Impact of Age on the Importance of Systolic and Diastolic Blood Pressures for Stroke Risk

The MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project

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Abstract—This study investigates age-related shifts in the relative importance of systolic (SBP) and diastolic (DBP) blood pressures as predictors of stroke and whether these relations are influenced by other cardiovascular risk factors. Using 34 European cohorts from the MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project with baseline between 1982 and 1997, 68 551 subjects aged 19 to 78 years, without cardiovascular disease and not receiving antihypertensive treatment, were included. During a mean of 13.2 years of follow-up, stroke incidence was 2.8%. Stroke risk was analyzed using hazard ratios per 10-mm Hg/5-mm Hg increase in SBP/DBP by multivariate-adjusted Cox regressions, including SBP and DBP simultaneously. Because of nonlinearity, DBP was analyzed separately for DBP ≥71 mm Hg and DBP <71 mm Hg. Stroke risk was associated positively with SBP and DBP ≥71 mm Hg (SBP/DBP ≥71 mm Hg; hazard ratios: 1.15/1.06 [95% CI: 1.12–1.18/1.03–1.09]) and negatively with DBP <71 mm Hg (0.88[0.79–0.98]). The hazard ratio for DBP decreased with age (P<0.001) and was not influenced by other cardiovascular risk factors. Taking into account the age×DBP interaction, both SBP and DBP ≥71 mm Hg were significantly associated with stroke risk until age 62 years, but in subjects older than 46 years the superiority of SBP for stroke risk exceeded that of DBP ≥71 mm Hg and remained significant until age 78 years. DBP <71 mm Hg became significant at age 50 years with an inverse relation to stroke risk. In Europeans, stroke risk should be assessed by both SBP and DBP until age 62 years with increased focus on SBP from age 47 years. From age 62 years, emphasis should be on SBP without neglecting the potential harm of very low DBP. **(*Hypertension*. 2012;60:1117-1123.)** ● **Online Data Supplement**

Key Words: blood pressure ■ age ■stroke ■ risk factors ■ epidemiology

Hypertension affects ≈30% of the world's population.[1] Despite being a modifiable cardiovascular risk factor, blood pressure (BP) control is still poor, and uncertainties remain over which BP measure, systolic BP (SBP) or diastolic BP (DBP), is the most important risk factor for a cardiovascular event in different ages. Recent discussions have focused increased attention on SBP, especially in the elderly.[2,3]

It is well documented in the literature that BP profiles change with age.[4] DBP rises until age 50 years and then declines, whereas SBP rises from adolescence until old age, suggesting a different relative importance of DBP and SBP with aging. The Framingham Heart Study[5] was the first to show that there was a declining relative importance of DBP and a corresponding increase in the importance of SBP in coronary heart disease risk with advancing age. Since then, many studies[6–15] have shown the superiority of either SBP or pulse pressure (PP) in the elderly. In younger ages, the pattern was less clear. Only some studies showed the superiority of DBP,[5,7,12] whereas others showed the superiority of SBP[6,14] or both BPs.[8–11,13]

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An appendix with the details of MORGAM Project can be found in the online-only Data Supplement.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.201400/-/DC1.

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All previous studies[6–15] analyzed the associations between BP and cardiovascular disease risk using subgroups of age rather than using age as a continuous variable. The latter would have offered a clearer picture of the age at which the relative importance of SBP begins to exceed DBP, and the age at which the superiority of SBP is established. Moreover, because BP is a stronger risk factor for stroke than for coronary heart disease,[16] and because only few previous studies[8,11,14,15] examined incident stroke, none of which were in Europeans who have a high rate of hypertension,[17] more studies on the relationship among SBP, DBP, and stroke risk in European populations are desired.

In addition, because arterial stiffness is the main determinant of SBP in older patients[18] and is dependent on other cardiovascular risk factors, such as sex, smoking status, diabetes mellitus, body mass index (BMI), and cholesterol,[19] it is possible that the superiority of SBP is established at an earlier age in individuals with more of these cardiovascular risk factors present.

This report uses the MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project, which consists of large European population-based cohorts of men and women aged 19 to 78 years, with uniform standardized data collection and strict diagnostic criteria for incident stroke, to investigate the following: (1) the relative importance of SBP and DBP in stroke risk with advancing age, (2) the age at which the relative importance of SBP exceeds DBP in stroke risk, (3) whether this shift to the superiority of SBP is influenced by other cardiovascular risk factors, and (4) the relative importance of PP and mean arterial pressure (MAP) in stroke risk with advancing age.

Methods

Cohorts

The present study used baseline and follow-up data on fatal and nonfatal stroke from 34 cohorts in 10 European countries from the MORGAM Project[20] (Table S1 in the online-only Data Supplement). The cohorts in the MORGAM Project had either been a part of the World Health Organization MONICA Project or had used the same standardized MONICA survey procedures for data collection as described in the MORGAM manual.[21] Exclusion criteria at baseline included antihypertensive drug treatment (n=9716), or a history of stroke (ischemic or hemorrhagic; n=549), or coronary heart disease (myocardial infarction, angina pectoris, coronary artery bypass graft, or coronary angioplasty; n=1653), leaving a total of 68 551 participants for analyses.

The use of antihypertensive drugs, daily smoking, and diabetes mellitus at baseline were self-reported. BMI was calculated as weight (in kilograms) divided by the square of the height (in meters squared). BP was measured twice in the right arm in the sitting position using a standard or random zero mercury sphygmomanometer after a 5-minute rest[22] except in 5 cohorts where BP was measured only once. The mean of the first and second SBP and DBP was used when possible. Total serum cholesterol was measured in serum samples by local laboratories.[22]

The end point included fatal and nonfatal stroke. Observations continued until death or the end of a fixed follow-up period (1994–2007 depending on the cohort). The mean follow-up time was 13.2 years. Fatal cases were identified by national or regional health information systems. In most cohorts, nonfatal cases were identified by hospital discharge registers. Most MORGAM centers used the World Health Organization MONICA diagnostic criteria[22] to validate the stroke events occurring during follow-up. Details including quality assessments of MORGAM end points and baseline data have been described previously.[23,24]

Statistical Analyses

SAS (SAS Institute Inc, Cary, NC) version 9.2 was used for all analyses.

Three age-adjusted Cox regression models were used to compare the associations of baseline SBP per 10-mm Hg increase and baseline DBP per 5-mm Hg increase with stroke risk: model A included only SBP or DBP; model B included both SBP and DBP; and model C included both SBP and DBP, as well as adjustment for the potential confounders sex, smoking status, diabetes mellitus, cholesterol, and BMI.

Models B and C assessed independent associations of SBP and DBP with stroke risk. In all the analyses, the models were stratified by country allowing for the baseline hazard to vary between countries.

First, interactions between age and BP (ie, age×SBP) were examined, as well as whether they were influenced by other cardiovascular risk factors (ie, age×SBP×sex). When there was evidence of effect modification by cardiovascular risk factors, this was taken into account in the further analyses. Additional effect modifiers were examined for the age×BP interaction: (1) country, (2) high-/low-risk countries according to HeartScore,[25] and (3) Eastern/Western European countries. Next, the hazard ratios (HRs) for SBP and DBP were compared across different baseline age categories (19–39, 40–49, 50–59, and 60–78 years) and then with baseline age as a continuous variable in order to determine the age at which the HR for stroke for SBP significantly exceeds the HR for stroke for DBP. Further analyses assessed the risk of stroke using HRs per 1-mm Hg increase in SBP and DBP. The same analyses were carried out per 5-mm Hg increase in PP (calculated as SBP-DBP) and MAP (calculated as SBP/3+2DBP/3).

The use of different scales for SBP and DBP was consistent with previous work[11,14] and was mainly attributed to the noncomparability of the 2 BP measures, because SBP is approximately twice as high as DBP. Furthermore, because the SD of SBP is twice that of DBP, some previous studies have calculated HR per SD change in BP. However, because of variations in the SD of SBP and DBP across different countries, it was not used in the present study to standardize the comparisons of SBP and DBP.

All explanatory variables met the proportional hazards assumption of the Cox regression model, assessed by inspecting Schoenfeld residuals. The linearity of the continuous variables was assessed using quadratic and cubic effects, as well as cubic splines (a piecewise fitting of polynomial equations). The relation of DBP to stroke risk was J-shaped with the lowest stroke risk at a DBP of ≈71 mm Hg. Stroke risk was greater with DBPs both higher and lower than 71 mm Hg. Based on inspection of the above mentioned cubic spline with knots placed at the fifth, 23rd, 41st, 59th, 77th, and 95th centiles, we modeled DBP as a linear spline with 1 knot at 71 mm Hg, and thus separate results are reported for DBP ≥71 mm Hg and DBP <71 mm Hg.

A sensitivity analysis was performed excluding the 5 cohorts, where BP was measured only once. For all analyses, a 2-tailed $P<0.05$ was considered statistically significant.

Results

Study Characteristics

Risk factors such as BMI, cholesterol, and BP increased across age groups for the 68 551 participants ($P<0.0001$; Table 1). During 13.2 years of follow-up, 2.8% (1192 men and 700 women) had an incident stroke event. The stroke incidence rates per 1000 person years generally increased with rising categories of baseline BP ($P<0.0001$) and age ($P<0.0001$; Figure S1 in the online-only Data Supplement).

Factors Influencing the Association Between BP and Stroke Risk

The associations among SBP, DBP, MAP, and stroke risk were significantly influenced by age (all $P<0.01$; model A); and remained significant after adjustment for the other BP measure (all $P<0.05$; model B). However, in the

Table 1. Distribution of Risk Factors According to Age Group

	Age, y				
Risk factors	19–78	19–39	40–49	50–59	60–78
N	68 551	21 453 (31.3)	15 895 (23.2)	23 226 (33.9)	7977 (11.6)
Men	38 821 (56.6)	10 406 (48.5)	7836 (49.3)	16 255 (70.0)	4324 (54.2)
Smoker	20 357 (29.7)	7610 (37.3)	4940 (31.1)	5876 (25.3)	1931 (24.2)
Diabetics	1775 (2.6)	197 (0.92)	324 (2.04)	851 (3.7)	403 (5.05)
Body mass index, kg/m^2	26.0 (4.2)	24.6 (3.9)	26.3 (4.1)	26.8 (4.0)	27.1 (4.4)
Total cholesterol, mmol/L	5.7 (1.2)	5.2 (1.1)	5.7 (1.1)	6.0 (1.1)	6.2 (1.2)
Systolic blood pressure, mm Hg	131.7 (19.5)	124.1 (15.2)	129.5 (17.8)	135.8 (20.1)	144.4 (21.7)
Diastolic blood pressure, mm Hg	81.5 (11.5)	77.3 (10.9)	82.6 (11.4)	83.9 (11.3)	83.9 (11.2)
Pulse pressure, mm Hg	50.1 (14.2)	46.8 (11.9)	46.9 (12.0)	51.9 (14.7)	60.4 (16.8)
Mean arterial pressure, mm Hg	98.2 (13.0)	92.9 (11.1)	98.3 (12.6)	101.2 (13.1)	104.0 (13.3)

Values are expressed as numbers (percentages) or mean (SD).

multivariate-adjusted model, only associations among DBP, MAP, and stroke risk remained significant (both $P<0.05$; model C). Although we found an effect modification by sex on ages has an influence on the MAP/stroke association (all $P<0.05$; models A and B), it did not remain significant in the multivariate-adjusted model (model C; Table S2). Furthermore, there was no effect modification by country variables. A sensitivity analysis, excluding the 5 cohorts where BP was measured only once, showed the same results as above (data not shown).

SBP Versus DBP

For the total population, stroke risk was associated positively with SBP and DBP ≥71 mm Hg and negatively with DBP <71 mm Hg (all $P<0.05$; models A through C, Table 2). Age was also independently associated with stroke risk in models A through C (all $P<0.0001$; data not shown).

Age Categories

When SBP and DBP were considered separately in the regression model, both SBP and DBP ≥71 mm Hg were significantly associated with stroke risk across the 4 age groups (all $P<0.0001$; model A). However, when both BPs were considered jointly (models B and C), SBP became nonsignificant in the 19 to 39 year olds, although there was no effect modification by age after multivariate adjustment (model C). For DBP ≥71 mm Hg, the association with stroke risk became nonsignificant in the 50 to 59 year olds (model C) and in the 60 to 78 year olds (models B and C; Table 2). For DBP <71 mm Hg, the inverse association between DBP and stroke risk was significant in the 60 to 78 year olds in all 3 models.

Table 2. Hazard Ratios for Subsequent Strokes (Fatal and Nonfatal) From a Cox Regression Model in Different Age Groups at Baseline

	19–78		19–39		40–49		50–59		60–78	
Age, y	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Mean SBP, mm Hg										
Model A*	1.18 (1.16–1.21)	<0.0001	1.27 (1.16–1.38)	<0.0001	1.27 (1.21–1.35)	<0.0001	1.20 (1.16–1.24)	<0.0001	1.15 (1.11–1.20)	<0.0001
Model B†	1.14 (1.11–1.17)	<0.0001	1.06 (0.93–1.20)	0.38	1.20 (1.10–1.30)	<0.0001	1.16 (1.11–1.21)	<0.0001	1.16 (1.11–1.21)	<0.0001
Model C‡	1.15 (1.12–1.18)	<0.0001	1.02 (0.90–1.16)	0.76	1.20 (1.11–1.31)	<0.0001	1.17 (1.12–1.23)	<0.0001	1.17 (1.12–1.22)	<0.0001
Mean DBP, if ≥71 mm Hg										
Model A*	1.15 (1.13–1.18)	<0.0001	1.24 (1.16–1.33)	<0.0001	1.22 (1.16–1.28)	<0.0001	1.16 (1.12–1.20)	<0.0001	1.10 (1.06–1.15)	<0.0001
Model B†	1.07 (1.04–1.10)	<0.0001	1.21 (1.10–1.33)	<0.0001	1.09 (1.02–1.17)	0.01	1.06 (1.01–1.10)	0.02	1.00 (0.96–1.05)	0.91
Model C‡	1.06 (1.03–1.09)	<0.0001	1.19 (1.08–1.31)	0.0004	1.08 (1.01–1.16)	0.03	1.04 (0.99–1.09)	0.10	1.00 (0.95–1.05)	0.94
Mean DBP, if <71 mm Hg										
Model A*	0.89 (0.90–0.99)	0.031	1.25 (0.93–1.68)	0.15	0.81 (0.63–1.04)	0.10	0.92 (0.76–1.11)	0.37	0.79 (0.67–0.94)	0.006
Model B†	0.87 (0.78–0.97)	0.01	1.23 (0.92–1.66)	0.17	0.77 (0.60–0.99)	0.04	0.88 (0.73–1.06)	0.19	0.79 (0.67–0.97)	0.004
Model C‡	0.88 (0.79–0.98)	0.02	1.28 (0.95–1.73)	0.11	0.78 (0.61–1.01)	0.06	0.91 (0.75–1.10)	0.31	0.80 (0.68–0.94)	0.007

HR indicates hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Data were adjusted for age.

†Data were adjusted for age and the other blood pressure (BP) measure: SBP and DBP are adjusted for each other.

‡Data were adjusted for age, the other BP measure, and cardiovascular risk factors: sex, smoking status, diabetes mellitus, cholesterol, and body mass index.

Continuous Age

Next, we compared the independent associations among SBP, DBP, and the risk of stroke across different ages using baseline age as a continuous variable (Table 3). For illustrative purposes, the results are depicted graphically for model B in Figure 1 (models B and C displayed similar graphical results). The risk of stroke for each 10-mm Hg increase in SBP significantly exceeded that of DBP ≥71 mm Hg per 5-mm Hg increase at age 52 years (model B) and 47 years (model C). The association between DBP ≥71 mm Hg and stroke risk was strongest in the youngest ages and declined with age becoming nonsignificant at age 62 years. In contrast, SBP remained significantly associated with stroke risk across all ages, with a slight increase with advancing age (model B). However, after multivariate-adjustment, the risk of stroke for each 10-mm Hg increase in SBP remained the same across all ages (model C). The risk of stroke was inversely associated with DBP <71 mm Hg. The association was stronger in the elderly and became significant from ages 48 (model B) and 50 years (model C).

Further descriptive analyses showed that only 452 aged ≥62 (0.7%) had DBP <71 mm Hg. These participants (0.7%) had a mean SBP±SD of 129±19 mm Hg. SBP ≥140 mm Hg was seen in 109 (24%) of these participants, and only 30 (6.6%) had SBP ≥160 mm Hg.

A separate analysis, assessing the risk of stroke per 1-mm Hg increase in SBP and DBP, respectively, did not find a superiority of SBP before DBP ≥71 mm Hg becoming nonsignificant at 62 years of age (data not shown).

PP Versus MAP

As seen in Table 4, PP was significantly associated with stroke risk independent of age and MAP (model B and illustrated graphically in Figure 2) and remained significant after multivariate adjustment (model C). The significant influence of age on the MAP/stroke association was found to be different in men and women (model B); however, after multivariate adjustment, the effect modification by sex became nonsignificant (model C). The association between MAP and stroke risk was strongest in the youngest ages and declined with advancing age, becoming nonsignificant after the age of 69 years in men and 73 years in women (model B). The BP/stroke associations with advancing age in model C resembled those for men in model B except that here MAP was also significantly associated with stroke risk in the elderly.

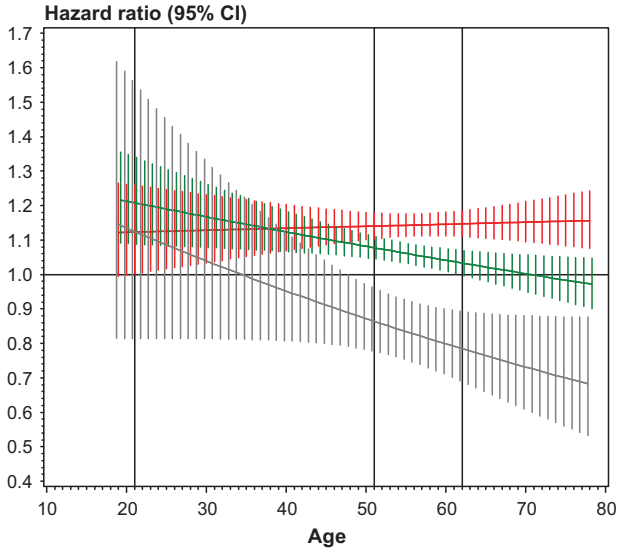

Figure 1. Hazard ratios for risks of stroke (fatal or nonfatal) by a 10-mm Hg increase in systolic blood pressure (SBP) (red) or by a 5-mm Hg increase in diastolic blood pressure (DBP) given its either ≥71 mm Hg (green) or below 71 mm Hg (grey) across different ages. SBP and DBP are adjusted for each other and age. The vertical line at age 51 years indicates the age after which the hazard ratio (HR) for SBP becomes significantly higher than the HR for DBP when DBP ≥71 mm Hg. The vertical line at age 62 years indicates the age at which the HR for DBP when DBP ≥71 mm Hg becomes nonsignificant.

Table 3. Comparison of Significant HRs of SBP and DBP With Advancing Age

		DBP		SBP	
BP, mm Hg With Significant HR	Age, y	HRs Range	95% CI Range	HRs Range	95% CI Range
Model B†					
DBP ≥71	19–20	1.21–1.22	1.09–1.36		
DBP ≥71 and SBP	21–51	1.08–1.21	1.04–1.34	1.12–1.14	1.002–1.26
SBP exceeds DBP ≥71	52–61	1.04–1.07	1.002–1.10	1.14–1.15	1.11–1.18
SBP	62–78			1.15–1.16	1.08–1.24
DBP <71*	48–78	0.68–0.89	0.53–0.99		
Model C‡					
DBP ≥71 and SBP	19–46	1.08–1.17	1.05–1.27	1.15	1.12–1.18
SBP exceeds DBP ≥71	47–61	1.04–1.08	1.002–1.11	1.15	1.12–1.18
SBP	62–78			1.15	1.12–1.18
DBP <71*	50–78	0.70–0.89	0.54–0.99		

BP indicates blood pressure; DBP, diastolic BP; SBP, systolic BP; HR, hazard ratio. All HRs and 95% CIs with $P<0.05$.

*Data show the protective effect of DBP per 5-mm Hg increase.

†Data were adjusted for the other BP measure: SBP and DBP are adjusted for each other.

‡Data were adjusted for age, the other BP measure, and cardiovascular risk factors: smoking status, diabetes mellitus, cholesterol, and body mass index.

Table 4. Comparison of Significant HRs of MAP and PP With Advancing Age

BP, mm Hg With Significant HR	Age, y	MAP HRs Range	MAP 95% CI Range	PP HRs Range	PP 95% CI Range
Model B†					
Men					
MAP exceeds PP	19–58	1.10–1.30	1.07–1.42	1.05	1.03–1.06
MAP and PP	59–69	1.05–1.09	1.0023–1.12	1.05	1.03–1.06
PP	70–78			1.05	1.03–1.06
Women					
PP	19–26			1.05	1.03–1.06
MAP and PP	27–73	1.07–1.09	1.0008–1.19	1.05	1.03–1.06
PP	74–78			1.05	1.03–1.06
Model C‡					
MAP exceeds PP	19–64	1.09–1.21	1.06–1.30	1.04	1.02–1.06
MAP and PP	65–78	1.05–1.09	1.0008–1.12	1.04	1.02–1.06

HR indicates hazard ratio; MAP, mean arterial pressure; PP, pulse pressure. All HRs and 95% CIs with $P<0.05$.
†Data were adjusted for the other BP measure: PP and MAP are adjusted for each other.
‡Data were adjusted for age, the other BP measure, and cardiovascular risk factors: smoking status, diabetes mellitus, cholesterol, and body mass index.

Discussion

This study suggests the presence of age-related shifts in the independent relative importance of SBP and DBP as risk factors for fatal and nonfatal stroke in European populations that are not influenced by the geographical location or the presence of other cardiovascular risk factors.

In participants with DBP ≥71 mm Hg, both SBP and DBP were significantly associated with stroke risk until age 62 years, after which only SBP continued to remain significant.

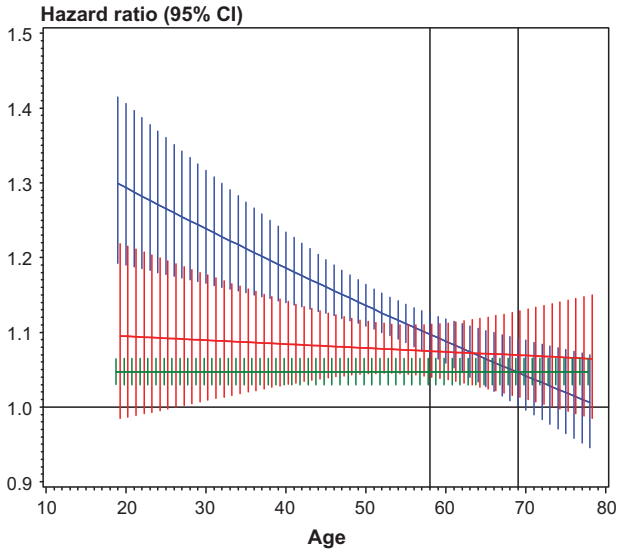

Figure 2. Hazard ratios for risks of fatal stroke by a 5-mm Hg increase in mean arterial pressure (MAP) across different ages in men (blue) and women (red), or by a 5-mm Hg increase in pulse pressure (PP) (green). MAP and PP are adjusted for each other, as well as age and sex. The vertical line at age 58 years indicates the age until which the hazard ratio (HR) for MAP is significantly higher than the HR for PP in men. The vertical line at age 69 years indicates the age after which the HR for MAP becomes nonsignificant in men.

However, already from the age of 52 years, the relative importance of SBP for stroke risk significantly exceeded that of DBP. Interestingly, the superiority of SBP occurred even earlier at the age of 47 years after multivariate adjustment. Although there was no superiority of SBP over DBP before the age of 62 years when using HRs per 1-mm Hg increase in SBP and DBP, respectively, we believe that the use of the present scale of 10-mm Hg SBP/5-mm Hg DBP is justifiable (see Methods).

The superiority of SBP in stroke risk with advancing age was consistent with the results from the Asia Pacific Cohort Studies Collaboration,[11] which showed that the strongest relationship for SBP was in older men aged 50 to 69 years and in women of all ages. In contrast, another large-scale study by the prospective collaborative study group[14] did not find an age-related shift in stroke risk and concluded that SBP was slightly more informative than DBP, irrespective of age group. However, this study did not include DBP and SBP simultaneously in the regression model, which would have allowed for a direct comparison between these 2 BP measures. Furthermore, inclusion of participants below the age of 40 years might have shown an age-related shift.

In participants with DBP <71 mm Hg, a significant inverse association between DBP and stroke risk was seen from middle age, indicating that the risk of stroke decreased for each 5-mm Hg increase in DBP. For these participants, not only SBP but also DBP had a relative importance with advancing age. However, the clinical relevance of this epidemiological observation is questionable because it concerns few subjects (0.7%), with only 6.6% of them having moderate-to-severe hypertension. Furthermore, a study by Staessen et al[26] showed that subjects with isolated systolic hypertension had a clear effect of BP reduction. Consistently, Fagard et al[27] showed that antihypertensive treatment could be intensified to prevent cardiovascular events in elderly patients with systolic hypertension, at least until DBP reached 55 mm Hg.

The age-related shifts between SBP and DBP remained consistent, regardless of the geographical location or the presence of cardiovascular risk factors, such as sex, diabetes mellitus, smoking status, high cholesterol, or high BMI. This was consistent with a previous study,[14] which showed that cardiovascular risk factors were not found to have any influence on the proportional differences in vascular mortality associated with a given absolute difference in usual BP.

The J-shaped relation of DBP to stroke risk found in the present study was consistent with some[27,28] but not all[15] previous work. The increased risk of cardiovascular disease when DBP is low is presumably attributed to insufficient diastolic pressure gradient, especially in the elderly, which cannot be compensated by blood flow auto regulation, thus leading to a reduction of vital organ perfusion. In addition, a low DBP probably reflects the parallel rise in SBP that occurs as arteries stiffen with advancing age.[29] Both problems will be more pronounced in the elderly and may explain why the increased stroke risk associated with low DBP increased with aging.

The observation that SBP was positively and DBP (DBP <71 mm Hg) was negatively related to stroke risk with advancing age has been shown previously[6,7,9,12,13] and suggests the increased importance of PP in the elderly. This was not confirmed in the present study. Although we found that PP, independent of MAP, was significantly associated with stroke risk in ages 19 to 78 years, the risk of stroke for each 5-mm Hg increase was marginal and remained the same across all ages.

Moreover, although only PP was significantly associated with stroke risk after the age of 69 years in men and 73 years in women, this superiority of PP over MAP did not remain after multivariate adjustment. In addition, the effect modification by sex on the timing of the shift in the relative importance of MAP to PP was only by 4 years, which we do not consider clinically important. Furthermore, compared with SBP, we did not find that PP had a superior role in stroke risk in the elderly. Although we did not directly compare SBP and PP in the same model, we found that the associations between SBP and stroke risk were at least twice as strong compared with those for PP (HR range, 1.14–1.15 versus 1.04–1.05, respectively). This finding was consistent with previous work,[8,11,14,15] which showed that PP was less useful in predicting long-term stroke risk than SBP.

Limitations

We eliminated participants who were on antihypertensive therapy so as not to underestimate the relationship of BP to stroke risk and distort age-related shifts between the BP measures. However, this could have produced a selection bias because the number of excluded participants was not equal in all ages/age strata. Furthermore, BP measurements were only taken at baseline and, therefore, may have underestimated the associations between BP and stroke risk. Instead, replicate measurements of BP would have taken into account longer-term fluctuations or changes within the person over time, and thus, indicated the real association between the usual level of BP and stroke risk (regression dilution bias).[30] Nonetheless, as shown by Miura et al,[8] a single BP reading is strongly predictive of future cardiovascular events. Moreover, the inability to separate hemorrhagic from ischemic stroke is a major limitation. However, it was not possible to separate these strokes because accurate stroke subtype definition was not possible in all cases or populations. Data from previous work[8,14] showed similar age-specific associations for cerebral hemorrhage and cerebral ischemia, indicating that it might be appropriate to combine these 2 types of strokes to assess the BP/stroke association. Finally, our findings may not apply to non-Europeans, individuals with cardiovascular disease, or those who are in treatment with antihypertensive medication.

Perspectives

Our findings suggest that stroke risk in apparently healthy Europeans aged 19 to 78 years should be assessed by both SBP and DBP until the age of 62 years, although with increased focus on SBP from the age of 47 years and especially after the age of 62 years. Because previous studies[26,27] clearly have demonstrated the importance of treating isolated systolic hypertension even with low DBP, our observation that DBP <71 mm Hg was significantly associated with increased stroke risk from the age of 50 years should be interpreted with caution until more research is available. From a clinical point of view, it is more important to make assessments to prevent all cardiovascular events and not just stroke. Therefore, we intend in future research to address the age-related shifts of different BPs to other cardiovascular end points and all-cause mortality.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Graphical illustration of age-related prognostic shifts from a combination of DBP and SBP to SBP
- The risk factor independence of the prognostic superiority of SBP versus DBP
- Incorporating the J-shaped relation of DBP in our analyses and showing that DBP was significantly associated to stroke risk in all ages, independent of SBP

What Is Relevant?

- A way to simplify stroke risk assessment in both European men and women aged 19–78 years

Summary

Stroke risk assessment should focus on both DBP and SBP below the age of 62 years and on SBP above this age, with increased emphasis on SBP from age 47 years.

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ONLINE SUPPLEMENTS

IMPACT OF AGE ON THE IMPORTANCE OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE FOR STROKE RISK

THE MORGAM PROJECT

Short title: Blood pressure, age and risk of stroke

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Table S1. Characteristics of the MORGAM Cohorts Included in the Analyses

Country	Population	Type of Cohorts (No. of Cohorts)	Age Range at Baseline*	Survey Period	Years of Follow-Up	Number of subjects†	Total Years of Observation‡,§	No. of Fatal and Nonfatal Strokes‡,§		
								Men	Women	Total
Denmark	DEN-GLO Glostrup	MONICA centre (3)	30, 40, 50, 60	1982-1992	9-19	6129	91 419	143	108	251
Finland	FIN-EAS Eastern Finland and Oulu	MONICA centre and MONICA procedures (4)	25-64 25-74	1982-1997	11-26	14 493	256 467	397	270	667
	FIN-WES Turku-Loimaa and Helsinki	MONICA centre and MONICA procedures (4)	25-64 25-74	1982-1997	11-26	9342	157 152	207	157	364
Sweden	SWE-NSW Northern Sweden	MONICA centre (3)	24-65 24-74	1986-1994	5-14	4412	40 639	34	32	66
United Kingdom	UNK-BEL Belfast	MONICA procedures, men only (1)	49-60	1991-1994	10	2319	22 101	46	0	46
	UNK-CAE Caerphilly	Non-MONICA , men only (1)	48-67	1984-1988	13-17	1510	19 024	86	0	86
France	FRA-LIL Lille	PRIME (MONICA procedures), men only (1)	49-64	1991-1993	10	1990	19 085	30	0	30
	FRA-STR Strasbourg	PRIME (MONICA procedures), men only (1)	49-60	1991-1993	10	2053	19 638	16	0	16

	FRA-TOU Toulouse	PRIME (MONICA procedures), men only (1)	49-60	1991-1993	10	2104	20 145	13	0	13
Italy	ITA-BRI Brianza	MONICA centre (3)	25-66	1986-1994	9-16	4066	49 847	30	17	47
	ITA-PAM Pamela	MONICA procedures (1)	25-75	1990-1993	9-12	1578	17 165	20	7	27
	ITA-ROM Area Latina	MONICA centre and MONICA procedures (3)	19-78	1983-1995	8-19	7239	104 881	85	63	148
Spain	SPA-CAT Catalonia	MONICA centre and MONICA procedures (1)	24-68	1986-1988	10-12	2330	21 992	27	19	46
Poland	POL-WAR Warsaw	MONICA centre (3)	34-65	1983-1993	2-11	4250	25 325	22	6	28
Lithuania	LTU-KAU Kaunas	MONICA centre (3)	33-65	1983-1993	6-16	3725	34 515	40	20	60
Russia	RUS-NOV Novosibirsk	MONICA centre and MONICA procedures (1)	24-65	1994-1995	4-5	1154	4664	6	1	7
All MORGAM Cohorts						68 551	902 444	1192	700	1892

[*]The age range was continuous except in Den-GLO, where the age was around 30, 40, 50 or 60 years at baseline. Three cohorts in FIN-EAS, FIN-WES, and SWE-NSW used the age range 25-64, while one cohort used the age range 25-74.

[†]Number of subjects used in the analyses.

[‡]Analysis data set

[§]In those cohorts where follow-up for non fatal events was ended prior to the follow-up for fatal events (either due to upper age limit or due to coverage of calendar period by the event register which was used for the follow-up), fatal follow-up was also considered only up to that time. The upper age limit for the follow-up for non fatal events for LTU-KAU and POL-WAR was 65 years. For RUS-NOV and SWE-NSW, the upper age limit was 74 years. For POL-WAR, the follow-up of non fatal events ended on 31.12.1994.

Table S2. The Influences of Cardiovascular Risk Factors on the Interaction Between Age and Blood Pressure on Subsequent Fatal and Non-fatal Stroke

Interactions	Model A[*] *P* Value	Model B[†] *P* Value	Model C[‡] *P* Value
age*SBP	0·007	0·02	0·13
age*SBP*sex	0·28	0·35	0·45
age*SBP*smoking	0·84	0·66	0·73
age*SBP*diabetes	0·15	0·12	0·13
age*SBP*cholesterol	0·54	0·77	0·92
age*SBP*BMI	0·29	0·48	0·54
age*SBP*country	0·67	0·79	0·61
age*SBP*country[1]	0·21	0·19	0·42
age*SBP*country[2]	0·77	0·72	0·84
age*DBP	0·0009	0·0001	0·001
age*DBP*sex	0·095	0·051	0·083
age*DBP*smoking	0·20	0·29	0·43
age*DBP*diabetes	0·88	0·89	0·29
age*DBP*cholesterol	0·87	0·73	0·72
age*DBP*BMI	0·16	0·19	0·24
age*DBP*country	0·52	0·56	0·40
age*DBP*country[1]	0·35	0·35	0·31
age*DBP*country[2]	0·81	0·75	0·73
age*PP	0·77	0·95	0·47
age*PP*sex	0·27	0·64	0·55
age*PP*smoking	0·39	0·17	0·24
age*PP*diabetes	0·096	0·058	0·56
age*PP*cholesterol	0·21	0·35	0·40
age*PP*BMI	0·12	0·23	0·21
age*PP*country	0·997	0·98	0·97
age*PP*country[1]	0·99	0·80	0·82
age*PP*country[2]	0·32	0·31	0·46
age*MAP	0·008	0·0009	0·01
age*MAP*sex	0·042	0·044	0·074
age*MAP*smoking	0·43	0·41	0·41
age*MAP*diabetes	0·55	0·58	0·63
age*MAP*cholesterol	0·90	0·88	0·96
age*MAP*BMI	0·37	0·37	0·47
age*MAP*country	0·53	0·52	0·34

age*MAP*country[1]	0·22	0·20	0·37
age*MAP*country[2]	0·99	0·98	0·89

P<0·05 indicates a significant interaction term in the Cox regression model.
[*]Adjusted for age.
[†]Adjusted for age and the other blood pressure (BP) measure: systolic BP (SBP) and diastolic BP (DBP) are adjusted for each other; and pulse pressure (PP) and mean arterial pressure. (MAP) are adjusted for each other.
[‡]Adjusted for age, the other BP measure, and cardiovascular risk factors: sex, smoking status, diabetes, cholesterol and body mass index.
Country[1] high risk countries (Denmark, Finland, United Kingdom, Poland, Lithuania, Russia, and Sweden) versus low risk countries (Italy, Spain, and France).
Country[2] Western European countries (Denmark, Finland, United Kingdom, Sweden, Italy, Spain, and France) versus Eastern European countries (Poland, Lithuania, and Russia).

Appendix

Sites and key personnel of contributing MORGAM Centres.

Denmark
Glostrup, Capital Region, Research Centre for prevention and Health, Glostrup University Hospital: T. Jørgensen (principal investigator), C. Agger, A. Borglykke, M. Olsen;

Finland
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PRIME/Toulouse, Department of Epidemiology, Faculty of Medicine, Toulouse-Purpan, Toulouse: J. Ferrières (Principal Investigator), J-B. Ruidavets and V. Bongard;
PRIME/Lille, Department of Epidemiology and Public Health, Pasteur Institute of Lille: P. Amouyel (principal investigator), M. Montaye, J. Dallongeville;

Italy
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Pamela, Dipartimento de Medicina, Prevenzione e Biotecnologie Sanitarie, Università degli Studi Milano-Bicocca, Monza: R. Sega, G. Mancia, R. Facchetti;
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Russian Federation
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Spain
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Sweden
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United Kingdom
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Caerphilly, Queen´s University Belfast, Belfast, Northern Ireland: J. Yarnell (principal investigator);
PRIME/Belfast, Queen´s University Belfast, Belfast, Norhern Ireland: F. Kee (principal investigator);
MORGAM Coordinating Centre, Queen's University Belfast, Belfast, Northern Ireland: A. Evans, S. Cashman;

MORGAM Management Group:
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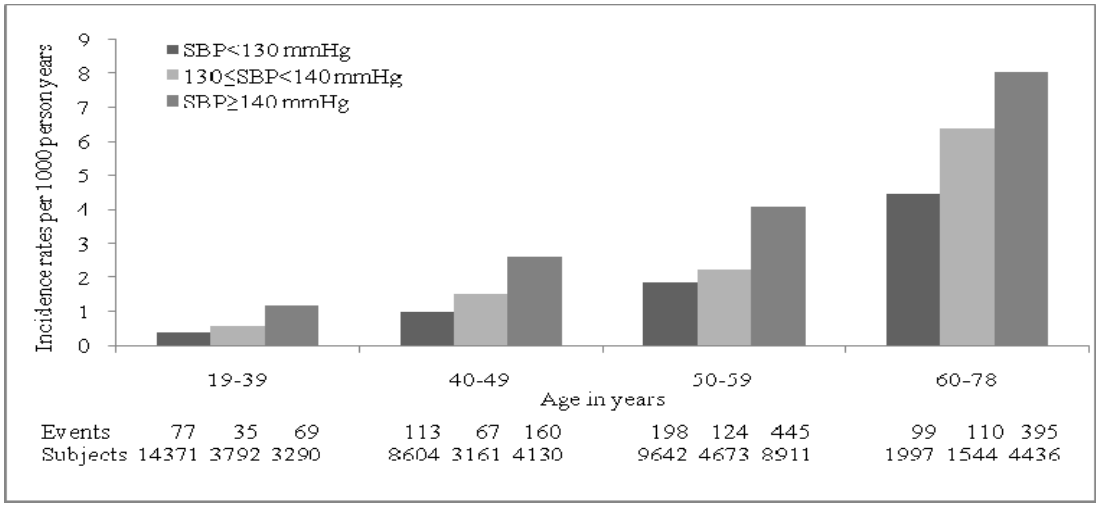

Figure S1a: Incidence rates per 1000 person years for fatal and non-fatal stroke in different systolic blood pressure (SBP) and age categories at baseline.

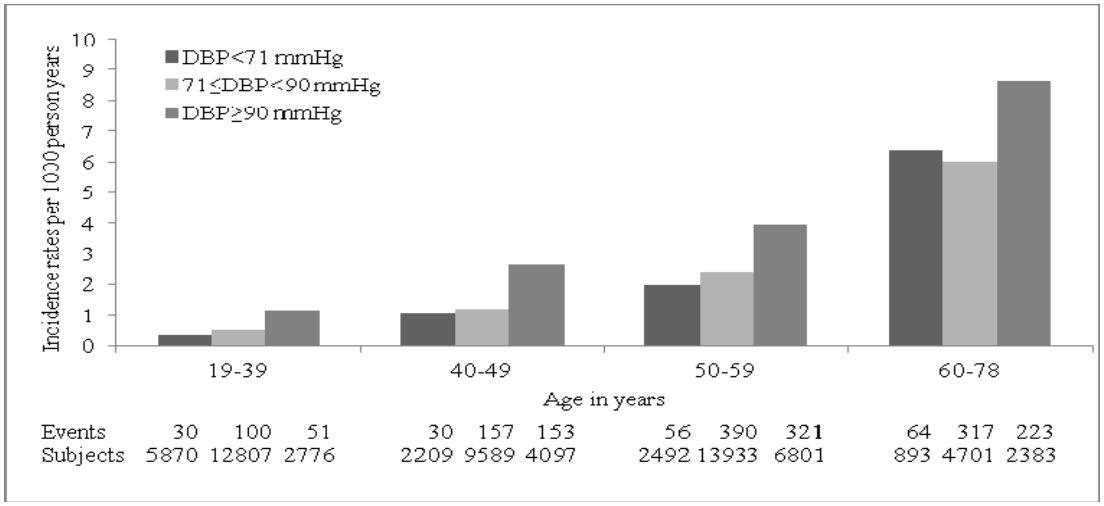

Figure S1b: Incidence rates per 1000 person years for fatal and non-fatal stroke in different diastolic blood pressure (DBP) and age categories at baseline.