Moderate morning rise in blood pressure has lowest risk of stroke but only in females.

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Short Title: Risk associated with morning surge

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Abstract

Background: The morning period which is recognized as the highest risk for cardiovascular events is associated with a surge in blood pressure. However, it is unclear what aspect of this rise is important.

Aim: To determine whether the rate of rise (RoR), the magnitude (day night difference) or the product (BPPower) is associated with increased cardiovascular risk.

Methods: We developed a logistic equation method to fit individual 24-hour patterns of blood pressure to determine RoR, amplitude and BPPower using the ambulatory recordings from the Ohasama study 564 males and 971 females (16.6 years follow up).

Results: Males had a higher risk of cardiovascular events than females (24%, 16%, P<0.001). Age and night BP were strong linear risk predictors. In males sorting risk by quintiles of BPPower (adjusted for age, night BP smoking status) revealed no clear linear or nonlinear pattern. However, in females BPPower had a U-shaped relationship with the lowest risk being the 2-3rd quintile for all cardiovascular events ($P_{quadratic}$=0.01) including cardiovascular death ($P_{quadratic}$=0.03) and non-fatal stroke ($P_{quadratic}$=0.02). A similar but less clear trend was observed with the RoR but only stroke (infarct) reached significance ($P_{quadratic}$=0.03) while sorting by Range showed a U shaped pattern in combined cardiovascular events ($P_{quadratic}$=0.04). **Conclusion:** These findings suggest that the morning BPPower is an important independent risk factor for predicting cardiovascular events and stroke but only in females with median levels having the lowest risk.

Key words: Cardiovascular risk, stroke, circadian rhythm, ambulatory blood pressure, hypertension, logistic equation, blood pressure, female, male.

Introduction

The morning period which coincides with the rapid rise in blood pressure and heart rate, has long been known to be a time of greatest cardiovascular risk with higher incidence of stroke, transient ischaemic attacks, myocardial infarction and sudden cardiac death.[1]. The mechanism is thought to involve the circadian variation in haemodynamic, autonomic and hormonal systems that creates a hyper-coagulable hyper-arrhythmic high risk environment [1]. This scenario, combined with long-standing cardiac or vascular hypertrophy, may explain the excessive cardiovascular events in the morning. There is therefore much interest in determining whether there is a direct link between the early morning blood pressure surge and cardiovascular outcome. An important study by Kario and colleagues found that a higher morning blood pressure surge is associated with stroke and that this was independent of ambulatory blood pressure levels and the night time blood pressure reduction [2]. In non-treated hypertensive patients, the morning surge was also associated with greater left ventricular weight [3] and with greater risk of cardiovascular complications [4]. However, other outcome studies found that not only was a greater morning blood pressure surge not a predictor for greater cardiovascular risk, but that a blunted morning blood pressure surge was associated with increased risk [5]. Precisely what is the best definition and how its related to different outcomes has been of great interest but has led to a variety of outcomes [6]. The method used in these studies to determine the morning surge calculated the difference between the 2-hour period after waking with the minimum during the night or with the pre-awake values. In either case the estimate is mainly reflecting the day night difference and doesn't consider the rate of rise as an independent factor. Another approach used in the European investigator study [7], was to calculate the slope of the blood pressure between the hours of 4 am and 10 am. In this case a higher rate was associated with a lesser risk of cardiovascular endpoints [7] but its not clear how well the regression between fixed times reflect the morning trend in blood pressure. It is not clear what exactly is the most important aspect of the morning surge that is creating the risk. It may be the degree of blood pressure reached or the rate at which it rises or an interaction of measures.

Our approach has been to use a mathematical method applied to ambulatory blood pressure monitoring (ABPM) recordings to measure the magnitude of the morning surge in blood pressure using a 6 parameter logistic equation that estimates the night and day plateaus and the rate of rise (RoR) and the rate of fall in blood pressure [8]. The difference between the plateaus is a measure of the amplitude of the morning rise. We have reported that the rate of rise and amplitude are greater in hypertensive patients [9] and is associated with levels of plasma cholesterol [10, 11]. Importantly, in a collaborative study with Tongji University School of Medicine in Shanghai we examined 170 hypertensive and 170 normotensive subjects ambulatory recordings and found that the rate of the morning surge is associated with a 1.3 times greater risk of cardiovascular and stroke events [12]. We have further developed a single measure of the impact of the morning surge which is a rate amplitude product called the morning BPPower [13] and examined which clinical measures were predictors of this new measure [10]. This new power measures reflects the impact of the rise in blood pressure when it is most rapid and largest and is not defined by waking time or fixed clock times.

The intention of the current study was to determine whether the blood pressure power is an independent risk factor for cardiovascular events in a large well-established cohort of patients. The Ohasama is a community based

prospective population study of over 1500 subjects begun in 1987 where ambulatory blood pressure as well as home measurements have been used to determine factors predicting cardiovascular events [14]. Indeed the morning blood pressure was shown to be predictive of stroke in this group particularly in treated hypertensive subjects [15]. Further, an exaggerated morning pressor surge (amplitude > 25 mmHg) was shown to be associated with a 4 fold greater risk of hemorrhagic stroke [16]. These findings appear to be at odds with the study by Verdechia [5] but the latter used a composite pool of events and found a higher risk with reduced pre-awake systolic blood pressure surge. Thus, in the present study we applied the logistic method to determine the cardiovascular risk associated with the rate of rise, the power of the morning rise as well as the amplitude.

Methods

We analyzed 1535 ambulatory blood pressure recordings from participants from the longitudinal observation study sampled from the general population in Ohasama Japan [17]. Of these 564 were male and 971 were female. Precise details of the study are available elsewhere [18-22].

Cardiovascular measurements

Ambulatory blood pressure was recorded using an oscillometric ABPM 630 device unit (Nippon, Colin, Japan) which were set to measure blood pressure every 30 minutes with the subjects instructed to continue normal daily activities during recordings. Data points from the first and last hour were included and 1535 recording were analyzed and none excluded. On average 43.9 points were included in the analysis (range 23-63, total study included 219,215 points). Importantly no data points were excluded. The recordings were analysed by the program "ABPM" which fitted a 6 parameter double logistic equation [8]:

$$\hat{y} = P1 + \frac{P2}{1+e^{P3(P4-x)}} + \frac{P2}{1+e^{P5(P6-x)}} \qquad (1)$$

where P1 is estimated plateau at night, P2 is the difference between the day and night plateau and P! + P2 was the estimated day time plateau. Note that this differs from the average day and night values as these were determined by the data included in specific times, with 7AM to 10PM being day and 10 PM to 7 AM considered night. Two parameters were used to estimate the rate of transition between the plateau. P3 is the rate of transition from day to night, P5 is the rate of transition between night and day and P4 and P6 are the time of the middle of these transitions (respectively). The maximum slope of the curve during the transitions was defined as $P_2*P_3/4$ for day to night and $P_2*P_5/4$ for the transition from night to day. The latter is also referred to as RoR. The best estimate of each parameter was determined using the least squares Marquardt algorithm. The fitting process did not require user intervention due to the preprogrammed parameter constraints which were used to guide the algorithm to find the correct values as previously described [8].

The power function BPPower (equation 2) is the first derivative of the logistic curve multiplied by the amplitude which is the day night difference between plateaus.

$$\hat{y} = \frac{P2\times P2\times P5\times e^{P5(P6-x)}}{\left(1+e^{P5(P6-x)}\right)^2} \qquad (2)$$

The maximum power at the midpoint peak of the curve can be calculated as in equation 3

$$\hat{y} = \frac{P2\times P2\times P5}{4} \qquad (3)$$

For this study as per previous studies, the main analysed blood pressure for power analysis and outcome was the mean rather than systolic or diastolic.

Outcome measures

All outcomes were obtained at follow up (average 8.5 years) and were classified according to the recommendations of the 10th revision of the World Health Organization's International Classification of Diseases. Cardiovascular death was defined as mortality related to disease of the circulatory system (International Classification of Diseases-10 code "I") [8]. Other non-fatal events included stroke, (ischemic and hemorrhagic), sub arachnoid hemorrhage and transient ischemic attack. A measure of all cardiovascular events was calculated as cardiovascular death plus non-fatal stroke and transient ischemic attack.

Statistical analysis

Data are presented as mean±standard deviation (SD) of the between-patient variation. The association between ABPM measures and outcomes were examined by comparing quintiles by analysis of variance for continuous outcome variables or Chi-Squared test for nominal data. Outcome measures were adjusted for night mean BP, age and smoking status. Non-normally distributed measures (BPPower and RoR) were cube root transformed. The between quintiles variance was further partitioned into linear and quadratic contrasts. Differences were considered significant when $P<0.05$. In addition, we performed a univariate and multivariate analysis that included in the latter, the significant univariate covariates. We used Akaike's information criterion and the Bayesian information criterion to include predictors in the baseline multivariate model.

RESULTS

Subject characteristics

A total 1535 subjects of which approximately one third were male and two thirds were female were included in

the study. Average age of 62 years and a body mass index of 23.5 kg/m^2 were similar in male and female participants. Clinic measured systolic blood pressure and diastolic blood pressure was 133/76 mmHg and was higher in males than females (Table 1, P<0.001). There were no differences in the percentage of males and females taking antihypertensive therapy (39% and 34 % respectively, P=0.62) nor were there differences in history of heart disease (1%) but history of stroke (5%), history of diabetes (17%), plasma levels of cholesterol (5 mmol/l) and glucose (6.4 nmol/l) were higher in males than females (Table 1, P<003). There was also a pronounced higher rate of smoking in males (48%) than females (1%, P < 0.001, Table 1) and a 10-fold greater number of males consuming alcohol than females (44% versus 3%, P <0.001, Table 1).

Outcomes after follow-up

Of the 1535 subjects, 345 had died in the average 8.5 year follow up period (22%) with the proportion of males (32%) being greater than females (17%) (Table 1). Of the deaths, 126 (36%) were related to cardiovascular causes which was also greater in males (P=0.005, Table 1). There was a total of 154 non-fatal strokes and 10 transient ischemic attacks (10.7% non-fatal event rate, 1.3% per year, Table 1). Thus, there were a total of 290 cardiovascular events (18.9%) which were more common in males (24%) than females (16%, P<0.001, Table 1)

24-hour blood pressure measurements from ABPM

The average 24 hour mean blood pressure of 88 mmHg (SD=9.1, n=1535) was higher in males and females as was the average day (92 mmHg) and average night (83 mmHg, Table 2, P<0.001 for all). Systolic blood pressure measured by ABPM during the day was lower than clinic measured blood pressure in both males and females (compare Table 1 and 2) and for diastolic blood pressure in males (P<0.001) but diastolic clinic and day ABPM was similar in females (Paired t test, P=0.4).

The double logistic curve fitting procedure calculated the average difference in blood pressure between day and night plateau as 22 mmHg (n=1535, SD=12), the morning rate of rise in MAP of 8.9 mmHg/hr (SD=9) and the morning power as 224 mmHg^2/hr (SD=278). While the day night difference and the rate of morning rise were similar in males or females although there was a trend for them to be greater in females (P=0.08 and P=0.06 respectively). However, the morning BPPower was 23% greater in females (P =0.01, Table 2).

Relationship between age, blood pressure and outcome.

When the outcome events were sorted by age and allocated to quintiles there is a clear linear relationship with all cardiovascular events including death and non-fatal stroke (P<0.001, Figure 1 upper panels). The oldest quintile subjects (average age=77 years) had 15 times greater number of events than the youngest quintile (average age= 46 years).

Sorting by night blood pressure (after adjustment for age) similarly showed a higher cardiovascular event rate (104 events) in the highest quintile (average mean=103 mmHg) than the lowest quintile with 31 events (71 mmHg, Figure 1 lower panels). There was a linear trend with age adjusted night blood pressure in these outcome measures (P<0.05 for all, Figure 1).

Relationship between Outcomes and ABPM power of morning surge in males.

An analysis was performed separately on males and females to determine whether the patterns were similarly distributed in both sexes. Assigning quintiles to the males according to BPPower after adjustment for age, night blood pressure and smoking status, showed no differences between quintiles for any of the outcome measures except for non-fatal stroke (Table 3, Figure 2). In this case there was a very low risk in the lowest quintile and a 3-fold higher risk in the second lowest quintile of BPPower. Across the quintiles there were no differences in body mass index, history of heart, stroke or diabetes, alcohol intake, total cholesterol, LDL or glucose (Supplementary Table S1). The lowest risk quintile with the smallest BPPower, had less antihypertensive treatment and a higher rate of smoking and lower clinic diastolic blood pressure. Restricting males to non-drinkers eliminated this pattern of cardiovascular events (Supplement Figure S1). In this case however, the middle quintile showed the highest risk of a cardiovascular event. A similar pattern was seen for quintiles of morning RoR in mean blood pressure (Figure 2).

Relationship between Outcomes and ABPM power of morning surge in females.

In contrast to males, there was difference between quintiles for all cardiovascular events in females when sorted by morning BPPower (age, night blood pressure and smoking status adjusted, P<0.001, Table 4, Figure 3). This formed a U-shaped relationship over the quintiles for the combined cardiovascular events (P<0.001), mainly due to this pattern in cardiovascular death (P<0.001), non-fatal stroke (P=0.014) and infarct stroke (P=0.03). The lowest quintile in the females with the lowest morning power showed the highest values for all outcomes with the middle having the least events (Figure 3). Across the quintiles there were no differences in body mass index, history of heart, stroke, alcohol intake, total cholesterol, LDL or glucose (Supplementary Table S2). However, there was a U-shaped relationship with use of antihypertensive therapy ($P_{quadratic}$ =0.01). The highest use of calcium channel blockers was in the lowest quintile and the highest use of angiotensin converting enzyme inhibitors were observed in the highest quintile (Supplementary Table S2). However, a similar U-shaped trend for all cardiovascular events and cardiovascular

deaths was observed when the analysis was restricted to untreated females (Supplement Figure S2) although the total cardiovascular events was 4-fold lower (52 in 639, 8.1% in untreated; n=103 in 331, 31% in treated). A similar pattern was seen for quintiles of morning RoR in mean blood pressure except that a significant quadratic trend was only observed for all cardiovascular events (Figure 3).

Relationship between Outcomes and ABPM power of morning surge in subjects combined.

In addition to the separate analysis of males and females, the trends in the combined group were also analysed. The outcome and ABPM data were sorted by BPPower and allocated to quintiles each of 307 individuals (Table 4, Supplement Figure S3). BPPower was adjusted for night mean blood pressure, age and smoking status (Supplementary Table S3, Supplementary Figure S3). There was a linear increase in average day and 24-hour mean blood pressure from the lowest quartile of BPPower to the highest but not night blood pressure as expected as an adjustment variable (Supplementary Table S3). There were marked differences between quintiles in "all cardiovascular events" (P<0.001) due to a U-shaped relationship (quadratic P=0.0008) rather than a linear trend (P=0.34) with the lowest risk of events being the middle quintile (42 events) and the highest at the extremes particularly the lowest quintile of BPPower (80 events) but also the highest quintile (66 events) (Supplementary Table S3). There were some differences between quintiles in antihypertensive therapy with higher use of ACE inhibitors in the upper quintiles but other histories and blood biochemistry were similar across quintiles (Supplementary Table S4).

Relationship between Outcomes and ABPM estimated BP Range.

The outcome and ABPM data were also sorted by the estimated difference (range) between the day and night plateaus as determined by the fitting of the logistic curve (BP Range) and allocated to quintiles for males (Figure 4 upper panels) and females (Figure 4 lower panels). Range was adjusted for night mean blood pressure, age and smoking status (Figure 4). In males there were no differences between quintiles for "all cardiovascular events" (P=0.067), cardiovascular death (P=0.06) or non-fatal stroke was detected (P=0.14, Figure 4). Further there was no a linear or quadratic trend for any outcome. In females, there was a U-shaped relationship detected in all cardiovascular events (Figure 4, P=0.041) but this didn't reach statistical significance in the subgroups of outcome such as cardiovascular deaths or non-fatal stroke.

Baseline univariate- and multivariate analysis.

In the univariate analysis of cardiovascular risk as calculated by all cardiovascular events in all subjects, only age, night BP, smoking and being male indicated as being a predictor. Range, rate of rise and BPPower were not predictors with odds ratio close to one (Supplementary Table S5). In a multivariate analysis which included all the significant univariate predictors, only age and night BP remained significant predictors (P<0.0001, Supplementary Table S5).

A further analysis confined to female subjects showed a similar trend to all participants. Age and night BP were predictors in a univariate analysis and also in a multivariate analysis indicating they are independent predictors. In females, range, rate of rise and BPPower were not predictors with odds ratio close to one (Supplementary Table S6).

Discussion

In the present study we have used a double-logistic curve fitting procedure to assess whether the power of the morning surge which is the rate of rise multiplied by the amplitude, is associated with cardiovascular events in a Japanese population study. The major findings were that the morning BPPower is indeed associated with risk of cardiovascular death or non-fatal strokes but not in a linear manner. The relationship showed a U-shaped pattern with the lowest risk in the middle and the highest risk at the extremes of the measure. Thus, very large or very low BPPower had the highest event rate of cardiovascular events. A surprising aspect was that this pattern was observed only in females whether they had been treated for hypertension or not, but not with males. Thus, it appears that the morning surge in BP as determined using the power function which is the product of the rate of rise in blood pressure and the amplitude of the rise is an independent risk factor in females for stroke at the high and low end of the scale.

Interestingly, a univariate or multivariate analysis failed to find and association of BPPower with all cardiovascular events presumably because the relationship is U shaped and not linear. This analysis did find age and night BP were independent predictors which is in line with their strong linear association with risk as shown in Fig 1.

There are a number of factors that are known to contribute to cardiovascular events in the morning period which is the time of the greatest risk [2, 23-31]. Marler and colleagues observed that more strokes occurred in the period 10 am to midday than any other 2 hour period [23]. Previous studies with the Ohasama cohort have examined morning and evening blood pressure using home self-measurement techniques and found a high risk of stroke with morning or sustained hypertension whether treated or untreated [15]. An earlier study using ambulatory blood pressure recordings of the Ohasama cohort found a prognostic risk of death in non-dippers or those that increased blood pressure at night but did not find any greater risk of those with extreme dipping (large day night difference) [19]. In elderly Japanese with hypertension, from the Kansai region, a higher risk of stroke was observed in extreme dippers (large difference between day and night) and reverse dippers [27]. As they

essentially divided the group into quartiles they therefore described a U-shaped curve of risk. In that study, age, 24 hour blood pressure, smoking status as well as dipping status were predictors of stroke but not being male, antihypertensive therapy, diabetes or dyslipidemia [27]. Thus, it was appropriate that we adjusted for age, blood pressure and smoking status in the current study. In the present study we used night mean blood pressure as this measure appears to be a more accurate predictor of cardiovascular risk [7]. In the present study we did not adjust for dipping status since the amplitude of the day night difference is part of the BPPower function and therefore cannot be a cofounding factor as well. Thus, the BPPower encapsulates the risk associated with the rate and the amplitude of the morning surge.

The previous approach by Kario and colleagues, used an estimate of the morning surge being either the difference between the blood pressure 2 hours after waking and the 2-hour period surrounding the lowest value at night or between the 2 hours prior to waking. Only the former was associated with greater risk of stroke [2]. A subsequent analysis of the Ohasama cohort which determined the amplitude of the morning pressor surge of systolic blood pressure which was taken as the difference between the 2 hours before waking to the 2 hours after waking found no consistent trend with total stoke [16]. However, this study did observe an association between a very large morning surge and cerebral hemorrhage but not cerebral infarction. This finding is somewhat limited by the very low number of hemorrhagic strokes in the cohort (27 of 143). Further, there was a clear difference between the number of men and women in the quintiles with a high percentage of men with low morning amplitude and a high percentage of women in the large morning amplitude quintile [16].

The measures used in previous studies are partly a measure of the amplitude and rate of rise but is not a precise measure of either. It is also dependent on the accuracy of the awake time. For these reasons we developed the logistic fitting analysis and estimate of the power of the morning surge being the product of the rate and amplitude. It is not dependent on estimating the waking time, clock times or the variability of nocturnal blood pressure [8, 13, 25]. We have shown that the BPPower is higher in hypertensive subjects, white-coat patients and also differentially affected by antihypertensive treatment [13]. We had previously found that the rate of rise in morning blood pressure was an independent risk factor for cardiovascular events, but we had not used the BPPower until the current study [12].

Another consideration was that we used mean blood pressure rather than systolic or diastolic [10, 13, 24, 25] as the latter two measures are estimated by algorithm in oscillometric devices but the mean is determined accurately as the peak of the fluctuations [32, 33]. Interestingly, oscillometric mean blood pressure well reflected aortic mean pressure as a whole but the oscillometric technique overestimates the mean in men by about 4 mmHg and underestimates the value in women by about the same amount. These technical differences would not impact the current study where we analyzed men and women separately but may well influence combined analysis.

The precise reason for the sex difference in the cardiovascular risk in the current study is not obvious. We observed no clear relationship between morning power and cardiovascular risk in the men but a very strong U-shaped relationship in females. Known differences in higher rates of smoking or drinking in males did not account for the difference since the lack of association also was evident in non-drinking males and BPPower was adjusted for smoking, age and night blood pressure. A possible explanation is that the adjustment for age, blood pressure and smoking status accounted for most of the risk associated with the morning period in males. This doesn't appear to be the case for women where a U-shaped pattern of risk was evident with the highest risk in the lowest and highest quintiles and the least risk in the second lowest quintile. There were no factors including body mass index, history of heart disease, stroke or diabetes, cholesterol levels or plasma glucose were different between the quintiles of BPPower except for use of antihypertensive therapy which was highest in the high-risk quintiles of BPPower. Interestingly, Calcium channel blockers were most prescribed in the lowest quintile and angiotensin converting enzyme inhibitors most prescribed in the highest quintile. While the association might suggest that women of highest risk of stroke were given more likely to be on therapy, this cannot be the explanation for the U-shaped risk patter. The reason is that the same U-shaped pattern was observed in women not on antihypertensive therapy.

We have previously shown that plasma low density cholesterol (LDL) is a predictor of the morning surge both in a cross-sectional study as well as a follow up analysis where the increase in LDL independently predicted a larger BPPower [10]. However, we didn't find any difference between the total cholesterol or LDL levels in females (or males for that matter) between quintiles ordered by BPPower in the Ohasama cohort. Thus, while LDL is a predictor of the morning surge (estimated by power, this is not the reason for patterns we observed in females or males. One reason we may not have observed such a relationship is that LDL as a predictor of BPPower only explains a small percentage of the variance.

A recent study by Panwar and colleagues found using a population based cohort that during a 7 year follow up of 18000 black and white US adults over 45 years of age, there was a U shaped relationship between stroke and hemoglobin levels in females but not in males [34]. The reason for the difference in stroke association between males and females was not investigated in that study, but the authors speculated that higher hemoglobin in females could be a marker for blood viscosity, oxidative stress and

platelet activation and lower levels an indication of poor health [35]. A resonance hypothesis has been suggested that states that reduced baroreceptor sensitivity combined with small artery remodeling and aging combined with the timing of peaks of short term and long term variability when synchronized leads to a large dynamic surge which might trigger an event [36]. This is similar to the concept that we proposed in deriving the power of the morning surge which may also be contributing to increased turbulence or sheer stress which has been suggested previously [37]. Indeed, we have previously found that a morning BPPower is highest in those with a more reactive sympathetic nervous system [38]. The latter is also associated with greater plasma catecholamines and cortisol in the morning and increased platelet aggregability but there is no-correlation between the hormonal changes and the sensitivity of platelets to adrenaline [39]. This suggests an extrinsic action of platelet aggregability which has been suggested to involve both alpha and beta receptors [37]. The key question however, is still why this mechanism is more evident in females.

In conclusion the present analysis confirms the importance of age and blood pressure as risk factors for cardiovascular events but also shows that in females the rate of rise in blood pressure and particularly the power of the morning surge is an independent risk factor after accounting for age, night blood pressure, smoking status, alcohol intake and antihypertensive treatment. The interesting aspect of the risk is that it is U shaped in women with the highest risk at the lowest and highest levels of BPPower and is not at all linear. The practical lesson from these studies are that there is additional risk from a large morning surge but this is only apparent in females and relates to both the rate and the magnitude of the morning surge. The upper 20% are clearly at the highest risk of events, in particular strokes, but clear optimal thresholds need to be developed using larger cohorts and particularly in other population groups.

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Table 1. Subject characteristics, clinic blood pressure, lipid parameters and medicine usage.

Mean (SD) or n (%)	Total	Male	Female	P
Number	1535	564	971	
Clinic SBP (mmHg)	133.3 (19.3)	136.9 (19.1)	131.2 (19.1)	***<0.001***
Clinic DBP (mmHg)	75.7 (11.9)	78.7 (12.1)	74 (11.4)	***<0.001***
Heart Rate (b/min)	71 (10.6)	70.3 (11.4)	71.6 (9.8)	>0.5
Age (years)	61.7 (10.7)	62.6 (10.8)	61.2 (10.6)	0.14
Body Mass Index (kg/m2)	23.4 (3.1)	22.9 (2.7)	23.7 (3.2)	***<0.001***
Antihypertensive therapy n(%)	549(35.8)	217(38.5)	332(34.2)	>0.5
ACE Inhibitor	48(3.1)	25(4.4)	23(2.4)	0.25
Angiotensin Receptor Blocker	0(0)	0(0)	0(0)	
CA Chanel Blocker	337(22)	134(23.8)	203(20.9)	>0.5
Diuretic	123(8)	51(9)	72(7.4)	>0.5
History of Heart Disease n(%)	20(1.3)	10(1.8)	10(1)	>0.5
History of Stroke n(%)	80(5.2)	46(8.2)	34(3.5)	***<0.001***
History of Diabetes n(%)	267(17.4)	124(22)	143(14.7)	***0.003***
Current Smoking n(%)	285(18.6)	272(48.2)	13(1.3)	***<0.001***
Consumes Alcohol n(%)	278(18.1)	250(44.3)	28(2.9)	***<0.001***
Total Cholesterol (mmol/l)	5.0(0.9)	4.7(0.9)	5.1(0.9)	***<0.001***
Plasma Glucose (mmol/l)	6.4(1.9)	7.0(2.5)	6.2(1.5)	***<0.001***
Deaths	345 (22.5)	183 (32.4)	162 (16.7)	***<0.001***
Cardiovascular Death	126 (8.2)	61 (10.8)	65 (6.7)	***0.005***
Non Cardiovascular Death	219 (14.3)	122 (21.6)	97 (10)	***<0.001***
All Cardiovascular Events	290 (18.9)	135 (23.9)	155 (16)	***<0.001***
Non fatal stroke	154 (10)	70 (12.4)	84 (8.7)	***0.02***
Stroke (Infarct)	119 (7.8)	58 (10.3)	61 (6.3)	***0.005***
Haemorrhagic Stroke	27 (1.8)	11 (2)	16 (1.6)	>0.5
Sub-Arachnoid Haemorrhage	8 (0.5)	1 (0.2)	7 (0.7)	0.15
Transient ischaemic attack	10 (0.7)	4 (0.7)	6 (0.6)	>0.5

Abbreviations: ACE angiotensin converting enzyme inhibitor, CA calcium. P is the Probability between males and females calculated by Student's t-test for continuous variables and Chi squared test for the nominal data. Numbers are mean (SD) or n (%). All cardiovascular events include cardiovascular death, non-fatal stroke and transient ischaemic attack.

Table 2. Average results from the circadian analysis of 24 hour mean arterial blood pressure measurements analyzed by the double logistic method for all, male and female subjects.

Mean (SD)	**Total**	**Male**	**Female**	**P**
Number	1535	564	971	
Mean Blood Pressure				
Average 24 Hour Mean BP (mmHg)	88.4 (9.1)	90.7 (9)	87 (9)	***<0.001***
Average Day Mean BP (mmHg)	92.2 (9.8)	94.2 (9.7)	91 (9.7)	***<0.001***
Average Mean BP at Night (mmHg)	83.2 (9.8)	86.2 (9.8)	81.5 (9.5)	***<0.001***
Range (mmHg)*	22.2 (11.6)	21.2 (11.9)	22.7 (11.5)	0.08
Morning Rate of Rise (mmHg/hr)* ϕ	8.9 (8.8)	8.01 (8.4)	9.5 (9.1)	0.06
Morning Power (mmHg2/hr)* ϕ	224.3 (278.2)	198.7 (267.5)	243.2 (324.8)	***0.01***
Systolic Blood Pressure				
Average 24 Hour Mean BP (mmHg)	122.4 (13)	125 (12.7)	120.8 (12.9)	***<0.001***
Average Day Mean BP (mmHg)	126.9 (13.6)	129.1 (13.3)	125.7 (13.7)	***<0.001***
Average Mean BP at Night (mmHg)	116.2 (14.4)	119.7 (14.4)	114.2 (14)	***<0.001***
Range (mmHg)*	29 (17.3)	28 (17.6)	29.7 (17)	0.31
Morning Rate of Rise (mmHg/hr)* ϕ	11.8 (12.2)	10.91 (11.3)	12.3 (12.5)	>0.5
Morning Power (mmHg2/hr)* ϕ	399.1 (555.3)	354.1 (440.9)	427.5 (607.3)	>0.5
Diastolic Blood Pressure				
Average 24 Hour Mean BP (mmHg)	71.4 (7.7)	73.6 (7.6)	70.1 (7.4)	***<0.001***
Average Day Mean BP (mmHg)	74.8 (8.4)	76.7 (8.4)	73.7 (8.2)	***<0.001***
Average Mean BP at Night (mmHg)	66.8 (8.1)	69.4 (8)	65.2 (7.7)	***<0.001***
Range (mmHg)*	19.1 (10)	18.6 (10.2)	19.5 (9.7)	0.42
Morning Rate of Rise (mmHg/hr)* ϕ	7.8 (7.6)	7.05 (7.3)	8.2 (7.7)	***0.01***
Morning Power (mmHg2/hr)* ϕ	169.2 (222.5)	152 (204.5)	180.3 (229.4)	***0.02***

Values are mean (SD). Abbreviations: blood pressure, Blood Pressure. P probability for the difference between males and females calculated by Student's t test. ϕstatistics performed on cubic root to normalize the distribution. *Values adjusted for average night mean blood pressure, age and smoking status.

Risk associated with morning surge

Table 3 Analysis of 24 hour mean blood pressure measurements and outcomes of **564 male subjects** divided into quintiles according to BPPower.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Pquintiles	PLinear	PQuadratic
Morning Power (mmHg2/hr)	-27.3 (129.4)	66.7 (15.5)	130.4 (25)	241.2 (43.2)	574.2 (359.6)	P<0.001	P<0.001	P<0.001
Number	113	113	113	113	113			
Average 24 Hour (mmHg)	87.2 (7.4)	91 (9.4)	90.3 (9.4)	92.5 (8.3)	92.7 (9.1)	P<0.001	P<0.001	>0.5
Average Day (mmHg)	88.9 (7.7)	93.8 (9.6)	94.1 (9.9)	96.7 (9.2)	97.3 (9.7)	P<0.001	P<0.001	0.29
Average Night (mmHg)	85.1 (8.7)	87.2 (10.2)	85.1 (10.1)	87 (9.2)	86.5 (10.6)	>0.5	>0.5	>0.5
Day Night Difference	3.8 (7.2)	6.6 (6.5)	8.9 (7.1)	9.7 (7.9)	10.8 (8.5)	P<0.001	P<0.001	0.31
AASI (symmetrical)	0.3 (0.14)	0.32 (0.09)	0.32 (0.08)	0.34 (0.08)	0.34 (0.08)	0.07	***0.01***	>0.5
Double Logistic Estimates Range (mmHg)	9.9 (13.3)	18.3 (8.5)	22.9 (10.2)	25.1 (9.3)	29.4 (9.1)	P<0.001	P<0.001	***0.017***
Morning Rate of Rise (mmHg/hr)	-0.52 (5.9)	3.7 (2.4)	6.3 (3)	10.7 (3.8)	19.6 (7.7)	P<0.001	P<0.001	P<0.001
Deaths	38	32	33	37	43	>0.5	0.48	0.34
Cardiovascular Death	10	16	12	12	11	>0.5	>0.5	>0.5
Non Cardiovascular Death	28	16	21	25	32	0.09	0.38	0.14
Non fatal stroke	7	22	15	12	14	***0.047***	>0.5	0.26
Stroke (Infarct)	6	19	11	11	11	0.08	>0.5	0.31
Haemorrhagic Stroke	1	3	4	1	2	>0.5	>0.5	0.48
Sub-Arachnoid Haemorrhage	0	0	0	0	1	0.41	0.41	0.48
Transient ischaemic attack	2	1	0	0	1	0.47	>0.5	0.34
All cardiovascular events	19	39	27	24	26	***0.031***	>0.5	0.285

All cardiovascular events include cardiovascular death, non-fatal stroke and transient ischaemic attack. Numbers are mean (SD) or n. P is the difference between quintiles, for linear trend and for quadratic (U-shaped) trend calculated by analysis of variance for continuous variables and Chi squared test for the nominal data.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Pquintiles	PLinear	PQuadratic
Morning Power (mmHg2/hr)	8.2 (47.8)	85.9 (19.7)	158.4 (24.5)	292.3 (47.7)	677 (310)	P<0.001	P<0.001	P<0.001
Number	193	193	193	193	193			
Average 24 Hour (mmHg)	86.1 (8)	85.1 (8.7)	86.7 (9.1)	87.2 (9.2)	89.7 (8.9)	P<0.001	P<0.001	0.13
Average Day (mmHg)	88.1 (8.4)	89.2 (9.4)	91 (9.8)	91.6 (9.8)	95.2 (9.5)	P<0.001	P<0.001	>0.5
Average Night (mmHg)	83.4 (8.9)	79.7 (8.6)	80.9 (9.5)	81 (9.9)	82 (9.3)	***0.02***	>0.5	***0.01***
Day Night Difference	4.7 (6.4)	9.4 (5.6)	10.1 (6.4)	10.6 (6.9)	13.1 (6.7)	P<0.001	P<0.001	0.08
AASI (symmetrical)	0.35 (0.09)	0.34 (0.08)	0.34 (0.07)	0.34 (0.08)	0.35 (0.07)	>0.5	>0.5	>0.5
Double Logistic Estimates								
Range (mmHg)	15.2 (11.7)	21.8 (7.8)	23.2 (9.7)	24.8 (9.3)	30 (9)	P<0.001	P<0.001	>0.5
Morning Rate of Rise (mmHg/hr)	1.28 (3.3)	4.1 (2.3)	7.6 (3.3)	13 (4.3)	22.2 (7.2)	P<0.001	P<0.001	P<0.001
Deaths	58	22	26	25	28	P<0.001	***0.01***	***0.01***
Cardiovascular Death	24	8	8	9	14	***0.002***	0.24	***0.03***
Non-Cardiovascular Death	34	14	18	16	14	***0.001***	***0.04***	0.21
Non-fatal stroke	23	12	9	15	25	***0.014***	>0.5	***0.02***
Stroke (Infarct)	19	8	7	10	17	***0.03***	>0.5	***0.04***
Haemorrhagic Stroke	3	2	2	4	5	>0.5	0.46	>0.5
Sub-Arachnoid Haemorrhage	1	2	0	1	3	0.44	>0.5	0.45
Transient ischaemic attack	2	0	2	1	1	>0.5	>0.5	>0.5
All Cardiovascular events	49	20	19	25	40	P<0.001	>0.5	***0.001***

Table 4 Analysis of 24 hour mean blood pressure measurements and outcomes of **971 female subjects** divided into quintiles according to BPPower.
All cardiovascular events include cardiovascular death, non-fatal stroke and transient ischaemic attack. Numbers are total (SD) or n. P is the difference between quintiles, for linear trend and for quadratic (U-shaped) trend calculated by analysis of variance for continuous variables and Chi squared test for the nominal data.

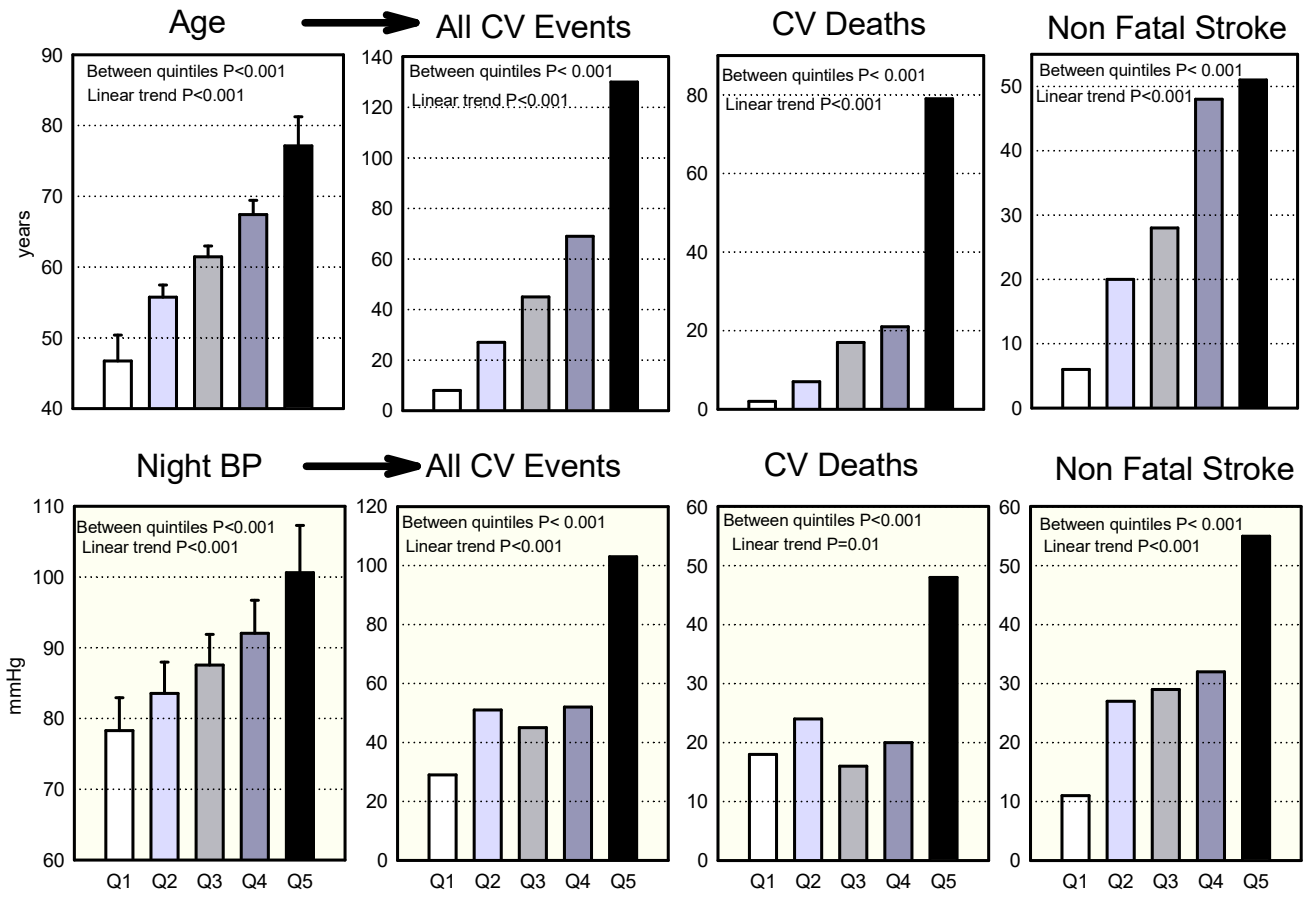

Figure 1
Upper Panels: Average quintiles (Q1-5, n=307 per quintile) sorted by age for all cardiovascular (CV) events, CV deaths and non-fatal stroke in males and females (n=1535). Lower Panels: Average quintiles sorted by night mean blood pressure (adjusted for age) in males and females. Values are mean and SD (for continuous variables) and n for nominal data. P values are shown for between all quintiles, linear and quadratic trend from a Chi squared test.

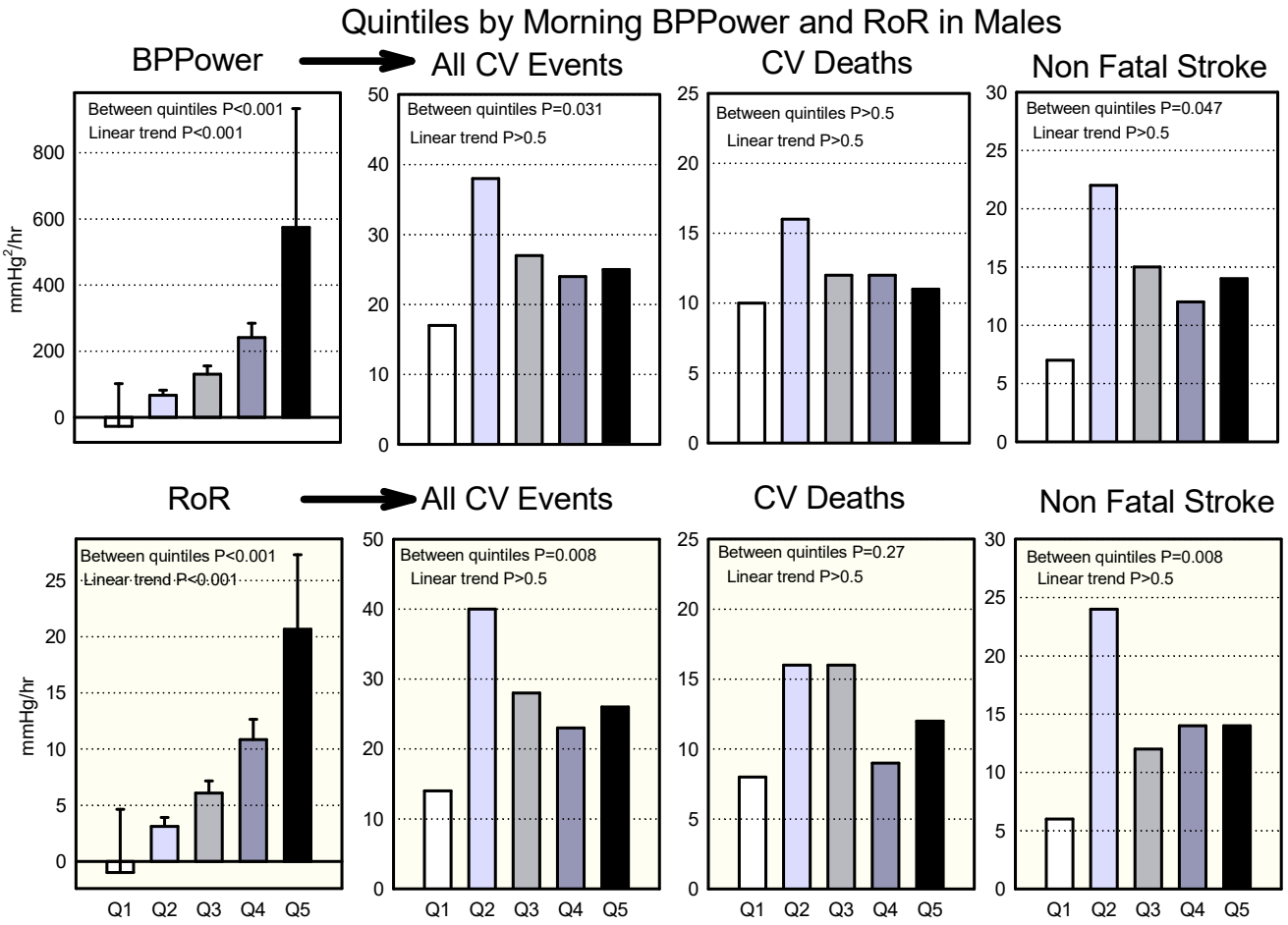

Figure 2

Upper Panels: Average quintiles (Q1-5, n=113 per quintile) sorted by morning BPPower (adjusted for age, night mean arterial pressure and smoking status) for all cardiovascular (CV) events, CV deaths and non-fatal stroke in males and females (n=564). Lower Panels: Average quintiles sorted by rate of morning rise in mean blood pressure (adjusted for age, night mean arterial pressure and smoking status) in males and females. Values are mean and SD (for continuous variables) and n for nominal data. P values are shown for between all quintiles, linear and quadratic trend from a Chi squared test.

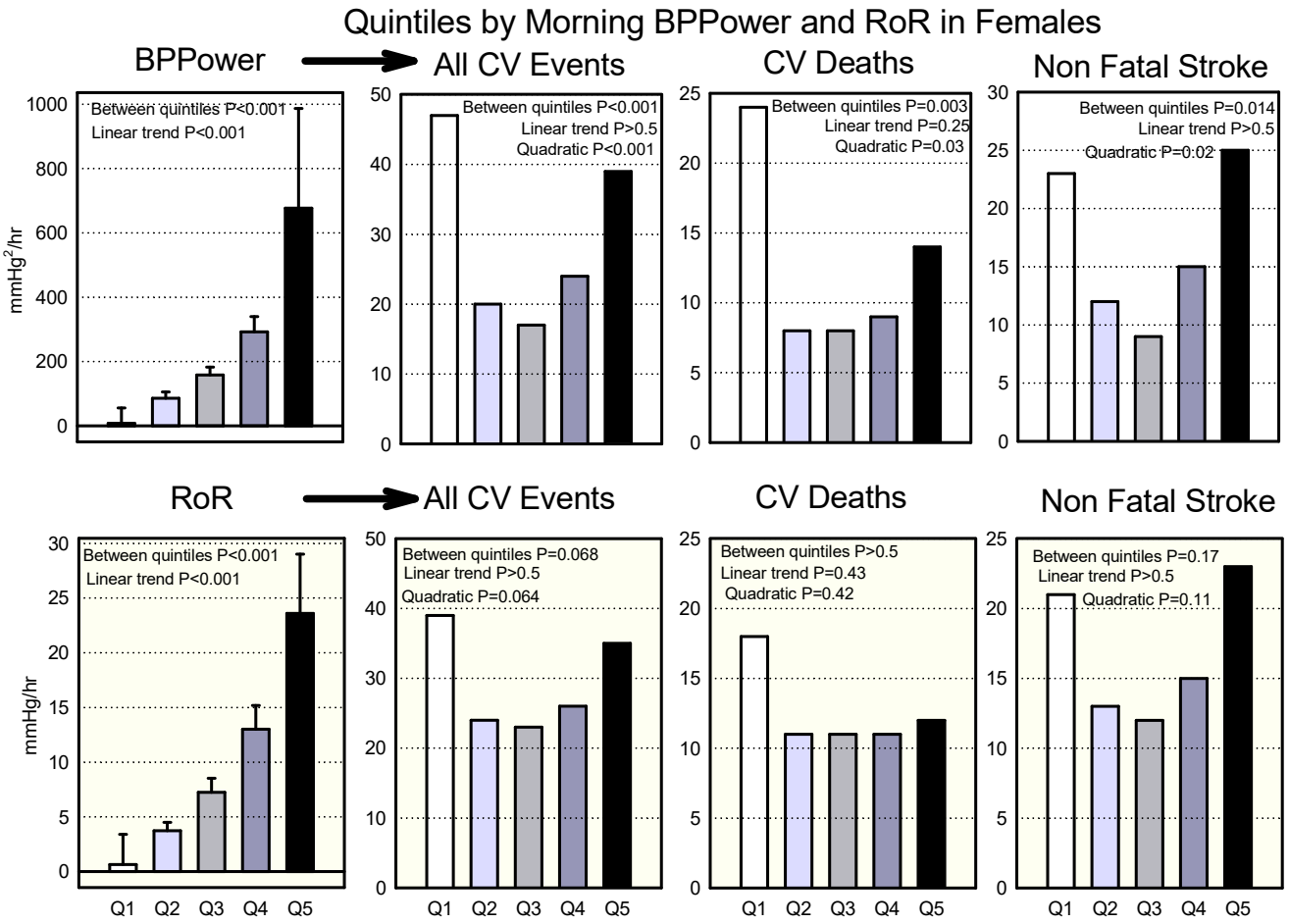

Figure 3

Upper Panels: Average quintiles (Q1-5, n=193 per quintile) sorted by morning BPPower (adjusted for age, night mean arterial pressure and smoking status) for all cardiovascular (CV) events, CV deaths and non-fatal stroke in females (n=971). Lower Panels: Average quintiles sorted by rate of morning rise in mean blood pressure (adjusted for age, night mean arterial pressure and smoking status) in females. Values are mean and SD (for continuous variables) and n for nominal data. P values are shown for between all quintiles, linear and quadratic trend from a Chi squared test.

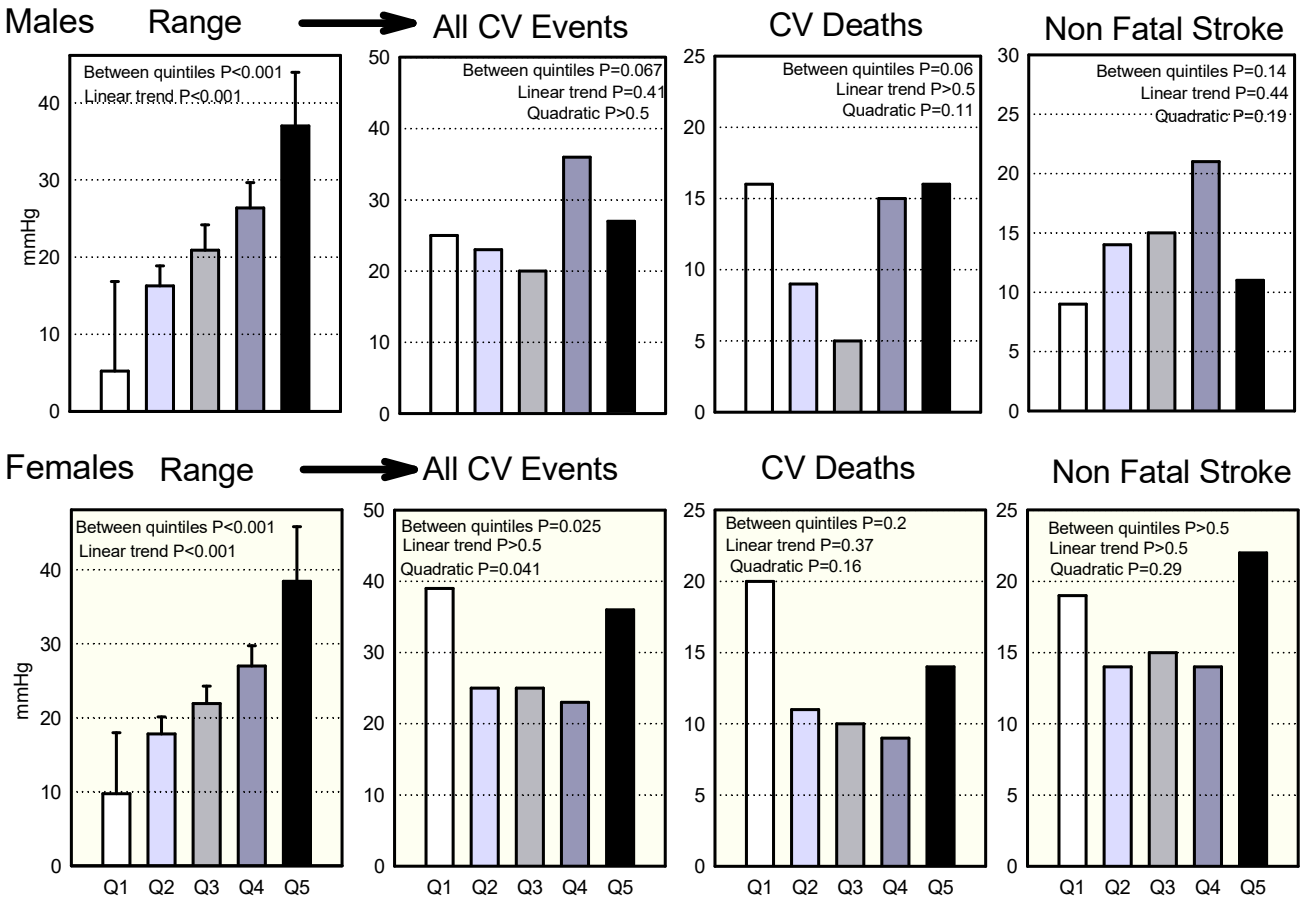

Figure 4

Upper Panels: Average quintiles (Q1-5, n=113 per quintile) sorted by Range (adjusted for age, night mean arterial pressure and smoking status) for all cardiovascular (CV) events, CV deaths and non-fatal stroke in males (n=564). Lower Panels: Average quintiles (Q1-5, n=193 per quintile) sorted by Range (adjusted for age, night mean arterial pressure and smoking status) in females (n=971). Values are mean and SD (for continuous variables) and n for nominal data. P values are shown for between all quintiles, linear and quadratic trend from a Chi squared test.