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Predictive importance of blood pressure characteristics with increasing age in healthy men and women: The MORGAM Project

Short title: Prognostic importance of BP by age and sex

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Abbreviations

ACM, all-cause mortality; AUC_{ROC}, area under the receiver-operating-characteristic curve; BMI, body mass index; BP, blood pressure; CEP, composite cardiovascular endpoint; Chol, serum total cholesterol; CI, confidence interval; cNRI, continuous net reclassification improvement; CVD, cardiovascular death; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; MBP, mean blood pressure; MONICA, Multi-national MONItoring of Trends and Determinants in CArdiovascular Disease; MORGAM, MOnica, Risk, Genetics, Archiving and Monograph; NRI, net reclassification improvement; NS, non-significant; PP, pulse pressure; SCORE, Systematic COronary Risk Evaluation; SBP, systolic blood pressure.

Abstract

It remains unclear which blood pressure (BP) characteristics best predict cardiovascular risk in different age groups and between sexes. We leveraged data from the MORGAM Project to investigate determinants of BP characteristics and their prognostic importance, in younger and older (</≥50 years) men and women. The study population comprised 107,599 individuals (53% men) aged 19-97 years without established cardiovascular disease, not on antihypertensive treatment, recruited between 1982-2008 in 38 cohorts. Covariates of BP characteristics were explored using multivariable linear regression. Prognostic importance was examined using multivariable Cox proportional-hazards regression, area under the receiver-operating-characteristic curve (AUC_{ROC}), and net reclassification improvement (NRI). The primary endpoint was a composite cardiovascular endpoint (CEP), defined as fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction. The positive association between age and systolic BP (SBP) was more pronounced among individuals ≥50 years while the same was true for diastolic BP (DBP) in those <50 years (P-interaction<0.001). Higher SBP and mean BP were significantly associated with CEP, irrespective of age group (P<0.001), but DBP only demonstrated an independent relationship in the younger group (P<0.001). Brachial pulse pressure was associated with CEP in the older age group (P<0.001). In subjects <50 years, DBP significantly improved AUC_{ROC} compared with SCORE variables (including SBP) alone (0.842 versus 0.840,P=0.03), enhanced continuous NRI (0.150, 95% confidence interval, 0.087-0.215) and improved the prognostic value of the ESC/ESH hypertension definition (categorical NRI=0.0255,P=0.005). In conclusion, DBP may provide additional prognostic utility beyond SBP, in predicting composite cardiovascular events among younger individuals.

Key words

Blood pressure characteristics, Arterial stiffness, Age, Sex, Prognosis, SCORE, Net reclassification index

Background

Hypertension is a major modifiable risk factor for cardiovascular disease and all-cause mortality (1-3). Through the years, several blood pressure characteristics, including systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) have received attention because of their potential ability to predict cardiovascular events (4). These BP characteristics are affected to a varying degree by age-related changes in the cardiovascular system, e.g., arterial stiffening, increased peripheral resistance, and atherosclerosis (5), changes that themselves are associated with subsequent cardiovascular disease (6-10).

SBP generally increases throughout life, whereas DBP begins to decline after the age of 50 years, resulting in PP increase (5). This is due to arterial stiffening that increases with age. PP may better reflect large artery stiffness, and mean BP (MBP) may better reflect cardiac output and peripheral resistance than SBP and DBP (7). Aging increases arterial stiffening in both sexes, but sex hormones and menopause may modify the pace at which this happens (5, 11). In addition, arterial stiffening occurs irrespective of BP levels (12). Accordingly, it remains unclear which BP characteristics best predict cardiovascular risk in different age groups and between men and women.

We leveraged data from the large, multinational MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project to investigate 1) covariates of classical BP characteristics (SBP, DBP, and MBP) and indirect measures of arterial stiffness (brachial PP, SBP/DBP-ratio, and brachial PP/MBP-ratio) in younger and older men and women; 2) the relative importance of these BP characteristics independently and combined, in predicting incident cardiovascular events and all-cause mortality; and 3) whether the predictive power of BP characteristics were affected by sex and age.

Methods

We used baseline and 10-year follow-up data from the MORGAM Project, which consists of large population cohort studies from many countries. The data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Approval of the Principal Investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access to the data. In addition, a detailed description of the project, included cohorts, and quality assessment have been published previously (13, 14).

Cohorts and baseline variables

Baseline data were gathered from 1982-2002 and originated from 38 population-based cohorts in 11 European countries (**Supplemental Table S1**, please see http://hyper.ahajournals.org). These cohorts had either been part of the World Health Organization's MONICA (MONitoring trends and determinants In CArdiovascular disease) Project or had used the same standardized MONICA survey procedures for data collection as described in the MORGAM manual (15).

We excluded 17,552 subjects in whom information on the following variables was missing: history of diabetes mellitus (n=1753), history of cardiovascular disease (n=781), use of antihypertensive medication (n=4224), the cardiovascular risk factors age, sex, current smoking, total cholesterol and SBP included in the Systematic COronary Risk Evaluation (SCORE) model (n=9528) (16), and failure to obtain information from national or regional health information systems for the composite cardiovascular endpoint (CEP) or death before 10 years (n=1266). We further excluded individuals with a history of cardiovascular disease or diabetes as well as those on

antihypertensive therapy at baseline (n=16,440), leaving a total of 107,599 apparently healthy subjects aged 19-97 years available for analysis.

All participants were examined only once at baseline. In most cohorts, BP was measured twice in the right arm, in the sitting position and after 5 minutes of rest, using standard or random zero mercury sphygmomanometers and the standardized procedures and joint training of the measurers of the WHO MONICA Project. The mean of the first and second SBP and DBP was used. In the cohorts FRA-LIL, FRA-STR, FRA-TOU, UNK-BEL, GER-AUG (only cohort 24), and NOR-TRO, BP was measured using an automated device, and in the cohorts FRA-LIL, FRA-STR, FRA-TOU, UNK-BEL, and GER-ESR, BP was measured only once. Details on the BP collection procedures and quality assessments have been described previously (17). MBP was calculated as DBP + 0.4*(SBP-DBP), and brachial PP as difference of the mean of the first and second measurement of SBP and DBP. Antihypertensive therapy at baseline, smoking habits, and history of diabetes were self-reported. History of cardiovascular disease included ischemic or hemorrhagic stroke, or coronary heart disease (myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting). Angina pectoris was included in the definition of coronary heart disease for the Warsaw and Brianza cohort 3 when it could not be separated from myocardial infarction. Total cholesterol and high-density lipoprotein (HDL) cholesterol concentrations were measured in serum samples by local laboratories with external international quality control in all cohorts except for GER-AUG (cohort 24) and GER-ESR.

Endpoints

The primary endpoint was CEP, defined as fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction. Death from coronary heart disease included the categories “definite or possible myocardial infarction or coronary death”, and “unclassifiable

death". The latter category represents death (mostly sudden) with no evidence of cardiac origin and no competing cause. Secondary endpoints were all-cause mortality (ACM) and cardiovascular death (CVD), the latter defined as fatal stroke or death from coronary heart disease. Observations continued until an endpoint was reached or the end of the 10-year follow-up period (1992-2012 depending on the cohort). Events were identified by national or regional health information systems. To validate events occurring during follow-up, most centers used the MONICA criteria or other similar diagnostic criteria, taking into account also troponins in the diagnosis of myocardial infarction after these were introduced to clinical practice (18). Before a cohort was accepted to MORGAM, both the coverage of follow-up and the used diagnostic criteria were evaluated to ensure that follow-up data were reasonably comparable between the cohorts. Supplemental Tables S2 and S3 summarize the follow-up procedures used by each centre for death and for coronary and stroke events. For the supplemental tables please see http://hyper.ahajournals.org. The details of the follow-up procedures and diagnostic criteria used in each cohort have been published (14) as has the quality assessment of the follow-up data (17), although the latter does not include the very last years of data used in the present study.

Statistical analyses

Categorical variables were presented as numbers (percentages), and continuous variables were summarized by medians (25^{th}, 75^{th} percentile). Multivariable linear regression models were used to examine the associations of age, sex, body mass index, total cholesterol, HDL cholesterol, and smoking status with all six BP characteristics. Standardized regression coefficients (i.e., per 1 standard deviation increase) were reported as the measures of association.

Next, we calculated unadjusted and adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) for the association of each BP characteristic with each endpoint,

using Cox proportional-hazards regression models. We adjusted for country and the variables of SCORE, with the following modifications to the BP characteristic: analyses of SBP were adjusted for DBP and vice versa, and analyses of MBP were adjusted for brachial PP and vice versa. The ability of selected BP characteristics to enhance prognostication beyond sex, age, SBP (only for analyses involving DBP), MBP (only for analyses involving PP), total cholesterol, smoking status, and country, was further examined using discrimination ability (comparison of area under the receiver operating characteristic curve derived from logistic regression models; AUC_{ROC}) and continuous net reclassification improvement (NRI). Furthermore, the predictive value of using both SBP and DBP compared to only using SBP in the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) and the 2017 American College of Cardiology/American Heart (ACC/AHA) guidelines definition of hypertension was tested calculating categorical NRI.

All explanatory variables met the proportional-hazards assumption of Cox regression, as assessed by Schoenfeld residuals. Sex- and age-related interactions were explored for both types of regression analyses, using the likelihood-ratio test. We stratified the analyses at age 50 years since it is well-known that BP profiles change around this age (5). A two-sided P-value <0.05 was considered statistically significant. No adjustment for multiple testing was made. All analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA) and Stata/IC 15 (StataCorp LP, College Station, TX, USA).

Results

Demographic and clinical characteristics

The final sample consisted of 107,599 individuals (53% men) aged 19-97 years without cardiovascular disease who were not on antihypertensive medications. Baseline characteristics of study participants stratified for sex, age, and incident CEP are shown in **Table 1**. Men in both age

groups (≥50 years versus <50 years) who experienced a CEP had a greater burden of cardiovascular risk factors, such as active smoking, higher total cholesterol concentration, SBP, MBP, and brachial PP when compared with their counterparts who did not have an event. The same was evident in women, where the burdens of active smoking, higher total cholesterol level, SBP, MBP, and brachial PP were greater in women with an incident CEP compared with those without, irrespective of age group.

Covariates of blood pressure characteristics

Results from cross-sectional analyses stratified by age group (≥50 years versus <50 years) are presented in **Table 2**. Considering age, the positive association between age as a continuous variable and SBP was more pronounced among individuals ≥50 years while the same was true for DBP in those <50 years (P-interaction<0.001 for both). The association between age and MBP was consistently positive in the entire study population, albeit slightly more pronounced in the older age group, leading to a significant interaction (P-interaction<0.001). Furthermore, (continuous) age was positively associated with the indirect estimates of arterial stiffness (brachial PP, SBP/DBP and brachial PP/MBP) in subjects ≥50 years of age, and negatively associated in those aged <50 years (P-interaction<0.001).

Male sex was associated with higher SBP, DBP, MBP and brachial PP, except brachial PP in the age group ≥50 years where the association was reversed. Particularly strong associations for male sex were found with SBP and MBP among subjects <50 years. SBP/DBP and brachial PP/MBP were positively associated with male sex in individuals <50 years and negatively in those who were ≥50 years. All interactions between sex and age group in predicting BP characteristics were significant (P-interaction<0.001).

Risk of incident events

At 10 years, a total of 4385 individuals had experienced a CEP (4.1% of the study sample, 3212 men and 1173 women), and 5082 had died from any cause (4.7%, 3468 men and 1614 women). The cause of death was cardiovascular in 1015 subjects (0.9%, 733 men and 282 women). **Figures 1a-d** illustrate the unadjusted impact of SBP and DBP, and **Figures 2a-d** show the unadjusted impact of MBP and brachial PP, on the incidence of CEP and ACM stratified by age ≥ and <50 years, respectively.

Prediction, discrimination, and reclassification of events by blood pressure characteristics

Figure 3 shows the independent prediction, discrimination, and net reclassification of events by BP characteristics. SBP was significantly associated with all three event types, irrespective of age group, while DBP was only associated significantly with CEP and ACM, and exclusively in the younger age group after adjustment for country and SCORE variables. Among subjects <50 years, DBP significantly improved AUC_{ROC} compared with SCORE variables and country alone, in predicting CEP. This was further corroborated by continuous NRI analysis. Similar findings were obtained for ACM, but not CVD. Like SBP, MBP was associated with all event types in both age groups, while brachial PP was only associated with events in the older age group after adjusting for country, age, sex, smoking, serum cholesterol and MBP. Model performance was not enhanced by the addition of PP. In fact, MBP generally carried discrimination abilities akin to SBP and DBP combined especially in the younger age group. Brachial PP, SBP/DBP and PP/MBP mainly predicted events in the older age group, and predictive capabilities as assessed by AUC_{ROC} were generally lower than those obtained using other BP characteristics. Associated interaction analyses are provided in **Table 3**.

Finally, exploratory categorical NRI analyses for the addition of DBP to SBP in the prediction model, using the 2018 ESC/ESH and the 2017 ACC/AHA guidelines definition of hypertension are provided in **Supplemental Table 4** and **Supplemental Table 5**, respectively. Please see http://hyper.ahajournals.org. When categorized, the conventional DBP threshold improved NRI predicting CEP among individuals <50 years of age.

Discussion

In this large, multinational cohort study, we found that both age and sex were associated with all BP characteristics in a complex fashion, though with older age and male sex generally being associated with higher BP values. DBP added significant discriminative value to the cardiovascular risk estimated by the individual SCORE variables in predicting composite cardiovascular events as well as death among individuals <50 years of age, but not in those aged ≥50 years.

Sex differences in BP characteristics might in part be accounted for by sex hormones. Androgen- and estrogen receptors are expressed on vascular smooth muscle cells (19, 20), and estrogen may alleviate arterial stiffening (11). Furthermore, menopause augments the age-dependent increase in arterial stiffening and PP (21, 22), supporting our findings in the older age group, in which sex differences appeared to diminish. Finally, aortic size and the lower height and body size of women may play key roles as BP amplification from central to peripheral arteries increases with body height (23, 24).

Considering age-related changes in BP characteristics, a rise in DBP occurs primarily in subjects younger than 50 years, likely due to increased peripheral vascular resistance (5). However, as the large arteries become stiffer and the buffering capacity of aorta diminishes, SBP increases and DBP decreases or levels out, leading to higher PP (25). Indeed, we also found stronger, positive relationships between age and both SBP and brachial PP in the older age group.

MBP appeared to increase steadily with age which can be explained by DBP increasing among persons <50 years and SBP increasing in those of older age.

The Multiple Risk Factor Intervention Trial (MRFIT) showed that any combination of PP, SBP or DBP was a better indicator of incident cardiovascular risk than any single characteristic in men aged 35-57 years without diabetes or prior myocardial infarction (26). The Framingham study included both sexes across a broader age range and concluded that combining PP with MBP or SBP with DBP produced models that were superior to those with single BP characteristics for predicting cardiovascular disease (27). A large Swedish study of 1.2 million young men (mean age 18.4 years), who had military conscription examinations between 1969 and 1995, showed that the relation of DBP to mortality risk was stronger than that of SBP (28). Most recently, a study of 1.3 million adults from the Kaiser Permanente Northern California health system found significant contributions of both systolic and diastolic hypertension to cardiovascular risk. However, age-stratified results were not reported, nor were measures of discrimination (29). Our results extend these findings by showing that use of SBP alone is adequate among individuals of at least 50 years of age, which is also the age group where the majority of adverse events took place. However, DBP provides additional value among those younger than 50 years. Alternatively, MBP could be used alone, irrespective of age, in that its discrimination ability was akin to that of SBP and DBP combined. Although brachial PP has been suggested as a surrogate marker of arterial stiffening (30, 31), potentially superior to SBP in predicting risk among the elderly (32-35), we found no benefit of using brachial PP over other BP characteristics (26, 36). Lastly, we observed no value in the ratios of SBP/DBP and brachial PP/MBP beyond SBP.

Contemporary guidelines differ slightly in their approach to the use of BP characteristics. Both the 2018 ESC/ESH and the 2017 ACC/AHA guidelines for hypertension include treatment targets for SBP and DBP (3, 37), but risk estimation tools like SCORE endorsed

by ESC/ESH (38) and the pooled cohort equations for calculation of atherosclerotic cardiovascular disease risk recommended by ACC/AHA (39) primarily rely on SBP, although DBP can be used optionally in the pooled cohort equations for individualized patient advice. However, according to our results, the effect on NRI of adding DBP in people <50 years is larger using the 2018 ESC/ESH definition of hypertension as compared to the ACC/AHA definition. Conversely, some experts have suggested abandoning DBP measurement in therapeutic decision making (40), but based on our results, this could lead to loss of clinically meaningful information in younger patients.

Strengths and limitations

Major strengths of the study are the large sample size of 107,599 participants, inclusion of both men and women across a wide age range from eleven countries, and long-term follow-up with a large number of cardiovascular events. Standardized baseline measurements and harmonized endpoint assessments available from the MORGAM cohorts with individual validation of the diagnosis in the majority of events also strengthen the study.

However, some limitations should be considered. First, BP was only measured at baseline which may result in underestimation of the effects of each BP component due to regression dilution bias, even though a single BP measurement is strongly predictive of future events (41). Second, our primary endpoint differed slightly from that originally used to derive the SCORE model, but risk factors for these different conditions appear to be similar. As SCORE itself may allow more room for model improvement as compared with more comprehensive risk prediction equations, the SCORE variables have been used individually in the risk models. Third, the fact that some of the participants could have been treated with antihypertensive therapy during follow-up is a limitation as we were not able to account for this. In addition, lipid lowering treatment became common practice towards the end of the enrolment period, which concerns 3 out of the 38 cohorts,

and this may have changed the cholesterol profile of some of the subjects. The initiation of lipid lowering treatment during the follow-up period may also have diluted the relative risk estimates for cholesterol. Fourth, different cohorts were enrolled from 1980 to 2000, and therefore secular trends in the risk factors and disease incidence may have influenced the observed associations. However, the enrolment period was 10 years or less in each country, and the analyses were adjusted for country as well, which eliminates most of these effects over the 20-year enrolment period. An exception to this was Finland, in which the enrolment period was 20 years. Fifth, some of the "apparently healthy" subjects may have had unrecognized chronic kidney disease or heart failure. However, the prevalence of clinically significant chronic kidney disease or heart failure was expected to be very low as we had excluded subjects with a history of cardiovascular disease or diabetes as well as those on antihypertensive therapy at baseline. Sixth, whereas some of the patients used to derive the SCORE were receiving antihypertensive drugs at entry, the present study was conducted in untreated subjects. However, we do not believe this to affect our analyses since we did not use the SCORE risk equation per se, but rather its individual variables in a multivariable Cox regression model adjusted for country. Seventh, despite the use of MONICA criteria, there was some variation in the identification of endpoints between the countries. For instance, for non-fatal myocardial infarction the variation was due to the use of non-specific diagnostic tools as well as differences in the healthcare systems between countries. This variation was presumably attenuated after the introduction and widespread implementation of cardiac troponins. Furthermore, for subjects who died outside the healthcare setting (predominantly sudden deaths), the percentage of events with no evidence of cardiac origin and no competing cause of death (unclassifiable deaths) varied substantially between countries. Finally, our sample primarily consisted of white Europeans; therefore, our results may not be generalizable to other racial or ethnic groups.

Perspectives

In conclusion, older age and male sex were generally associated with higher BP values. DBP had significant additive value on top of SCORE variables (including SBP) in predicting both CEP and ACM among individuals <50 years of age, but not in those aged ≥50 years. Therefore, DBP may provide prognostic utility beyond SBP in predicting CEP and ACM among younger individuals.

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Disclosures

VS has received honoraria from Novo Nordisk and Sanofi for consultations. He also has ongoing research collaboration with Bayer Ltd. (All unrelated to the present study). SSg has received

speakers and consultant honoraria from Actelion Ltd. MHO has from 2013-2018 received a part time clinical research grant from the Novo Nordic Foundation. MP has the followings relationships – Advisory Board and Speaking Honoraria: AstraZeneca; Speaking Honoraria: Bayer, Boehringer Ingelheim.

Supplemental Materials

Sites and key personnel of contributing MORGAM Centers

Online Tables S1-S5

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Novelty and Significance

What is new?

Classical blood pressure characteristics (SBP, DBP, MBP) and indirect measures of arterial stiffness (brachial PP, SPB/DBP-ratio, and brachial PP/MBP-ratio) were associated differently with age and sex and had different prognostic values in young versus older subjects. Whereas SBP alone was adequate among individuals ≥50 years of age, DBP provided additional value among those < 50 years. Alternatively, MBP could be used alone, irrespective of age, in that its discrimination ability was akin to that of SBP and DBP combined. There were no superior benefits of using brachial PP or the ratios of SBP/DBP and brachial PP/MBP.

What is relevant?

DBP may provide additional prognostic value beyond SBP in predicting composite cardiovascular events as well as all-cause mortality among younger individuals.

Summary

DBP added significant discriminative value on top of SCORE variables (including SBP) in predicting outcomes among individuals <50 years of age, but not in those aged ≥50 years.

Figure legends

Figure 1 Impact of systolic and diastolic blood pressure on the incidence of the composite cardiovascular endpoint (A,B) as well as all-cause mortality (C,D)in men and women younger and older than 50 years, respectively, based on blood pressure quarters. The MORGAM Project. CEP: composite cardiovascular endpoint consisting of fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction, SBP: systolic blood pressure (mmHg), DBP: diastolic blood pressure (mmHg), W: women, M: men.

Figure 2 Impact of mean blood pressure and brachial pulse pressure on the incidence of the composite cardiovascular endpoint (A,B) as well as all-cause mortality (C,D) in men and women younger and older than 50 years, respectively, based on blood pressure quarters. The MORGAM Project. CEP: composite cardiovascular endpoint consisting of fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction, MBP: mean blood pressure (mmHg), PP: pulse pressure (mmHg), W: women, M: men.

Figure 3 Adjusted hazard ratio (A,C,E) and discrimination (B,D,F) of the composite cardiovascular endpoint, cardiovascular death, and all-cause mortality as well as continuous net reclassification for all three events (G) by blood pressure characteristics in subjects younger or older than 50 years. The MORGAM Project. The composite cardiovascular endpoint consists of fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction, and cardiovascular death consists of fatal stroke or death from coronary heart disease. SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, PP: pulse pressure, HR: hazard ratio, CI:

confidence interval, AUCROC: area under the receiver operating characteristic curve, cNRI: continuous net reclassification improvement, SCORE: The variables of SCORE (Systematic COronary Risk Evaluation) risk equation for cardiovascular death.

HR is per 1 standard deviation, adjusted for country, age, sex, smoking, serum cholesterol, and a blood pressure estimate as described in the methods section.

Comparison of AUCROC for a model comprising SCORE variables + diastolic blood pressure with a model comprising SCORE variables alone.

NS: non-significant, i.e., P>0.05

Tables

Table 1: Baseline characteristics stratified by sex, age, and incident composite cardiovascular events. The MORGAM Project.

Baseline variables	No incident CEP (men)		Incident CEP (men)		No incident CEP (women)		Incident CEP (women)	
	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years
Number of participants (%)	32015 (56)	21730 (38)	738 (1.3)	2474 (4.3)	34650 (68)	14819 (29)	213 (0.4)	960 (2)
Smokers (%)	13201 (41)	6373 (29)	449 (61)	992 (40)	11175 (32)	2761 (19)	116 (54)	291 (30)
Age, years	36 (30-42)	56 (53-60)	44 (39-47)	58 (55-63)	36 (30-42)	58 (53-62)	44 (39-47)	64 (58-72)
BMI, kg/m^2	25 (23-27)	26 (24-28)	27 (24-29)	27 (24-29)	23 (21-26)	26 (24-30)	25 (21-28)	26 (24-30)
Chol, mmol/l	5.5 (4.8-6.3)	5.9 (5.2-6.6)	6.4 (5.7-7.4)	6.2 (5.5-7.0)	5.2 (4.6-5.9)	6.3 (5.6-7.1)	5.6 (5.0-6.7)	6.8 (5.9-7.6)
HDL-C, mmol/l	1.25 (1.1-1.5)	1.27 (1.1-1.5)	1.18 (1.0-1.4)	1.2 (1.0-1.4)	1.53 (1.3-1.8)	1.56 (1.3-1.8)	1.45 (1.2-1.7)	1.5 (1.2-1.8)
SBP, mmHg	130 (121-140)	134 (122-148)	139 (126-149)	143 (130-160)	120 (112-130)	137 (123-152)	130 (120-143)	150 (135-169)
DBP, mmHg	80 (72-87)	83 (76-91)	87 (80-96)	86 (78-94)	75 (68-82)	82 (75-89)	82 (75-90)	85 (78-94)
PP, mmHg	50 (42-58)	50 (42-60)	50 (42-59)	57 (46-70)	46 (40-53)	54 (45-66)	48 (41-57)	65 (54-77)

MBP, mmHg	99 (93-107)	104 (96-113)	107 (99-116)	109 (100-119)	93 (86-100)	104 (95-114)	102 (94-111)	111 (102-123)
SBP*100/DBP	162 (151-176)	161 (151-173)	156 (148-169)	167 (154-181)	161 (151-173)	166 (155-180)	150 (160-169)	174 (162-191)
PP*100/MBP	50 (42-58)	49 (42-57)	46 (40-54)	53 (45-61)	49 (43-56)	52 (45-51)	48 (42-54)	57 (50-66)
ACM (%)	523 (1.6)	1858 (8.6)	175 (24)	912 (37)	309 (0.9)	888 (6)	47 (22)	370 (39)
CVD (%)	0	0	129 (17)	604 (24)	0	0	39 (18)	243 (25)

Values are presented as numbers (percentages) or median (25^{th}, 75^{th} percentile).

ACM: all-cause mortality, BMI: body mass index, CEP: primary composite cardiovascular endpoint (fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction), Chol: serum total cholesterol, CVD: cardiovascular death (fatal stroke or death from coronary heart disease), DBP: diastolic blood pressure, HDL-C: serum high-density lipoprotein cholesterol, MBP: mean blood pressure, PP: pulse pressure, SBP: systolic blood pressure.

Table 2: Covariates of blood pressure characteristics using multiple regression analyses in subjects younger or older than 50 years. The MORGAM Project.

Baseline variables	SBP		DBP		SBP/DBP	
	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years
Age	0.063$^{<0.001}$	0.269$^{<0.001}$	0.230$^{<0.001}$	0.017$^{<0.001}$	-0.241$^{<0.001}$	0.323$^{<0.001}$
Sex, male	0.266$^{<0.001}$	0.022$^{<0.001}$	0.162$^{<0.001}$	0.109$^{<0.001}$	0.090$^{<0.001}$	-0.093$^{<0.001}$
BMI	0.209$^{<0.001}$	0.217$^{<0.001}$	0.220$^{<0.001}$	0.237$^{<0.001}$	-0.046$^{<0.001}$	0.004^{NS}
Chol	0.097$^{<0.001}$	0.095$^{<0.001}$	0.106$^{<0.001}$	0.102$^{<0.001}$	-0.033$^{<0.001}$	0.003^{NS}
HDL-C	0.052$^{<0.001}$	0.046$^{<0.001}$	0.001^{NS}	0.033$^{<0.001}$	0.053$^{<0.001}$	0.019$^{<0.001}$
Smoking, active	-0.026$^{<0.001}$	-0.008^{NS}	-0.039$^{<0.001}$	-0.029$^{<0.001}$	0.021$^{<0.001}$	0.022$^{<0.001}$
Adj. R^2	0.160$^{<0.001}$	0.138$^{<0.001}$	0.209$^{<0.001}$	0.072$^{<0.001}$	0.079$^{<0.001}$	0.122$^{<0.001}$
	PP		**MBP**		**PP/MBP**	
	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years

Age	-0.140$^{<0.001}$	0.345$^{<0.001}$	0.164$^{<0.001}$	0.170$^{<0.001}$	-0.240$^{<0.001}$	0.323$^{<0.001}$
Sex, male	0.200$^{<0.001}$	-0.050$^{<0.001}$	0.232$^{<0.001}$	0.067$^{<0.001}$	0.085$^{<0.001}$	-0.095$^{<0.001}$
BMI	0.067$^{<0.001}$	0.116$^{<0.001}$	0.235$^{<0.001}$	0.247$^{<0.001}$	-0.051$^{<0.001}$	0.003^{NS}
Chol	0.027$^{<0.001}$	0.053$^{<0.001}$	0.111$^{<0.001}$	0.107$^{<0.001}$	-0.031$^{<0.001}$	0.003^{NS}
HDL-C	0.068$^{<0.001}$	0.037$^{<0.001}$	0.028$^{<0.001}$	0.044$^{<0.001}$	0.055$^{<0.001}$	0.020$^{<0.001}$
Smoking, active	0.003^{NS}	0.011$^{0.03}$	-0.036$^{<0.001}$	-0.019$^{<0.001}$	0.023$^{<0.001}$	0.025$^{<0.001}$
Adj. R^2	0.055$^{<0.001}$	0.153$^{<0.001}$	0.210$^{<0.001}$	0.107$^{<0.001}$	0.079$^{<0.001}$	0.122$^{<0.001}$

BMI: body mass index, Chol: serum total cholesterol, DBP: diastolic blood pressure, HDL-C: serum high-density lipoprotein cholesterol, MBP: mean blood pressure, PP: pulse pressure, SBP: systolic blood pressure. Superscript denotes the P-value, NS: non-significant, i.e., P≥0.05.

Table 3: Interaction analyses in Cox regression models. The MORGAM Project.

Baseline BP characteristics	Interaction for age (< 50 versus ≥ 50 years)			Interaction for sex		
	CEP	**ACM**	**CVD**	**CEP**	**ACM**	**CVD**
SBP	$0.990^{<0.001}$	$0.995^{0.02}$	$0.987^{0.002}$	0.999^{NS}	$1.003^{0.02}$	0.998^{NS}
DBP	$0.966^{<0.001}$	$0.972^{<0.001}$	$0.962^{<0.001}$	0.998^{NS}	1.003^{NS}	0.996^{NS}
PP	$1.020^{<0.001}$	$1.023^{<0.001}$	$1.018^{0.008}$	0.998^{NS}	$1.003^{0.05}$	0.997^{NS}
MBP	$0.978^{<0.001}$	$0.984^{<0.001}$	$0.975^{<0.001}$	0.998^{NS}	$1.004^{0.04}$	0.997^{NS}

ACM: all-cause mortality, CEP: primary composite cardiovascular endpoint (fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction), CVD: cardiovascular death (fatal stroke or death from coronary heart disease), BP: blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, PP: pulse pressure, SBP: systolic blood pressure.

NS: non-significant, i.e., P≥0.05.

Predictive importance of blood pressure characteristics with increasing age in healthy men and women: The MORGAM ~~Prospective Cohort~~ Project

Short title: Prognostic importance of BP by age and sex

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Abbreviations
ACM, all-cause mortality; AUC_{ROC}, area under the receiver-operating-characteristic curve; BMI, body mass index; BP, blood pressure; CEP, composite cardiovascular endpoint; Chol, serum total cholesterol; CI, confidence interval; cNRI, continuous net reclassification improvement; CVD, cardiovascular death; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; MBP, mean blood pressure; MONICA, Multi-national MONItoring of Trends and Determinants in CArdiovascular Disease; MORGAM, MOnica, Risk, Genetics, Archiving and Monograph; NRI, net reclassification improvement; NS, non-significant; PP, pulse pressure; SCORE, Systematic COronary Risk Evaluation; SBP, systolic blood pressure.

Abstract

It remains unclear which blood pressure (BP) characteristics best predict cardiovascular risk in different age groups and between sexes. We leveraged data from the MORGAM Project to investigate determinants of BP characteristics and their prognostic importance, in younger and older (</≥50 years) men and women. The study population comprised 107,599 individuals (53% men) aged 19-97 years without established cardiovascular disease, not on antihypertensive treatment, recruited between 1982-2008 in 38 cohorts. Covariates of BP characteristics were explored using multivariable linear regression. Prognostic importance was examined using multivariable Cox proportional-hazards regression, area under the receiver-operating-characteristic curve (AUC_{ROC}), and net reclassification improvement (NRI). The primary endpoint was a composite cardiovascular endpoint (CEP), defined as fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction. The positive association between age and systolic BP (SBP) was more pronounced among individuals ≥50 years while the same was true for diastolic BP (DBP) in those <50 years (P-interaction<0.001). Higher SBP and mean BP were significantly associated with CEP, irrespective of age group (P<0.001), but DBP only demonstrated an independent relationship in the younger group (P<0.001). Brachial pulse pressure was associated with CEP in the older age group (P<0.001). In subjects <50 years, DBP significantly improved AUC_{ROC} compared with SCORE variables (including SBP) alone (0.842 versus 0.840,P=0.03), enhanced continuous NRI (0.150, 95% confidence interval, 0.087-0.215) and improved the prognostic value of the ESC/ESH hypertension definition (categorical NRI=0.0255,P=0.005). In conclusion, DBP may provide additional prognostic utility beyond SBP, in predicting composite cardiovascular events among younger individuals.

Key words

Blood pressure characteristics, Arterial stiffness, Age, Sex, Prognosis, SCORE, Net reclassification index

Background

Hypertension is a major modifiable risk factor for cardiovascular disease and all-cause mortality (1-3). Through the years, several blood pressure characteristics, including systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) have received attention because of their potential ability to predict cardiovascular events (4). These BP characteristics are affected to a varying degree by age-related changes in the cardiovascular system, e.g., arterial stiffening, increased peripheral resistance, and atherosclerosis (5), changes that themselves are associated with subsequent cardiovascular disease (6-10).

SBP generally increases throughout life, whereas DBP begins to decline after the age of 50 years, resulting in PP increase (5). This is due to arterial stiffening that increases with age. PP may better reflect large artery stiffness, and mean BP (MBP) may better reflect cardiac output and peripheral resistance than SBP and DBP (7). Aging increases arterial stiffening in both sexes, but sex hormones and menopause may modify the pace at which this happens (5, 11). In addition, arterial stiffening occurs irrespective of BP levels (12). Accordingly, it remains unclear which BP characteristics best predict cardiovascular risk in different age groups and between men and women.

We leveraged data from the large, multinational MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project to investigate 1) covariates of classical BP characteristics (SBP, DBP, and MBP) and indirect measures of arterial stiffness (brachial PP, SBP/DBP-ratio, and brachial PP/MBP-ratio) in younger and older men and women; 2) the relative importance of these BP characteristics independently and combined, in predicting incident cardiovascular events and all-cause mortality; and 3) whether the predictive power of BP characteristics were affected by sex and age.

Methods

We used baseline and 10-year follow-up data from the MORGAM Project, which consists of large population cohort studies from many countries. The data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Approval of the Principal Investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access to the data. ~~The present study was based on baseline and 10-year follow-up data from the MORGAM Project, the objective of which was to develop cardiovascular risk scores based on well-known, traditional risk factors, and to determine whether genetic variability and biomarker assessment enhanced risk stratification.~~ In addition, a~~A~~ detailed description of the project, included cohorts, and quality assessment have been published previously (13, 14). ~~The data originating from the MORGAM Project are not publicly available (15).~~

Cohorts and baseline variables

Baseline data were gathered from 1982-2002 and originated from 38 population-based cohorts in 11 European countries (**Supplemental Table S1**, please see http://hyper.ahajournals.org). These cohorts had either been part of the World Health Organization's MONICA (MONitoring trends and determinants In CArdiovascular disease) Project or had used the same standardized MONICA survey procedures for data collection as described in the MORGAM manual (15).

We excluded 17,552 subjects in whom information on the following variables was missing: history of diabetes mellitus (n=1753), history of cardiovascular disease (n=781), use of antihypertensive medication (n=4224), the cardiovascular risk factors age, sex, current smoking, total cholesterol and SBP included in the Systematic COronary Risk Evaluation (SCORE) model

(n=9528) (16), and ~~loss to follow-up~~failure to obtain information from national or regional health information systems for the composite cardiovascular endpoint (CEP) or death before 10 years (n=1266). We further excluded individuals with a history of cardiovascular disease or diabetes as well as those on antihypertensive therapy at baseline (n=16,440), leaving a total of 107,599 apparently healthy subjects aged 19-97 years available for analysis.

All participants were examined only once at baseline. In most cohorts, BP was measured twice in the right arm, in the sitting position and after 5 minutes of rest, using standard or random zero mercury sphygmomanometers and the standardized procedures and joint training of the measurers of the WHO MONICA Project. The mean of the first and second SBP and DBP was used. In the cohorts FRA-LIL, FRA-STR, FRA-TOU, UNK-BEL, GER-AUG (only cohort 24), and NOR-TRO, BP was measured using an automated device, and in the cohorts FRA-LIL, FRA-STR, FRA-TOU, UNK-BEL, and GER-ESR, BP was measured only once. Details on the BP collection procedures and quality assessments have been described previously (17). MBP was calculated as DBP + 0.4*(SBP-DBP), and brachial PP as difference of the mean of the first and second measurement of SBP and DBP. Antihypertensive therapy at baseline, smoking habits, and history of diabetes were self-reported. History of cardiovascular disease included ischemic or hemorrhagic stroke, or coronary heart disease (myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting). Angina pectoris was included in the definition of coronary heart disease for the Warsaw and Brianza cohort 3 when it could not be separated from myocardial infarction. Total cholesterol and high-density lipoprotein (HDL) cholesterol concentrations were measured in serum samples by local laboratories with external international quality control in all cohorts except for GER-AUG (cohort 24) and GER-ESR.

Endpoints

The primary endpoint was CEP, defined as fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction. Death from coronary heart disease included the categories "definite or possible myocardial infarction or coronary death", and "unclassifiable death". The latter category represents death (mostly sudden) with no evidence of cardiac origin and no competing cause. Secondary endpoints were all-cause mortality (ACM) and cardiovascular death (CVD), the latter defined as fatal stroke or death from coronary heart disease. Observations continued until an endpoint was reached or the end of the 10-year follow-up period (1992-2012 depending on the cohort). Events were identified by national or regional health information systems. To validate events occurring during follow-up, most centers used the MONICA criteria or other similar diagnostic criteria, taking into account also troponins in the diagnosis of myocardial infarction after these were introduced to clinical practice (18). Before a cohort was accepted to MORGAM, both the coverage of follow-up and the used diagnostic criteria were evaluated to ensure that follow-up data were reasonably comparable between the cohorts. Supplemental Tables S2 and S3 summarize the follow-up procedures used by each centre for death and for coronary and stroke events. For the supplemental tables please see http://hyper.ahajournals.org. The details of the follow-up procedures and diagnostic criteria used in each cohort have been published (14) as has the quality assessment of the follow-up data (17), although the latter does not include the very last years of data used in the present study. ~~Details of the data collection procedures and quality assessments of MORGAM endpoints have been described previously (14, 17).~~

Statistical analyses

Categorical variables were presented as numbers (percentages), and continuous variables were summarized by medians (25^{th}, 75^{th} percentile). Multivariable linear regression models were used to

examine the associations of age, sex, body mass index, total cholesterol, HDL cholesterol, and smoking status with all six BP characteristics. Standardized regression coefficients (i.e., per 1 standard deviation increase) were reported as the measures of association.

Next, we calculated unadjusted and adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) for the association of each BP characteristic with each endpoint, using Cox proportional-hazards regression models. We adjusted for country and the variables of SCORE, with the following modifications to the BP characteristic: analyses of SBP were adjusted for DBP and vice versa, and analyses of MBP were adjusted for brachial PP and vice versa. The ability of selected BP characteristics to enhance prognostication beyond sex, age, SBP (only for analyses involving DBP), MBP (only for analyses involving PP), total cholesterol, smoking status, and country, was further examined using discrimination ability (comparison of area under the receiver operating characteristic curve derived from logistic regression models; AUC_{ROC}) and continuous net reclassification improvement (NRI). Furthermore, the predictive value of using both SBP and DBP compared to only using SBP in the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) and the 2017 American College of Cardiology/American Heart (ACC/AHA) guidelines definition of hypertension was tested calculating categorical NRI.

All explanatory variables met the proportional-hazards assumption of Cox regression, as assessed by Schoenfeld residuals. Sex- and age-related interactions were explored for both types of regression analyses, using the likelihood-ratio test. We stratified the analyses at age 50 years since it is well-known that BP profiles change around this age (5). A two-sided P-value <0.05 was considered statistically significant. No adjustment for multiple testing was made. All analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA) and Stata/IC 15 (StataCorp LP, College Station, TX, USA).

Results

Demographic and clinical characteristics

The final sample consisted of 107,599 individuals (53% men) aged 19-97 years without cardiovascular disease who were not on antihypertensive medications. Baseline characteristics of study participants stratified for sex, age, and incident CEP are shown in **Table 1**. Men in both age groups (≥50 years versus <50 years) who experienced a CEP had a greater burden of cardiovascular risk factors, such as active smoking, higher total cholesterol concentration, SBP, MBP, and brachial PP when compared with their counterparts who did not have an event. The same was evident in women, where the burdens of active smoking, higher total cholesterol level, SBP, MBP, and brachial PP were greater in women with an incident CEP compared with those without, irrespective of age group.

Covariates of blood pressure characteristics

Results from cross-sectional analyses stratified by age group (≥50 years versus <50 years) are presented in **Table 2**. Considering age, the positive association between age as a continuous variable and SBP was more pronounced among individuals ≥50 years while the same was true for DBP in those <50 years (P-interaction<0.001 for both). The association between age and MBP was consistently positive in the entire study population, albeit slightly more pronounced in the older age group, leading to a significant interaction (P-interaction<0.001). Furthermore, (continuous) age was positively associated with the indirect estimates of arterial stiffness (brachial PP, SBP/DBP and brachial PP/MBP) in subjects ≥50 years of age, and negatively associated in those aged <50 years (P-interaction<0.001).

Male sex was associated with higher SBP, DBP, MBP and brachial PP, except brachial PP in the age group ≥50 years where the association was reversed. Particularly strong

associations for male sex were found with SBP and MBP among subjects <50 years. SBP/DBP and brachial PP/MBP were positively associated with male sex in individuals <50 years and negatively in those who were ≥50 years. All interactions between sex and age group in predicting BP characteristics were significant (P-interaction<0.001).

Risk of incident events

At 10 years, a total of 4385 individuals had experienced a CEP (4.1% of the study sample, 3212 men and 1173 women), and 5082 had died from any cause (4.7%, 3468 men and 1614 women). The cause of death was cardiovascular in 1015 subjects (0.9%, 733 men and 282 women).

~~Supplemental~~ **Figures 1a-d** illustrate the unadjusted impact of SBP and DBP, and ~~Supplemental~~ **Figures 2a-d** show the unadjusted impact of MBP and brachial PP, on the incidence of CEP and ACM stratified by age ≥ and <50 years, respectively.

Prediction, discrimination, and reclassification of events by blood pressure characteristics

Figure~~Table~~ **3** shows the independent prediction, discrimination, and net reclassification of events by BP characteristics. SBP was significantly associated with all three event types, irrespective of age group, while DBP was only associated significantly with CEP and ACM, and exclusively in the younger age group after adjustment for country and SCORE variables. Among subjects <50 years, DBP significantly improved AUC_{ROC} compared with SCORE variables and country alone, in predicting CEP. This was further corroborated by continuous NRI analysis. Similar findings were obtained for ACM, but not CVD. Like SBP, MBP was associated with all event types in both age groups, while brachial PP was only associated with events in the older age group after adjusting for country, age, sex, smoking, serum cholesterol and MBP. Model performance was not enhanced by the addition of PP. In fact, MBP generally carried discrimination abilities akin to SBP and DBP

combined especially in the younger age group. Brachial PP, SBP/DBP and PP/MBP mainly predicted events in the older age group, and predictive capabilities as assessed by AUC_{ROC} were generally lower than those obtained using other BP characteristics. Associated interaction analyses are provided in **Table 34**.

Finally, exploratory categorical NRI analyses for the addition of DBP to SBP in the prediction model, using the 2018 ESC/ESH and the 2017 ACC/AHA guidelines definition of hypertension are provided in **Supplemental Table 45** and **Supplemental Table 56**, respectively. Please see http://hyper.ahajournals.org. When categorized, the conventional DBP threshold improved NRI predicting CEP among individuals <50 years of age.

Discussion

In this large, multinational cohort study, we found that both age and sex were associated with all BP characteristics in a complex fashion, though with older age and male sex generally being associated with higher BP values. DBP added significant discriminative value to the cardiovascular risk estimated by the individual SCORE variables in predicting composite cardiovascular events as well as death among individuals <50 years of age, but not in those aged ≥50 years.

Sex differences in BP characteristics might in part be accounted for by sex hormones. Androgen- and estrogen receptors are expressed on vascular smooth muscle cells (19, 20), and estrogen may alleviate arterial stiffening (11). Furthermore, menopause augments the age-dependent increase in arterial stiffening and PP (21, 22), supporting our findings in the older age group, in which sex differences appeared to diminish. Finally, aortic size and the lower height and body size of women may play key roles as BP amplification from central to peripheral arteries increases with body height (23, 24).

Considering age-related changes in BP characteristics, a rise in DBP occurs primarily in subjects younger than 50 years, likely due to increased peripheral vascular resistance (5). However, as the large arteries become stiffer and the buffering capacity of aorta diminishes, SBP increases and DBP decreases or levels out, leading to higher PP (25). Indeed, we also found stronger, positive relationships between age and both SBP and brachial PP in the older age group. MBP appeared to increase steadily with age which can be explained by DBP increasing among persons <50 years and SBP increasing in those of older age.

The Multiple Risk Factor Intervention Trial (MRFIT) showed that any combination of PP, SBP or DBP was a better indicator of incident cardiovascular risk than any single characteristic in men aged 35-57 years without diabetes or prior myocardial infarction (26). The Framingham study included both sexes across a broader age range and concluded that combining PP with MBP or SBP with DBP produced models that were superior to those with single BP characteristics for predicting cardiovascular disease (27). A large Swedish study of 1.2 million young men (mean age 18.4 years), who had military conscription examinations between 1969 and 1995, showed that the relation of DBP to mortality risk was stronger than that of SBP (28). Most recently, a study of 1.3 million adults from the Kaiser Permanente Northern California health system found significant contributions of both systolic and diastolic hypertension to cardiovascular risk. However, age-stratified results were not reported, nor were measures of discrimination (29). Our results extend these findings by showing that use of SBP alone is adequate among individuals of at least 50 years of age, which is also the age group where the majority of adverse events took place. However, DBP provides additional value among those younger than 50 years. Alternatively, MBP could be used alone, irrespective of age, in that its discrimination ability was akin to that of SBP and DBP combined. Although brachial PP has been suggested as a surrogate marker of arterial stiffening (30, 31), potentially superior to SBP in predicting risk among the elderly (32-35), we found no benefit of

using brachial PP over other BP characteristics (26, 36). Lastly, we observed no value in the ratios of SBP/DBP and brachial PP/MBP beyond SBP.

Contemporary guidelines differ slightly in their approach to the use of BP characteristics. Both the 2018 ESC/ESH and the 2017 ACC/AHA guidelines for hypertension include treatment targets for SBP and DBP (3, 37), but risk estimation tools like SCORE endorsed by ESC/ESH (38) and the pooled cohort equations for calculation of atherosclerotic cardiovascular disease risk recommended by ACC/AHA (39) primarily rely on SBP, although DBP can be used optionally in the pooled cohort equations for individualized patient advice. However, according to our results, the effect on NRI of adding DBP in people <50 years is larger using the 2018 ESC/ESH definition of hypertension as compared to the ACC/AHA definition. Conversely, some experts have suggested abandoning DBP measurement in therapeutic decision making (40), but based on our results, this could lead to loss of clinically meaningful information in younger patients.

Strengths and limitations

Major strengths of the study are the large sample size of 107,599 participants, inclusion of both men and women across a wide age range from eleven countries, and long-term follow-up with a large number of cardiovascular events. Standardized baseline measurements and harmonized endpoint assessments available from the MORGAM cohorts with individual validation of the diagnosis in the majority of events also strengthen the study.

However, some limitations should be considered. First, BP was only measured at baseline which may result in underestimation of the effects of each BP component due to regression dilution bias, even though a single BP measurement is strongly predictive of future events (41). Second, our primary endpoint differed slightly from that originally used to derive the SCORE model, but risk factors for these different conditions appear to be similar. As SCORE itself may

allow more room for model improvement as compared with more comprehensive risk prediction equations, the SCORE variables have been used individually in the risk models. Third, the fact that some of the participants could have been treated with antihypertensive therapy during follow-up is a limitation as we were not able to account for this. In addition, lipid lowering treatment became common practice towards the end of the enrolment period, which concerns 3 out of the 38 cohorts, and this may have changed the cholesterol profile of some of the subjects. The initiation of lipid lowering treatment during the follow-up period may also have diluted the relative risk estimates for cholesterol. Fourth, different cohorts were enrolled from 1980 to 2000, and therefore secular trends in the risk factors and disease incidence may have influenced the observed associations. However, the enrolment period was 10 years or less in each country, and the analyses were adjusted for country as well, which eliminates most of these effects over the 20-year enrolment period. An exception to this was Finland, in which the enrolment period was 20 years. Fifth, some of the "apparently healthy" subjects may have had unrecognized chronic kidney disease or heart failure. However, the prevalence of clinically significant chronic kidney disease or heart failure was expected to be very low as we had excluded subjects with a history of cardiovascular disease or diabetes as well as those on antihypertensive therapy at baseline. Sixth, whereas some of the patients used to derive the SCORE were receiving antihypertensive drugs at entry, the present study was conducted in untreated subjects. However, we do not believe this to affect our analyses since we did not use the SCORE risk equation per se, but rather its individual variables in a multivariable Cox regression model adjusted for country. Seventh, despite the use of MONICA criteria, there was some variation in the identification of endpoints between the countries. For instance, for non-fatal myocardial infarction the variation was due to the use of non-specific diagnostic tools as well as differences in the healthcare systems between countries. This variation was presumably attenuated after the introduction and widespread implementation of cardiac troponins. Furthermore, for

subjects who died outside the healthcare setting (predominantly sudden deaths), the percentage of events with no evidence of cardiac origin and no competing cause of death (unclassifiable deaths) varied substantially between countries. Finally, our sample primarily consisted of white Europeans; therefore, our results may not be generalizable to other racial or ethnic groups.

Perspectives

In conclusion, older age and male sex were generally associated with higher BP values. DBP had significant additive value on top of SCORE variables (including SBP) in predicting both CEP and ACM among individuals <50 years of age, but not in those aged ≥50 years. Therefore, DBP may provide prognostic utility beyond SBP in predicting CEP and ACM among younger individuals.

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Disclosures

VS has received honoraria from Novo Nordisk and Sanofi for consultations. He also has ongoing research collaboration with Bayer Ltd. (All unrelated to the present study). SSg has received speakers and consultant honoraria from Actelion Ltd. MHO has from 2013-2018 received a part time clinical research grant from the Novo Nordic Foundation. MP has the followings relationships – Advisory Board and Speaking Honoraria: AstraZeneca; Speaking Honoraria: Bayer, Boehringer Ingelheim.

Supplemental Materials

Sites and key personnel of contributing MORGAM Centers

Online Tables S1-S5

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Novelty and Significance

What is new?

Classical blood pressure characteristics (SBP, DBP, MBP) and indirect measures of arterial stiffness (brachial PP, SPB/DBP-ratio, and brachial PP/MBP-ratio) were associated differently with age and sex and had different prognostic values in young versus older subjects. Whereas SBP alone was adequate among individuals ≥50 years of age, DBP provided additional value among those < 50 years. Alternatively, MBP could be used alone, irrespective of age, in that its discrimination ability was akin to that of SBP and DBP combined. There were no superior benefits of using brachial PP or the ratios of SBP/DBP and brachial PP/MBP.

What is relevant?

DBP may provide additional prognostic value beyond SBP in predicting composite cardiovascular events as well as all-cause mortality among younger individuals.

Summary

DBP added significant discriminative value on top of SCORE variables (including SBP) in predicting outcomes among individuals <50 years of age, but not in those aged ≥50 years.

Figure legends

Figure 1 Impact of systolic and diastolic blood pressure on the incidence of the composite cardiovascular endpoint (A,B) as well as all-cause mortality (C,D)in men and women younger and older than 50 years, respectively, based on blood pressure quarters. The MORGAM Project. CEP: composite cardiovascular endpoint consisting of fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction, SBP: systolic blood pressure (mmHg), DBP: diastolic blood pressure (mmHg), W: women, M: men.

Figure 2 Impact of mean blood pressure and brachial pulse pressure on the incidence of the composite cardiovascular endpoint (A,B) as well as all-cause mortality (C,D) in men and women younger and older than 50 years, respectively, based on blood pressure quarters. The MORGAM Project. CEP: composite cardiovascular endpoint consisting of fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction, MBP: mean blood pressure (mmHg), PP: pulse pressure (mmHg), W: women, M: men.

Figure 3 Adjusted hazard ratio (A,C,E) and discrimination (B,D,F) of the composite cardiovascular endpoint, cardiovascular death, and all-cause mortality as well as continuous net reclassification for all three events (G) by blood pressure characteristics in subjects younger or older than 50 years. The MORGAM Project. The composite cardiovascular endpoint consists of fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction, and cardiovascular death consists of fatal stroke or death from coronary heart disease. SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, PP: pulse pressure, HR: hazard ratio, CI:

confidence interval, AUCROC: area under the receiver operating characteristic curve, cNRI: continuous net reclassification improvement, SCORE: The variables of SCORE (Systematic COronary Risk Evaluation) risk equation for cardiovascular death.

HR is per 1 standard deviation, adjusted for country, age, sex, smoking, serum cholesterol, and a blood pressure estimate as described in the methods section.

Comparison of AUCROC for a model comprising SCORE variables + diastolic blood pressure with a model comprising SCORE variables alone.

NS: non-significant, i.e., P>0.05

Tables

Table 1: Baseline characteristics stratified by sex, age, and incident composite cardiovascular events. The MORGAM Project.

Baseline variables	No incident CEP (men)		Incident CEP (men)		No incident CEP (women)		Incident CEP (women)	
	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years
Number of participants (%)	32015 (56)	21730 (38)	738 (1.3)	2474 (4.3)	34650 (68)	14819 (29)	213 (0.4)	960 (2)
Smokers (%)	13201 (41)	6373 (29)	449 (61)	992 (40)	11175 (32)	2761 (19)	116 (54)	291 (30)
Age, years	36 (30-42)	56 (53-60)	44 (39-47)	58 (55-63)	36 (30-42)	58 (53-62)	44 (39-47)	64 (58-72)
BMI, kg/m^2	25 (23-27)	26 (24-28)	27 (24-29)	27 (24-29)	23 (21-26)	26 (24-30)	25 (21-28)	26 (24-30)
Chol, mmol/l	5.5 (4.8-6.3)	5.9 (5.2-6.6)	6.4 (5.7-7.4)	6.2 (5.5-7.0)	5.2 (4.6-5.9)	6.3 (5.6-7.1)	5.6 (5.0-6.7)	6.8 (5.9-7.6)
HDL-C, mmol/l	1.25 (1.1-1.5)	1.27 (1.1-1.5)	1.18 (1.0-1.4)	1.2 (1.0-1.4)	1.53 (1.3-1.8)	1.56 (1.3-1.8)	1.45 (1.2-1.7)	1.5 (1.2-1.8)
SBP, mmHg	130 (121-140)	134 (122-148)	139 (126-149)	143 (130-160)	120 (112-130)	137 (123-152)	130 (120-143)	150 (135-169)
DBP, mmHg	80 (72-87)	83 (76-91)	87 (80-96)	86 (78-94)	75 (68-82)	82 (75-89)	82 (75-90)	85 (78-94)
PP, mmHg	50 (42-58)	50 (42-60)	50 (42-59)	57 (46-70)	46 (40-53)	54 (45-66)	48 (41-57)	65 (54-77)

MBP, mmHg	99 (93-107)	104 (96-113)	107 (99-116)	109 (100-119)	93 (86-100)	104 (95-114)	102 (94-111)	111 (102-123)
SBP*100/DBP	162 (151-176)	161 (151-173)	156 (148-169)	167 (154-181)	161 (151-173)	166 (155-180)	150 (160-169)	174 (162-191)
PP*100/MBP	50 (42-58)	49 (42-57)	46 (40-54)	53 (45-61)	49 (43-56)	52 (45-51)	48 (42-54)	57 (50-66)
ACM (%)	523 (1.6)	1858 (8.6)	175 (24)	912 (37)	309 (0.9)	888 (6)	47 (22)	370 (39)
CVD (%)	0	0	129 (17)	604 (24)	0	0	39 (18)	243 (25)

Values are presented as numbers (percentages) or median (25^{th}, 75^{th} percentile).

ACM: all-cause mortality, BMI: body mass index, CEP: primary composite cardiovascular endpoint (fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction), Chol: serum total cholesterol, CVD: cardiovascular death (fatal stroke or death from coronary heart disease), DBP: diastolic blood pressure, HDL-C: serum high-density lipoprotein cholesterol, MBP: mean blood pressure, PP: pulse pressure, SBP: systolic blood pressure.

Table 2: Covariates of blood pressure characteristics using multiple regression analyses in subjects younger or older than 50 years. The MORGAM Project.

Baseline variables	SBP		DBP		SBP/DBP	
	Age <50 years	**Age ≥50 years**	**Age <50 years**	**Age ≥50 years**	**Age <50 years**	**Age ≥50 years**
Age	0.063$^{<0.001}$	0.269$^{<0.001}$	0.230$^{<0.001}$	0.017$^{<0.001}$	-0.241$^{<0.001}$	0.323$^{<0.001}$
Sex, male	0.266$^{<0.001}$	0.022$^{<0.001}$	0.162$^{<0.001}$	0.109$^{<0.001}$	0.090$^{<0.001}$	-0.093$^{<0.001}$
BMI	0.209$^{<0.001}$	0.217$^{<0.001}$	0.220$^{<0.001}$	0.237$^{<0.001}$	-0.046$^{<0.001}$	0.004^{NS}
Chol	0.097$^{<0.001}$	0.095$^{<0.001}$	0.106$^{<0.001}$	0.102$^{<0.001}$	-0.033$^{<0.001}$	0.003^{NS}
HDL-C	0.052$^{<0.001}$	0.046$^{<0.001}$	0.001^{NS}	0.033$^{<0.001}$	0.053$^{<0.001}$	0.019$^{<0.001}$
Smoking, active	-0.026$^{<0.001}$	-0.008^{NS}	-0.039$^{<0.001}$	-0.029$^{<0.001}$	0.021$^{<0.001}$	0.022$^{<0.001}$
Adj. R^2	0.160$^{<0.001}$	0.138$^{<0.001}$	0.209$^{<0.001}$	0.072$^{<0.001}$	0.079$^{<0.001}$	0.122$^{<0.001}$
	PP		**MBP**		**PP/MBP**	
	Age <50 years	**Age ≥50 years**	**Age <50 years**	**Age ≥50 years**	**Age <50 years**	**Age ≥50 years**

Age	-0.140$^{<0.001}$	0.345$^{<0.001}$	0.164$^{<0.001}$	0.170$^{<0.001}$	-0.240$^{<0.001}$	0.323$^{<0.001}$
Sex, male	0.200$^{<0.001}$	-0.050$^{<0.001}$	0.232$^{<0.001}$	0.067$^{<0.001}$	0.085$^{<0.001}$	-0.095$^{<0.001}$
BMI	0.067$^{<0.001}$	0.116$^{<0.001}$	0.235$^{<0.001}$	0.247$^{<0.001}$	-0.051$^{<0.001}$	0.003^{NS}
Chol	0.027$^{<0.001}$	0.053$^{<0.001}$	0.111$^{<0.001}$	0.107$^{<0.001}$	-0.031$^{<0.001}$	0.003^{NS}
HDL-C	0.068$^{<0.001}$	0.037$^{<0.001}$	0.028$^{<0.001}$	0.044$^{<0.001}$	0.055$^{<0.001}$	0.020$^{<0.001}$
Smoking, active	0.003^{NS}	0.011$^{0.03}$	-0.036$^{<0.001}$	-0.019$^{<0.001}$	0.023$^{<0.001}$	0.025$^{<0.001}$
Adj. R^2	0.055$^{<0.001}$	0.153$^{<0.001}$	0.210$^{<0.001}$	0.107$^{<0.001}$	0.079$^{<0.001}$	0.122$^{<0.001}$

BMI: body mass index, Chol: serum total cholesterol, DBP: diastolic blood pressure, HDL-C: serum high-density lipoprotein cholesterol, MBP: mean blood pressure, PP: pulse pressure, SBP: systolic blood pressure. Superscript denotes the P-value, NS: non-significant, i.e., P≥0.05.

Table 3: Adjusted hazard ratio, discrimination, and continuous net reclassification of events by blood pressure characteristics in subjects younger or older than 50 years. The MORGAM Project.

	CEP		ACM		CVD	
	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years	Age <50 years	Age ≥50 years
HR (95% CI) for SBP per mmHg	1.010$^{<0.001}$ (1.005-1.016)	1.014$^{<0.001}$ (1.011-1.016)	1.006$^{0.03}$ (1.001-1.011)	1.007$^{<0.001}$ (1.005-1.009)	1.018$^{0.004}$ (1.006-1.031)	1.015$^{<0.001}$ (1.011-1.020)
HR (95% CI) for DBP per mmHg	1.023$^{<0.001}$ (1.014-1.031)	1.002 (0.998-1.006)	1.014$^{0.001}$ (1.006-1.022)	1.001^{NS} (0.997-1.005)	1.019^{NS} (0.999-1.039)	1.002^{NS} (0.994-1.009)
AUC_{roc} (SCORE including SBP)	0.840 (0.828-0.852)	0.733 (0.725-0.741)	0.732 (0.717-0.747)	0.754 (0.745-0.762)	0.849 (0.823-0.875)	0.787 (0.772-0.802)
AUC_{roc} (SCORE including both SBP and DBP)	0.842$^{0.03*}$ (0.830-0.854)	0.733^{NS} (0.725-0.741)	0.739$^{0.002*}$ (0.723-0.754)	0.754^{NS} (0.745-0.762)	0.852^{NS} (0.826-0.877)	0.787^{NS} (0.772-0.802)
cNRI (DBP added to SCORE variables)	0.150 (0.087 to 0.215)	-0.034 (-0.047 to 0.048)	0.099 (0.037 to 0.176)	0.019 (-0.037 to 0.053)	0.135 (-0.139 to 0.281)	-0.053 (-0.098 to 0.081)
HR (95% CI) for MBP per mmHg	1.033$^{<0.001}$ (1.027-1.039)	1.016$^{<0.001}$ (1.013-1.019)	1.020$^{<0.001}$ (1.014-1.026)	1.008$^{<0.001}$ (1.005-1.011)	1.037$^{<0.001}$ (1.024-1.051)	1.017$^{<0.001}$ (1.012-1.023)
HR (95% CI) for	0.997^{NS}	1.007$^{<0.001}$	0.998^{NS}	1.004$^{0.004}$	1.003^{NS}	1.008$^{0.001}$

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PP per mmHg	(0.991-1.003)	(1.005-1.010)	(0.992-1.004)	(1.001-1.006)	(0.989-1.017)	(1.003-1.014)
AUC_{ROC} (SCORE	0.842	0.732	0.738	0.753	0.852	0.786
including MBP, but	(0.830-0.854)	(0.723-0.740)	(0.723-0.754)	(0.745-0.762)	(0.826-0.878)	(0.770-0.801)
not SBP)						
AUC_{ROC} (SCORE	0.842[NS]	0.733[NS]	0.739[NS]	0.754[NS]	0.852[NS]	0.787[NS]
including both PP	(0.830-0.854)	(0.725-0.741)	(0.723-0.754)	(0.745-0.762)	(0.826-0.878)	(0.772-0.802)
and MBP, but not						
SBP)						
HR (95% CI) for	0.996[NS]	1.006[<0.001]	0.998[NS]	1.003[<0.001]	1.000[NS]	1.006[<0.001]
SBPx100/DBP per	(0.992-1.000)	(1.004-1.007)	(0.994-1.001)	(1.001-1.005)	(0.990-1.009)	(1.003-1.009)
unit						
AUC_{ROC}	0.832	0.721	0.733	0.751	0.835	0.777
	(0.819-0.844)	(0.712-0.729)	(0.718-0.748)	(0.743-0.760)	(0.806-0.864)	(0.762-0.792)
HR (95% CI) for	0.993[0.04]	1.010[<0.001]	0.996[NS]	1.005[<0.001]	0.999[NS]	1.011[<0.001]
PPx100/MBP per	(0.987-1.000)	(1.007-1.013)	(0.990-1.002)	(1.002-1.008)	(0.984-1.014)	(1.005-1.017)
unit						
AUC_{ROC}	0.832 (0.819-	0.720	0.733	0.751	0.835	0.777

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	0.844)	(0.712–0.729)	(0.718–0.749)	(0.743–0.760)	(0.806–0.864)	(0.762–0.792)

Comparison of AUC_{roc} for a model comprising SCORE variables + diastolic blood pressure with a model comprising SCORE variables alone.

***HR** adjusted for country, age, sex, smoking, serum cholesterol, and a blood pressure estimate as described in the methods section.*

Table 34: Interaction analyses in Cox regression models. The MORGAM Project.

Baseline BP characteristics	Interaction for age (< 50 versus ≥ 50 years)			Interaction for sex		
	CEP	**ACM**	**CVD**	**CEP**	**ACM**	**CVD**
SBP	$0.990^{<0.001}$	$0.995^{0.02}$	$0.987^{0.002}$	0.999^{NS}	$1.003^{0.02}$	0.998^{NS}
DBP	$0.966^{<0.001}$	$0.972^{<0.001}$	$0.962^{<0.001}$	0.998^{NS}	1.003^{NS}	0.996^{NS}
PP	$1.020^{<0.001}$	$1.023^{<0.001}$	$1.018^{0.008}$	0.998^{NS}	$1.003^{0.05}$	0.997^{NS}
MBP	$0.978^{<0.001}$	$0.984^{<0.001}$	$0.975^{<0.001}$	0.998^{NS}	$1.004^{0.04}$	0.997^{NS}

ACM: all-cause mortality, CEP: primary composite cardiovascular endpoint (fatal or non-fatal stroke, death from coronary heart disease, or non-fatal myocardial infarction), CVD: cardiovascular death (fatal stroke or death from coronary heart disease), BP: blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, PP: pulse pressure, SBP: systolic blood pressure.

NS: non-significant, i.e., P≥0.05.

~~Table 5: Categorical net reclassification improvement using the 2018 ESC/ESH guideline definition of hypertension.~~

			CEP			ACM			CVD	
Age		SBP<140 and DBP<90	SBP<140 and DBP≥90	SBP≥140	SBP<140 and DBP<90	SBP<140 and DBP≥90	SBP≥140	SBP<140 and DBP<90	SBP<140 and DBP≥90	SBP≥140
<50 years	No. of +events	462	72	417	633	68	353	70	13	85
	No. of −events	51631	3361	11673	51460	3365	11737	52023	3420	12005
	Event rate	0.9%	2.1%	3.4%	1.2%	2.0%	2.9%	0.1%	0.4%	0.7%
	NRI for use of DBP		0.0255 $^{P=0.005}$			0.0140 ^{NS}			0.0267 ^{NS}	
≥50 years	No. of +events	1224	163	2047	1614	155	2259	275	30	542
	No. of −events	19396	1964	15189	19006	1972	14977	20345	2097	16694
	Event rate	5.9%	7.7%	11.9%	7.8%	7.3%	13.1%	1.3%	1.4%	3.1%
	NRI for use of DBP		0.0063 ^{NS}			0.0164 $^{P<0.001}$			0.0182% $^{P=0.006}$	

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Table 6: Categorical net reclassification improvement using the 2017 American College of Cardiology/American Heart Association guideline definition of hypertension.

			CEP			ACM			CVD	
Age		SBP<130 and DBP<80	SBP<130 and DBP≥80	SBP≥130	SBP<130 and DBP<80	SBP<130 and DBP≥80	SBP≥130	SBP<130 and DBP<80	SBP<130 and DBP≥80	SBP≥130
<50 years	No. of +events	195	141	615	352	154	548	34	19	115
	No. of −events	32091	9581	24993	31934	9568	25060	32252	9703	25493
	Event rate	0.6%	1.5%	2.4%	1.1%	1.6%	2.1%	0.1%	0.2%	0.4%
	NRI for use of DBP		0.0045^{NS}			0.0024^{NS}			-0.0308^{NS}	
≥50 years	No. of +events	517	274	2643	737	312	2979	118	55	674
	No. of −events	9308	4653	22588	19006	1972	14977	9707	4872	24557
	Event rate	5.3%	5.6%	10.5%	7.5%	6.3%	11.8%	1.2%	1.1%	2.7%
	NRI for use of DBP		0.0475$^{P<0.001}$			0.0509$^{P<0.001}$			0.0596$^{P<0.001}$	