Hypertension

EPIDEMIOLOGY/POPULATION STUDIES

Predictive Importance of Blood Pressure Characteristics With Increasing Age in Healthy Men and Women

The MORGAM Project

Julie K.K. Vishram-Nielsen, Anna M. Dyrvig Kristensen, Manan Pareek, Stephane Laurent, Peter M. Nilsson, Allan Linneberg, Sara V. Greve, Luigi Palmieri, Simona Giampaoli, Chiara Donfrancesco, Frank Kee, Giuseppe Mancia, Giancarlo Cesana, Giovanni Veronesi, Guido Grassi, Kari Kuulasmaa, Veikko Salomaa, Tarja Palosaari, Susana Sans, Jean Ferrieres, Jean Dallongeville, Stefan Söderberg, Marie Moitry, Wojciech Drygas, Abdonas Tamosiunas, Annette Peters, Hermann Brenner, Sameline Grimsgaard, Matti Savallampi, Michael H. Olsen, On behalf of the MORGAM Project†

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 (MONICA [Monitoring of Trends and Determinants in Cardiovascular Disease], Risk, Genetics, Archiving and Monograph) 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 to 97 years without established cardiovascular disease, not on antihypertensive treatment, recruited between 1982 and 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, and net reclassification improvement. The primary end point was a composite cardiovascular end point (CEP), defined as fatal or nonfatal stroke, death from coronary heart disease or nonfatal myocardial infarction. The positive association between age and systolic BP was more pronounced among individuals ≥50 years while the same was true for diastolic BP in those <50 years (P interaction <0.001). Higher systolic BP and mean BP were significantly associated with cardiovascular end point, irrespective of age group (P<0.001), but diastolic BP only demonstrated an independent relationship in the younger group (P<0.001). Brachial pulse pressure was associated with cardiovascular end point in the older age group (P<0.001). In subjects <50 years, diastolic BP significantly improved area under the receiver operating characteristic curve compared with Systematic Coronary Risk Evaluation variables (including systolic BP) alone (0.842 versus 0.840, P=0.03), enhanced continuous net reclassification improvement (0.150 [95% CI, 0.087–0.215]) and improved the prognostic value of the European Society of Cardiology/European Society of Hypertension hypertension definition (categorical net reclassification improvement=0.0255, P=0.005). In conclusion, diastolic BP may provide additional prognostic utility beyond systolic BP, in predicting composite cardiovascular events among younger individuals. (***Hypertension*.2021;77:1076-1085.DOI:10.1161/HYPERTENSIONAHA.120.16354.)** • **Data Supplement**

Key Words: blood pressure ■ cardiovascular disease ■ myocardial infarction ■ prognosis ■ risk factor

Correspondence to: Michael H. Olsen, Cardiology Section, Department of Internal Medicine, Holbaek Hospital, Smedelundsgade 60, 4300 Holbaek, Denmark. Email michael.olsen@dadlnet.dk

*J.K.K. Vishram-Nielsen and A.M.D. Kristensen are joint first authors.

†A list of all MORGAM Project members is given in the Data Supplement.

This article was sent to Marc L. De Buyzere, Guest Editor, for review by expert referees, editorial decision, and final disposition.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.120.16354.

For Sources of Funding and Disclosures, see page 1084.

Hypertension is available at www.ahajournals.org/journal/hyp

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.

Nonstandard Abbreviation and Acronyms

ACC/AHA	American College of Cardiology/American Heart Association
ACM	all-cause mortality
BP	blood pressure
CEP	composite cardiovascular end point
DBP	diastolic blood pressure
ESC/ESH	European Society of Cardiology/European Society of Hypertension
HDL	high-density lipoprotein
MBP	mean blood pressure
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
MORGAM	MONICA, Risk, Genetics, Archiving and Monograph
MRFIT	Multiple Risk Factor Intervention Trial
NRI	net reclassification improvement
PP	pulse pressure
SBP	systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation

Hypertension is a major modifiable risk factor for cardiovascular disease and all-cause mortality (ACM).[1–3] Through the years, several blood pressure (BP) characteristics, including systolic BP (SBP), diastolic BP (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, for example, 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 MORGAM (MONICA [Monitoring of Trends and Determinants in Cardiovascular Disease], Risk, Genetics, Archiving and Monograph) project to investigate (1) covariates of classical BP characteristics (SBP, DBP, and MBP) and indirect measures of arterial stiffness, some established (brachial PP) and some hypothetical (brachial SBP/DBP-ratio and brachial PP/MBP-ratio),[5,7] in younger and older men and women; (2) the relative importance of these BP characteristics independently and combined, in predicting incident cardiovascular events and ACM; 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 to 2002 and originated from 38 population-based cohorts in 11 European countries (Table S1 in the Data Supplement). These cohorts had either been part of the World Health Organization's MONICA 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 (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 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 to 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 World Health Organization MONICA Project. The mean of the first and second SBP and DBP was used. In the cohorts France-Lille, France-Strasbourg, France-Toulouse, United Kingdom-Belfast, Germany-Augsburg, (only cohort 24), and Norway-Tromsø, BP was measured using an automated device, and in the cohorts France-Lille, France-Strasbourg, France-Toulouse, United Kingdom-Belfast, and Germany-ESTHER, 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 HDL (high-density lipoprotein) 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.

End Points

The primary end point was CEP, defined as fatal or nonfatal stroke, death from coronary heart disease, or nonfatal 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 end points were ACM and cardiovascular death, the latter defined as fatal stroke or death from coronary heart disease. Observations continued until an end point 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. Tables S2 and S3 summarize the follow-up procedures used by each center for death and for coronary and stroke events. For the tables please see the Data Supplement. 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 (25th, 75th 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 6 BP characteristics. Standardized regression coefficients (ie, per 1 SD increase) were reported as the measures of association.

Next, we calculated unadjusted and adjusted hazard ratios with corresponding 95% CIs for the association of each BP characteristic with each end point, 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) and continuous net reclassification improvement (NRI). Furthermore, the predictive value of using both SBP and DBP compared with 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 Association (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 2-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) and Stata/IC 15 (StataCorp LP, College Station, TX).

RESULTS

Demographic and Clinical Characteristics

The final sample consisted of 107 599 individuals (53% men) aged 19 to 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 BP 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) reflecting that DBP increased more than SBP with increasing age in subjects <50 years.

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). Figure 1A through 1D illustrate the unadjusted impact of SBP and DBP, and Figure 2A through 2D 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 BP Characteristics

Figure 3 shows the independent prediction, discrimination, and net reclassification of events by BP characteristics. SBP was significantly associated with all 3 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 area under the receiver operating characteristic curve 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 cardiovascular death. 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 area under the receiver operating characteristic curve 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 Tables S4 and S5, respectively. 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

Table 1. Baseline Characteristics Stratified by Sex, Age, and Incident Composite Cardiovascular Events

Baseline variables	No incident CEP (men)		Incident CEP (men)		No incident CEP (women)		Incident CEP (women)	
	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y
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, y	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, mm Hg	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, mm Hg	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, mm Hg	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, mm Hg	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)

The MORGAM Project. Values are presented as numbers (percentages) or median (25th, 75th percentile). ACM indicates all-cause mortality; BMI, body mass index; CEP, primary composite cardiovascular end point (fatal or nonfatal stroke, death from coronary heart disease, or nonfatal 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; MORGAM, MONICA, Risk, Genetics, Archiving and Monograph; PP, pulse pressure; and SBP, systolic blood pressure.

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,

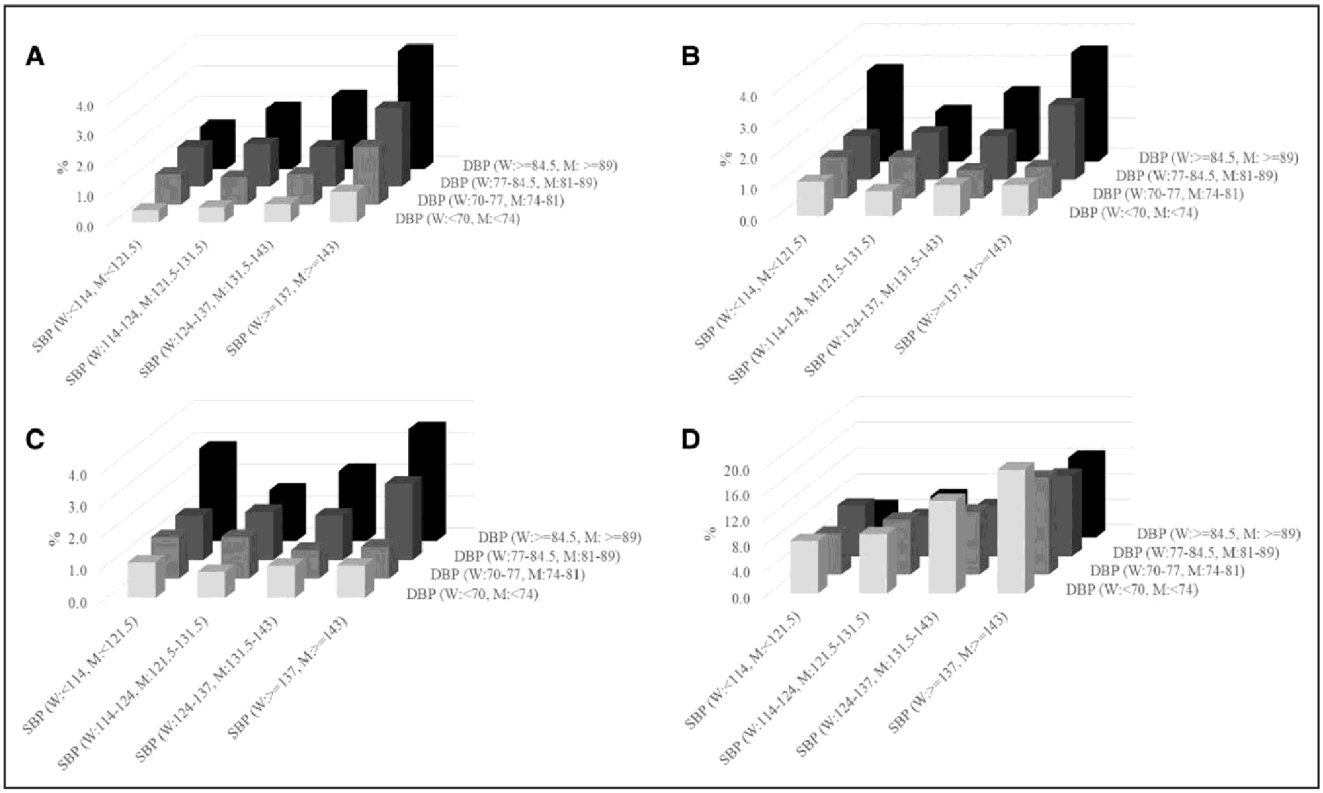

Figure 1. Impact of systolic and diastolic blood pressure on the incidence of the composite cardiovascular end point (CEP) as well as all-cause mortality (ACM) in men and women younger and older than 50 y based on blood pressure quarters.
A) CEP in ages younger than 50 y; **B**) CEP in ages older than 50 y; **C**) ACM in ages younger than 50 y; and **D**) ACM in ages older than 50 y.

Table 2. Covariates of Blood Pressure Characteristics Using Multiple Regression Analyses in Subjects Younger or Older Than 50 Years

	SBP		DBP		SBP/DBP		PP		MBP		PP/MBP	
Baseline variables	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y
Age	0.063$^{<0.001}$	0.269$^{<0.001}$	0.230$^{<0.001}$	0.017$^{<0.001}$	−0.241$^{<0.001}$	0.323$^{<0.001}$	−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	0.266$^{<0.001}$	0.022$^{<0.001}$	0.162$^{<0.001}$	0.109$^{<0.001}$	0.090$^{<0.001}$	−0.093$^{<0.001}$	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	0.209$^{<0.001}$	0.217$^{<0.001}$	0.220$^{<0.001}$	0.237$^{<0.001}$	−0.046$^{<0.001}$	0.004^{NS}	0.067$^{<0.001}$	0.116$^{<0.001}$	0.235$^{<0.001}$	0.247$^{<0.001}$	−0.051$^{<0.001}$	0.003^{NS}
Chol	0.097$^{<0.001}$	0.095$^{<0.001}$	0.106$^{<0.001}$	0.102$^{<0.001}$	−0.033$^{<0.001}$	0.003^{NS}	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	0.052$^{<0.001}$	0.046$^{<0.001}$	0.001^{NS}	0.033$^{<0.001}$	0.053$^{<0.001}$	0.019$^{<0.001}$	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	−0.026$^{<0.001}$	−0.008^{NS}	−0.039$^{<0.001}$	−0.029$^{<0.001}$	0.021$^{<0.001}$	0.022$^{<0.001}$	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	0.160$^{<0.001}$	0.138$^{<0.001}$	0.209$^{<0.001}$	0.072$^{<0.001}$	0.079$^{<0.001}$	0.122$^{<0.001}$	0.055$^{<0.001}$	0.153$^{<0.001}$	0.210$^{<0.001}$	0.107$^{<0.001}$	0.079$^{<0.001}$	0.122$^{<0.001}$

The MORGAM project. BMI indicates body mass index; Chol, serum total cholesterol; DBP, diastolic blood pressure; HDL-C, serum high-density lipoprotein cholesterol; MBP, mean blood pressure; MORGAM, MONICA, Risk, Genetics, Archiving and Monograph; NS, nonsignificant; PP, pulse pressure; and SBP, systolic blood pressure.

Superscript denotes the *P* value, that is, *P*≥0.05.

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 MRFIT (Multiple Risk Factor Intervention Trial) 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 to 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[16] and the pooled cohort equations for calculation of atherosclerotic cardiovascular disease risk recommended by ACC/AHA[38] 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 with the ACC/AHA definition. Conversely, some experts have suggested abandoning DBP measurement in therapeutic decision making,[39] but based on our results, this could lead to loss of clinically meaningful information in younger patients.

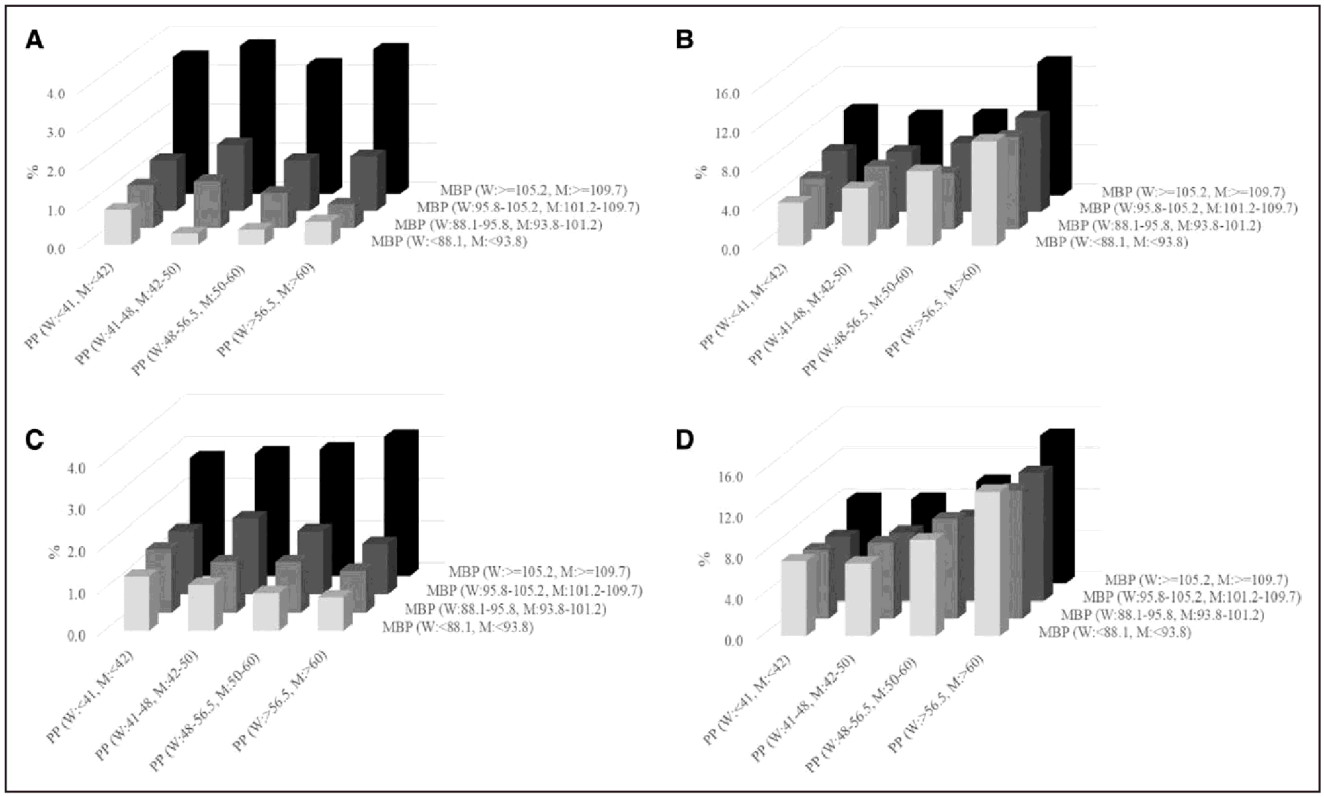

Figure 2. Impact of mean blood pressure and brachial pulse pressure on the incidence of the composite cardiovascular end point (CEP) as well as all-cause mortality (ACM) in men and women younger and older than 50 y based on blood pressure quarters.

A) CEP in ages younger than 50 y; **B**) CEP in ages older than 50 y; **C**) ACM in ages younger than 50 y; and **D**) ACM in ages older than 50 y.

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 11 countries and long-term follow-up with a large number of cardiovascular events. Standardized baseline measurements and harmonized end point 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.[40] Second, our primary end point 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

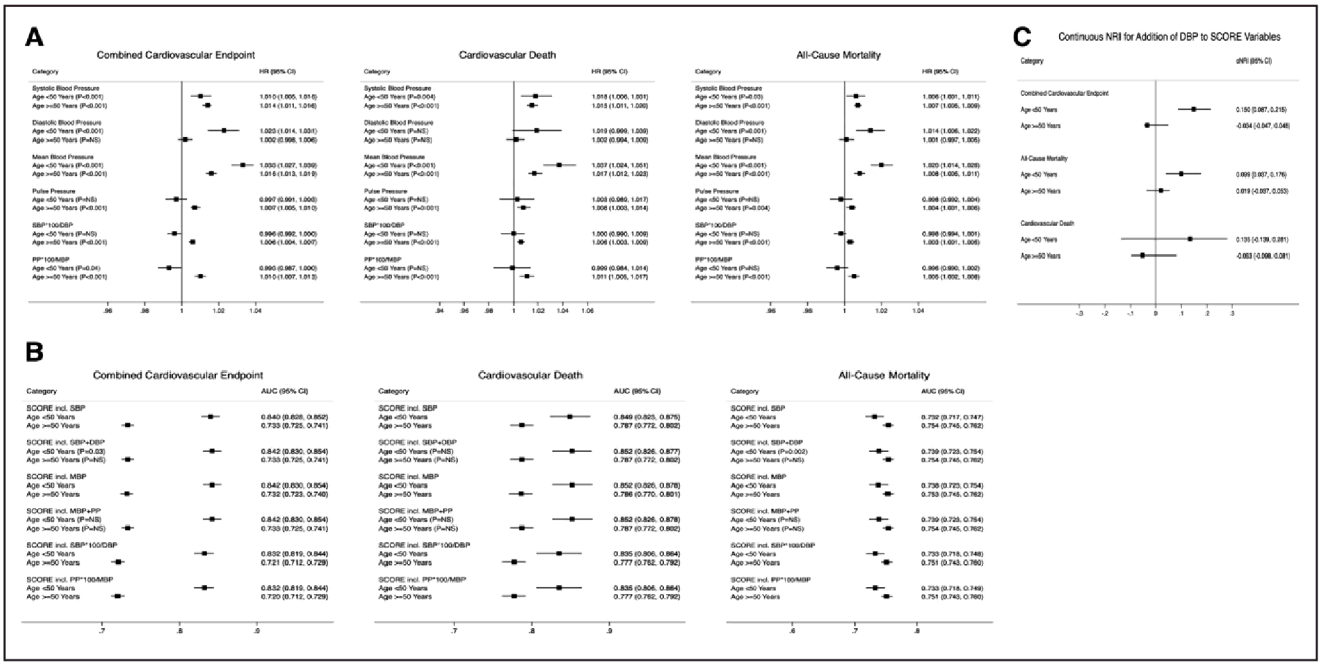

Figure 3. The independent prediction, discrimination, and net reclassification of events by blood pressure (BP) characteristics. Adjusted hazard ratio (HR; **A**) and discrimination (**B**) of the composite cardiovascular end point, cardiovascular death, and all-cause mortality as well as continuous net reclassification for all three events (**C**) by blood pressure characteristics in subjects younger or older than 50 y. The MORGAM (MONICA [Monitoring of Trends and Determinants in Cardiovascular Disease], Risk, Genetics, Archiving and Monograph) Project. The composite cardiovascular end point consists of fatal or nonfatal stroke, death from coronary heart disease, or nonfatal myocardial infarction, and cardiovascular death consists of fatal stroke or death from coronary heart disease. HR is per 1 SD, adjusted for country, age, sex, smoking, serum cholesterol, and a blood pressure estimate as described in the methods section. Comparison of area under the receiver operating characteristic curve (AUCROC) for a model comprising SCORE variables+diastolic blood pressure with a model comprising SCORE variables alone. cNRI indicates continuous net reclassification improvement; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; SBP, systolic blood pressure; and SCORE: The variables of SCORE (Systematic Coronary Risk Evaluation) risk equation for cardiovascular death. Nonsignificant (NS), that is, $P>0.05$.

MONICA criteria, there was some variation in the identification of end points between the countries. For instance, for nonfatal myocardial infarction the variation was due to the use of nonspecific diagnostic tools as well as differences in the health care systems between countries. This variation was presumably attenuated after the introduction and widespread implementation of cardiac troponins. Furthermore, for subjects who died outside the health care 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,

Table 3. Interaction Analyses in Cox Regression Models

Baseline BP characteristics	Interaction for age (<50 vs ≥50 y)			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}

The MORGAM Project. NS, that is, $P\geq0.05$. ACM indicates all-cause mortality; BP, blood pressure; CEP, primary composite cardiovascular end point (fatal or nonfatal stroke, death from coronary heart disease, or nonfatal myocardial infarction); CVD, cardiovascular death (fatal stroke or death from coronary heart disease); DBP, diastolic BP; MBP, mean BP; MORGAM, MONICA, Risk, Genetics, Archiving and Monograph; NS, nonsignificant; PP, pulse pressure; and SBP, systolic BP.

DBP may provide prognostic utility beyond SBP in predicting CEP and ACM among younger individuals.

ARTICLE INFORMATION

Received September 16, 2020; accepted December 31, 2020.

Affiliations

From the Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region of Denmark, Copenhagen, Frederiksberg (J.K.K.V.-N., A.L.); Department of Cardiology, Rigshospitalet (J.K.K.V.-N.) and Department of Clinical Medicine, Faculty of Health and Medical Sciences (A.L.), University of Copenhagen, Denmark; Department of Cardiology, North Zealand Hospital, Hillerød, Denmark (A.M.D.K., M.P.); Department of Internal Medicine, Yale New Haven Hospital, Yale University School of Medicine, New Haven, CT (M.P.); Department of Clinical Pharmacology and INSERM U 970, team 7, Paris CV Research Center (PARCC), Hôpital Européen Georges Pompidou, France (S.L.); Department for Clinical Sciences Medicine, University Hospital, Malmö, Sweden (P.M.N.); Cardiovascular and Metabolic Preventive Clinic, Department of Endocrinology, Odense University Hospital, Denmark (S.V.G.); Department of Cardiovascular, Endocrine-metabolic Diseases and Aging, Istituto Superiore di Sanità (ISS), Rome, Italy (L.P., S. Giampaoli, C.D.); Centre for Public Health, The Queen´s University of Belfast, Northern Ireland (F.K.); University of Milano-Bicocca and Policlinico di Monza, Italy (G.M.); Research Centre on Public Health (G.C.) and Clinica Medica, Department of Medicine and Surgery (G.G.), University of Milano Bicocca, Villa Serena, Monza, Italy; Research Centre in Epidemiology and Preventive Medicine (EPIMED), Department of Medicine and Surgery, University of Insubria, Italy (G.V.); Finnish Institute for Health and Welfare (THL), Helsinki, Finland (K.K., V.S., T.P., M.S.); Catalan Department of Health, Barcelona, Spain (S. Sans); Department of Cardiology, Toulouse University School of Medicine, Rangueil Hospital, France (J.F.); Institut Pasteur de Lille, France (Jean Dallongeville); Department of Public Health and Clinical Medicine, Cardiology and Heart Centre, Umeå University, Sweden (S. Söderberg); Department of Epidemiology and Public Health, University of Strasbourg and University Hospital of Strasbourg, France (M.M.); Department of Epidemiology, CVD Prevention and Health Promotion, National Institute of Cardiology, Warsaw, Poland (W.D.); Lithuanian University of Health Sciences, Institute of Cardiology, Kaunas (A.T.); German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany (A.P.); German Cancer Research Center, Heidelberg, Germany (H.B.); Network Aging Research, University of Heidelberg, Germany (H.B.); Department of Community Medicine, UiT the Arctic University of Norway, Tromsø, Norway (S. Grimsgaard); Department of Internal Medicine, Holbaek Hospital, Denmark (M.H.O.); and Centre of Individualized Medicine in Arterial Diseases (CIMA), Department of Regional Health Research, University of Southern Denmark (M.H.O.).

Acknowledgments

We thank the participants and the staff of the cohorts for their continuing dedication and efforts.

Sources of Funding

We did not receive any funding for this study, but overall this work has been sustained by the MORGAM (MONICA [Monitoring of Trends and Determinants in Cardiovascular Disease], Risk, Genetics, Archiving and Monograph) Project´s recent funding: European Community FP 7 projects Consortium on Health and Ageing: Network of cohorts in Europe and the United States (HEALTH-F3-2010-242244) and BiomarCaRE (278913). This has supported data harmonization and part of the activities of the MORGAM Data Centre, at THL in Helsinki, Finland. MORGAM Participating Centers are funded by regional and national governments, research councils, charities, and other local sources. Dr Salomaa was supported by the Finnish Foundation for Cardiovascular Research. SSg was supported by the Swedish Heart and Lung foundation and by the County council of Västertotten. Dr Pareek has the followings relationships—Advisory Board and Speaking Honoraria: AstraZeneca; Speaking Honoraria: Bayer, Boehringer Ingelheim.

Disclosures

Dr Salomaa 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). Dr Söderberg has received speakers and consultant honoraria from Actelion Ltd. Dr Olsen has from 2013 to 2018 received a part time clinical research grant from the Novo Nordic Foundation. Dr Pareek 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

REFERENCES

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380:2224–2260. doi: 10.1016/S0140-6736(12)61766-8
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913. doi: 10.1016/s0140-6736(02)11911-8
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339
4. Kannel WB. Historic perspectives on the relative contributions of diastolic and systolic blood pressure elevation to cardiovascular risk profile. *Am Heart J.* 1999;138(3 pt 2):205–210. doi: 10.1016/s0002-8703(99)70311-x
5. Franklin SS, Gustin W IV, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation.* 1997;96:308–315. doi: 10.1161/01.cir.96.1.308
6. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J.* 2006;27:2588–2605. doi: 10.1093/eurheartj/ehl254
7. Palatini P, Casiglia E, Gąsowski J, Głuszek J, Jankowski P, Narkiewicz K, Saladini F, Stolarz-Skrzypek K, Tikhonoff V, Van Bortel L, et al. Arterial stiffness, central hemodynamics, and cardiovascular risk in hypertension. *Vasc Health Risk Manag.* 2011;7:725–739. doi: 10.2147/VHRM.S25270
8. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension.* 2002;39:10–15. doi: 10.1161/hy0102.099031
9. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation.* 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655
10. Vishram JK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Broda G, Palmieri L, Giampaoli S, Donfrancesco C, et al; 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. doi: 10.1161/HYPERTENSIONAHA.112.201400
11. Rajkumar C, Kingwell BA, Cameron JD, Waddell T, Mehra R, Christophidis N, Komesaroff PA, McGrath B, Jennings GL, Sudhir K, et al. Hormonal therapy increases arterial compliance in postmenopausal women. *J Am Coll Cardiol.* 1997;30:350–356. doi: 10.1016/s0735-1097(97)00191-5
12. Nilsson PM, Laurent S, Cunha PG, Olsen MH, Rietzschel E, Franco OH, Ryliškytė L, Strazhesko I, Vlachopoulos C, Chen CH, et al; Metabolic syndrome, Arteries REsearch (MARE) Consortium. Characteristics of healthy vascular ageing in pooled population-based cohort studies: the global Metabolic syndrome and Artery REsearch Consortium. *J Hypertens.* 2018;36:2340–2349. doi: 10.1097/HJH.0000000000001824
13. Evans A, Salomaa V, Kulathinal S, Asplund K, Cambien F, Ferrario M, Perola M, Peltonen L, Shields D, Tunstall-Pedoe H, et al; MORGAM Project. MORGAM (an international pooling of cardiovascular cohorts). *Int J Epidemiol.* 2005;34:21–27. doi: 10.1093/ije/dyh327
14. Kulathinal S, Niemelä M, Niiranen T, Saarela O, Palosaari T, Tapanainen H, Kuulasmaa K; contributors from Participating Centres, for the MORGAM Project. *Description of MORGAM Cohorts.* MORGAM Project e-Publications;

2014. https://www.thl.fi/publications/morgam/cohorts/index.html. Accessed September 14, 2020.
15. MORGAM Project. *MORGAM Manual*. MORGAM Project e-Publications; 2019. www.thl.fi/publications/morgam/manual/contents.htm. Accessed September 14, 2020.
16. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003. doi: 10.1016/s0195-668x(03)00114-3
17. Niemelä M, Kulathinal S, Kuulasmaa K, eds, for the MORGAM Project. *Description and Quality Assessment of MORGAM Data*. MORGAM Project e-Publications; 2012. https://www.thl.fi/publications/morgam/qa/contents.htm. Accessed September 14, 2020.
18. Tunstall-Pedoe H, ed. *Monica Monograph and Multimedia Sourcebook*. World Health Organization; 2003.
19. Karas RH, Patterson BL, Mendelsohn ME. Human vascular smooth muscle cells contain functional estrogen receptor. *Circulation*. 1994;89:1943–1950. doi: 10.1161/01.cir.89.5.1943
20. Wu J, Hadoke PW, Mair I, Lim WG, Miller E, Denvir MA, Smith LB. Modulation of neointimal lesion formation by endogenous androgens is independent of vascular androgen receptor. *Cardiovasc Res*. 2014;103:281–290. doi: 10.1093/cvr/cvu142
21. Zaydun G, Tomiyama H, Hashimoto H, Arai T, Koji Y, Yambe M, Motobe K, Hori S, Yamashina A. Menopause is an independent factor augmenting the age-related increase in arterial stiffness in the early postmenopausal phase. *Atherosclerosis*. 2006;184:137–142. doi: 10.1016/j.atherosclerosis.2005.03.043
22. Takahashi K, Miura S, Mori-Abe A, Kawagoe J, Takata K, Ohmichi M, Kurachi H. Impact of menopause on the augmentation of arterial stiffness with aging. *Gynecol Obstet Invest*. 2005;60:162–166. doi: 10.1159/000086570
23. Smulyan H, Asmar RG, Rudnicki A, London GM, Safar ME. Comparative effects of aging in men and women on the properties of the arterial tree. *J Am Coll Cardiol*. 2001;37:1374–1380. doi: 10.1016/s0735-1097(01)01166-4
24. London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex on arterial hemodynamics and blood pressure. Role of body height. *Hypertension*. 1995;26:514–519. doi: 10.1161/01.hyp.26.3.514
25. Nowak KL, Rossman MJ, Chonchol M, Seals DR. Strategies for achieving healthy vascular aging. *Hypertension*. 2018;71:389–402. doi: 10.1161/HYPERTENSIONAHA.117.10439
26. Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, Grimm R, Cohen J, Stamler J; MRFIT Research Group. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 2002;287:2677–2683. doi: 10.1001/jama.287.20.2677
27. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:243–250. doi: 10.1161/CIRCULATIONAHA.108.797936
28. Sundström J, Neovius M, Tynelius P, Rasmussen F. Association of blood pressure in late adolescence with subsequent mortality: cohort study of Swedish male conscripts. *BMJ*. 2011;342:d643. doi: 10.1136/bmj.d643
29. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, Melles RB, Bhatt DL. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med*. 2019;381:243–251. doi: 10.1056/NEJMoa1803180
30. Benetos A. Pulse pressure and cardiovascular risk. *J Hypertens Suppl*. 1999;17:S21–S24.
31. Franklin SS. Ageing and hypertension: the assessment of blood pressure indices in predicting coronary heart disease. *J Hypertens Suppl*. 1999;17:S29–S36.
32. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation*. 1999;100:354–360. doi: 10.1161/01.cir.100.4.354
33. Khattar RS, Swales JD, Dore C, Senior R, Lahiri A. Effect of aging on the prognostic significance of ambulatory systolic, diastolic, and pulse pressure in essential hypertension. *Circulation*. 2001;104:783–789. doi: 10.1161/hc3201.094227
34. Lee ML, Rosner BA, Weiss ST. Relationship of blood pressure to cardiovascular death: the effects of pulse pressure in the elderly. *Ann Epidemiol*. 1999;9:101–107. doi: 10.1016/s1047-2797(98)00034-9
35. Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH. Pulse pressure and mortality in older people. *Arch Intern Med*. 2000;160:2765–2772. doi: 10.1001/archinte.160.18.2765
36. Miura K, Dyer AR, Greenland P, Daviglus ML, Hill M, Liu K, Garside DB, Stamler J; Chicago Heart Association. Pulse pressure compared with other blood pressure indexes in the prediction of 25-year cardiovascular and all-cause mortality rates: the Chicago Heart Association Detection Project in Industry Study. *Hypertension*. 2001;38:232–237. doi: 10.1161/01.hyp.38.2.232
37. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension*. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065
38. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
39. Sever P. Abandoning diastole. *BMJ*. 1999;318:1773. doi: 10.1136/bmj.318.7200.1773
40. Miura K, Soyama Y, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Yoshita K, Kagamimori S, Nakagawa H. Comparison of four blood pressure indexes for the prediction of 10-year stroke risk in middle-aged and older Asians. *Hypertension*. 2004;44:715–720. doi: 10.1161/01.HYP.0000145108.23948.7b