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See Editorial Commentary, pp 377–378

Abstract—To analyze sex-specific relative and absolute risks associated with blood pressure (BP), we performed conventional and 24-hour ambulatory BP measurements in 9357 subjects (mean age, 52.8 years; 47% women) recruited from 11 populations. We computed standardized multivariable-adjusted hazard ratios for associations between outcome and systolic BP. During a course of 11.2 years (median), 1245 participants died, 472 of cardiovascular causes. The number of fatal combined with nonfatal events was 1080, 525, and 458 for cardiovascular and cardiac events and for stroke, respectively. In women and men alike, systolic BP predicted outcome, irrespective of the type of BP measurement. Women compared with men were at lower risk (hazard ratios for death and all cardiovascular events=0.66 and 0.62, respectively; $P<0.001$). However, the relation of all cardiovascular events with 24-hour BP ($P=0.020$) and the relations of total mortality ($P=0.023$) and all cardiovascular ($P=0.0013$), cerebrovascular ($P=0.045$), and cardiac ($P=0.034$) events with nighttime BP were steeper in women than in men. Consequently, per a 1-SD decrease, the proportion of potentially preventable events was higher in women than in men for all cardiovascular events (35.9% vs 24.2%) in relation to 24-hour systolic BP (1-SD, 13.4 mm Hg) and for all-cause mortality (23.1% vs 12.3%) and cardiovascular (35.1% vs 19.4%), cerebrovascular (38.3% vs 25.9%), and cardiac (31.0% vs 16.0%) events in relation to systolic nighttime BP (1-SD, 14.1 mm Hg). In conclusion, although absolute risks associated with systolic BP were lower in women than men, our results reveal a vast and largely unused potential for cardiovascular prevention by BP-lowering treatment in women. **(*Hypertension*. 2011;57:397-405.) • Online Data Supplement**

Key Words: blood pressure ■ epidemiology ■ morbidity ■ risk factors ■ women

In the United States, cardiovascular disease kills ≈500 000 women each year, ≈1 every minute.[1] Whereas 1 in 30 American women die of breast cancer, ≈1 in 3 dies from largely preventable cardiovascular disorders.[1,2] Ninety percent of women have 1 or more risk factors for developing heart disease, but blood pressure (BP) remains the major reversible cardiovascular risk factor.

Conventional BP measurement by auscultation of the Korotkoff sounds is fraught with potential sources of error. Compared with conventional sphygmomanometry, ambula-

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From the Centro de Nefrología and Departamento de Fisiopatología (J.B.), Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay; the Studies Coordinating Centre (J.B., L.T., T.R., T.K., J.A.S.), Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium; Research Center for Prevention and Health and Department of Clinical Physiology (T.W.H.), Nuclear Medicine and PET, Copenhagen University Hospital, Faculty of Health Sciences, Rigshospitalet, Copenhagen, Denmark; Center for Epidemiological Studies and Clinical Trials (Y.L., J.W.) and Center for Vascular Evaluation (Y.L.), Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; the Tohoku University Graduate School of Pharmaceutical Science and Medicine (M.K., T.O., Y.I.), Sendai, Japan; the Shiga University School of Medical Science (T.O.), Otsu, Japan; the Section of Geriatrics (K.B.B., L.L.), Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; the Copenhagen University Hospital (J.J., C.T.P.), Copenhagen, Denmark; Cambridge University Hospitals (E.D.), Addenbrook's Hospital, Cambridge, United Kingdom; First Department of Cardiology and Hypertension (K.S.S., K.K.J), Jagiellonian University Medical College, Kraków, Poland; Department of Clinical and Experimental Medicine (V.T., E.C.), University of Padova, Padova, Italy; Institute of Internal Medicine (T.K., S.M., Y.N.), Novosibirsk, Russian Federation; Laboratorio de Neurociencias (G.M.), Universidad del Zulia, Maracaibo, Venezuela; the Asociación Española Primera de Socorros Mutuos (E.S.), Montevideo, Uruguay; Aarhus University and Division of Cardiology (H.I.), Holbak Hospital, Holbak, Denmark; the Conway Institute of Biomolecular and Biomedical Research (E.O.), University College Dublin, Dublin, Ireland; Department of Epidemiology (T.R., J.A.S.), Maastricht University, Maastricht, The Netherlands.

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Laboratory of Hypertension, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Block D, Level 00, Box 7001, B-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be or jan.staessen@epid.unimaas.nl

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tory BP recordings have higher reproducibility and therefore provide a better estimate of a subject's usual BP and cardiovascular prognosis.[3–5] To our knowledge, no previous population study assessed the absolute and relative risks associated with BP on both conventional and ambulatory measurement in women compared with men and assessed the number of cardiovascular complications potentially preventable by lowering the ambulatory BP in women and men.

Methods

Study Population

As described in detail elsewhere,[6] we constructed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO). Studies were eligible for inclusion if they involved a random population sample, if baseline information on the ambulatory BP and cardiovascular risk factors was available, and if the subsequent follow-up included both fatal and nonfatal outcomes.

At the time of writing this report, the IDACO database included prospective studies from 11 centers (11 785 subjects). In line with previous reports, we excluded 252 participants (2.1%) because they were <18 years old at the moment of enrolment and 219 (1.9%) because their conventional BP had not been measured. We also excluded 493 (4.2%) and 1464 (12.4%) participants because their ambulatory recording included <30 readings during the whole day or <5 readings during nighttime, respectively. Thus, the number of subjects statistically analyzed totaled 9357. The participants were 2142 residents from Copenhagen, Denmark[7]; 1124 subjects from Noorderkempen, Belgium[8]; 1097 older men from Uppsala, Sweden[9]; 244 subjects from Novosibirsk, the Russian Federation[10,11]; 1312 inhabitants from Ohasama, Japan[12]; 349 villagers from the JingNing County, China[13]; 1372 subjects from Montevideo, Uruguay[14]; 165 subjects from Pilsen, the Czech Republic[11]; 934 subjects from Dublin, Ireland[15]; 310 subjects from Padova, Italy[11]; and 308 subjects from Kraków, Poland.[11]

BP Measurement

A detailed description of the methods used for conventional and ambulatory BP measurement is provided in the Expanded Methods section available online only at http://hyper.ahajournals.org. Hypertension was a conventional BP of at least 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs.

Other Measurements

In all cohorts, we administered a questionnaire to obtain information on each subject's medical history and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods.

Ascertainment of Events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in previous publications.[6,9,12–14] Fatal and nonfatal strokes did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac events comprised coronary end points and fatal and nonfatal heart failure. The composite cardiovascular end point included all aforementioned end points plus cardiovascular mortality. In all outcome analyses, we only considered the first event within each category. The International Classification of Disease code numbers used to differentiate these events are available in Table I of the online-only Data Supplement available at http://hyper.ahajournals.org.

Table 1. Baseline Characteristics of Participants by Sex

Characteristics	Women (n=4397)	Men (n=4960)
No. with characteristic (%)		
Hypertension	1527 (34.7)	2339 (47.2)
Antihypertensive drug treatment	848 (19.3)	955 (19.3)
Diabetes mellitus	243 (5.5)	371 (7.5)
Current smokers	945 (21.5)	1731 (34.9)
Current drinkers	1578 (35.9)	3040 (61.3)
Previous cardiovascular disease	232 (5.3)	496 (10.0)
Age, y	50.3±15.2	55.0±15.9
Body mass index, kg/m^2	24.8±4.5	25.8±3.9
Blood pressure, mm Hg		
Conventional systolic	125.6±20.1	134.5±19.8
24-hour systolic	119.9±13.4	127.0±13.8
Daytime systolic	126.0±14.3	133.7±14.8
Nighttime systolic	108.7±14.1	115.2±15.1
Conventional diastolic	77.1±11.4	81.7±11.3
24-hour diastolic	71.6±8.1	75.6±8.3
Daytime diastolic	76.8±8.8	80.7±9.0
Nighttime diastolic	62.3±8.6	66.4±9.2
Serum cholesterol, mmol/L	5.63±1.18	5.64±1.16

All between-sex differences were significant ($P<0.0001$) with the exception of serum cholesterol ($P=0.59$) and antihypertensive treatment ($P=0.059$). Hypertension was a conventional BP of at least 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs. Diabetes mellitus was use of antidiabetic drugs, a fasting blood glucose concentration ≥7.0 mmol/L, a random blood glucose concentration of ≥11.1 mmol/L, a self-reported diagnosis, or diabetes documented in practice or hospital records. Plus/minus values are mean±SD.

Statistical Methods

For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute, Cary, NC). For comparison of means and proportions, we applied the large-sample z test and the χ^2 statistic, respectively. Statistical significance was a probability value of 0.05 or less on 2-sided tests.

Because in middle-aged and older subjects systolic BP is a stronger risk factor than is diastolic BP,[16–18] we limited our analyses to systolic BP. We first plotted incidence rates by quintiles of the distributions of systolic BP while standardizing for cohort and age by the direct method. In dichotomous analyses, we considered 50 years of age as a cut-off limit because cardiovascular risk increases in postmenopausal women and because 50 years is close to the median age at menopause.[19] We used Kaplan-Meier survival function estimates, plotted according to current recommendations,[20] and the log-rank test to estimate and compare incidence rates by sex. We applied Cox regression to compute standardized hazard ratios (HRs), which express the risk for a 1-SD change in the independent variables. We checked the proportional-hazards assumption by the Kolmogorov-type supremum test and by testing the interaction terms between follow-up duration and the risk variable of interest. The HRs were adjusted for cohort, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. In analyses stratified by cohort, we pooled the participants recruited in the framework of the European Project on Genes in Hypertension (Kraków, Novosibirsk, Padova, and Pilsen).[11]

Results

Baseline Characteristics

The study population consisted of 6324 Europeans (67.6%), 1661 Asians (17.8%), and 1372 South Americans (14.7%).

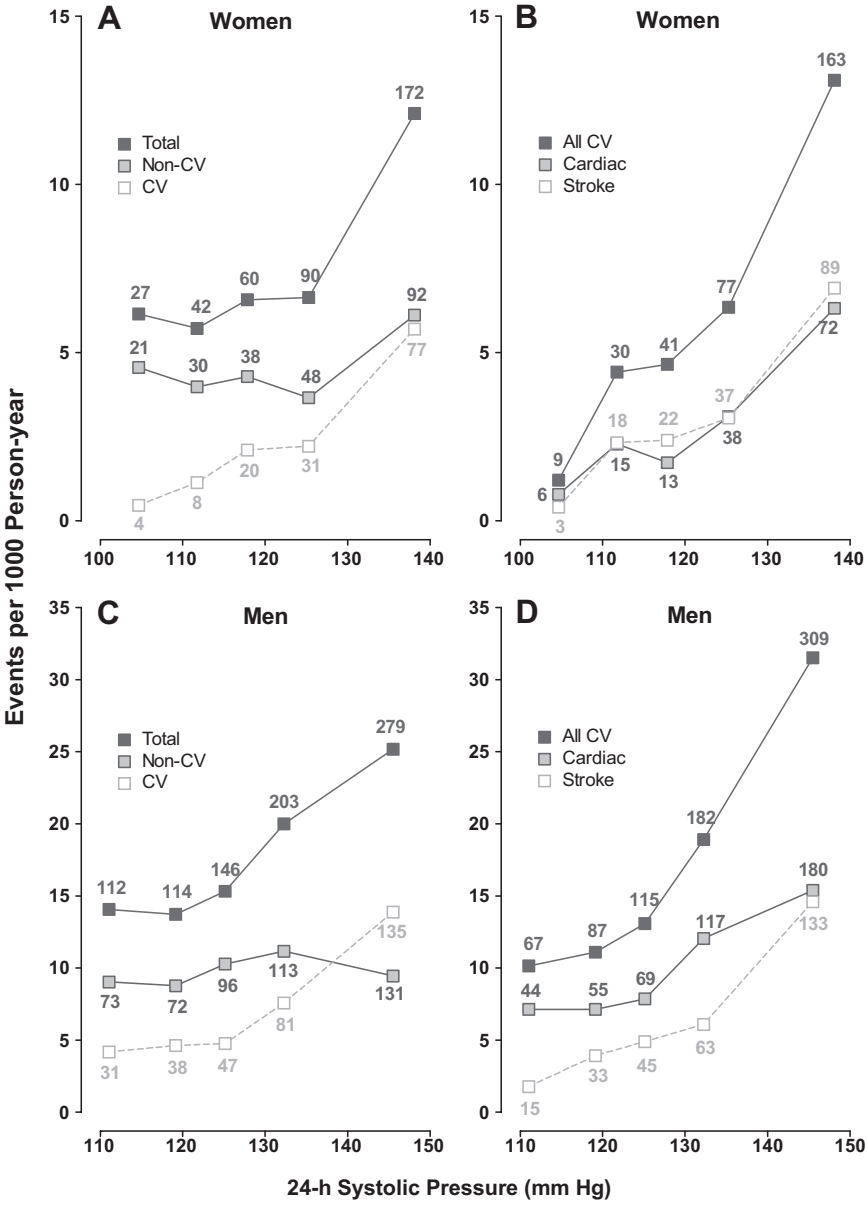

Figure 1. Incidence of total mortality (A, C) and all cardiovascular events (B, D) in relation to the 24-hour systolic BP in 4397 women (A, B) and 4960 men (C, D). Incidence rates were standardized for cohort and age by the direct method. Mortality rates are plotted separately for total, noncardiovascular (non-CV), and cardiovascular (CV) mortality. Cardiovascular events refer to the composite of all fatal plus nonfatal cardiovascular events. The number of end points contributing to the rates is presented.

The 9357 participants included 4397 women (47.0%) and 3866 patients with hypertension on conventional BP measurement (41.3%). Mean (±SD) age was 52.8±15.7 years. The conventional BP averaged 130.4±20.4 mm Hg systolic and 79.5±11.6 mm Hg diastolic. For the 24-hour BP, these values were 123.7±14.1 and 73.7±8.4 mm Hg, respectively. At enrolment, 2676 participants (28.6%) were current smokers and 4618 (49.4%) reported intake of alcohol.

Table 1 shows the baseline characteristics of the participants by sex. With the exception of serum total cholesterol and antihypertensive treatment, women and men differed in their baseline characteristics. Cardiovascular risk factors were less frequent among women than in men. Among 1527 hypertensive women, 679 (44.5%) were untreated, 462 (30.3%) were treated but uncontrolled, and 386 (25.3%) were treated and controlled. Among 2339 hypertensive men, 1384 (59.2%) were untreated, 662 (28.3%) were treated but uncontrolled, and 239 (19.2%) were treated and controlled.

Table II (online only) lists the baseline characteristics of women and men by age class, with median year at menopause (50 years) as the cut-off. Comparing younger and older subjects revealed that all baseline characteristics in both sexes differed by age group. The only exception was the proportion of nondippers, defined as a night-to-day systolic pressure ratio of <0.90. Nondipping was significantly more frequent ($P<0.01$) among older women (31.3% vs 25.9%) and older men (29.7% vs 25.7%) than in younger subjects. In continuous analyses of the night-to-day ratio, however, the age differences disappeared in women (0.87 vs 0.86; $P=0.25$) as well as in men (0.86 vs 0.86; $P=0.47$).

Incidence of Events

In the overall study population, median follow-up was 11.2 years (5th to 95th percentile interval, 2.5 to 17.6 years). During 100 396 person-years of follow-up, 1245 participants died (12.4 per 1000 person-years), and 1080 experienced a

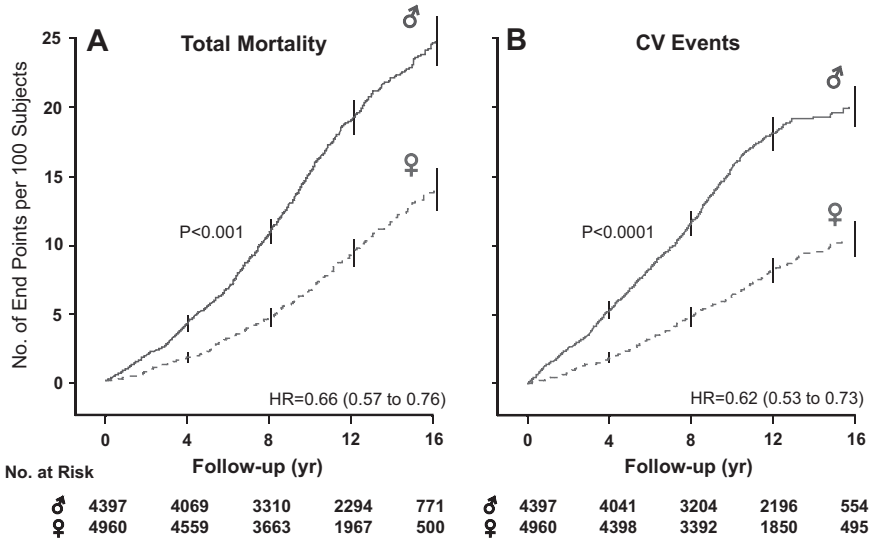

Figure 2. Kaplan-Meier survival function estimates for total mortality (A) and the composite of all fatal plus nonfatal cardiovascular events (B) in 4397 women and 4960 men. Follow-up time spans the 5th to 95th percentile interval. Numbers refer to women and men at risk at the beginning of each 4-year interval. Vertical lines represent the SE of the survival function estimates. HR refers to the hazard ratio, which expresses the risk of women compared with men, with adjustment applied for cohort, age, body mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, presence of diabetes mellitus, and antihypertensive drug treatment at baseline.

fatal or nonfatal cardiovascular complication (10.8 per 1000 person-years). The cause of death was cardiovascular in 472 participants, noncardiovascular in 714, renal failure in 17, and unknown in 42. Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 88 and 370, respectively, and cardiac events consisted of 171 fatal and 438 nonfatal events.

Sex-Specific Incidence of Events in Unadjusted Analyses

Exploratory analyses, in which we plotted the incidence of events standardized for cohort and age, showed association between the incidence of total mortality and cardiovascular events and BP on conventional and ambulatory measurement in women as well as men (Figure 1). The cohort- and age-standardized rates were significantly higher in the top than in the bottom quintile ($P \leq 0.0023$) except for noncardiovascular mortality, which was not associated with BP in women ($P=0.31$) or men ($P=0.77$). The Kaplan-Meier survival function estimates showed a significantly lower incidence of total, cardiovascular, and noncardiovascular mortality ($P \leq 0.001$) and of all cardiovascular, cerebrovascular, cardiac, and coronary events ($P \leq 0.0001$) in women than in men (Figure 2).

Sex-Specific Incidence of Events in Multivariable-Adjusted Analyses

Relative Risk

Table 2 shows the multivariable-adjusted standardized HRs for mortality by sex. In women and men, systolic BP on conventional, 24-hour, and nighttime measurement was a significant predictor of total and cardiovascular mortality.

Table 2. Multivariable-Adjusted Standardized HRs for Mortality in Relation to Systolic BP by Sex

Cause of Death	No.	Conventional	24-Hour	Daytime	Nighttime
Total					
Women	391	1.12 (1.00–1.25)*	1.25 (1.12–1.38)‡	1.17 (1.05–1.30)†	1.30 (1.17–1.44)‡
Men	854	1.14 (1.06–1.23)‡	1.12 (1.04–1.19)‡	1.06 (0.99–1.13)	1.14 (1.07–1.20)‡
P		0.89	0.097	0.19	0.023
Noncardiovascular					
Women	229	1.02 (0.88–1.19)	1.13 (0.98–1.30)	1.05 (0.91–1.21)	1.22 (1.06–1.39)†
Men	485	1.01 (0.91–1.12)	0.98 (0.90–1.08)	0.95 (0.86–1.04)	1.04 (0.96–1.13)
P		0.082	0.054	0.15	0.025
Cardiovascular					
Women	140	1.36 (1.15–1.61)‡	1.52 (1.28–1.80)‡	1.45 (1.23–1.71)‡	1.50 (1.27–1.76)‡
Men	332	1.33 (1.19–1.49)‡	1.31 (1.18–1.44)‡	1.23 (1.11–1.37)‡	1.26 (1.16–1.37)‡
P		0.75	0.24	0.25	0.13

P indicates the significance of the sex difference in the HRs. No. refers to the number of deaths. The numbers at risk were 4397 women and 4960 men. The HRs (95% CIs) express the risk associated with a 1-SD increase in systolic BP. In women, the SDs of systolic BP were 20.1, 13.4, 14.3, and 14.1 mm Hg for the conventional, 24-hour, daytime, and nighttime BPs; in men, the corresponding SDs were 19.8, 13.8, 14.8, and 15.1 mm Hg, respectively. All models were adjusted for cohort, age, body mass index, smoking and drinking, serum total cholesterol, a history of cardiovascular disease, the presence of diabetes mellitus, and antihypertensive drug treatment at baseline. There were 42 deaths of unknown cause and 17 fatal renal deaths.

Significance of the HRs: *$P<0.05$, †$P<0.01$, and ‡$P<0.001$.

Table 3. Multivariable-Adjusted Standardized HRs for Cardiovascular Events in Relation to Systolic BP by Sex

Event	No.	Conventional	24-Hour	Daytime	Nighttime
All cardiovascular					
Women	320	1.26 (1.12–1.42)‡	1.56 (1.39–1.74)‡	1.45 (1.29–1.61)‡	1.54 (1.38–1.71)‡
Men	760	1.28 (1.19–1.38)‡	1.32 (1.23–1.40)‡	1.27 (1.19–1.36)‡	1.24 (1.17–1.31)‡
P		0.95	0.020	0.11	0.0013
Stroke					
Women	169	1.44 (1.24–1.67)‡	1.67 (1.44–1.94)‡	1.56 (1.34–1.81)‡	1.62 (1.40–1.88)‡
Men	289	1.42 (1.26–1.60)‡	1.51 (1.36–1.67)‡	1.45 (1.30–1.61)‡	1.35 (1.24–1.47)‡
P		0.98	0.30	0.52	0.045
Cardiac					
Women	144	1.05 (0.87–1.26)	1.47 (1.24–1.74)‡	1.35 (1.14–1.61)‡	1.45 (1.24–1.70)‡
Men	465	1.24 (1.13–1.37)‡	1.24 (1.14–1.35)‡	1.22 (1.11–1.33)‡	1.19 (1.11–1.29)‡
P		0.41	0.10	0.35	0.034
Coronary					
Women	86	1.15 (0.91–1.46)	1.51 (1.22–1.88)‡	1.46 (1.17–1.81)‡	1.44 (1.17–1.77)‡
Men	357	1.15 (1.02–1.28)*	1.18 (1.07–1.30)‡	1.19 (1.07–1.31)‡	1.12 (1.03–1.23)†
P		0.86	0.12	0.21	0.090

P indicates the significance of the sex difference in the HRs. No. refers to the number of fatal and nonfatal events. See the footnote to Table 2 for details.

Significance of the HRs: *$P<0.05$, †$P<0.01$, and ‡$P<0.001$.

Daytime systolic BP predicted total mortality in women and cardiovascular mortality in both sexes. The HRs relating total mortality to the 24-hour systolic BP or to the nighttime systolic BP were, respectively, slightly ($P=0.097$) or significantly ($P=0.023$) larger in women than in men (Table 2), whereas those associated with the conventional ($P\leq0.89$) and daytime ($P\leq0.19$) BPs were similar in both sexes. Except for nighttime BP in women, systolic BP did not predict noncardiovascular mortality and was significantly ($P<0.001$) higher in subjects dying of cardiovascular causes than in those dying of noncardiovascular diseases. For the 24-hour systolic BP, these levels were 132.9±14.4 versus 127.4±15.8 mm Hg ($P=0.0008$) in women and 135.7±16.3 versus 129.8±14.2 mm Hg ($P<0.0001$) in men.

Table 3 shows the multivariable-adjusted standardized HRs for all and cause-specific cardiovascular events by sex. In women and men, the 24-hour, daytime, and nighttime systolic BPs were significant predictors of all cardiovascular events, stroke, and cardiac and coronary complications. The conventional systolic BP predicted all cardiovascular events and stroke in women and men and cardiac and coronary events, but only in men. The HRs expressing the risk of the composite cardiovascular end point in relation to the 24-hour systolic BP ($P=0.020$) and the risk of all cardiovascular ($P=0.0013$), cerebrovascular ($P=0.045$), and cardiac ($P=0.034$) events in relation to the nighttime systolic BP were higher in women than in men (Table 3).

The absolute 10-year risk of death, a composite cardiovascular end point, a fatal or nonfatal stroke, or a fatal or nonfatal cardiac event in relation to the 24-hour and nighttime systolic BPs appear in Figure 3 and online-only Figure I. The continuous-risk functions were fitted by Cox regression with adjustment for cohort, age, body mass index, smoking and drinking, serum total cholesterol, a history of cardiovascular disease, the presence of diabetes mellitus, and antihypertensive drug treatment at baseline. To illustrate the fit of the continuous risk function, Figures 3 and I also include the HRs expressing the risk by quintiles of the BP distributions. Absolute risk was lower in women than in men, but the increase in risk with BP was slightly or significantly steeper in women than men.

Number of Prevented Events

Estimates of the number of end points potentially prevented by a 1-SD decrease in systolic BP on 24-hour or nighttime measurement appear in Figure 4. Because women experienced fewer events than did men, we expressed the number of preventable events as a percentage of the total number in either sex. The proportion of potentially preventable events was higher in women than in men for the composite cardiovascular end point (35.9% vs 24.2%; $P=0.018$) in relation to the 24-hour systolic BP, for all-cause mortality (23.1% vs 12.3%; $P=0.021$), and for all cardiovascular (35.1% vs 19.4%; $P=0.001$), cerebrovascular (38.3% vs 25.9%; $P=0.043$), and cardiac (31.0% vs 16.0%; $P=0.027$) events in relation to systolic BP at night.

Sensitivity Analyses

In sensitivity analyses, we excluded 1 cohort at a time (Tables III and IV available online only at http://hyper.ahajournals.org), and we stratified all participants according to baseline characteristics (online-only Tables V and VI). With 1 cohort excluded, all HRs expressing the risk associated with systolic BP were larger in women than in men, although because of the lower number of subjects in the analysis, not all HRs remained significant. The analyses stratified according to baseline

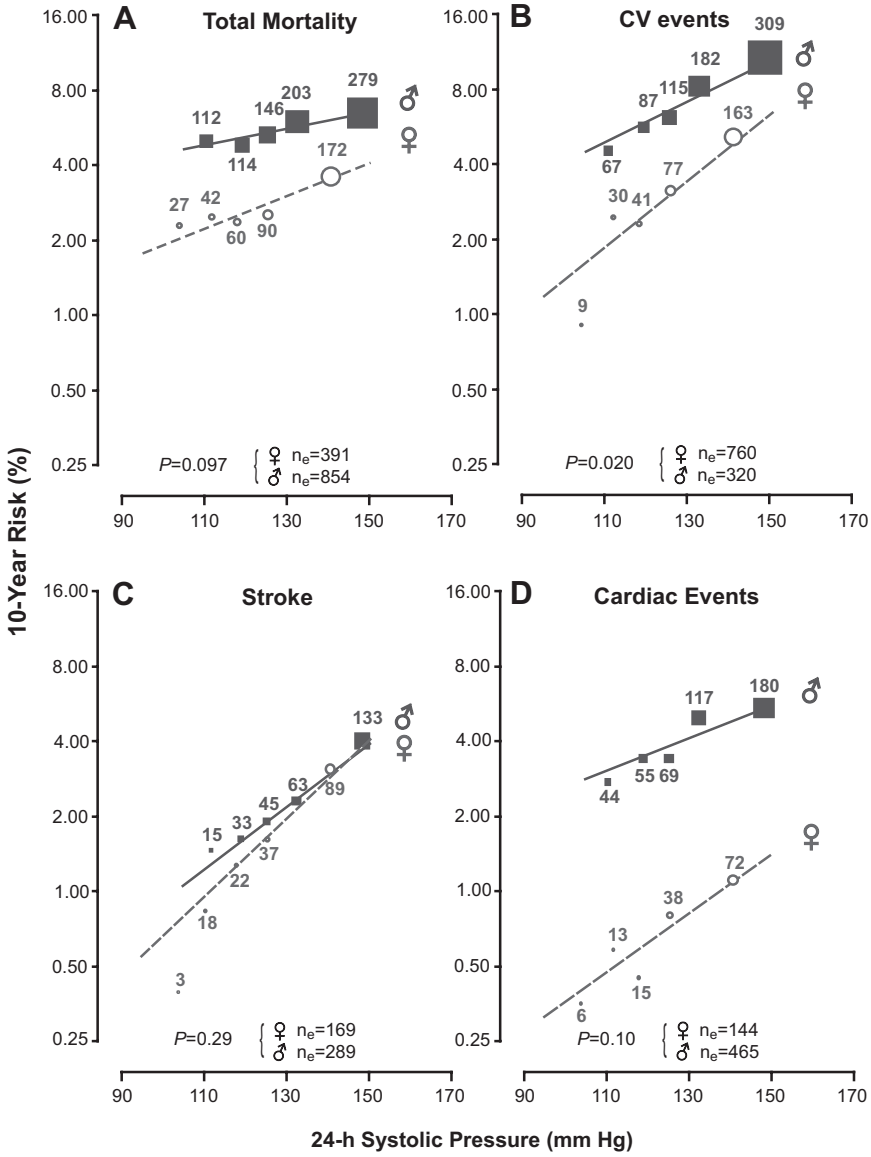

Figure 3. Absolute 10-year risk of death (A), a composite cardiovascular (CV) end point (B), a fatal or nonfatal stroke (C), or a fatal or nonfatal cardiac event (D) in relation to the 24-hour systolic BP. The continuous risk functions cover the 5th to 95th percentile interval of the 24-hour systolic BP and were fitted by Cox regression with adjustment for cohort, age, body mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, presence of diabetes mellitus, and antihypertensive drug treatment at baseline. Circles (women) and squares (men) represent the multivariable-adjusted HRs in quintiles of the distribution of the 24-hour systolic BP and have a size proportional to the inverse of the variance of the HR. The number of events in each quintile is given next to each circle or square; n_e is the total number of events by disease category and sex. The probability values for interaction were derived from multivariable-adjusted Cox models as given in Tables 2 and 3.

characteristics, in general, showed slightly or significantly higher HRs in women than in men except for total mortality below age 50, in subjects with cardiovascular disease at baseline, and except for the composite cardiovascular end point in South American and Asian participants.

Discussion

The key finding of our current meta-analysis of individual data is that although absolute risk was lower in women than in men, the increase in risk with the 24-hour and nighttime BPs was steeper in women than in men. The proportion of events potentially preventable by BP lowering was therefore higher in women than in men for the composite cardiovascular end point in relation to the 24-hour systolic BP, for all fatal plus nonfatal end points, and for fatal plus nonfatal cerebrovascular and cardiac events in relation to systolic BP at night.

We did a PubMed search using the key words "women" AND "blood pressure" AND "risk." Of the 49 "hits," we selected 5 articles,[21–25] all based on population studies. Already in 1969,[21] the Framingham investigators noticed that after 14 years of follow-up, the incidence of coronary heart disease was lower in women than in men (5.9% vs 14.2%). Subsequent population studies confirmed that women are at lower risk of angina pectoris,[21] myocardial infarction,[21–24] stroke,[24] and cardiovascular complications,[25] but few studies reported detailed comparisons of relative and absolute risk between the sexes. None of the 5 reviewed studies[21–25] addressed the association between risk and BP on ambulatory measurement.

In the Reykjavik Study,[23] absolute risk was lower in women than in men: 7.3% versus 19.1%. In multivariable-adjusted analyses, the HRs relating the risk of myocardial infarction to office systolic BP were 1.013 (95% CI, 1.009 to 1.017) in women and 1.010 (95% CI, 1.007 to 1.013) in men; for a 20-mm Hg increase in systolic BP, as in the current study, these estimates would translate into values of 1.29 and 1.22, respectively. Because the Icelandic investigators did not report significance for the sex interaction term in the multivariable analyses,[23] we used a normal approximation to

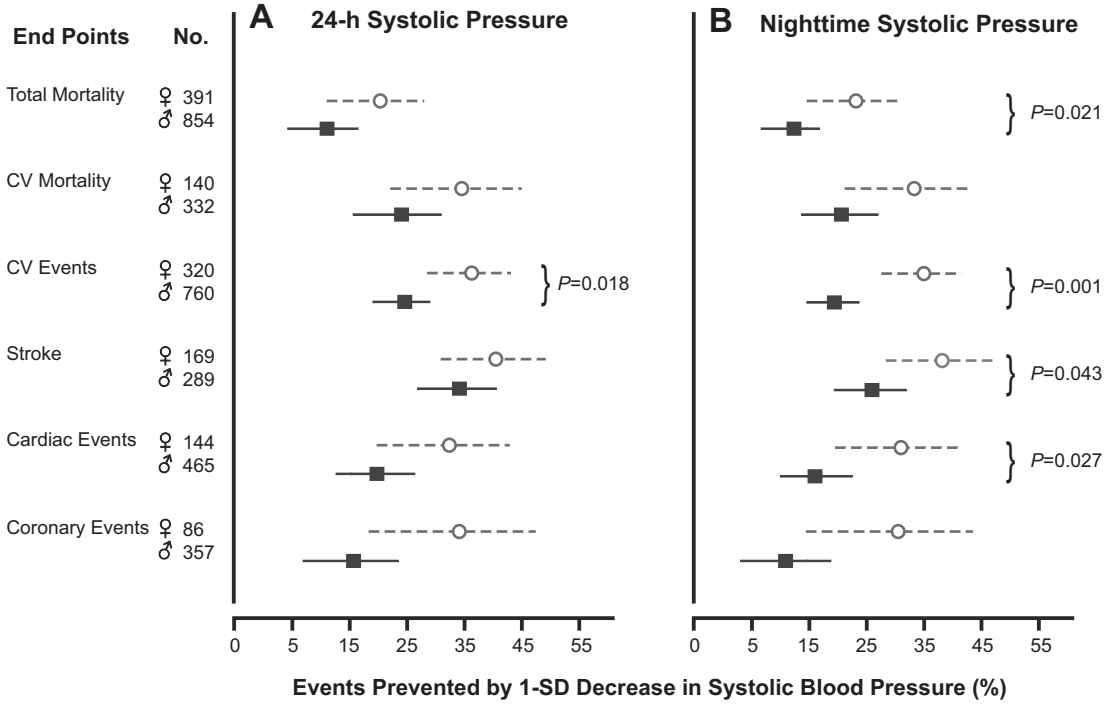

Figure 4. Changes in the incidence of mortality and cardiovascular (CV) events that would be associated with a 1-SD decrease in the 24-hour systolic BP (A) or in the nighttime BP (B) in women (circles) and men (squares). Estimates were derived from the multivariable-adjusted Cox models presented in Tables 2 and 3 and the observed number of each end point. Probability values indicate significant sex differences.

estimate the sex difference in the adjusted HRs. The z statistic was 1.18 ($P=0.24$). The Rotterdam Study included 6004 women and men age 55 years or more.[22] The authors did not state the number of women and men included in their analyses but reported that there was no evidence for a sex difference in the association of systolic or diastolic BP with the risk of myocardial infarction (P for interaction ≥ 0.44). The Japanese Arteriosclerosis Longitudinal Study Group[24] performed a meta-analysis involving 27 163 women and 21 061 men. The standardized HRs relating stroke and myocardial infarction to systolic BP were 1.46 (95% CI, 1.35 to 1.58) and 1.25 (95% CI, 0.99 to 1.58) in women and 1.51 (95% CI, 1.41 to 1.63) and 1.23 (95% CI, 1.06 to 1.44) in men. With the normal approximation to compute the significance of the sex difference, the z values were 0.62 ($P=0.54$) for stroke and -0.11 ($P=0.91$) for myocardial infarction. In Singaporean women and men with the metabolic syndrome,[25] the incidence of cardiovascular complications was 3.7 events per 1000 person-years in 108 women (4 events) and 15.9 events per 1000 person-years in 136 men (19 events). However, the HRs describing the associations of cardiovascular complications with BP were not reported.

In keeping with our previous findings,[4,26] nighttime compared with daytime BP was a stronger predictor of outcome. Why relative risk increased more with nighttime BP in women than in men remains to be elucidated. In the International Database of the Ambulatory Blood Pressure,[27] after adjustment for age and other significant covariables, the nocturnal fall in systolic BP was smaller in 3590 women than in 3730 men (15.1 vs 16.7 mm Hg) and women had a greater night-to-day ratio of systolic BP (0.883 vs 0.875). With similar adjustments applied in the current database, we confirmed the curvilinear association of the nocturnal BP fall and the night-to-day ratio with age (online-only Figure II), but we did not find a significant difference between the sexes in the nocturnal fall in systolic BP (women vs men, 17.9 vs 18.0 mm Hg; $P=0.75$) or in the systolic night-to-day BP ratio (0.862 vs 0.866, $P=0.12$; Table II). These previous[27] and current observations exclude the hypothesis that sex-specific diurnal patterns in BP might explain the higher HRs associated with the nighttime systolic BP in women compared with men. We did not have information on the menopausal state of women at baseline or follow-up. However, the evidence currently available suggests that the cardiovascular effects usually attributed to menopause are a consequence of aging rather than of a change in the hormonal environment.[28]

The present study must be interpreted within the context of its potential limitations. First, BP was measured under differing conditions in the cohorts. However, in all but 1 cohort,[9] BP was measured in the sitting position, and in all cohorts, the average of the first 2 measurements was used for analysis. In addition, all of the centers implemented rigorous quality-control programs for BP measurement. Second, BP was only measured at baseline. It needs to be confirmed that that our current results hold true when BP collected during follow-up would be accounted for. The IDACO consortium is currently collecting follow-up measurements of the conventional and ambulatory BPs. Unfortunately, these data are not yet available. However, use of BP-lowering drugs after enrolment can only have weakened the prognostic significance of the BP at baseline. On the plus side, our study is the first to address sex-specific differences in the association between outcome

and BP based on ambulatory monitoring. Other strong points of our study are the large sample, including populations from Europe, Asia, and South America, and the large number of events.

Perspectives

In line with our current findings, most epidemiologic studies[21–25] are concordant in showing that women experience cardiovascular complications at an older age and at a lower rate than do men. Although in Europe[29] and elsewhere in the world women have a higher life expectancy than men do, men consistently report a higher proportion of healthy life years, when compared with women. In our current study population, 74.7% of hypertensive women and 87.4% of hypertensive men were either untreated or uncontrolled at baseline. Against this background, what our current study highlights is the large proportion of events potentially preventable in hypertensive women by BP-lowering treatment. Although absolute risk is lower in women than in men, the proportion of preventable cardiovascular complication is from 30% to 100% higher in women than in men. The lower absolute risk in women should therefore not be considered an excuse for therapeutic laxity. Women and their healthcare providers should be aware of this and request a wider use of ambulatory BP measurement to diagnose and take control of BP. This approach will help women live a longer life with higher quality.

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Disclosures

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EXPANDED METHODS and DATA SUPPLEMENT
Ambulatory Blood Pressure Monitoring in 9357 Subjects from 11 Populations Highlights Missed Opportunities for Cardiovascular Prevention in Women

Short title: Sex-Specific Risks Associated with Blood Pressure

José Boggia, Lutgarde Thijs, Tine W. Hansen, Yan Li, Masahiro Kikuya, Kristina Björklund-Bodegård, Tom Richart, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypek, Valérie Tikhonoff, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Gladys Maestre, Edgardo Sandoya, Kalina Kawecka-Jaszcz, Yutaka Imai, Jiguang Wang, Hans Ibsen, Eoin O'Brien, Jan A. Staessen, on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators

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Correspondence to:
Jan A. Staessen, MD, PhD, FESC, FAHA,
Studies Coordinating Centre,
Laboratory of Hypertension,
University of Leuven,
Campus Sint Rafaël,
Kapucijnenvoer 35,
Block d, Level 00, Box 7001,
B-3000 Leuven, Belgium

Telephone: +32-16-34-7104 (office)
+32-15-41-1747 (home)
+32-47-632-4928 (mobile)
Facsimile: +32-16-34-7106 (office)
+32-15-41-4542 (home)
email: jan.staessen@med.kuleuven.be
jan.staessen@epid.unimaas.nl

Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay (J.B.); the Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Belgium (Y.L., L.T., T.R., T.K., J.A.S.); Research Center for Prevention and Health and Department of Clinical Physiology, Nuclear Medicine and PET, Copenhagen University Hospital, Faculty of Health Sciences, Rigshospitalet, Copenhagen, Denmark (T.W.H.); Center for Epidemiological Studies and Clinical Trials (Y.L., J.W.); and Center for Vascular Evaluation (Y.L.), Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; the Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai, Japan (M.K., T.O., Y.I.); the Shiga University School of Medical Science, Otsu, Japan (T.O.); the Section of Geriatrics, Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden (K.B.B., L.L.); the Copenhagen University Hospital, Copenhagen, Denmark (J.J., C.T.P.); Cambridge University Hospitals, Addenbrook's Hospital, Cambridge, United Kingdom (E.D.); First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland (K.S.S., K.K.J); Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy (V.T., E.C.); Institute of Internal Medicine, Novosibirsk, Russian Federation (T.K., S.M., Y.N.); Laboratorio de Neurociencias, Universidad del Zulia, Maracaibo, Venezuela (G.M.); the Asociación Española Primera de Socorros Mutuos, Montevideo, Uruguay (E.S.); Aarhus University and Division of Cardiology, Holbak Hospital, Holbak, Denmark (H.I.); the Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland (E.O.); and Department of Epidemiology, Maastricht University, Maastricht, The Netherlands (T.R., J.A.S.). The IDACO investigators are listed in the data supplement available online at http://hyper.ahajournals.org.

Correspondence to Dr Jan A. Staessen, Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Block D, Box 7001, BE-3000 Leuven, Belgium.
E-mail: jan.staessen@med.kuleuven.be

Expanded Methods

Study Population

As described in detail elsewhere,[1] we constructed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO). Studies were eligible for inclusion, if they involved a random population sample, if baseline information on the ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included both fatal and nonfatal outcomes.

At the time of writing this report, the IDACO database included prospective studies from 11 centers (11,785 subjects). In line with previous reports, we excluded 252 participants (2.1%), because they were less than 18 years old at the moment of enrolment and 219 (1.9%) because their conventional blood pressure had not been measured. We also excluded 493 (4.2%) and 1464 (12.4%) participants, because their ambulatory recording included less than 30 readings over the whole day or less than 5 readings during nighttime, respectively. Thus, the number of subjects statistically analyzed totaled 9357. The participants were 2142 residents from Copenhagen, Denmark;[2] 1124 subjects from Noorderkempen, Belgium;[3] 1097 older men from Uppsala, Sweden;[4] 244 subjects from Novosibirsk, the Russian Federation;[5,6] 1312 inhabitants from Ohasama, Japan;[7] 349 villagers from the JingNing county, China;[8] 1372 subjects from Montevideo, Uruguay;[9] 165 subjects from Pilsen, the Czech Republic;[6] 934 subjects from Dublin, Ireland;[10] 310 subjects from Padova, Italy;[6] and 308 subjects from Kraków, Poland.[6]

Blood Pressure Measurement

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,[2-6,8,10] with validated auscultatory[7] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[9] (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with participants in the sitting[2,3,5-10] or supine[4] position. Conventional blood pressure was the average of two consecutive readings obtained either at the person's home[3,5,6,8,9] or at an examination center.[2,4,7,10] Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs.[11]

We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day,[7,10] or at intervals ranging from 15[2] to 30[4] minutes during daytime and from 30[2] to 60[4] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[4] or an oscillometric technique (Spacelabs 90202 and 90207, Takeda TM-2421, and ABPM-630) in the other cohorts.[2,3,5-10]

The same SAS macro processed all ambulatory recordings, which generally stayed unedited. The Ohasama recordings were edited sparsely according to previously published criteria.[12] While accounting for the daily pattern of activities of the participants, we defined daytime as the interval from 10 AM to 8 PM in Europeans[2-6,10] and South Americans,[9] and from 8 AM to 6 PM in Asians.[7,8] The corresponding nighttime intervals ranged from midnight to 6 AM [2-6,9,10] and from 10 PM to 4 AM,[7,8] respectively. These fixed intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and nighttime blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels. Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings. In dichotomous analyses, we considered 50 years of age as a cut-off limit, because cardiovascular risk increases in postmenopausal women and because 50 years is close to the median age at menopause.[13]

Other Measurements

In all cohorts, we administered a questionnaire to obtain information on each subject's medical history, and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/L[2-7,9,10] a random blood glucose concentration of at least 11.1 mmol/L,[3,7,8] a self-reported diagnosis,[3,8,9] or diabetes documented in practice or hospital records.[9]

Ascertainment of Events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in previous publications.[6,9,12-14] Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac events comprised coronary endpoints and fatal and nonfatal heart failure. The composite cardiovascular endpoint included all aforementioned endpoints plus cardiovascular mortality. In all outcome analyses, we only considered the first event within each category. The International Classification of Disease code numbers used to differentiate these events are available in Table S1.

Statistical Methods

For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute, Cary, NC). For comparison of means and proportions, we applied the large-sample z-test and the χ^2-statistic, respectively. Statistical significance was a *P*-value of 0.05 or less on two-sided tests.

Because in middle-aged and older subjects, systolic blood pressure is a stronger risk factor than diastolic blood pressure,[16-18] we limited our analyses to systolic blood pressure. We first plotted incidence rates by fifths of the distributions of systolic blood pressure, while standardizing for cohort and age by the direct method. In dichotomous analyses, we considered 50 years of age as a cut-off limit, because cardiovascular risk increases in postmenopausal women and because 50 years is close to the median age at menopause.[19] We used Kaplan-Meier survival function estimates, plotted according to current recommendations,[20] and the log-rank test to estimate and compare incidence rates by sex. We applied Cox regression to compute standardized hazard ratios, which express the risk for a 1-SD change in the independent variables. We checked the proportional hazards assumption by the Kolmogorov-type supremum test, and by testing the interaction terms between follow-up duration and the risk variable of interest. The hazard ratios were adjusted for cohort, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. In analyses stratified by cohort, we pooled the participants recruited in the framework of the European Project on Genes in Hypertension (Kraków, Novosibirsk, Padova, and Pilsen).[11]

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Legend to Figures

Figure S1. Absolute 10-year risk of death (A), a composite cardiovascular (CV) endpoint (B), a fatal or nonfatal stroke (C), or a fatal or nonfatal cardiac event (D) in relation to the nighttime systolic blood pressure.
The continuous risk functions cover the 5th to 95th percentile interval of the nighttime systolic blood pressure and were fitted by Cox regression with adjustment for cohort, age, body mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, presence of diabetes mellitus, and antihypertensive drug treatment at baseline. Circles (women) and squares (men) represent the multivariable-adjusted hazard rates by fifths of the distribution of the nighttime systolic blood pressure and have a size proportional to the inverse of the variance of the hazard ratio. The number of events in each quintile is given next to each circle or square; ne is the total number of events by disease category and sex. The P-values for interaction were derived from multivariable-adjusted Cox models as given in Tables 2 and 3.

Figure S2. Night-to-day ratio of systolic blood pressure and nocturnal fall in systolic blood pressure by sex and age group. For each sex and age group, the number of subjects contributing to the mean is given. BP indicates blood pressure.

Table S1. International Classification of Diseases (ICD) Codes Applied in each Cohort

Cohort	Stroke	Myocardial infarction	Angina pectoris	Heart failure
Copenhagen	*ICD8* 430-434 and 436, *ICD10* I60-I64	*ICD8* 410, *ICD10* I21-I22	*ICD8* 411-414, *ICD10* I20 and I23-I25	*ICD8* 427.0, 427.1, 428.0, 429.0, 519.1 and 782.4, *ICD10* I50 and J81
Noorderkempen	*ICD8* 430-434, 436 and 438	*ICD8* 410	*ICD8* 413	*ICD8* 427.0, 427.1, 428.0, 429.0, 519.1 and 782.4
Uppsala	*ICD9* 430-434 and 436, *ICD10* I60-I64	*ICD9* 410, *ICD10* I21	*ICD9* 413 and 411.1, *ICD10* I20	*ICD9* 429, *ICD10* I50
Dublin	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413, 411.1 and 414	*ICD9* 428
Novosibirsk	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413 and 411.1	*ICD9* 428
Pilsen	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413 and 411.1	*ICD9* 428
Padova	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413 and 411.1	*ICD9* 428
Kraków	*ICD9* 430-438	*ICD9* 410	*ICD9* 413	*ICD9* 428.0-428.4
Montevideo	*ICD10* I60-I64	*ICD10* I21-I22	*ICD10* I20	*ICD10* I50 and J81
Ohasama	*ICD10* I60-I64	……	……	……
JingNing	*ICD9* 430-431 and 434	*ICD9* 410	*ICD9* 413	*ICD9* 428, 427.0 and 427.1

…… Not assessed, because of the low incidence in the Ohasama cohort.

Table S2: Baseline Characteristics by Sex and Age Group

Characteristics	Women			Men		
	<50 yr (n=1953)	≥50 yr (n=2444)	All (n= 4397)	<50 yr (n=1722)	≥50 yr (n=3238)	All (n= 4960)
Number with characteristic (%)						
Hypertension	257 (13.2)	1270 (52.0)	1527 (34.7)	367 (21.3)	1972 (60.9)	2339 (47.2)
Antihypertensive treatment	103 (5.27)	745 (30.5)	848 (19.3)	67 (3.9)	888 (27.4)	955 (19.3)
Diabetes mellitus	51 (2.6)	192 (7.9)	243 (5.5)	44 (2.6)	327 (10.1)	371 (7.5)
Current smokers	526 (26.6)	419 (17.1)	945 (21.5)	675 (39.2)	1056 (32.6)	1731 (34.9)
Current drinkers	738 (37.8)	840 (34.4)	1578 (35.9)	990 (57.5)	2050 (63.3)	3040 (61.3)
History of CV disease	47 (2.4)	185 (7.6)	232 (5.3)	53 (3.1)	443 (13.7)	496 (10.0)
Mean values±SD						
Age, y	36.1±8.5	61.7±6.2	50.3±15.2	36.3±8.4	65.0±7.9	55.0±15.9
Body mass index, kg/m2	23.9±4.3	25.6±4.5	24.8±4.5	25.34±3.9	26.1±3.8	25.8±3.9
Blood pressure, mm Hg						
Conventional systolic	115.6±14.7	133.6±20.2	125.6±20.1	124.3±14.7	140.0±20.0	134.5±19.8
24-hour systolic	113.7±10.1	124.8±13.6	119.9±13.4	121.4±10.3	130.0±14.5	127.0±13.8
Daytime systolic	119.9±11.1	130.9±14.6	126.0±14.3	128.0±11.5	136.7±15.5	133.7±14.8
Nighttime systolic	103.3±10.3	113.1±15.1	108.7±14.1	110.2±10.9	117.9±16.3	115.2±15.1
Conventional diastolic	74.3±10.2	79.4±11.8	77.1±11.4	78.6±10.9	83.3±11.2	81.7±11.3
24-hour diastolic	70.1±7.5	72.9±8.3	71.6±8.1	73.8±7.9	76.5±8.3	75.6±8.3
Daytime diastolic	75.7±8.1	87.7±9.2	76.8±8.8	79.7±8.8	81.2±9.1	80.7±9.0
Nighttime diastolic	60.2±8.0	63.9±8.8	62.3±8.6	63.7±8.5	67.9±9.3	66.4±9.2
Night-to-day ratio	0.86±0.06	0.87±0.09	0.86±0.08	0.86±0.07	0.86±0.09	0.86±0.08
Non-dippers	505 (25.9)	765 (31.3)	1270 (28.9)	442 (25.7)	961 (29.7)	1403 (28.3)
Serum cholesterol, mmol/L	5.17±1.03	5.94±1.18	5.63±1.18	5.42±1.21	5.74±1.12	5.64±1.16

CV indicates cardiovascular. Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs. Diabetes mellitus was use of antidiabetic drugs, a fasting blood glucose concentration of ≥7.0 mmol/L, a random blood glucose concentration of ≥11.1 mmol/L, a self-reported diagnosis, or diabetes documented in practice or hospital records. We considered 50 years of age as a cut-off limit, because it is the median age at menopause.[19] All baseline characteristics differed by age group in both sexes. The only exception was the proportion of nondippers, defined as night-to-day systolic pressure ratio of ≥0.90. Nondipping was significantly more frequent (P<0.01) among older women (31.3% *vs* 25.9%) and men (29.7% *vs* 25.7%) than in younger subjects. In continuous analyses of the night-to-day ratio, however, the age differences disappeared in women (0.87 *vs* 0.86; P=0.25) as well as in men (0.86 *vs* 0.86; P=0.47).

Table S3. Multivariable-Adjusted Standardized Hazard Ratios for All-Cause Mortality in Relation to the 24-h and Nighttime Systolic Blood Pressures by Sex with One Cohort Excluded at a Time

Excluded cohort	Deaths (n)	At risk (n)	24-h	Nighttime
None				
Women	391	4397	1.25 (1.12–1.38)‡	1.30 (1.18–1.44)‡
Men	854	4960	1.12 (1.04–1.19)†	1.14 (1.07–1.20)‡
P	1245	9357	0.097	0.023
Copenhagen (n=2142)				
Women	258	3371	1.16 (1.02–1.33)*	1.27 (1.11–1.45)‡
Men	616	3844	1.11 (1.03–1.20)†	1.13 (1.06–1.21)‡
P	874	7215	0.25	0.039
Noorderkempen (n=1124)				
Women	340	3828	1.24 (1.11–1.38)‡	1.30 (1.17–1.44)‡
Men	768	4405	1.11 (1.04–1.19)†	1.12 (1.05–1.19)‡
P	1108	8233	0.15	0.033
EPOGH (n=1027)				
Women	380	3830	1.26 (1.13–1.40)‡	1.31 (1.18–1.44)‡
Men	842	4500	1.11 (1.04–1.19)†	1.14 (1.07–1.20)‡
P	1222	8330	0.068	0.019
Uppsala (n=1097)				
Women	391	4397	1.25 (1.12–1.38)‡	1.30 (1.18–1.44)‡
Men	556	3863	1.14 (1.04–1.24)†	1.18 (1.08–1.28)‡
P	947	8260	0.16	0.096
Dublin (n=934)				
Women	372	3935	1.25 (1.12–1.39)‡	1.31 (1.18–1.45)‡
Men	837	4488	1.12 (1.05–1.19)†	1.14 (1.07–1.21)‡
P	1209	8423	0.076	0.013
Montevideo (n=1372)				
Women	344	3678	1.26 (1.12–1.41)‡	1.31 (1.18–1.46)‡
Men	811	4307	1.12 (1.05–1.20)‡	1.14 (1.08–1.21)‡
P	1155	7985	0.17	0.054
Ohasama (n=1312)				
Women	265	3534	1.31 (1.16–1.49)‡	1.32 (1.18–1.49)‡
Men	704	4511	1.12 (1.04–1.20)†	1.14 (1.07–1.21)‡
P	969	8045	0.074	0.052
JingNing (349)				
Women	387	4206	1.23 (1.10–1.37)‡	1.28 (1.16–1.42)‡
Men	844	4802	1.11 (1.04–1.19)†	1.13 (1.07–1.20)‡
P	1231	9005	0.13	0.031

P indicates the significance of the sex difference in the hazard ratios. The hazard ratios (95% confidence interval) express the risk associated with a 1-SD increase in systolic blood pressure. EPOGH includes the cohorts recruited in Kraków (n=308), Novosibirsk (n=244), Padova (n=310) and Pilsen (n=165). All models were adjusted for cohort, age, body mass index, smoking and drinking status, serum total cholesterol, history of cardiovascular disease, presence of diabetes mellitus, and antihypertensive drug treatment at baseline. Significance of the hazard ratios: * $P<0.05$, † $P<0.01$, and ‡ $P<0.001$.

Table S4. Multivariable-Adjusted Standardized Hazard Ratios for the Composite Cardiovascular Endpoint in Relation to the 24-h and Nighttime Systolic Blood Pressures by Sex with One Cohort Excluded at a Time

Excluded cohort	Events (n)	At risk (n)	24-h	Nighttime
None				
Women	320	4397	1.56 (1.39–1.74)‡	1.54 (1.38–1.71)‡
Men	760	4960	1.32 (1.23–1.40)‡	1.24 (1.17–1.31)‡
P	1080	9357	0.020	0.0013
Copenhagen (n=2142)				
Women	229	3371	1.52 (1.33–1.74)‡	1.49 (1.31–1.70)‡
Men	566	3844	1.31 (1.22–1.41)‡	1.22 (1.15–1.30)‡
P	795	7215	0.034	0.0066
Noorderkempen (n=1124)				
Women	278	3828	1.54 (1.37–1.73)‡	1.53 (1.37–1.71)‡
Men	703	4405	1.31 (1.22–1.40)‡	1.24 (1.17–1.31)‡
P	981	8233	0.022	0.0010
EPOGH (n=1027)				
Women	310	3830	1.54 (1.37–1.72)‡	1.52 (1.36–1.69)‡
Men	738	4500	1.32 (1.24–1.41)‡	1.25 (1.18–1.32)‡
P	1048	8330	0.037	0.0035
Uppsala (n=1097)				
Women	320	4397	1.56 (1.39–1.74)‡	1.54 (1.38–1.71)‡
Men	446	3863	1.40 (1.28–1.54)‡	1.37 (1.25–1.50)‡
P	766	8260	0.22	0.12
Dublin (n=934)				
Women	310	3935	1.56 (1.39–1.75)‡	1.55 (1.39–1.72)‡
Men	751	4488	1.31 (1.23–1.41)‡	1.24 (1.17–1.31)‡
P	1061	8423	0.019	0.0009
Montevideo (n=1372)				
Women	270	3678	1.57 (1.39–1.78)‡	1.57 (1.40–1.77)‡
Men	695	4307	1.31 (1.23–1.41)‡	1.24 (1.17–1.32)‡
P	965	7985	0.067	0.0049
Ohasama (n=1312)				
Women	206	3534	1.63 (1.43–1.87)‡	1.31 (1.14–1.52)‡
Men	666	4511	1.29 (1.21–1.38)‡	1.22 (1.15–1.30)‡
P	872	8045	0.005	0.0005
JingNing (349)				
Women	317	4206	1.54 (1.38–1.72)‡	1.52 (1.36–1.69)‡
Men	755	4802	1.31 (1.23–1.40)‡	1.24 (1.17–1.31)‡
P	1072	9008	0.025	0.0019

Significance of the hazard ratios: * $P<0.05$, † $P<0.01$, and ‡ $P<0.001$. For further explanation, see Table S3.

Table S5. Multivariable-Adjusted Standardized Hazard Ratios for All-Cause Mortality in Relation to the 24-h Systolic and Nighttime Systolic Blood Pressures by Sex and Baseline Characteristics

Strata	Deaths (n)	At risk (n)	24-h	Nighttime
Normotension				
Women	147	2870	1.29 (1.04–1.59)*	1.30 (1.07–1.60)†
Men	266	2621	1.02 (0.84–1.23) 0.86	1.12 (0.96–1.31) 0.150
P	413	5491	0.21	0.34
Hypertension (HT)				
Women	244	1527	1.26 (1.10–1.44)‡	1.33 (1.18–1.51)‡
Men	588	2339	1.10 (1.02–1.19)*	1.12 (1.05–1.20)†
P	832	3866	0.073	0.011
Untreated HT				
Women	78	679	1.43 (1.13-1.82)†	1.37 (1.10-1.72)†
Men	277	1384	1.09 (0.99-1.22) 0.16	1.11 (1.01-1.23)*
P	355	2063	0.016	0.09
Controlled HT				
Women	70	386	1.20 (0.90–1.59) 0.22	1.35 (1.04–1.76)†
Men	88	293	1.22 (0.93–1.60) 0.44	1.18 (0.91–1.52) 0.22
P	158	679	0.87	0.48
Uncontrolled HT				
Women	96	462	1.24 (0.97–1.57)0.08	1.40 (1.15–1.71)‡
Men	223	662	1.10 (0.96–1.25)0.18	1.11 (0.99–1.24)‡
P	319	1124	0.21	0.024
<50 years				
Women	22	1953	1.08 (0.60–1.95)	1.15 (0.64–2.05)
Men	38	1722	1.08 (0.68–1.69)	1.32 (0.89–1.96)
P	60	3675	0.64	0.50
≥50 years				
Women	369	2444	1.25 (1.12–1.39)‡	1.31 (1.18–1.44)‡
Men	816	3238	1.11 (1.04–1.19)†	1.12 (1.06–1.20)‡
P	1185	5682	0.09	0.020
No previous CV disease				
Women	345	4165	1.30 (1.16–1.45)‡	1.34 (1.21–1.50)‡
Men	674	4464	1.12 (1.04–1.21)†	1.14 (1.07–1.22) ‡
P	1019	8629	0.047	0.012
Previous CV disease				
Women	46	232	1.04 (0.75–1.44) 0.806	1.10 (0.82–1.49) 0.514
Men	180	496	1.10 (0.95–1.27) 0.223	1.11 (0.98–1.27) 0.115
P	226	728	0.66	0.92
European				
Women	214	2624	1.32 (1.15–1.52)‡	1.31 (1.15–1.50)‡
Men	651	3700	1.12 (1.04–1.21)†	1.13 (1.06–1.21)‡
P	865	6324	0.15	0.14
South American				
Women	47	719	1.13 (0.85–1.50) 0.39	1.16 (0.87–1.56) 0.297
Men	43	653	1.02 (0.76–1.37) 0.90	1.06 (0.80–1.40) 0.89
P	90	1372	0.37	0.38
Asian				
Women	130	1054	1.17 (0.97–1.43) 0.103	1.35 (1.13–1.63)†
Men	160	607	1.14 (0.96–1.35) 0.13	1.18 (1.01–1.38)*
P	290	1661	0.55	0.19

Significance of the hazard ratios: * $P<0.05$, † $P<0.01$, and ‡ $P<0.001$. For further explanation, see Table S3.

Table S6. Multivariable-Adjusted Standardized Hazard Ratios for the Composite Cardiovascular Endpoint in Relation to the 24-h and Nighttime Systolic Blood Pressures by Sex and Baseline Characteristics

Strata	Events (n)	At risk (n)	24-h	Nighttime
Normotension				
Women	93	2870	1.53 (1.19–1.97)‡	1.49 (1.17–1.91)†
Men	184	2621	1.44 (1.16–1.80)†	1.28 (1.07–1.53)†
P	277	5491	0.89	0.53
Hypertension (HT)				
Women	227	1527	1.52 (1.33–1.74)‡	1.52 (1.35–1.73)‡
Men	576	2339	1.26 (1.17–1.35)‡	1.20 (1.13–1.28)‡
P	803	3866	0.022	0.0021
Untreated HT				
Women	70	679	1.85 (1.44-2.37)‡	1.70 (1.34-2.15)‡
Men	262	1384	1.31 (1.18-1.46)‡	1.23 (1.12-1.35)‡
P	332	2063	0.0049	0.018
Controlled HT				
Women	59	386	1.34 (1.00–1.80)*	1.45 (1.10–1.92)†
Men	90	293	1.52 (1.16–1.98)†	1.21 (0.95–1.56)0.12
P	149	679	0.73	0.20
Uncontrolled HT				
Women	98	462	1.34 (1.07–1.66)†	1.39 (1.16–1.68)‡
Men	224	662	1.22 (1.07–1.38)†	1.21 (1.09–1.34)‡
P	322	1124	0.66	0.28
<50 years				
Women	22	1953	2.20 (1.40–3.53)†	2.12 (1.29–3.50)†
Men	28	1722	1.45 (0.93–2.27)	1.31 (0.84–2.04)
P	50	3675	0.61	0.49
≥50 years				
Women	298	2444	1.52 (1.36–1.71)‡	1.51 (1.36–1.69)‡
Men	732	3238	1.31 (1.23–1.40)‡	1.24 (1.18–1.33)‡
P	1030	5682	0.092	0.001
No previous CV disease				
Women	272	4165	1.61 (1.43–1.82)‡	1.57 (1.40–1.76)‡
Men	585	4464	1.35 (1.26–1.45)‡	1.28 (1.20–1.36)‡
P	857	8629	0.028	0.0046
Previous CV disease				
Women	48	232	1.31 (0.99–1.81)*	1.33 (1.02–1.75)*
Men	175	496	1.20 (1.05–1.39)†	1.15 (1.01–1.30)*
P	223	728	0.47	0.17
European				
Women	153	2624	1.68 (1.43–1.98)‡	1.65 (1.42–1.92)‡
Men	596	3700	1.28 (1.20–1.38)‡	1.22 (1.14–1.29)‡
P	749	6324	0.030	0.005
South American				
Women	50	719	1.36 (1.03–1.80)*	1.25 (0.94–1.65)
Men	65	653	1.46 (1.15–1.85)†	1.37 (1.09–1.72)†
P	115	1372	0.43	0.44
Asian				
Women	117	1054	1.43 (1.18–1.73)‡	1.46 (1.21–1.76)‡
Men	99	607	1.64 (1.33–2.02)‡	1.56 (1.29–1.89)‡

P	216	1661	0.48	0.78

Significance of the hazard ratios: * $P<0.05$, † $P<0.01$, and ‡ $P<0.001$. For further explanation, see Table S3.

Figure S1

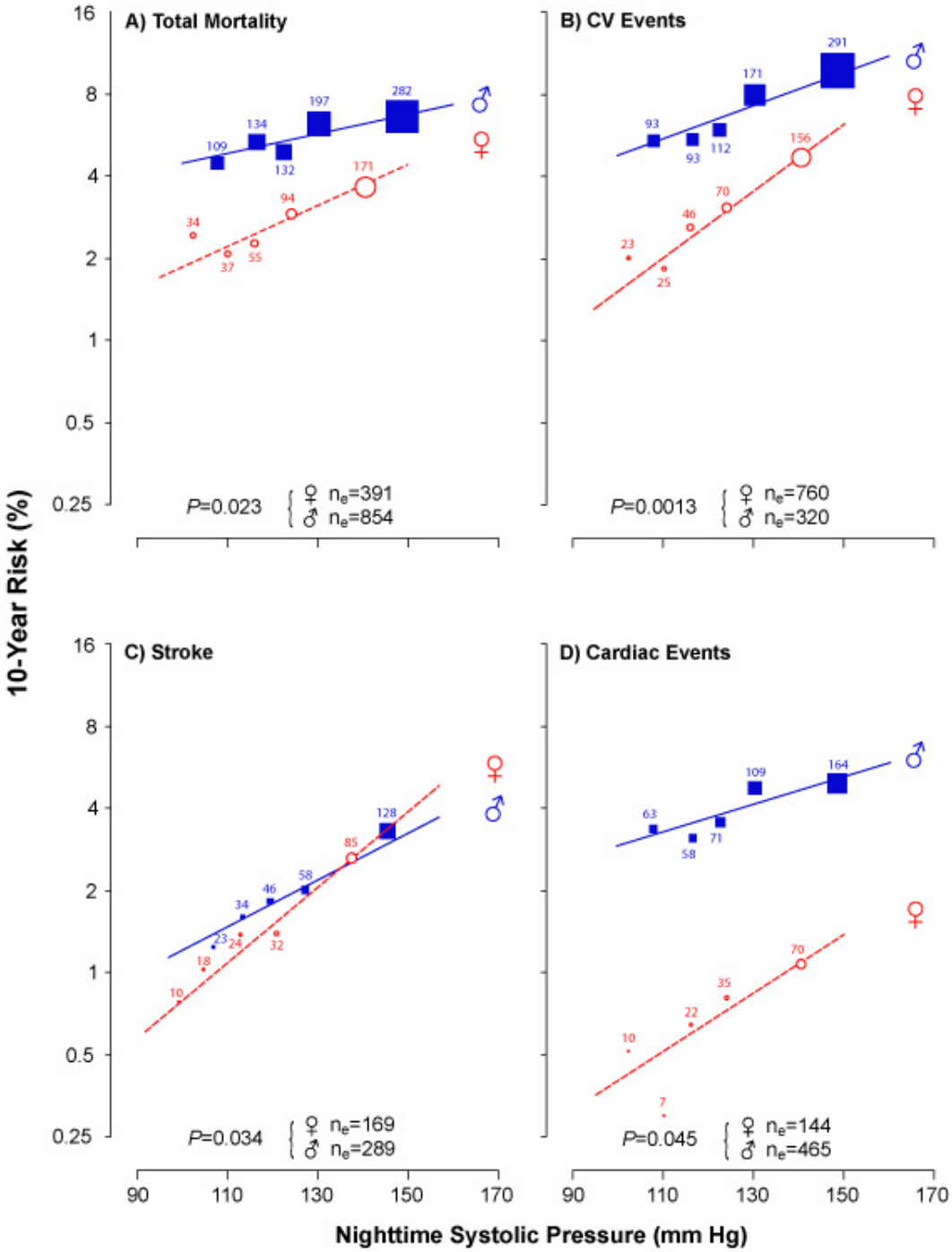

Figure S2