR) were published [59,60], and showed the clinical benefits of lowering elevated SBP (isolated systolic hypertension ≥ 160 mmHg) to reduce the risk of cardiovascular events in elderly patients 60 years or older.

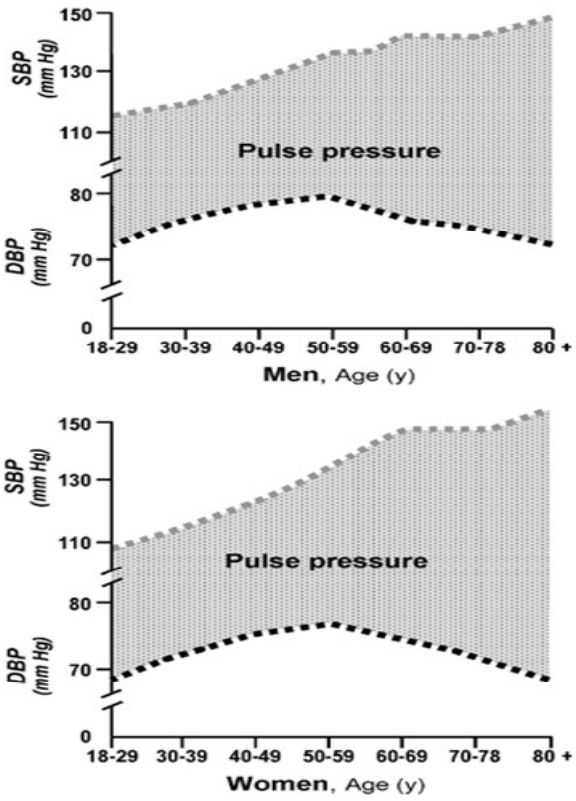
Age-related shifts in SBP and DBP

It is well documented in the literature that BP profiles change with age [67]. DBP rises until age 50 years and then declines, whereas SBP rises from adolescence until old age (figure 1) [56,68]. This shift in BP profiles with age is thought to be due to the progressive decrease in arterial compliance with advancing age, thereby reducing the buffering capacity of the arterial system and resulting in continuously increasing SBP levels and level off and then decline of DBP. The loss of vascular compliance is due to the arterial stiffening following age related structural changes in larger conduit arteries, arteriosclerosis. The increasing levels of SBP combined with the decreasing levels of DBP also results in a progressive increase in pulse pressure (PP=SBP-DBP) with advancing age (figure 1) [56,68]. In younger individuals, higher SBP and DBP are mainly caused by an increase in peripheral vascular resistance generated by functional and structural narrowing of the resistance arteries and arterioles [69,70]. Consequently, a high prevalence of isolated systolic hypertension is seen in advanced age, whereas the prevalence of isolated diastolic hypertension decreases with aging (figure 2) [71]. In fact, isolated systolic hypertension is present in approximately two thirds of hypertensive individuals above 60 years of age, while younger persons tend toward isolated diastolic hypertension or combined systolic- diastolic hypertension [63].

Age-related shifts in SBP and DBP and risk of CVD

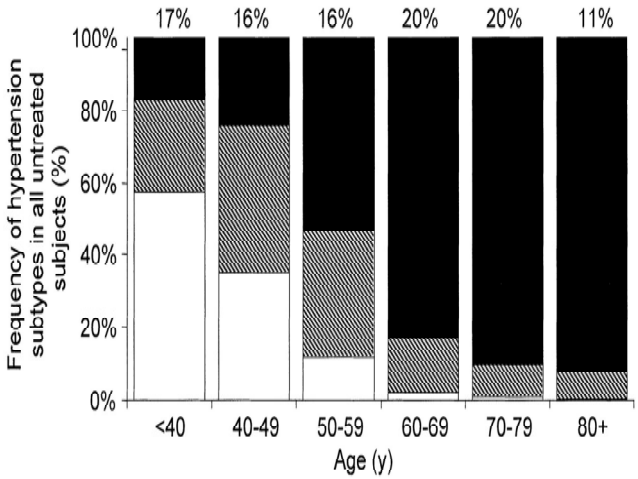
The Framingham Heart Study [72] was the first to show that there was a declining relative importance of DBP and a corresponding increase in the importance of SBP in CHD risk with advancing age, suggesting a different relative importance of DBP and SBP with aging. Since then, many studies [66,73-81] have shown the superiority of either SBP or PP in the elderly. In younger ages, the pattern is less clear. Some studies showed the superiority of DBP [72,74,79] others of SBP [66,73] and some of both BPs [75-78,80]. One of the most compelling studies of recent time, acknowledging the superiority of SBP as the most important risk factor in CVD risk, was published by the Prospective Collaborative Study Group

Figure 1: Mean SBP and DBP by age for men and women



Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; pulse pressure SBP-DBP; y, years. Modified from Black [56] and Burt et al [68].

Figure 2: Frequency of hypertension subtypes in untreated hypertensive individuals in different age groups

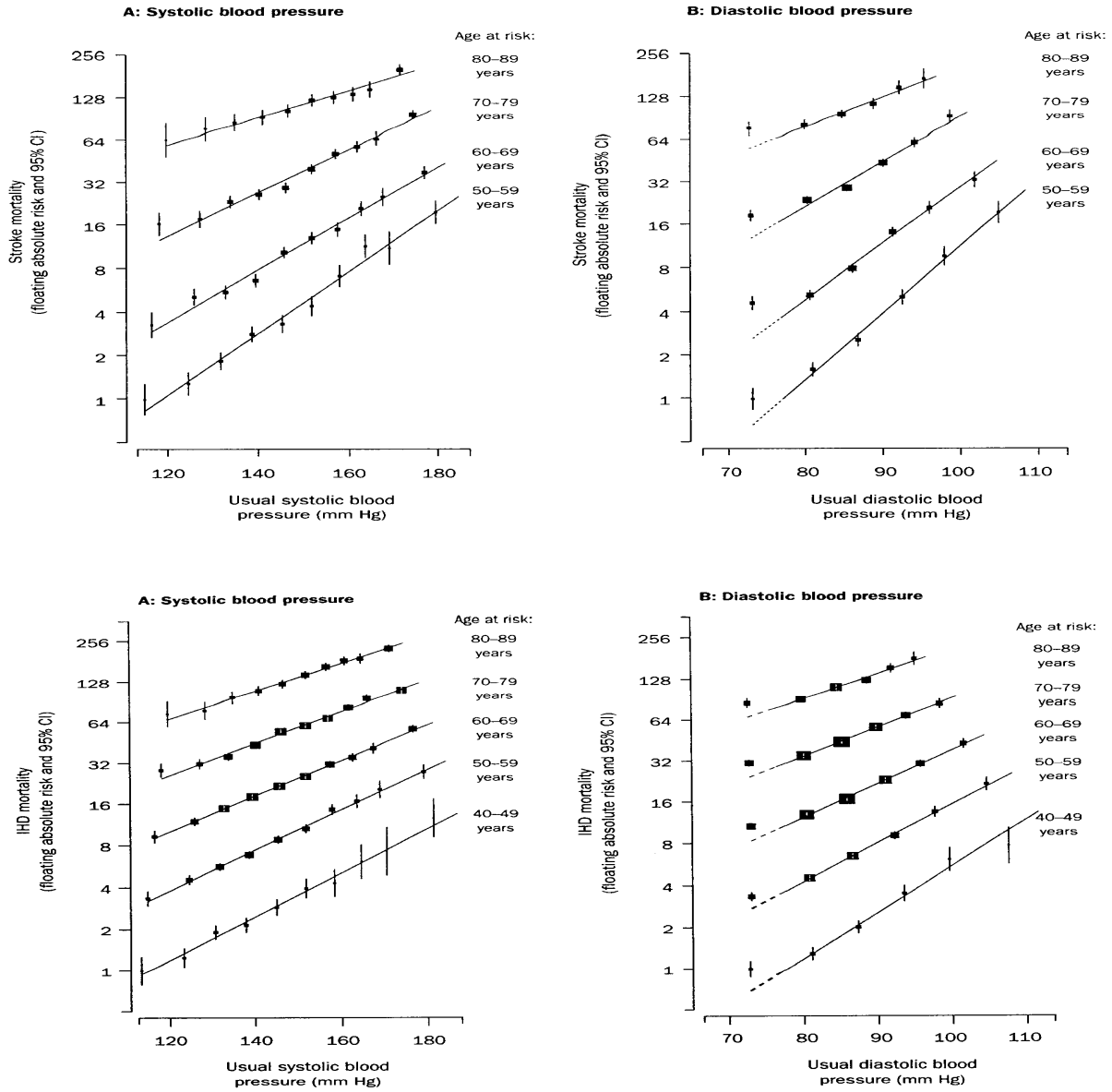


Numbers at the top of bars represent the overall percentage distribution of all subtypes of untreated hypertension in that age group. Black colour indicates isolated systolic hypertension (SBP ≥140 mmHg and DBP <90 mmHg); striped colour, systolic-diastolic hypertension (SBP ≥140 mmHg and DBP ≥90 mmHg); and white colour, isolated diastolic hypertension (SBP <140 mmHg and DBP ≥90 mmHg). From Franklin et al [71].

[66], which pooled 61 observational studies in more than 1 million participants. This group showed that SBP level at baseline was a significantly stronger predictor of strokes and CHD than DBP. In addition, they showed that BP was positively associated with cardiovascular mortality down to at least 115 / 75 mmHg in different age groups above 40 years. Throughout middle- and old age, a difference in BP of 20 / 10 mmHg was associated with more than a twofold difference in stroke mortality rates and a twofold difference in ischaemic heart disease (IHD) mortality rates (figure 3) [66].

One of the main similarities of all these previous studies [66,73-81] is that they analysed the association between BP and CVD risk using subgroups of age rather than using age as a continuous variable. This latter type of analysis, which would perhaps have offered a clearer picture of the age at which the relative importance of SBP begins to exceed DBP, and the age at which the superiority of SBP is established, forms the basis of papers I-II in the present thesis. Furthermore, since arterial stiffness is the main determinant of SBP in older patients [82] and may be dependent on other cardiovascular risk factors such as male gender, cigarette smoking, DM, high BMI, and elevated total cholesterol [83], it is possible that the superiority of SBP is established at an earlier age in individuals with more of these cardiovascular risk factors present.

Figure 3: Mortality rates of stroke and IHD in each decade of age versus usual SBP (A) and DBP (B) at the start of that decade



SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and IHD, ischaemic heart disease. From Lewington et al [66].

THE METABOLIC SYNDROME

Definition

Although the clustering of the cardiovascular risk factors hypertension, hyperglycaemia and hyperuricaemia was first described by Kylin in 1923 [84], it was not until his Banting Medal award lecture in 1988 [14] that Reaven firmly established the clinical importance of the clustering of dysglycemia, central adiposity, hypertension and dyslipidemia, known as the metabolic syndrome (MetS). Since then many expert groups have attempted to develop a unifying definition for MetS (table 2) [85-90].

The definition of MetS by the World Health Organization (WHO; 1999) and the European Group for study of Insulin Resistance (EGIR; 1999) are both based on insulin resistance as the underlying contributor to MetS [85-88], and require the presence of dysglycemia. A few years later, the National Education Program – Adult Treatment Panel (NCEP-ATP III, 2001; and the revised NCEP-ATP III, 2004) and the International Diabetes Federation (IDF; 2005) proposed more clinically oriented definitions of MetS and therefore, excluded the measurement of insulin resistance [85-90]. Instead, these newer definitions of MetS considered central obesity as the core underlying mechanism. In contrast to the NCEP-ATP III definition, the IDF definition of MetS is more "glucose-centric" since increased waist circumference (WC) is a requirement. The IDF proposed their definition after the results of the AusDiab study [91] had shown that only 9% of participants met the criteria of MetS by the three definitions, WHO, EGIR and NCEP-ATP III, and the aim was to establish a unified diagnostic tool, that could be used everywhere so that data can be compared properly across the world. The American Association of Clinical Endocrinologists (AACE; 2002) proposed yet another definition of MetS, namely a hybrid between the NCEP-ATP III and WHO criteria, and with no defined number of risk factors present; diagnosis was solely based on clinical judgment [86,87]. In an attempt to harmonize MetS, a more recent definition was proposed in 2009 [89] as a joint statement between the IDF Task Force on Epidemiology and Prevention and the American Heart Association / National Heart, Lung, and Blood Institute. This newer definition of MetS is based on the occurrence of any three or more out of five cardiovascular risk factors, and with no priority of WC as a prerequisite.

Table 2: Various definitions of the metabolic syndrome

MetS Criteria	WHO (1999)	EGIR (1999)	NCEP-ATPIII (2001)	AACE (2002)	NCEP-ATPIII (2004)	IDF (2005)	New Joint (2009)
Absolutely required:	One of: DM2, IGT, IFG, and/or IR	IR[¶]		MetS diagnosis dependes on clinical judgment based on risk factors[‡]		WC	
Other criteria:	≥ 2	≥ 2	≥ 3		≥ 3	2	≥ 3
Blood pressure (mmHg)	≥ 140/90 and/or	≥ 140/90 and/or	≥ 130/85 and/or	≥ 130/85	≥ 130/85 or	SBP ≥ 130 or DBP ≥ 85 or	SBP ≥ 130 and/or DBP ≥ 85 or
Antihypertensive drugs	yes	yes	yes		yes	yes	yes
Dyslipidemia Triglyceride (mmol/L)	≥ 1.695 and/or	≥ 2.0 and/or	≥ 1.7 and/or	≥ 1.69 and/or	≥ 1.7 and/or	≥ 1.7 and/or	≥ 1.7 and/or
HDL-C (mmol/L)	≤ 0.9 (M) ≤ 1.0 (W)	< 1.0 or	< 1.03 (M) < 1.29 (W)	< 1.04 (M) < 1.29 (W)	< 1.03 (M) < 1.29 (W)	< 1.03 (M) or < 1.29 (W) or	< 1.0 (M) or < 1.3 (W) or
Lipid lowering drugs		yes				yes	yes
Central obesity Waist:hip ratio	>0.90 (M) and/or >0.85 (W) and/or						
WC (cm)		≥ 94 (M) ≥ 80 (W)	≥ 102 (M) ≥ 88 (W)		> 102 (M) > 88 (W)	ethnicity specific[*] or	ethnicity specific[*]
BMI (kg/m^2)	> 30			≥ 25		> 30	
Dysglycemia DM 2	One of: yes	no				yes	
IGT (mmol/L)	≥ 7.8 and < 11.1	≥ 7.8 and < 11.1		> 7.8 and < 11.1			
IFG/ FG (mmol/L)	≥ 6.1 and < 7.0	≥ 6.1 and < 7.0	≥ 6.1	> 6.1 and < 7.0	≥ 5.6 or	≥ 5.6[†] or	≥ 5.6 or
IR	yes	yes					
Anti-diabetic drugs					yes	yes	yes
Microalbuminuria	UAER≥20 µg/min or ACR ≥30 mg/g						

WHO indicates the World Health Organization; EGIR, the European Group for study of Insulin Resistance; NCEP-ATPIII, the National Education Program – Adult Treatment Panel; IDF, the International Diabetes Federation; AACE, the American Association of Clinical Endocrinologists; MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; M, men; W, women; HDL-C, high density lipoprotein cholesterol; WC, waist circumference; BMI, body mass index; DM2, diabetes mellitus type 2; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; FG, fasting glucose; IR, insulin resistance; UAER, urinary albumin excretion rate; and ACR, albumin to creatinine ratio.

[*] Ethnicity specific: Europids, Sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations, WC ≥ 94 cm (M) and ≥ 80 cm (W); South Asians, Chinese, Ethnic South and Central Africans, WC ≥ 90 cm (M) and ≥ 80 cm (W); and Japanese, WC ≥ 85 cm (M) and ≥ 90 cm (W).

[¶] IR: defined as hyperinsulinaemia – top 25% of fasting insulin values among the non-diabetic population.

[†]If above 5.6 mmol/L, oral glucose tolerance test is strongly recommended but is not necessary to define the presence of the syndrome.
[‡]The presence of other risk factors: Family history of DM2, hypertension, or cardiovascular disease, polycystic ovary syndrome, sedentary lifestyle, advancing age, ethnic groups having high risk for DM2 or cardiovascular disease.
Modified [85-90].

Critical appraisal of MetS

A syndrome can be defined as a collection of components that cluster together or occur together with higher frequency than would be expected by chance alone, and assumes that the clustering is "more than the sum of its parts" [92]. In recent years, MetS has been criticized for not being a syndrome [33,88,92-95], since there is no agreement on whether insulin resistance, central obesity or some third cause such as pro-inflammatory or pro-thrombotic states due to elevations of C-reactive protein (CRP) or fibrinogen, respectively, is the unifying underlying pathophysiology of MetS. Furthermore, the clinical applicability of MetS has also been questioned [33,92-95]. Firstly, it is based on a dichotomization of cardiovascular risk factors, which have been shown to associate in a continuous fashion with increasing risk of CVD, thus weakening the prognostic value of these cardiovascular risk factors. Secondly, it is consistently outperformed by global risk assessment tools, such as the Framingham Risk Score and the Heart Systematic COronary Risk Evaluation (SCORE), that include additional cardiovascular risk factors like age, sex, and smoking together with personal and family history of CHD [33,92,94,96]. Thirdly, the cut-off values of each component of the cluster and the way of combining them to define MetS differ between the definitions (table 2), and are arbitrary and ambiguous [33]. Fourth, recent studies have shown that MetS does not confer a greater risk of CVD above and beyond its individual components [20,32-45], implying that clinicians should evaluate and treat all cardiovascular risk factors without regard to whether a patient meets the criteria of MetS.

MetS and risk of CVD

To some extent it has also been shown that MetS is influenced by the non-modifiable cardiovascular risk factors gender and age. For instance, from the previously mentioned meta-analyses [26-29], as well as other studies [30,31] there is some indication that MetS confer a higher CVD risk in women than in men. Furthermore, although it is known that MetS is strongly related to age [99-102], only few studies have investigated age and gender specific MetS prevalence [18,21,22,24], and none of these studies looked at the impact of age and gender on the prognostic significance of MetS. Thus it is important to clarify (1) whether prognostic interactions exist between age / gender and MetS, which could perhaps optimize its use in identifying individuals at high risk of CVD and thereby justify its use; and (2) whether there at certain levels are interactions between the individual components of MetS that may suggest new threshold values of the components and thereby a re-definition of MetS with these new partition values, which in turn could justify its use above and beyond its individual components. These two clarifications, of which the first is elucidated in paper III of the present PhD thesis, need consideration before the possible final burial of MetS.

INTERACTIONS BETWEEN CARDIOVASCULAR RISK FACTORS

A statistical interaction, also known as an effect modifier, is present when the causal effect of an exposure on an outcome "depends" on a third factor [47]. For example, if the association between BP and stroke risk depends on age, then age is an effect modifier. Interactions are usually assessed by regression models, such as logistic regression or Cox proportional hazards regression, and for these models constructed by multiplying the exposure and the effect modifier (i.e., BP*age; multiplicative model). In contrast, additive models consider the difference between risks.

Previous research in cardiovascular diseases has shown us, which risk factors typically lead to the development of cardiovascular disease. Since the damaging effect of these risk factors is partly additive, researchers have developed different risk stratification schedules, such as the Framingham Risk Score and the HeartScore, which are used to calculate the individual person´s risk of developing cardiovascular disease within the next 10 years. However, evidence [34,63,103-108] indicates that when concomitantly present, cardiovascular risk factors may potentiate each other (act synergistically), leading to a total cardiovascular risk that is greater than the sum of its individual components, and thus making these risk stratification charts, along with screening tools such as MetS, inadequate. For instance, Izzo et al [63] demonstrated this complex interplay between cardiovascular risk factors by showing that systolic hypertension interacts significantly with other major risk factors such as hypercholesterolemia and diabetes. In another study in hemodialyzed patients, Kimura et al [103] showed that elevated SBP significantly worsened survival in the presence of hypercholesterolemia and active smoking. In addition, Scuteri et al [105] showed that the components of MetS interact to synergistically impact vascular thickness and stiffness. Golden et al [34] showed the synergistic effects of SBP and hypertriglyceridemia on carotid intima-media thickness.

In the present PhD thesis, we use Cox proportional hazard regression (papers I-III) to test prognostic interactions in order to investigate (1) the influence of age and other cardiovascular risk factors on the association between BP and CVD risk, and (2) variations in MetS prognosis according to age and gender; and logistic regression (paper III) to test interactions in order to investigate age and gender-specific variations in MetS prevalence.

HYPOTHESES AND AIMS

PAPERS I-II

Hypothesis

The prognostic value of SBP surmounts that of DBP earlier in subjects with other cardiovascular risk factors. Therefore, the prognostic shift between SBP and DBP will be lower than 50 years of age in individuals who have other cardiovascular risk factors.

Aims

To investigate: (1) the relative importance of SBP and DBP in cardiovascular disease risk with advancing age; (2) the age at which the relative importance of SBP exceeds DBP in cardiovascular disease risk; (3) whether this shift to the superiority of SBP is influenced by other cardiovascular risk factors; and (4) the relative importance of PP and MAP in cardiovascular disease risk with advancing age.

Paper I examines the endpoint fatal and nonfatal (total) stroke, while paper II examines mortality from stroke, CHD, and all-causes.

PAPER III

Hypothesis
Age and gender interact with the prevalence and prognostic importance of MetS.

Aims
To investigate the importance of age and gender for prevalence and prognostic importance in regard to total CHD, total stroke, and CVD mortality of MetS, defined by the two most recent definitions.

MATERIALS AND METHODS
A detailed description of the cohorts used in the three studies is available in table S1 (online data supplements) of the corresponding papers I-II and in table 1 for paper III.

THE MORGAM PROJECT
Study population
The three papers were based on prospective cohorts, with baseline data collection between 1982 and 1997, from the MORGAM Project [8,9]. The cohorts in the MORGAM Project were primarily European, and consisted of men and women aged 19-78 years. Exclusion criteria at baseline included any major CVD and missing values on the following cardiovascular risk factors used as adjustment in the Cox regression model: age, sex, BP, smoking status, total cholesterol, BMI, and DM status. For papers I and II additional exclusion criteria involved those in antihypertensive drug treatment, while for paper III it was those with missing values on any of the MetS components. A brief overview of the study population in each paper is listed in the following table 3:

Table 3: Study characteristics

Paper	I	II	III
Number of:			
Participants	68 551	85 772	69 094
Cohorts	34	42	36
European countries	10	11	10
Non-European countries		1	
Years of follow-up	13·2	13·3	12·2
Endpoints	total stroke	mortality from stroke CHD all-causes	total stroke total CHD CVD mortality

Total indicates fatal and nonfatal; and CVD mortality, fatal stroke and fatal CHD.

Measurements
Antihypertensive drug treatment, daily smoking, and DM, at baseline, were self-reported. BMI was calculated as weight (kg) divided by the square of the height (m2). BP was measured twice in the right arm in the sitting position using a standard or random zero mercury sphygmomanometer after a 5-minute rest [7] except in five cohorts where BP was measured only once. The mean of the first and second SBP and DBP was used when possible. Total serum cholesterol, HDL-C, and triglycerides, were measured in serum samples by local laboratories [7].

Outcome
The specific endpoints examined in papers I-III are listed in table 3. Observations continued until death or the end of a fixed follow-up period (1994-2007) depending on the cohort. Fatal cases were identified by national or regional health information systems. In most cohorts, nonfatal cases were identified by hospital discharge registers. The MONICA criteria for stroke were based on clinical presentation and not on imaging techniques. A stroke event score for each cohort was defined to evaluate the reliability of total stroke events (a high stroke event score indicated increased reliability). Most MORGAM centres used the WHO MONICA diagnostic criteria [7] to validate the stroke events occurring during follow-up. The MORGAM criteria for CHD included definite and possible myocardial infarction or coronary death, unstable angina pectoris, cardiac revascularization, and unclassifiable death. Details including quality assessments of MORGAM endpoints and baseline data have been described previously [109,110].

STATISTICAL ANALYSES
Statistical Analysis Software (SAS Institute Inc, Cary, NC) version 9.2 was used for all analyses. Descriptive analyses of the distribution of cardiovascular risk factors in the baseline age groups 19-39 years, 40-49 years, 50-59 years, and 60-78 years, were expressed as number (percentage) and either as mean (standard deviation, SD; paper I and II) or as median and the 5th and 95th percentiles (paper III). Discrete variables were compared using the Chi-square test, while continuous variables were compared using Student´s t-test or non-parametric Man-Whitney test, according to the normality of the variables. Differences in continuous variables between groups were tested using one-way ANOVA. Due to differences in cohort follow-up time, the incidence rates per 1000 person years for a given event were reported instead of absolute number of events.

Survival was analyzed using Cox proportional hazard regression models with time from baseline as the time variable, and stratified by country allowing for the baseline hazard to vary among the countries. All explanatory variables met the proportional hazards assumption of the Cox regression model, assessed by inspecting Schoenfeld residuals. The linearity of the continuous variables was assessed using quadratic and cubic effects as well as linear and cubic splines (see below).

For all analyses a 2-tailed $P<0{\cdot}05$ was considered statistically significant.

Papers I-II
Univariate and multivariate age-adjusted Cox regression models were used to compare the associations of baseline SBP per 10-mmHg increase and DBP per 5-mmHg increase with the risk of an event. The multivariate age-adjusted model included either, SBP and DBP (Model B; paper I), or SBP and DBP as well as the potential confounders sex, smoking status, DM, cholesterol, and BMI (Models C and B; papers I and II, respectively).

Interactions between age and BP (i.e., age*SBP) were examined, as well as the possible influence by other cardiovascu-

lar risk factors such as sex (i.e., age*SBP*sex), smoking status, DM, cholesterol, and BMI. Statistically significant interactions were carried forward in the further analyses. Additional effect modifiers examined were: (1) country; (2) high- / low- risk countries according to HeartScore [108]; and (3) Eastern / Western countries. Next, the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for SBP and DBP were compared across different ages at baseline in order to determine the age, at which the HR for an event for SBP per 10-mmHg increase significantly exceeds that of DBP per 5-mmHg increase. The same analyses were repeated, to some extent, for PP per 5-mmHg increase (calculated as SBP-DBP) and for MAP per 5-mmHg increase (calculated as SBP/3+2DBP/3) in order to see whether any potential discrepancies between SBP and DBP with advancing age could be explained by especially PP.

Sub-analyses

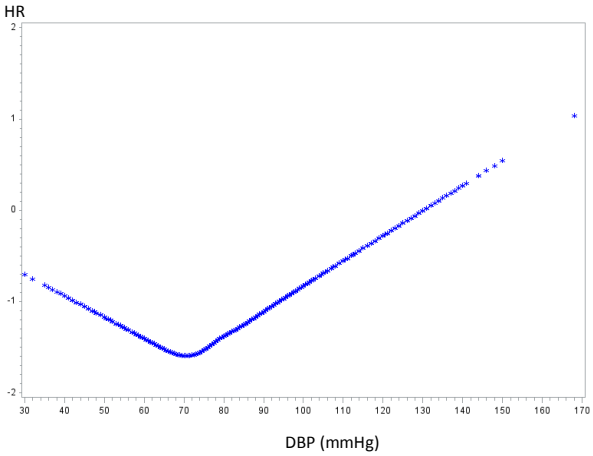
(1) Although the use of a 10-mmHg SBP / 5-mmHg DBP scale was fully justifiable as shown previously [7,8], and mainly due to the non-comparability of the two BP measures since SBP is approximately twice as high as DBP, the analyses were repeated using HRs per 1-mmHg increase in SBP and DBP.
(2) A sensitivity analysis was performed excluding the five cohorts where BP was measured only once.
(3) In order to explain any discrepancies between paper I and paper II, the reproducibility of the significant effect modifiers on the interaction between age and BP found in paper II was further examined in: (1) the dataset used in paper I; (2) Europeans only; and (3) countries with a high versus low stroke event score.

Splines

A spline is a piecewise fitting of polynomial equations, characterized by a high degree of smoothness where the polynomial pieces connect (known as knots) [111]. SBP and DBP were modelled as cubic splines with four to six knots when deviations from linearity were observed. For PP and MAP, there was no deviation from linearity.

In paper I, the relation of DBP to total stroke risk was J-shaped with the lowest risk at a DBP of about 71 mmHg. Total stroke risk was greater with DBPs both higher and lower than 71 mmHg. Based on inspection of the cubic spline with six knots placed at the fifth, 23rd, 41st, 59th, 77th, and 95th percentiles (figure 4), we modelled DBP as a linear spline with one knot at 71 mmHg, and thus separate results are reported for DBP≥71 mmHg and DBP<71 mmHg.

Figure 4: The relationship between DBP and total stroke risk using a cubic spline



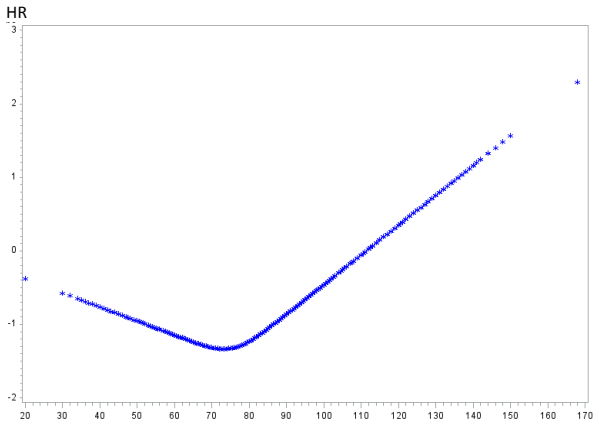
The lowest risk of total stroke is at a DBP of 71 mmHg. HR indicates hazard ratio per 5-mmHg increase in DBP; DBP, diastolic blood pressure; and total stroke, fatal and nonfatal stroke.

In paper II, the relation of DBP to mortality risk was J-shaped with the lowest mortality risk at a DBP of about 75 mmHg (stroke), 78 mmHg (CHD), and 82 mmHg (all-cause). For SBP, the relation to stroke mortality was linear, whereas the relation was J-shaped for CHD- and all-cause mortality with the lowest mortality at a SBP of about 116 mmHg and 120 mmHg, respectively. For both DBP and SBP, mortality risk was greater with BPs both higher and lower than the above mentioned thresholds. Based on inspection of the cubic splines with either four knots placed at the fifth, 35th, 65th, and 95th centiles (figure 5A-C,E) or six knots placed at the fifth, 23rd, 41st, 59th, 77th, and 95th percentiles (figure 5D), we modelled BP as a linear spline with one knot at 75 mmHg (for DBP and stroke mortality), 78 mmHg (for DBP and CHD mortality), 82 mmHg (for DBP and all-cause mortality), 116 mmHg (for SBP and CHD mortality), and 120 mmHg (for SBP and all-cause mortality). Thus, separate results are reported for BPs above and below the above mentioned thresholds.

The above J-shaped relations between BP and event risk were carried out for the total population in age-adjusted Cox regression models. However, when dividing the population into four separate age groups, as mentioned above, we found that the J-shaped relations were partially age dependent, such that the threshold value generally increased with advancing age.

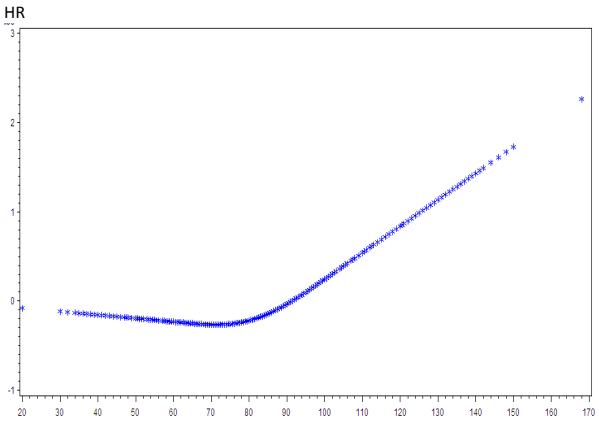
Figure 5: The relationship between BP and mortality risk using cubic splines

A.



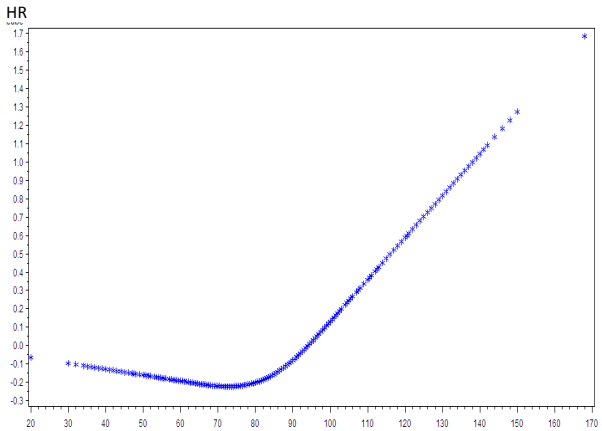
The lowest risk of stroke mortality is at a DBP of 75 mmHg.

B.



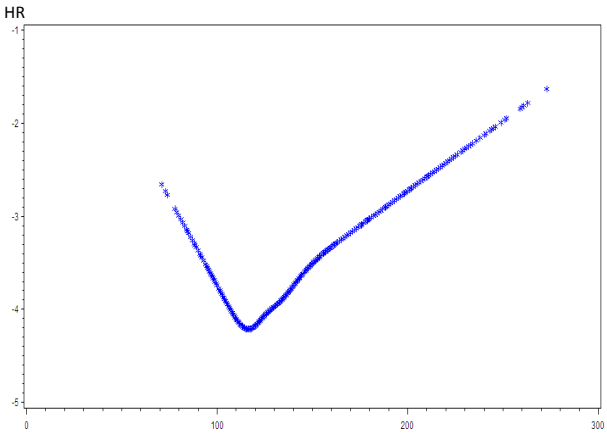
The lowest risk of CHD mortality is at a DBP of 78 mmHg.

C.



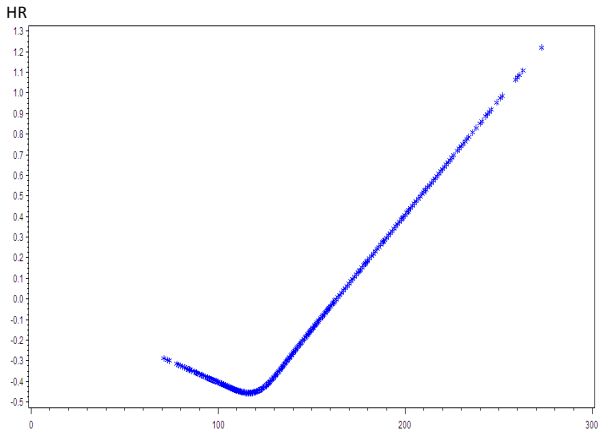
The lowest risk of all-cause mortality is at a DBP of 82 mmHg.

D.



The lowest risk of CHD mortality is at a SBP of 116 mmHg.

E.



The lowest risk of all-cause mortality is at a SBP of 120 mmHg.

HR indicates hazard ratio per 5-mmHg increase in DBP and per 10-mmHg increase in SBP, respectively; DBP, diastolic blood pressure; SBP, systolic blood pressure, and CHD, coronary heart disease.

Paper III

Due to differences in baseline age distribution among the different populations, the prevalence of MetS is presented for a fixed age-interval of 50-59 years, allowing for a meaningful comparison between the populations since this age range is covered by all the populations. Furthermore, due to significant interactions between age and gender for the prevalence of MetS and its components using adjusted logistic regression models (all P<0·0001; table 2, see paper III), separate analyses were carried out for men and women in various baseline age groups as mentioned above. Although interactions between country and age as well as country and gender were also significant for the prevalence of MetS and most of its components, regression analyses were not carried out separately for men and women within each country due to lack of statistical power. Multivariate Cox regression models, adjusting for total cholesterol, smoking- as well as fasting status, were used to compare the association of MetS with the risk of an event. Only the interaction between MetS and age for women with regards to CHD risk was significant (table 3, see paper III). Since fasting levels differed between cohorts, we used a categorized fasting variable as adjustment in the Cox model: (1) full fasting: overnight / at least 8 hours of fasting before blood sampling; (2) semi-fasting: between 4-8 hours of fasting; and (3) non-fasting: less than 4 hours of fasting.

Classification of MetS

We used modified versions of MetS according to both the IDF criteria [87] and the 2004 revised NCEP-ATP III criteria [90]. In order to maximize sample size, BMI was used in the main analyses; analyses were also replicated using WC. A scatter plot was drawn to find the BMI cut-offs which corresponded to WC with specific reference to a European population. Furthermore, since data on plasma glucose was not available, the presence of DM or use of anti-diabetic drugs was used instead. According to the IDF criteria, MetS was based on the presence of a BMI ≥ 30 kg/m2 in men and ≥ 25 kg/m2 in women and 2 or more of the following components: (1) BP ≥ 130 mmHg (systolic) or ≥ 85 mmHg (diastolic) or use of antihypertensive drugs; (2) triglyceride ≥ 1·7 mmol/l; (3) HDL cholesterol < 1·03 mmol/l in men and < 1·29 mmol/l in women; and (4) the presence of DM or use of anti-diabetic drugs. According to the NCEP-ATP III criteria, MetS was based on the presence of 3 or more of the 5 criteria which are identical to those provided by IDF. With specific reference to a European population, the cut-offs for WC was ≥ 94 cm in men and ≥ 80 cm in women according to the IDF criteria, and > 102 cm in men and > 88 cm in women according to the NCEP-ATP III criteria.

S*ub-analyses*

Analyses were replicated in subsets using WC instead of BMI, and using a reduced dataset excluding participants in anti-hypertensive drug treatment and non-fasting or semi-fasting participants.

MAIN RESULTS

Detailed results of the three papers, including descriptive analyses of cardiovascular risk factor distribution in various age groups, are available in the corresponding papers I-III and in their respective online data supplements (papers I-II). A summary of the main results, especially with focus on interaction analyses, are provided below.

PAPER I

During the average of 13·2 years of follow-up, the number of total stroke in men / women were 1192 / 700 (table S1; online data supplements). The significant interactions of age and other cardiovascular risk factors found for the association between BP and total stroke risk are summarized in table 4 below (taken from table S2; online data supplements), and used in the further analyses.

Table 4: Significant interactions between age, BP, and other cardiovascular risk factors for subsequent total stroke

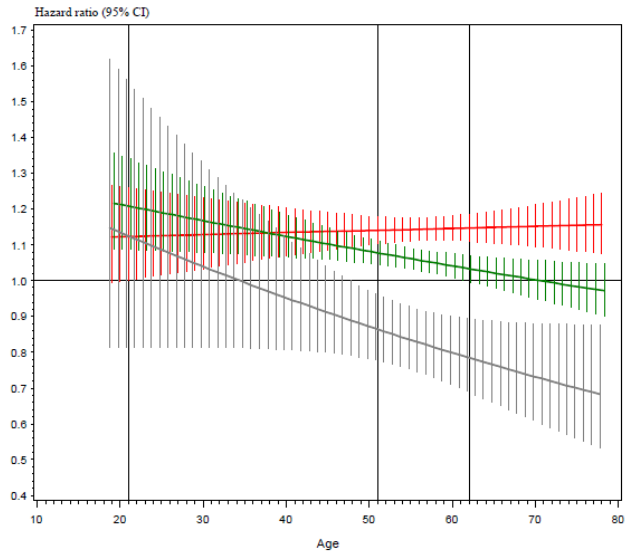
Interactions	Model B* *P* Value	Model C† *P* Value
age*SBP	0·02	NS
age*DBP	0·0001	0·001
age*MAP	0·0009	0·01
age*MAP*sex	0·04	NS

Total indicates fatal and nonfatal stroke; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; and MAP, mean arterial pressure.
P<0·05 indicates a significant interaction term in the Cox model while NS indicates non-significance.
*Model B: adjusted for age and the other BP measure: SBP and DBP are adjusted for each other; and PP (pulse pressure) and MAP are adjusted for each other.
†Model C: adjusted for age, the other BP measure, and the cardiovascular risk factors sex, smoking, diabetes, cholesterol, and body mass index.

The relative importance of SBP versus DBP in total stroke risk with advancing age

For the total population, total stroke risk was associated positively with SBP and DBP≥71mmHg and negatively with DBP<71mmHg (all P<0·05; Models B-C, table 2 – see paper I). Using baseline age as a continuous variable in the Cox model allowed us to explore the independent associations between SBP, DBP, and the risk of total stroke across different ages. As seen in figure 6 for Model B below (Models B and C displayed similar graphical results), the association between DBP≥71 mmHg and total stroke risk (green colour) became significant at age 19 years, was strongest in the youngest ages, and declined with age becoming non-significant at age 62 years. In contrast, SBP (red colour) remained significantly associated with total stroke risk across all ages, with a slight increase with advancing age, although its interaction with age became non-significant after multivariate adjustment (Model C). However, already from ages 52 / 47 years (Models B / C), the relative importance of SBPper 10-mmHg increase significantly exceeded that of DBP per 5-mmHg increase for total stroke risk, and from the age of 62 years only SBP remained significant. The risk of total stroke was inversely associated with DBP<71 mmHg (grey colour), reaching significant levels from mid-age and onwards (for the corresponding table to figure 6, see table 3 paper I).

Figure 6: HRs for risk of total stroke per 10-mmHg increase in SBP (red) or per 5-mmHg increase in DBP≥71mmHg (green) or DBP<71mmHg (grey) with advancing baseline age



HRs indicates hazard ratios; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
Model B: SBP and DBP are adjusted for each other and age.
The vertical line at age 51 years indicates the age after which the HR for SBP significantly exceeds the HR for DBP when DBP≥71 mmHg. The vertical line at age 62 years indicates the age at which the HR for DBP when DBP<71mmHg becomes non-significant.

The relative importance of PP versus MAP in total stroke risk with advancing age

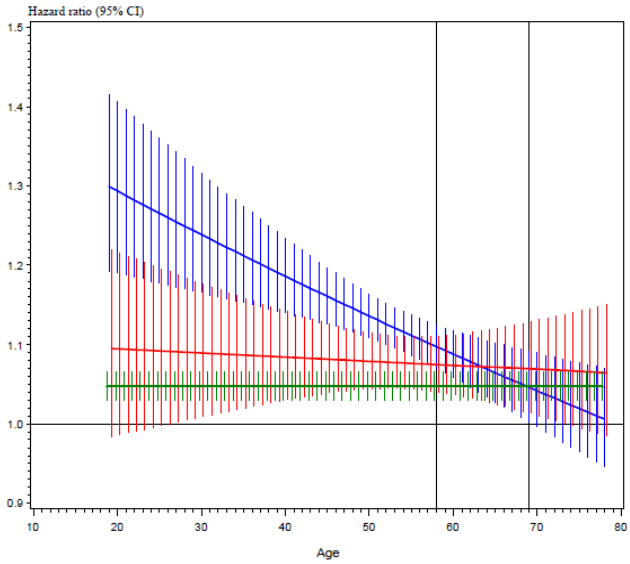
As seen in figure 7 for Model B, the association between PP and total stroke risk (green colour) was independent of age, and although it remained significant across all ages and continued to do so even after multivariate-adjustment (Model C), its association with total stroke risk was only marginal.

For MAP, the association with total stroke risk was influenced by interactions with both age and gender (age*MAP*sex) and as seen they were strongest in the youngest ages, and declined with advancing age becoming non-significant after the age of 69 years in men (blue colour) and age 73 years in women (red colour). However, in Model C only the interaction with age was significant, and here the association between MAP and total stroke risk continued to remain significant in the elderly (graphically the MAP / total stroke risk association with advancing age for Model C resembles that of men (blue colour) in Model B) (for the corresponding table to figure 7, see table 4 paper I).

PAPER II

During the average of 13·3 years of follow-up, the cases of mortality from stroke, CHD, and all-causes in men / women were 349 / 220, 1255 / 411, and 5369 / 2534 (table S1; online data supplements). The significant interactions of age and other cardiovascular risk factors found for the association between SBP, DBP, and mortality risk from stroke, CHD, and all-causes are summarized in table 5 below (taken from table S3; online data supplements), and used in the further analyses.

Figure 7: HRs for risk of total stroke per 5-mmHg increase in MAP in men (blue) and women (red) or per 5-mmHg increase in PP (green) with advancing baseline age



HRs indicates hazard ratios; MAP, mean arterial pressure; and PP, pulse pressure.
Model B: MAP and PP are adjusted for each other, as well as age and sex.
The vertical line at age 58 years indicates the age after which the HR for MAP significantly exceeds the HR for PP in men. The vertical line at age 69 years indicates the age after which the HR for MAP becomes non-significant in men.

Table 5 Significant interactions between age, BP, and other cardiovascular risk factors for subsequent mortality

Endpoint Interactions	fatal stroke *P* Value	fatal CHD *P* Value	All-cause mortality *P* Value
age*SBP	NS	0·009	0·01
age*SBP*sex	0·002	NS	NS
age*SBP*cholesterol	0·04	NS	NS
age*DBP	NS	0·005	<0·0001
age*DBP*country[†]	0·01	NS	NS

BP indicates blood pressure; CHD, coronary heart disease; SBP, systolic BP; and DBP, diastolic BP.
P<0·05 indicates a significant interaction term in the Cox model while NS indicates non-significance.
[*]Adjusted for age, the other BP measure (SBP and DBP are adjusted for each other) and the cardiovascular risk factors sex, smoking, diabetes, cholesterol, and body mass index.
[†]High-/low-risk country according to Heart SCORE. For further detail see tables S1 and S3 (online data supplements).

The same interaction analyses were repeated for PP and MAP (table S4; online data supplements). Generally PP and MAP interacted with age and other cardiovascular risk factors in a similar way as SBP and DBP. The main difference was the significant interaction with smoking on ages influence on the association between PP and all-cause mortality risk and with BMI on the influence of age on the association between MAP and CHD mortality risk.

The relative importance of SBP versus DBP in mortality risk with advancing age

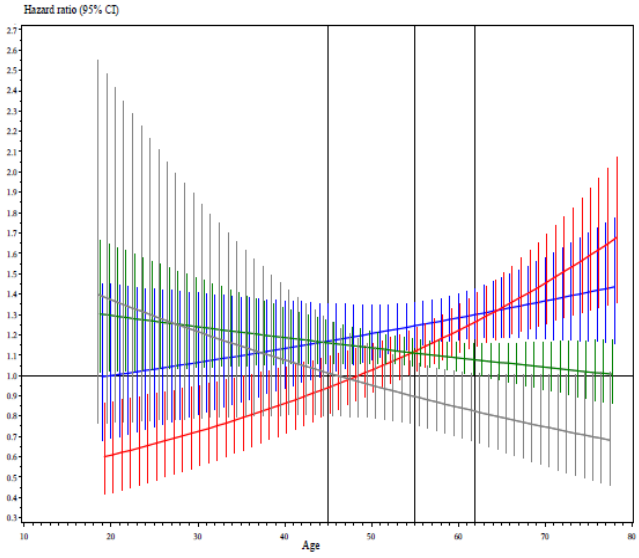
Using the multivariate-adjusted Cox model for the total population, stroke-, CHD, and all-cause mortality risk remained significantly associated with SBP, SBP≥116 mmHg, and SBP≥120 mmHg, respectively (all P<0·0001; table 1, see paper II). For DBP, only the associations between DBP≥75 mmHg and stroke mortality risk and DBP≥82 mmHg and all-cause mortality risk remained significant after multivariate adjustment (P<0·01). Below the above mentioned BP thresholds, inverse associations between BP and mortality risk were found. Using baseline age as a continuous variable in the Cox model allowed us to explore the independent associations between SBP, DBP, and the risk of mortality across different ages.

Stroke mortality risk

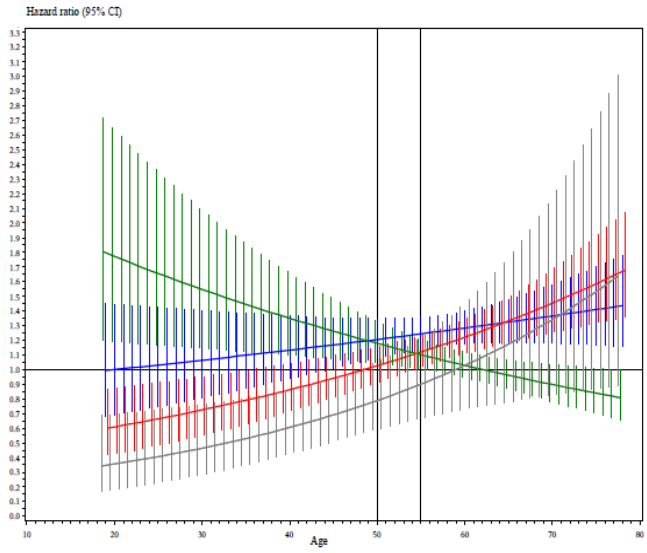
For the sake of simplicity, the cholesterol interaction is illustrated graphically below (figure 8) for serum cholesterol levels of 4 mmol/l (figure 8a-b), and 7 mmol/l (figure 8c-d), while serum levels 3 through 10 mmol/l are shown in the online data supplements figure S2.

The association between DBP≥75 mmHg and stroke mortality risk (green colour) reached significance at age 19 years, was strongest in the youngest ages (figure 8a-d) and declined with advancing age becoming non-significant at age 56 years in low-risk countries (figure 8b,d) and age 63 years in high-risk countries (figure 8a,c). For DBP<75 mmHg, the association with stroke mortality risk (grey colour) was inversely related, and only significant in ages 19-48 years in low-risk countries (figure 8b,d). The association between SBP and stroke mortality risk reached significance in ages 45 / 35 years for cholesterol levels 4 / 7 in men (blue colour) compared to the corresponding ages of 54 / 57 years in women (red colour), and remained significant until ages 78 / 69 years (figures 8a-b / 8c-d). As seen, the association between SBP and stroke mortality risk reached significance earlier in men compared to women and even earlier in men with a high cholesterol level (ages 35 vs. 57 years, respectively). Also, men from high risk countries and with a high cholesterol level had the lowest age (35 years; figure 8c) at which the HR for stroke mortality by a 10-mmHg increase in SBP exceeded that of DBP when DBP≥75 mmHg per 5-mmHg increase (for the corresponding table to figure 8, see table 2 paper I).

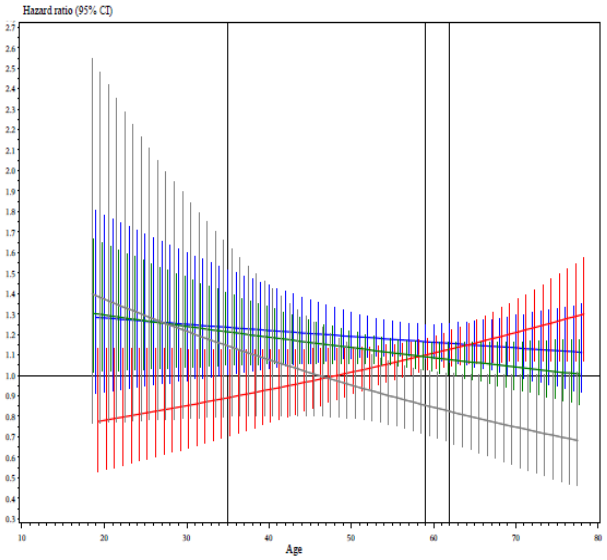
Figure 8: HRs for risk of stroke mortality per 10-mmHg increase in SBP in men (blue) and women (red) or per 5-mmHg increase in DBP>75 mmHg (green) or DBP<75 mmHg (grey) with advancing baseline age, according to cholesterol level and country risk



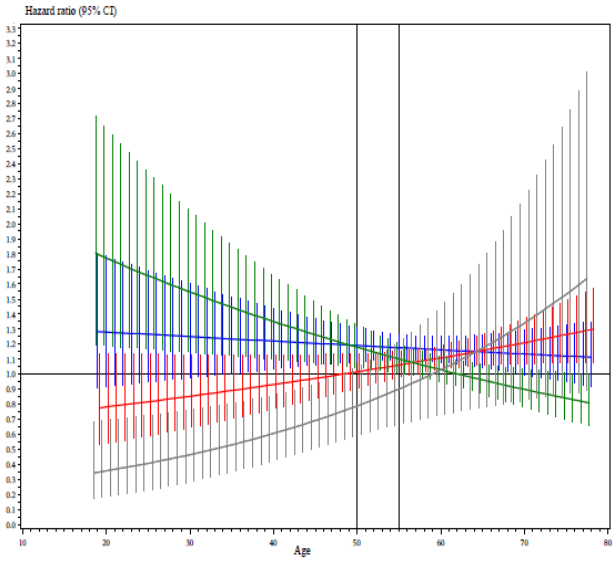
1A. Cholesterol 4 mmol/l and high-risk country



1B. Cholesterol 4 mmol/l and low-risk country



1C. Cholesterol 7 mmol/l and high-risk country



1D. Cholesterol 7 mmol/l and low-risk country

HRs indicates hazard ratios; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
Model: SBP and DBP are adjusted for each other, age, the cardiovascular risk factors sex, smoking status, diabetes mellitus, cholesterol, body mass index, and the two- and three- way interactions between SBP, age and sex, between SBP, age and cholesterol, and between DBP, age and country risk (see table 5 above).
The age at which the HR for SBP exceeds the HR for DBP when DBP≥75 mmHg is indicated by the first vertical line for men and the second vertical line (in high-risk countries only) for women. The third vertical line indicates the age after which the HR for DBP when DBP≥ mmHg becomes non-significant.

CHD mortality risk

Only SBP was significantly associated with CHD mortality risk, such that the association with SBP ≥116 mmHg was positive and significant in all ages although with strongest associations in the youngest ages (red colour; figure 9a), while the association with SBP<116 mmHg was negative and only significant in middle aged subjects (pink colour).

All-cause mortality risk

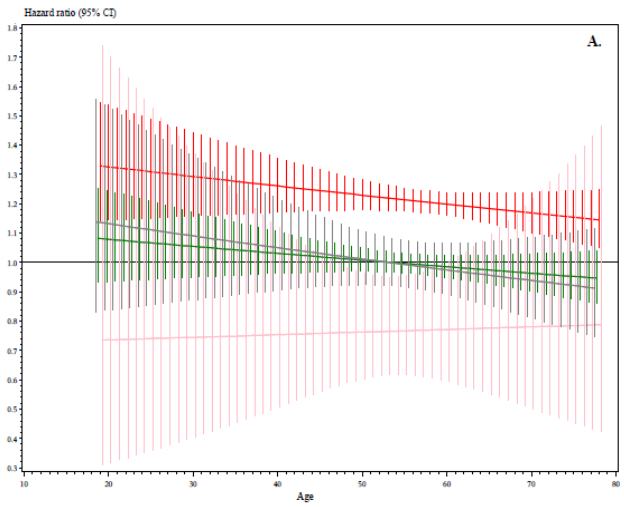
DBP≥82 mmHg was significantly associated with all-cause mortality risk in ages 19 to 58 years, and with the strongest association in the youngest ages (green colour; figure 9b). The inverse association between DBP<82 mmHg and all-cause mortality risk (grey colour) first became significant from age 59 years and onwards. The association between SBP≥120 and all-cause mortality risk was significant in ages 27 to 78 years (red colour), strengthened with advancing age and exceeded the HR of DBP≥82 mmHg at age 42 years (for the corresponding table to figure 9, see table 3 paper I).

Sub-analyses for papers I-II

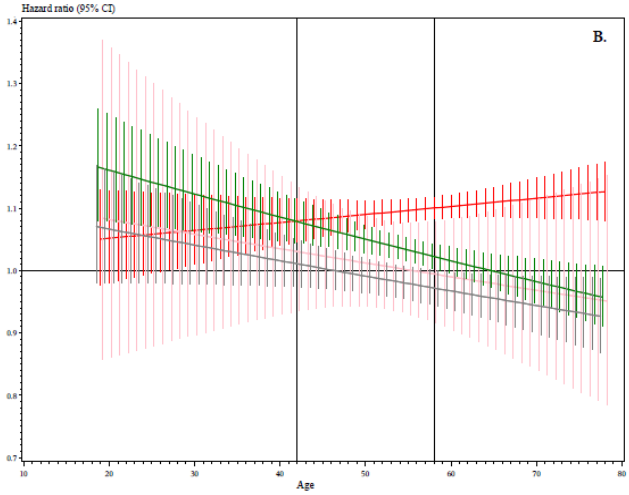
The above results were reproducible when excluding the five cohorts where BP was measured only once. Furthermore, assessing event risk using HRs per 1-mmHg increase in SBP and DBP, showed no superiority of SBP prior to the positive association between DBP and event risk becoming non-significant in the 6th decade.

In order to explain any discrepancies between papers I and II, the significant interactions for stroke mortality risk were replicated in secondary analyses including Europeans only, or countries with a high but not low stroke event score. In the reduced dataset used in paper I, the interaction with sex and high- / low-risk country, but not cholesterol, was replicated for stroke mortality risk. Re-analysis of the paper I endpoint total stroke risk showed no significant interactions with other cardiovascular risk factors regardless of the stroke event score.

Figure 9: HRs for risk of mortality due to CHD (A) and all-causes (B) per 10 mm-Hg increase in SBP or per 5-mmHg increase in DBP per 5-mmHg increase with advancing baseline age



SBP≥116 mmHg (red), SBP<116 mmHg (pink), DBP≥78 mmHg (green), and DBP<78 mmHg (grey).



SBP≥120 mmHg (red), SBP<120 mmHg, DBP≥82 mmHg (green), and DBP<82 mmHg (grey).

Model: SBP and DBP are adjusted for each other, age, the cardiovascular risk factors sex, smoking status, diabetes mellitus, cholesterol, and body mass index (see table 5 above).
The vertical line at age 42 years indicates the age at which the HR for SBP when SBP≥120 mmHg exceeds the HR for DBP when DBP≥82 mmHg. The vertical line at age 58 years indicates the age after which the HR for DBP when DBP≥82 mmHg becomes non-significant.

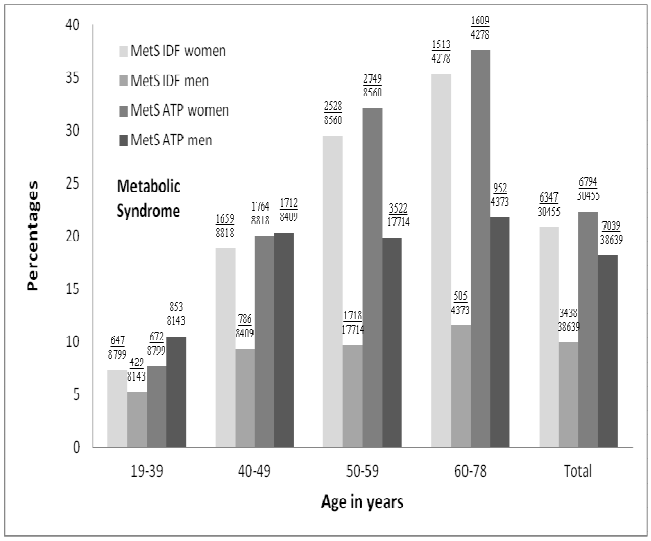
PAPER III

The prevalence of MetS

MetS prevalence, defined by IDF / NCEP-ATP III, varied greatly among populations (5·0-18·1% / 10·8-34·5% in men and 11·3-45·0% / 12·6-46·1% in women) and with a slightly higher prevalence in women compared to men, although this difference became smaller when using a BMI cut-off of 30 kg/m2 in both genders (table 1; see paper III). Furthermore, there was a higher prevalence of MetS when using the NCEP-ATP III criteria compared to the IDF. This difference between IDF and NCEP-ATP III was more pronounced in men (9·7% / 19·9%) than in women (29·5% / 32·1%).

Taking into account age group, the prevalence of MetS significantly increased across ages for both genders (P<0·0001; figure 10). The increase in MetS prevalence from age group 19-39 years to 60-78 years was almost 5-fold in women (7·4% / 7·6% to 35·4% / 37·6%, for IDF / NCEP-ATP III, respectively) and 2-fold in men (5·3% / 10·5% to 11·5% / 21·8%) reflecting less increase in men older than 49 years. Moreover, age also influenced the pattern of the MetS components in men and women, such that young women had a higher prevalence of obesity and low HDL-C, while younger men had a higher prevalence of elevated BP and elevated triglycerides. In older men and women, BP was the most prevalent component of MetS (figure 1; see paper III).

Figure 10: Frequency of MetS defined by both the IDF and the NCEP- ATP III criteria according to baseline age and gender



IDF indicates the International Diabetes Federation criteria; NCEP-ATP III, the National Cholesterol Education Program – Adult Treatment Panel III criteria. Numbers above each bar indicate total number of persons with MetS / total number of persons in the given age group; all *P*<0·0001 for each of the 4 MetS / gender combination across age groups. Within each age group, *P*<0·0001 between genders, except for MetS ATP in ages 40-49 years (*P*=0·57).

The association between MetS and CVD events

During the average of 12·2 years of follow-up, the number of total CHD, total stroke, and CVD mortality in men / women were 3222 / 1146, 1189 / 768, and 1412 / 638, respectively (table 1; see paper III).

The gender-specific HRs for the risk of total CHD, total stroke, and CVD mortality when MetS was defined by either IDF or NCEP-ATP III (table 6 below) were significantly associated with all three CVD events (all P<0·0001), independent of age, total cholesterol, and smoking- as well as fasting status, and comparable HRs were observed for both definitions of MetS. However, in women compared to men MetS defined by especially NCEP-ATPIII was closer associated with total CHD risk (HR 2·03 vs. 1·62), with CVD mortality risk (HR 2·06 vs. 1·65), and with total stroke risk (HR 1·77 vs. 1·53). Furthermore, whereas in men the HRs for a CVD event were independent of age (MetS*age, P>0·05; table 3, see paper III), in women the HRs for CHD declined with age (from HRs 3·23 / 3·98 to 1·55 / 1·56; MetS*age, P=0·01 / P=0·001 for IDF / NCEP-ATPIII) while the HRs for stroke tended to increase (from HRs 1·31 / 1·25 to 1·55 / 1·83; MetS*age, P>0·05).

Sub-analyses

Replicating the above analyses in subsets using WC instead of BMI, and using a reduced dataset excluding participants in antihypertensive treatment and non-fasting or semi-fasting participants, generally showed similar trends, although with slightly attenuated results for the prevalence of MetS.

Table 6: Hazard ratio for different definitions of the metabolic syndrome by age category and event type in men and women

	Men							Women						
	Number	MetS IDF			MetS ATP			Number	MetS IDF			MetS ATP		
	of events	HR	95%CI	*P*-value	HR	95%CI	*P*-value	of events	HR	95%CI	*P*-value	HR	95%CI	*P*-value
CHD														
19-39 years	140	140	0·84-2·55	0·18	1·50	0·99-2·27	0·05	40	3·23	1·51-6·89	0·0025	3·98	1·94-8·20	0·0002
40-49 years	672	672	1·28-1·98	<0·0001	1·65	1·40-1·95	<0·0001	234	2·56	1·96-3·35	<0·0001	2·66	2·04-3·48	<0·0001
50-59 years	1744	1744	1·50-1·95	<0·0001	1·65	1·49-1·83	<0·0001	539	1·88	1·58-2·23	<0·0001	2·02	1·70-2·40	<0·0001
60-78 years	666	666	1·03-1·60	0·02	1·46	1·23-1·72	<0·0001	333	1·55	1·24-1·94	0·0001	1·56	1·25-1·94	<0·0001
19-78 years[a]	3222	3222	1·45-1·77	<0·0001	1·62	1·50-1·75	<0·0001	1146	1·93	1·71-2·18	<0·0001	2·03	1·80-2·29	<0·0001
		140	0·84-2·55	0·18	1·50	0·99-2·27	0·05	40	3·23	1·51-6·89	0·0025	3·98	1·94-8·20	0·0002
Stroke														
19-39 years	47	47	0·98	0·30-3·19	0·97	1·88	0·91-3·89	38	1·31	0·45-3·78	0·62	1·25	0·43-3·61	0·68
40-49 years	196	196	1·54	1·01-2·34	0·04	1·37	1·00-1·88	129	1·33	0·88-2·00	0·17	1·35	0·90-2·01	0·14
50-59 years	579	579	1·60	1·27-2·02	<0·0001	1·76	1·47-2·09	304	1·74	1·38-2·21	<0·0001	1·95	1·54-2·46	<0·0001
60-78 years	367	367	1·38	1·03-1·84	0·032	1·25	0·99-1·58	297	1·55	1·22-1·96	0·0003	1·83	1·44-2·32	<0·0001
19-78 years[a]	1189	1189	1·51	1·28-1·78	<0·0001	1·53	1·35-1·73	768	1·58	1·36-1·84	<0·0001	1·77	1·52-2·05	<0·0001
		47	0·98	0·30-3·19	0·97	1·88	0·91-3·89	38	1·31	0·45-3·78	0·62	1·25	0·43-3·61	0·68
CVD mortality														
19-39 years	37	37	0·72	0·17-3·03	0·66	1·05	0·42-2·63	16	1·21	0·26-5·61	0·81	2·90	0·88-9·56	0·08
40-49 years	211	211	2·17	1·52-3·10	<0·0001	1·70	1·27-2·27	86	2·67	1·72-4·15	<0·0001	3·12	2·01-4·84	<0·0001
50-59 years	682	682	1·91	1·56-2·34	<0·0001	1·84	1·57-2·15	276	1·70	1·33-2·16	<0·0001	2·07	1·62-2·63	<0·0001
60-78 years	482	482	1·34	1·03-1·73	0·027	1·37	1·12-1·68	260	1·60	1·25-2·06	0·0002	1·71	1·33-2·20	<0·0001
19-78 years[a]	1412	1412	1·73	1·50-2·00	<0·0001	1·65	1·47-1·84	638	1·77	1·51-2·09	<0·0001	2·06	1·75-2·42	<0·0001

HR indicates hazard ratio; CHD, coronary heart disease; CVD, cardiovascular disease; MetS IDF, metabolic syndrome according to the International Diabetes Federation; and MetS ATP, metabolic syndrome according to the National Cholesterol Education Program – Adult Treatment Panel III.
Cox model adjusted for smoking (yes/no), cholesterol (continuous), and fasting (full / semi / no fasting).
[a]For the total population, the Cox model is adjusted for age, smoking (yes/no), total cholesterol (continuous), and fasting (full/ semi/ no fasting).

DISCUSSION

In the following section, the main findings of papers I-III are summarized and discussed in the context of previous research, followed by a discussion of some methodological considerations.

PAPERS I-II

Main findings

We demonstrated the presence of age-related shifts in the independent relative importance of SBP and DBP as risk factors for stroke (both total and fatal) and all-cause mortality, but not for CHD mortality, where SBP remained significant in all ages. The prognostic shift to the superiority of SBP was significantly established in the 6th decade, and only for stroke mortality risk was this shift influenced by other cardiovascular risk factors as well as the geographical location (i.e., high- / low-risk country), such that it occurred earlier in men from high-risk countries and with a high cholesterol level. In addition to the superiority of SBP with advancing age, we also found a significant independent relative importance of low DBP for the risk of total stroke and all-cause mortality from mid-age and onwards.

For total stroke risk, both PP and MAP had an independent relative importance with advancing age; although for PP this association was marginal and remained the same across all ages, and for MAP it first became significant in the elderly after multivariate adjustment. For mortality risk from stroke, CHD, and all-causes, PP and MAP generally interacted with age and other cardiovascular risk factors in a similar way as SBP and DBP, except for additional interactions with smoking (for age*PP→ risk of all-cause mortality) and BMI (for age*MAP→ for risk of fatal CHD), suggesting increased risk of mortality with advancing age.

The above results were reproducible in all sensitivity analyses.

Age-related superiority of SBP and influence of cardiovascular risk factors

In accordance with the Framingham Heart Study [72] and others [66,73-81], as stated in the background section, we showed the superiority of SBP as a risk factor for cardiovascular morbidity and mortality as well as for all-cause mortality with advancing age. However, we further extended these previous findings by using age as a continuous variable in the Cox model and thus elucidating the age-related shifts to the superiority of SBP. For stroke mortality risk we showed that the shift from DBP to SBP was dynamic such that it occurred at an earlier age in the presence of other cardiovascular risk factors. The earlier superiority of SBP seen in the presence of male gender, high cholesterol level, and high-risk country, was probably due to earlier stiffening of the arteries influencing the effects of SBP and DBP in opposite ways [82,83]. Interestingly, for women the positive association between SBP and stroke mortality risk did not reach significance before mid-age. This could be due to the hormonal protection up until around age 50 years or around the period of the menopause. For the risk of total stroke and all-cause mortality, age-related shifts between SBP and DBP remained consistent, regardless of the geographical location or the presence of other cardiovascular risk factors, whereas for the risk of CHD mortality no age-related shifts where seen since SBP remained superior in all ages.

The contradictory results, that age-related shifts to the superiority of SBP was influenced by other cardiovascular risk factors for stroke mortality risk (paper II) but not for total stroke risk (paper I) questioned the validity of the diagnosis of stroke, especially since the MONICA criteria for nonfatal stroke were based on clinical presentation and not on imaging techniques. However, using the MORGAM stroke event score, we found that the significant influences of cardiovascular risk factors on the association between BP and stroke mortality risk, but not on the association between BP and total stroke

risk, remained consistent in the cohorts with a high stroke event score. This suggests a real difference between these two endpoints and not just a diagnostic bias. Perhaps the impact of additional cardiovascular risk factors on the prognostic shift from DBP to SBP is more pronounced in patients with fatal strokes because it is these additional risk factors that increase the risk of a stroke becoming fatal. Although many previous studies [72,77-79,112] have shown that the impact of age on the associations between BP and events is different in men and women, to our knowledge few studies [66,104] have investigated the interaction of other cardiovascular risk factors in addition to gender. A study conducted by Nakamura et al [104] showed that a combination of current smoking and non-optimal levels of BP appears to have a synergistic impact on the risk of hemorrhagic stroke, at least among men and in the elderly. Somewhat similar, we found a significant interaction with smoking on ages influence on the association between PP and all-cause mortality risk, and an almost significant interaction for stroke mortality risk.

Our finding of an earlier prognostic shift to the superiority of SBP for stroke mortality risk in high-risk countries appears genuine despite the fact that the map of cardiovascular risk in Europe has changed during the last decade and former high-risk countries such as Denmark, Finland and the United Kingdom are now at low risk according to Joint Prevention Guidelines [113]. The genuinity lies in the fact that the division of countries into low or high risk as used in the present studies was consistent with the division of countries into low or high risk used 20 to 30 years ago when MORGAM cohorts were recruited.

Although the superior role of SBP as a risk factor for CVD events in the elderly has been elucidated in many studies, the independent relative importance of DBP in younger ages is less clear, as stated in the background section. The present findings indicated the independent relative importance of both DBP and SBP in young individuals. Although we showed that the associations between DBP and risk of total stroke as well as stroke- and all-cause mortality were superior in the very youngest ages, the strength of this association decreased with advancing age, suggesting that DBP and SBP were of similar importance already starting from the early to late twenties.

Inverse association of low DBP to event risk

We showed that for middle aged and elderly participants with low DBP there was a significant inverse association with the risk of total stroke (for DBP< 71 mmHg) and all-cause mortality (for DBP< 82 mmHg), such that the risk of these events decreased for each 5-mmHg increase in DBP. For these participants, not only SBP but also DBP had a relative importance with advancing age. These findings elucidate two important issues, namely (1) the J curve effect; and (2) PP. The age related stiffening of the conduit arteries leads to an increase in SBP and a decrease in DBP with older age.

J curve effect

The positive association between DBP and event risk above a certain threshold value, and the negative association with event risk below, describes a J-shaped relation of DBP to event risk, known as the J curve effect, which can be explained by the fact that below a certain threshold value perfusion of vital organs is impaired because auto-regulation of vasomotor tone cannot compensate for the excessive reduction in the pressure gradient.

However, the clinical relevance for antihypertensive treatment of this potential harmful effect of low DBP in relation to event risk is questionable because additional descriptive analyses (data not shown previously) for the endpoints total stroke / all-cause mortality showed that it concerns few subjects (0·7% / 6·6%), with mean SBP + SD of 128 + 18 mmHg / 131 + 17 mmHg, and only 5·4% / 5·5% of them having moderate to severe hypertension. Furthermore, although previous work [60,114-116], exploring the relationship of low DBP to CVD event risk has been contradictory, there is extensive evidence [60,114,115] that antihypertensive treatment, which is usually associated with very low DBPs, does reduce CVD events. For instance, a study by Staessen et al [60] showed the clear beneficial effect of BP reduction on such endpoints as total stroke, total CHD, and CVD morbidity and mortality in patients with isolated systolic hypertension. Furthermore, a recent meta-analysis [115] concluded that lowering DBP to less than 70 mmHg did not cause harm in patients with hypertension. In addition, Fagard et al [114] showed that antihypertensive treatment could be intensified to prevent CVD events in elderly patients with systolic hypertension, at least until DBP reached 55 mmHg. However, in contrast to these findings, Kannel et al [116] showed that in patients with hypertension, the risk of CVD events increased when DBP was less than 80 mmHg.

Most previous studies demonstrating a J-shaped relationship between DBP and CVD event risk, have shown these relations for CHD risk [81,117,118], and only very few for stroke risk [114,119]. The lack of a J-curve effect for stroke risk has been explained by the fact that cerebral blood flow is not seriously affected even with very low DBP due to cerebral auto-regulation, which maintains a constant cerebral blood flow so as to maintain the metabolic needs of the brain [120]. In addition, previous studies [114,121] have also shown J-shaped relations between DBP and non-CVD risk in both treated and untreated hypertensive patients, attributing it to poor health and reverse causation. Worth noting is that the J-shaped relation of DBP to event risk reported in these previous studies were in patients with hypertension. To our knowledge, no other study has shown J-shaped relations between DBP and event risk in apparently healthy participants, and therefore, we consider our findings novel.

Pulse pressure

The observation, that SBP was positively and DBP was negatively related to event risk with advancing age, has been shown previously [73,74,76,79,80], and suggests the increased importance of PP in the elderly. This was not confirmed in paper I, whereas in paper II we found that PP interacted significantly with age for stroke- and all-cause mortality, suggesting an increased risk of mortality for each 5-mmHg increase in PP with advancing age. Although in paper I we found that PP, independent of MAP, was significantly associated with total stroke risk in ages 19-78 years, the risk of total stroke for each 5-mmHg increase was marginal and remained the same across all ages. Moreover, although only PP was significantly associated with stroke risk after the age of 69 years in men and 73 years in women, this superiority of PP over MAP did not remain after multivariate-adjustment. In addition, the interaction with sex on the timing of the shift in the relative importance of MAP to PP was only by four years, which we do not

consider clinically important. Furthermore, compared to SBP, we did not find that PP had a superior role in total stroke risk in the elderly. Although we did not directly compare SBP and PP in the same model, we found that the association between SBP and total stroke risk was three times as strong compared to that for PP (HR 1·30 versus 1·10, respectively) in multivariate-adjusted Cox models per 1-SD increase. This finding was consistent with previous work [66,75,78,81], which showed that PP was less strongly associated with long-term stroke risk compared to SBP.

PAPER III

Main findings

Using modified versions of the IDF and the revised NCEP-ATP III criteria of MetS, the main findings of the present study were that the prevalence and prognostic significance of MetS showed great variations among countries and were influenced by both age and gender. With older age, the prevalence of MetS increased 5-fold in women and 2-fold in men and the pattern of the individual MetS components changed in women (obesity was surpassed by high SBP) but not in men in whom SBP was dominating in all ages. Independently of age, the prevalence of MetS based on the NCEP-ATP III criteria almost doubled that of IDF criteria in men whereas it was equal in women. The risk of a CVD event associated with MetS was (1) significant for all three CVD event types, (2) higher in women than in men especially when using the NCEP-ATP III criteria, and (3) independently of age in men whereas in women total CHD risk decreased and total stroke risk tended to increase with older age.

The above results were reproducible in all sensitivity analyses, although slightly attenuated.

Prevalence of MetS

Our finding, that MetS prevalence increased with age, is consistent with previous work [16,18,21,22,24,99]. Furthermore, the steeper age-related increase in MetS prevalence in women compared to men, has also been shown previously [18,21], and may be attributable to the steep increase in BP in women after menopause which initiates a more rapid decrease in endothelial function. Consistently, we found a shift in the dominance of the individual MetS components with age, from obesity in younger women to elevated BP in older women. Similarly, Lawlor et al [25] showed that the most prevalent component of MetS in postmenopausal women was elevated BP. Our finding of a less steep increase in prevalence of MetS in men could partly be due to the dominance of the BP component in all age groups. The relative difference between the genders in components of MetS with older age is consistent with previous work [22].

Country variations in prevalence of MetS have also been found in other studies [18,21,22,24,26-29,46]. For instance, comparing studies from Germany [18], Norway [21], and Greece [24] show variations in MetS prevalence from 9-16% in men below age 40 years to 34-45% in men between ages 60-69 years, and the corresponding prevalence in women was 5-8% and 35-46%. These age differences were slightly accentuated when using the IDF criteria. The country variation in the present study could not be explained by variations in age and gender indicating that it was due to some country specific differences in either genes, lifestyle and/or population selection.

Prognostic significance of MetS

Although the risk of all three CVD event types was significantly associated with MetS in both men and women, we showed that this risk was higher in women especially when using the NCEP-ATP III criteria. This is in line with previous work [26-31]. We further extended previous findings by showing that the CVD event risk was independently of age in men whereas in women total CHD risk decreased and total stroke risk tended to increase with older age. The generalized CVD event risk associated with MetS can be explained by the fact that MetS includes both metabolic risk factors promoting atherosclerosis and CHD and hemodynamic risk factors promoting arteriosclerosis and stroke [122,123]. In women the revised NCEP-ATP III criteria was more closely associated with outcome than MetS defined by the IDF criteria which might be explained by the fact that elevated BMI, which is mandatory for the IDF definition and very prevalent in women with MetS, is only weakly related to cardiovascular outcome. Furthermore, the weaker associations between CVD event risk and MetS defined by the IDF as well as NCEP-ATP III criteria found previously in women [15,25] could be due to the lack of age-stratification as well as the lack of inclusion of younger women. However, the increased risk, especially for total CHD among young women in the present study, could be a by-product reflecting low absolute risk and the greater importance of metabolic factors in otherwise lower risk groups. Indeed, Gami et al [27] showed in a meta-analysis that the association between MetS and incident CVD events and death was stronger in studies enrolling lower risk individuals. The apparent age independency of MetS associated CVD event risk in men, can be explained by an increase in mid-aged subjects due to sufficient exposure time and a decrease in older subjects due to selection bias. In women, MetS associated risk of total CHD and to some degree of CVD mortality decreased with older age which might be due to increasing competing risk such as cancer [124], whereas total stroke risk seemed to increase with age which might reflect that the contribution of SBP, the main predictor of stroke, to MetS increases considerably with older age in women.

METHODOLOGICAL CONSIDERATIONS

Statistical issues

A few statistical issues should be considered when interpreting the present results.

Collinearity

In papers I-II, including both SBP and DBP simultaneously in the Cox model raised the question of collinearity between these two variables, which could potentially reduce their predictive power or reliability [125]. However, we did not find that the correlation between these two variables was a major issue in the present work since the influence of SBP and DBP on event risk did not differ considerably in models where they were included separately compared to models where they were included simultaneously.

Statistical interactions

In papers I-II, the influence of age on the association between BP and event risk was carried out separately in the Cox model, correcting for the other BP measure (SBP adjusted for DBP, and DBP adjusted for SBP). However, we also tested whether these two BPs interacted synergistically (SBP*DBP). These analyses were carried out in age-adjusted as well as multivari-

ate-adjusted Cox models. The results indicated that the SBP*DBP interaction did not reach significance in any of the adjusted models (all P<0·05). Furthermore, the interaction between SBP*DBP*age also did not reach significance in any of the models (all P<0·05). Comparing the Akaike´s Information Criterion (AIC) values of models with the SBP*DBP interaction term to those models without this interaction term showed no improvement of model fit when including the interaction term.

Several factors play a role in disease causation, and therefore, in a person with multiple risk factors, one risk factor may compete with the other to cause an event (confounding). In papers I-III, we controlled for confounding by adjusting our models for the traditional cardiovascular risk factors, and it is also on these models that the main results and conclusion are based.

Strengths

The strength of the MORGAM Project lies in its large sample size of mostly European population-based cohorts, with an average follow-up time of at least 10 years encountering approximately 5000 major CVD events. The sample and case sizes surpassed that of many previous studies, and allowed for the performance of rigorous statistical analyses in men and women of various ages, including robust sensitivity analyses. Other strengths were the inclusion of a wide age range, an almost equal proportion of men and women, and the standardized baseline and endpoint assessment available from the well-characterized MORGAM cohorts, with individual validation of the diagnosis in the majority of fatal and nonfatal events.

Limitations

Some limitations should also be considered.

Papers I-II

We eliminated participants who were on antihypertensive therapy so as not to underestimate the relationship of BP to event risk and distort age-related shifts between the BP measures. However, this could have produced a selection bias since the proportion of excluded participants was not equal in all ages / age strata. Moreover, BP measurements were only taken at baseline, and therefore may have underestimated the associations between BP and event risk. Instead, replicate measurements of BP would have taken into account longer-term fluctuations or changes within the person over time, and thus, indicated the real association between the "usual" level of BP and stroke risk (regression dilution bias) [126]. Nonetheless, as shown by Miura et al [75], a single BP reading is strongly predictive of future cardiovascular events. In addition, the inability to separate hemorrhagic from ischemic stroke is a major limitation. However, there are several reasons as to why these two stroke types were combined. First, in several populations CT scanners were not widely available, or autopsy rates were low in patients dying out of the hospital, making accurate stroke sub-typing impossible. Second, the statistical power to determine risk for hemorrhagic stroke was low. Third, previous work [66,75] showed similar age-specific associations for cerebral hemorrhage and cerebral ischemia, indicating that it might be appropriate to combine these two types of strokes to assess the association between BP and stroke. Fourth, combining these two types of strokes is in line with previous MORGAM work [127].

Paper III

Since data on plasma glucose was not available, the self-reported presence of diabetes or use of anti-diabetic drugs was used instead. Therefore, we have underestimated the prevalence of diabetes. Although most of the "missed" cases would be defined as having MetS on account of the coexistence of other components of MetS, some might have been "missed" probably leading to an underestimation of the HR associated with MetS because subjects with diabetes generally are at high cardiovascular risk. Therefore, we do not believe that the underestimation of MetS influenced the prognostic interactions between age, gender and the risk of MetS. Although we used BMI instead of WC in order to maximize sample size, this was in line with other studies [19,22,26-29]. In a meta-analysis by Gami et al [27] it was shown that substitution of BMI for WC or waist-to-hip ratio in NCEP-based criteria did not appear to affect the results. Moreover, since fasting levels differed between cohorts, a categorized fasting variable was used as adjustment in the Cox model. In both of these cases, we carried out sensitivity analyses using WC instead of BMI, or including only full-fasting individuals, and showed similar, although slightly attenuated results. For the latter case, Hildrum et al [21] showed no statistically significant difference between the fasting and the non-fasting samples in the prevalence of the IDF- or ATP-proxies of MetS.

Papers I-III

The baseline age distribution of the various populations differed, and therefore any age difference observed may also reflect differences between the populations. We tried to minimize the influence of the populations by stratifying for country in the Cox model. Furthermore, when comparing MetS prevalence among the populations, we used a fixed age group, which was covered by all populations. However, since most populations are from age 25 years and onwards, our results for the youngest age group should be interpreted with caution due to lack of statistical power to detect associations.

Finally, our findings may not apply to non-Europeans (papers I-III), or patients with CVD (papers I-III), or who are in treatment with antihypertensive medication (papers I and II) since these two latter patient categories were excluded at baseline.

CONCLUSION

This PhD thesis demonstrates that prognostic interactions between cardiovascular risk factors can be used to obtain a deeper understanding of the complex interplay between these risk factors.

By examining interactions between age, gender, different BP measures and other important cardiovascular risk factors in a large European prospective cohort study of up to 86 000 men and women aged 19-78 years, we tested the following hypotheses:

(1) The superiority of SBP over DBP as a risk factor occurs at an earlier age if an individual presents with other cardiovascular risk factors (papers I-II).

(2) The prevalence and prognostic significance of MetS differ according to age and gender (paper III).

Based on our findings the main conclusions are summarized as follows:

Papers I-II: Age-related shifts exist for the independent relative importance of SBP and DBP as risk factors for total stroke and all-cause mortality, but not for CHD mortality where SBP remains superior in all ages. The prognostic shift to the superiority of SBP was significantly established in the 6th decade, and only for stroke mortality was this shift influenced by other cardiovascular risk factors, such that it occurred at an earlier age in men from high-risk countries and with a higher cholesterol level. However, at the same time, a potential harmful effect of low DBP observed for the risk of total stroke and all-cause mortality from mid-age and onwards could not be entirely ignored.

Paper III: The prevalence and prognostic significance of MetS showed great variations among countries and were influenced by both age and gender. With older age, the prevalence of MetS increased 5-fold in women and 2-fold in men. The risk of a CVD event associated with MetS was (1) higher in women than in men especially when using the NCEP-ATP III criteria, and (2) independently of age in men whereas in women total CHD risk decreased significantly and total stroke risk tended to increase (although not significant) with older age.

PERSPECTIVES

At a time where CVD still remains the leading cause of death worldwide, and risk factor control continues to be poor, there is a need for future studies to find better ways to optimize BP control and ways to identify high risk individuals. By elucidating the complex interplay between cardiovascular risk factors using prognostic interactions, the present work has raised several questions / new ideas which need to be addressed by future studies before any form for clinical implementation can take place.

For instance, papers I-II suggest one way to optimize BP control in order to prevent event risk, namely by assessing both SBP and DBP up until the 6th decade (age 62 years), although with increased focus on SBP from mid-age and even earlier when an individual possesses certain cardiovascular risk factors (especially to prevent stroke mortality). After the age of 62 years, the main focus should be on SBP. The potential harmful effect of low DBP, at least for the risk of total stroke, and all-cause mortality, from mid-age and onwards, should be weighed against studies showing the beneficial effects of treating isolated systolic hypertension even with low DBP.

In addition, the present studies also suggested different cut-off points of SBP and DBP (i.e., DBP> 71 mmHg and DBP <71 mmHg) for establishing the maximal association with event risk.

Future research should address the following:

(1) Replication of the present findings and reassessment of the magnitudes of the effect sizes through other large prospective cohort studies.

(2) Since the effects of treatment cannot be safely inferred from epidemiological data, randomized clinically controlled trials are needed to address whether the proposed different limits of “ideal BP” should be recommended as treatment goals depending on the age of the person.

(3) Whether the different cut-off points of SBP and DBP can better reclassify patients over and beyond the Framingham risk score or HeartScore.

(4) Explore the potential harmful effects of low DBP through randomized clinically controlled trials for CVD and non-CVD events.

(5) Replication of the present findings using different stroke sub-types as endpoints

(6) The applicability of the current findings in non-Europeans and other specific ethnicities.

Paper III suggests the existence of prognostic interactions between age, gender, and MetS, since the association of MetS to CHD risk varied according to these two non-modifiable risk factors. Before the possible final burial of Mets, future research should address the following:

(1) Replication of the present findings and reassessment through other large prospective cohort studies, preferably with available plasma glucose levels.

(2) Whether some of the elements (used as continuous variables) creating MetS interact with one another at certain levels which might suggest new threshold values of the components and thereby a re-definition of MetS with these new partition values.

(3) Whether MetS with these “new” threshold values associates stronger with event risk above and beyond its individual components.

(4) Whether MetS with “new” threshold values can better reclassify patients over and beyond the Framingham risk score or HeartScore.

It is hoped that answers to the above research questions will eventually lead to better targeted and more individualized prevention strategies.

LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AIC	Akaike´s Information Criterion
ATP-III	Adult Treatment Panel III
BP	Blood Pressure
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
EGIR	European Group for study of Insulin Resistance
ESH	European Society of Hypertension
ESC	European Society of Cardiology
HDL-C	High Density Lipoprotein Cholesterol

HR	Hazard Ratio
IDF	International Diabetes Federation
IHD	Ischaemic Heart Disease
JNC	Joint National Committee
MAP	Mean Arterial Pressure
MetS	Metabolic Syndrome
MONICA	MONItoring of trends and determinants in CArdiovascular disease
MORGAM	MOnica, Risk, Genetics, Archiving and Monograph
NCEP	National Cholesterol Education Program
PP	Pulse Pressure
SCORE	Systematic COronary Risk Evaluation
SBP	Systolic Blood Pressure
SD	Standard Deviation
WC	Waist Circumference
WHO	World Health Organization

SUMMARY

Background

Cardiovascular disease (CVD) still remains the leading cause of death worldwide, especially in Europe where the prevalence of hypertension is 60% higher compared with the United States and Canada and the clustering of hypertension and the metabolic disorders central adiposity, dyslipidemia and dysglycemia, known as the metabolic syndrome (MetS), affects 25% of the population. Despite the great initiatives of many primary prevention strategies, risk factor control is still poor. In an attempt to optimize risk factor control, two issues among others have been of great debate in the past decade: (1) the superiority of systolic blood pressure (SBP) as a risk factor in the elderly; and (2) the clinical relevance of MetS. However, in order to further elucidate these issues, we need to get a deeper understanding of how the cardiovascular risk factors interact with one another. Thus, prognostic interactions were used in the present PhD thesis to test the following hypotheses:

Primary hypotheses

(1) The superiority of SBP over diastolic blood pressure (DBP) as a risk factor occurs at an earlier age if an individual presents with other cardiovascular risk factors.

(2) The prevalence and prognostic significance of MetS differ according to age and gender.

The first hypothesis is explored in paper 1 (for the endpoint fatal and nonfatal (total) stroke) and paper II (for mortality from coronary heart disease (CHD), stroke, and all-causes), while the second hypothesis is explored in paper III (for total CHD, total stroke, and CVD mortality).

Methods

Using 34-42 cohorts from the MORGAM Project with baseline between 1982-1997, approximately 68 000-86 000 apparently healthy men and women aged 19-78 years, without CVD (papers I-III) and not receiving antihypertensive treatment (papers I-II) were included. During 12-13 years of follow-up, the incident events of total stroke were up to 1957, of total CHD were 4368, and of all-cause mortality were 7903.

In papers I-II, event risk was analyzed by multivariate-adjusted Cox regressions including SBP and DBP simultaneously, as well as other cardiovascular risk factors and any significant interactions between variables.

In paper III, MetS prevalence and prognostic significance was considered according to modified definitions of the International Diabetes Federation (IDF) and the revised National Cholesterol Education Program - Adult Treatment Panel (NCEP-ATP III), and the influence of possible interactions between age and gender on MetS prevalence and prognostic significance was explored using logistic as well as multivariate-adjusted Cox regressions. MetS was analyzed separately for men and women in various age-groups.

Results

Taking into account the significant interactions between cardiovascular risk factors, the results were as follows:

Papers I-II: Age-related shifts were shown for the independent relative importance of SBP and DBP as risk factors for stroke (both total and fatal) and all-cause mortality, but not for CHD mortality where SBP remained significant in all ages. The prognostic shift to the superiority of SBP was significantly established in the 6th decade, and only for stroke mortality was this shift influenced by other cardiovascular risk factors, such that it occurred at an earlier age in men from high-risk countries and with a higher cholesterol level. However, from mid-age and onwards, a potential harmful effect of low DBP for the risk of total stroke and all-cause mortality was present.

Paper III: The prevalence and prognostic significance of MetS showed great variations among countries and were influenced by both age and gender. With older age, the prevalence of MetS increased 5-fold in women from ages 19-39 years to 60-78 years and 2-fold in men. The CVD risk associated with MetS was (1) higher in women than in men especially when using the NCEP-ATP III criteria, and (2) independently of age in men whereas in women total CHD risk decreased significantly and the total stroke risk tended to increase (although not significant) with older age.

Conclusion

The present thesis elucidates through prognostic interactions the complex interplay between cardiovascular risk factors. Our results indicate the independent prognostic superiority of SBP in elderly Europeans, and only for stroke mortality risk this prognostic superiority of SBP was influenced by other cardiovascular risk factors such that it was established at an earlier age. The prevalence and prognostic significance of MetS differed according to both age and gender. In women, MetS was associated with higher relative event risks and the MetS associated relative CHD risk decreased with advancing age.

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