

European Heart Journal Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real world perspective from the prospective MONICA/KORA study

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Abstract

Aims

To investigate the clinical value of a lower blood pressure cut-off for Stage 1 (S1) hypertension (130-139 mmHg systolic or 80-89 mmHg diastolic) in comparison to the currently established Stage 2 (S2) cut-off ($\geq 140/90$ mmHg) in a population-based cohort.

Methods and Results

We assessed the hypertension prevalence and associated CVD events in a sample of 11,603 participants (52% men, 48% women; mean 47.6 years) from the MONICA/KORA prospective study. The implementation of the new S1 cut-off increased the prevalence of hypertension from 34% to 63%. Only 24% of S2 hypertension patients were under treatment. Within a follow-up period of 10 years (70,148 person-years), 370 fatal CVD events were observed. The adjusted CVD-specific mortality rate /1000 persons was 1.61 (95% CI 1.10-2.25) cases in S2 and 1.07 (95% CI 0.71-1.64) cases in S1 hypertension in comparison to normal blood pressure. Cox proportional regression models were significant for the association of S2 and CVD mortality (1.54, 95% CI 1.04-2.28, $p=.03$), also in the presence of competing risks (1.47, $p=.05$). However, statistical significance for S1 hypertension was not reached (0.93, 95% CI 0.61-1.44, $p=.76$). Among S2 participants, there was a significantly higher prevalence of depressed-mood in treated patients (47%) in comparison to non-treated patients (33%) ($p<.0001$).

Conclusion

The lower blood pressure cut-off substantially increased hypertension prevalence, while capturing a population with lower CVD mortality. Additionally, participants under treatment were more likely to have depressed-mood in comparison to non-treated participants, which might reflect a negative labelling effect.

Introduction

Among the established somatic and life-style related risk factors for cardiovascular (CVD) mortality, the risk of hypertension holds a top rank even surpassing that of smoking¹. Nevertheless, the exact cut-off values for defining hypertension continue to be a matter of debate. Currently, the European Society of Hypertension and the European Society of Cardiology (ESC) classifies the cut-off value of systolic blood pressure (SBP) of 120-129 and diastolic blood pressure (DBP) of 80-89 mmHg as “normal” and the 130-139/85-89 mmHg stratum as “high normal”². In contrast, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a new guideline in 2017, defining Stage 1 (S1) hypertension at 130 to 139 mmHg systolic or 80 to 89 mmHg diastolic, and Stage 2 (S2) hypertension as the former US and current ECS hypertension definition ($\geq 140/90$ mmHG)³. The ACC/AHA estimated that the proportion of US adult population labelled as having hypertension will increase from 32% to 46%^{3,4}.

The reclassification was mainly justified by the SBP Intervention Trial (SPRINT), including 9,361 adults over 50 years-old with SBP ≥ 130 mmHG, which showed that lowering SBP to 120 mmHg vs. 130 mmHg led to a substantial relative risk reduction in CVD events and mortality⁵. The reclassification was further supported by two meta-analyses of BP lowering randomised controlled trials (RCT)^{6,7}. However, contrary to these findings, the recent and most extended meta-analysis failed to find a favorable effect of BP lowering in subjects with baseline SBP < 140 mmHg for CVD events and mortality outcomes⁸.

Apart from highly homogenized patient populations included in RCTs, prospective epidemiological studies have also provided a view into the real-world situation. A meta-analysis of prospective studies supports the 2017 ACC/AHA guideline by showing that “prehypertension” (defined as SBP 120-139 mmHg) significantly increased the risk of CVD, but not of all-cause mortality⁹. However, the definition of prehypertension used in this study is not in line with the ACC/AHA reclassification of S1 or S2 hypertension.

Given the utmost importance of defining optimal cut-off values for hypertension and the contradictory state of the art, the present investigation used data from the prospective population-based MONICA/KORA study with a random sample of 11,603 participants to assess the proportion of

subjects, previously deemed as healthy, who now qualify as hypertensive. Furthermore, considering the adverse effects that labelling people as ill can have ¹⁰, we investigated the occurrence of fatal CVD events based on the 10-year follow-up of participants with S1 and S2 hypertension.

Methods

Participants

The study population was taken from the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)/ Cooperative Health Research in the Region of Augsburg (KORA) cohort study ¹¹. Three independent cross-sectional surveys including 13,427 participants (6,725 men and 6,702 women aged between 25-74 year-old) were conducted in 1984/1985, 1989/1990, and 1994/1995 as part of the multinational WHO MONICA project ¹¹. In the current analysis, missing data for depressed mood (N=939), cholesterol (N=238) and obesity (N=129), CVD mortality outcome (N=26) lead to a final sample of 11,603 participants (5,982 men and 5,621 women). A dropout analysis revealed that subjects with missing information were older ($p < 0.001$) compared to subjects with available information.

Assessment of hypertension

Adhering to the WHO MONICA protocol, blood pressure (BP) was measured on the right arm in a sitting position using a Hawksley random-zero sphygmomanometer, BP measurements were taken during the clinical interview after approximately half an hour at a 3-min interval. The average readings of the second and third measurement were considered for the analyses ¹². In line with the ACC/AHA Hypertension Guidelines, normal BP was set at SBP < 120 mmHg and DBP < 80 mmHg, elevated BP at SBP 120/129 mmHg and DBP < 80 mmHg, Stage 1 (S1) hypertension at SBP 130-139 mmHg or DBP 80-89 mmHg and Stage 2 (S2) hypertension at SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Crude hypertension values were used for analysis; hence, we considered actual BP, irrespective of antihypertensive medication status. Antihypertensive medication was classified as recommended by the German Hypertension Society.

Cardiovascular risk factors

Lifestyle factors: Smoking was defined as currently smoking at least one cigarette per day. Physical activity was defined by engaging in physical activity on average ≥ 1 h/week throughout the year.

Somatic factors: Total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were measured as mg/dL in serum by enzymatic methods (CHOD-PAP, Boehringer Mannheim, Germany) and hypercholesterolemia was defined as $TC \geq 240$ mg/dL. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and obesity was defined as having a $BMI \geq 30$ kg/m². Type 2 Diabetes Mellitus was self-reported by participants and verified by their medical records.

Depressed mood: Depressed mood was assessed using the depression and exhaustion subscale (DEEX), which combines eight items ranging from 0 to 3, leading to a Likert-like scoring range of 0–24¹³. Participants in the top tertile of the depressive symptom distribution stratified by sex were considered as suffering from depressed mood.

History of cardiovascular disease at baseline and high cardiovascular risk group

History of CVD at baseline was defined by self-report of myocardial infarction, heart failure, angina or stroke. Subjects with high CVD risk were defined by having 3 or more CVD risk factors¹⁴.

Follow-up and mortality endpoints

Death certificates were obtained from local health departments and coded for the underlying cause of death by a single trained person using the 9th revision of the International Classification of Diseases (ICD-9). In the present study, fatal CVD events (ICD-9: 390-459) were used as the endpoint. In the 10-year follow-up (70,148 person years), there were 370 cases of fatal CVD events. For mortality analyses, event times were calculated as time to death. Subjects without events or with loss to follow-up were censored at the time point of the last follow-up.

Statistical Analysis

Descriptive analyses

The proportion of the population with normal BP, elevated BP, S2 and S1 hypertension at baseline were calculated and Pearson's χ^2 test and Wilcoxon rank-sum test were used to assess sex,

age, treatment, depressed-mood, and additional risk differences. The S1 and S2 hypertension categories were stratified by sex and age groups (10-years), and significance of the obtained results were assessed using Cochran-Armitage Test for Trend. Similarly, trends in antihypertensive treatment by age groups were assessed.

Fatal cardiovascular disease events

Mortality rates of CVD adjusted for all primary risk factors were calculated for each BP category. Proportional hazards models were computed to assess the association of elevated BP, S2 and S1 hypertension with CVD mortality, where normal BP was considered as the reference group. Four stepwise multivariate models adjusted for (1) age, sex, survey (2) life-style factors (3) somatic factors (4) and depressed mood were calculated. Model 4 included all primary risk factors. A similar stepwise analysis was conducted for the combined S1 + S2 hypertension strata vs. normal BP. In order to ensure power of the analyses was at least 80%, a Logrank test was conducted for comparison of survival rates of CVD mortality in participants with S1 or S2 hypertension vs normal BP.

Sensitivity analyses calculated the impact of high CVD risk, relative risk of CVD for treated vs. non-treated participants, and the combined S2 + S1 variables vs. normal BP. Proportional hazards could be estimated by fitting models stratified by the risk factor categories and plotting the log-log survival curves for each risk factor, which were assessed for parallelism by visual inspection. As severe deviations from parallelism were not observed for any covariates of CVD events, proportional hazards were assumed. Competing risks were accounted for by Cumulative incidence functions (CIF) using Gray's test. Fine and Gray's sub-distribution hazard model was fitted by specifying event of interest, and by censoring for competing events (non-CVD mortality)¹⁵.

For all analyses, a p value < 0.05 was considered to be statistically significant. All statistical evaluations were performed using SAS (version 9.3). The analysis and the description in this manuscript follow the STROBE guidelines for cohort studies.

Results

Baseline characteristics of hypertension

We investigated a population based sample of 11,603 subjects, including 5,982 men (51.6%) and 5,621 women (48.4%) with a mean age of 47.26 years (± 13.3) at baseline. In the total sample,

3,914 (33.7%) patients had S2 hypertension. Once the ACC/AHA Guideline's cut-off values for S1 hypertension were applied, an additional 3,404 (29.3%) patients were diagnosed with hypertension, almost doubling the prevalence to 7,318 (63%).

Sex and age Analysis

As shown in [Figure 1](#), men had higher S2 (41%) and S1 (33%) hypertension in comparison to women (26% for both S2 and S1 hypertension). The prevalence of S2 hypertension increased with increasing age in both sexes, while the prevalence of S1 hypertension decreased with increasing age for men, and also after 45 years for women ($p < .0001$).

Baseline prevalence of cardiovascular disease risk factors

Participants with S2 hypertension presented the most adverse risk factor profile in comparison to other BP groups: they were more likely to be obese, physically inactive, have hypercholesterolemia, and type 2 diabetes ([Table 1](#); $p < .0001$ for all baseline characteristics and BP group associations). The prevalence of S1 criterion resulted in a similar, albeit less pronounced adverse risk factor profile. Correspondingly, the 'high CVD risk' category showed a clear dose-response relationship effect with increasing BP: 7% for normal BP, 10% for elevated BP, 14% for S1 and 21% for S2 hypertensive participants.

Blood pressure lowering treatment

In the S2 hypertension stratum, we identified 948 (24.1%) patients under treatment, while the remaining 2,971 (75.9%) did not receive treatment. Further analysis of non-treated participants revealed a clear age related trend, showing that the younger the patient, the less adherent to medication ([Figure 2b](#)). For instance, 325 (97.3%) participants between 25-35 years were non-treated, in comparison to 444 (56.4%) of participants over 65 years old.

Blood pressure and depression

In contrast to the other risk factors, higher BP was associated with having lower depressed-mood ([Table 1](#)). However, S2 patients under treatment, and thus labelled as hypertensive, were the exception to this finding¹⁶. Among S2 participants, there was a significantly higher prevalence of depressed-mood in treated patients (47%) in comparison to non-treated patients (33%) ($p < .0001$).

Cardiovascular disease mortality

In the primary model, the CVD-specific mortality per 1000 persons within the 10-year follow-up period was 1.61 cases in S2 hypertension (95% CI 1.10-2.25), 1.07 cases in S1 hypertension (95% CI 0.71-1.64), and 1.0 cases in elevated BP (95% CI 0.59-1.68) in reference to normal BP ([Figure 3](#)).

[Table 2](#) displays the risk of CVD mortality for participants with S2 hypertension, S1 hypertension, and S1 + S2 hypertension combined, in comparison to normal BP. In the S2 hypertension stratum, statistical significance for CVD risk was reached in each stepwise-adjustment of the Cox regression model, including the primary model adjusted for all risk factors (Model 4: HR 1.54, 95% CI 1.04-2.28, $p=0.03$).

In contrast, the risk of CVD mortality in both S1 hypertension (Model 4: HR 0.93, 95% CI 0.61-1.44, $p=0.76$) and elevated BP strata (Model 4: HR 0.77, 95% CI 0.44-1.34, $p=0.36$) vs. normal BP, did not reach statistical significance in any model. Furthermore, combining the S2 and S1 hypertension strata in comparison to normal BP also did not yield significant results between BP >130/80 and CVD mortality in the primary model (HR: 1.29, 95% CI 0.89-1.89, $p=0.18$).

Competing risks analyses showed that in the primary model, S2 hypertension was associated with CVD mortality risk by HR 1.47 ($p=0.05$), S1 hypertension by HR 1.01 ($p=0.95$), and elevated BP by HR 0.88 ($p=0.6$). The effect of competing events (non-CVD related mortality) had a HR of 1.19 ($p=0.2$) in S2 hypertension, and HR of 1.01 ($p=0.96$) in S1 hypertension.

Sensitivity analyses examining differences of CVD mortality between medically treated vs. non-treated participants with S2 and S1 hypertension were conducted. In the primary model, non-treated S2 participants were at two-fold risk of CVD mortality in comparison to treated S2 participants (HR: 2.00, 95% CI 1.14-3.49, $p=0.01$), whereas a significant difference of CVD mortality was not found in S1 participants who were treated vs. non-treated (HR: 1.33, 95% CI 0.73-2.42, $p=0.35$).

An additional sensitivity analyses considering the effect of CVD history showed HR of 1.54 (95% CI: 1.03-2.21, $p=0.03$) in S2 hypertension, HR 1.03 (0.68-1.57, $p=0.88$) in S1 hypertension.

Impact of concurrent cardiovascular disease risk factors

As shown in [Table 2](#), majority of confounding risk factors had a comparable or higher impact than hypertension on CVD related mortality. For S2 participants, a noteworthy finding was that obesity and depressed mood (HR 1.34, 95% CI 1.05-1.72) showed similar associations to the risk of

CVD mortality, demonstrating the high relevance of mental health on CVD related outcomes as comparable to the well-established risk factor of obesity. In comparison, significant associations between depressed mood, obesity and the risk of fatal CVD events were not found in participants with normal BP.

Discussion

The implementation of the 2017 ACC/AHA Guideline to a German community-dwelling population in the age range of 25-74 years increased the prevalence of hypertension from 34% to 63%. The increase reported herein is notably higher than the recent estimate by Muntner et al., of a rise in hypertension prevalence from 32% to 46% ⁴. Nonetheless, given the substantial burden that such high range of new patients would add to health care systems, is it unclear whether the new cut-off points are medically justified.

The present investigation confirms the validity of the S2 hypertension cut-off by showing significant prospective impact in CVD mortality. In contrast, the S1 hypertension cut-off failed to show statistically significant results. However, given the wide boundaries of the confidence intervals, we cannot disprove an increased CVD mortality risk that has been reported in various studies included in previous meta-analyses. Nonetheless, the CVD mortality rates in the S1 hypertension stratum were near the range of elevated BP and normal BP.

These results presented here are in contrast to a meta-analysis of 20 prospective studies including 1,129,098 participants performed by Y Huang et al. showing “prehypertension” (defined as SBP 120-139 mmHg) significantly increased the risk of CVD mortality ⁹. However, the significant effect reported in the meta-analysis was driven by four studies, while the remaining 14 studies failed to show significant findings.

The meta-analyses of relevant RCTs also present contradictory findings regarding the optimal BP cut-off for treatment. Our results contradicted the meta-analysis by Ettehad et al. including 612,815 participants from 123 RCTs showing that a SBP reduction of 10 mmHg reduced risk of CVD events and mortality across all SBP strata, independently of baseline SBP ⁷. A similar finding was achieved by Bundy et al. where 42 BP lowering RCTs with 144,220 participants were analyzed ⁶. Within these studies, the goal of BP reduction was set at SBP of 120-124 mmHg and a linear

association between mean achieved SBP reductions and CVD risks was evident, including for subjects with 130 mmHg SBP at baseline (HR: 0.71). However, the current investigation confirms the most recent and comprehensive meta-analysis by Brunström et al. which included 74 trials with over 300,000 patients. This meta-analysis shows that when baseline SBP is ≥ 140 mmHg, treatment of hypertension is associated with reduced risk of CVD and death. However, at levels < 140 , treatment did not lead to observed benefits, with an exception only for coronary heart disease patients ⁸.

The ACC/AHA Guidelines aim to decrease the prevalence of hypertension by introducing preventive BP lowering intervention for the S1 population before they reach S2. At first glance, it sounds sensible to target higher-risk individuals for risk factor modification; however, our findings suggest that it is not the optimal approach. First, room for improvement in adherence to antihypertensive medication remains high: 76% of S2 patients remained untreated, and among the medically treated S2 population, only 13% had successfully lowered BP at baseline. Furthermore, the situation remains concerning after follow-up of higher risk individuals identified at baseline. For example, a study by Markus et al., including 1,145 subjects from the population based MONICA/KORA S3 survey performed in 1994/1995, and at follow up in 2004/2005, shows that at baseline, 37.5% of participants were within the S2 hypertension stratum or receiving antihypertensive medication. However, after the 10-year follow up period, only 8.6% participants had lowered their BP below 140/90 mmHg, despite being aware of their BP status during the initial examination ¹⁷. Second, the baseline prevalence of CVD risk factors showed a clear dose-response relationship with BP; S2 participants led the unhealthiest lifestyle and had the highest CVD risk. This also implies that classifying as hypertensive does not lead to a decrease in unhealthy lifestyle factors, and a lower hypertension classification may not have relevance to initiating lifestyle interventions. Hence, the results demonstrate that having the firmly established ECS hypertension guideline did not lead to higher medical treatment or a healthier lifestyle, and it is doubtful whether a new guideline would lead to higher compliance with BP lowering initiatives.

The relative risk analysis conducted in the present investigation shows that S2 hypertension is not the only significant predictor of CVD risk; and in reality, other risk factors are comparable or present even higher risk. In line with previous findings by Ladwig et al., depressed mood is a

significant risk factor to consider, leading to a 34% increase in risk of fatal CVD events in the S2 hypertension stratum¹⁸. However, based on the cross-sectional baseline analysis, participants in the S2 stratum actually had less depressed mood in comparison to other BP groups, with an exception: among those using antihypertensive medication, half also reported to having depressed mood, compared to a third of those not using medication. In line with these findings, Herrmann-Lingen et al. showed that a higher BP per se was related to less depression, however patients labelled as hypertensive had more depressive symptoms than those without, partially due to medication and awareness of being ill¹⁶. Hence, high BP could have a protective effect against depression, as suggested by the decrease in depressed mood, however the substantial risk of depressed mood on CVD events is amplified from an awareness of being ill.

Furthermore, labelling has adverse effects on an individual's state of physical and mental health. A review by Pickering shows that diagnoses of hypertension has harmful consequences such as anger, anxiety, depression, deterioration of marital and home life, and worse perception of health in comparison to those without hypertension¹⁰. The landmark study of this phenomenon, performed by Haynes et al., includes steelworkers recently diagnosed with hypertension, and reports increased work absenteeism by 80% in the following year¹⁹. Furthermore, an experimental study by Rostrup et al., involving military recruits in Norway shows hypertension labelling leads to increase in BP at the next medical examination²⁰. Similarly, labelling of people within the S1 stratum as hypertensive could possibly result in the adoption of sick roles²¹.

Limitation

A limitation of this prospective study is that direct cause and effect relationships cannot be discerned. Furthermore, although we adjusted for a variety of important confounding variables, we cannot exclude that unknown risk factors may have biased the results. Similarly, the wide age range of the population could contribute to the wide confidence intervals in the current study, however, this was in line with the ACC/AHA guidelines which do not distinguish between different age groups. The strength of the study is the heterogeneity of a large number of subjects randomly drawn from the population and representative of all hypertensive patients in the community-dwelling population and hence in line with the ACC/AHA guidelines, as opposed to target groups with specific conditions in

RCTs. Additional strengths were the availability of data on lifestyle and multiple risk factors, which were measured according to a standardized protocol.

Conclusion

The current prospective epidemiological study has provided a view into the real world situation of S2 and S1 hypertension patients. The authors of this study recommend a shift of focus back towards BP lowering for patients within the S2 hypertension stratum. As is shown, the departure from the previous US and the current ESC guideline has captured a population that presents lower CVD-specific mortality, and statistically insignificant fatal CVD events. However, participants with S1 hypertension may present clinically significant risk factors that is associated to CVD mortality and should not be overlooked by health care workers (Table 2). Nevertheless, the burden on the health care system arising from a lower hypertension cut-off may not be justified considering the potential adverse effects.

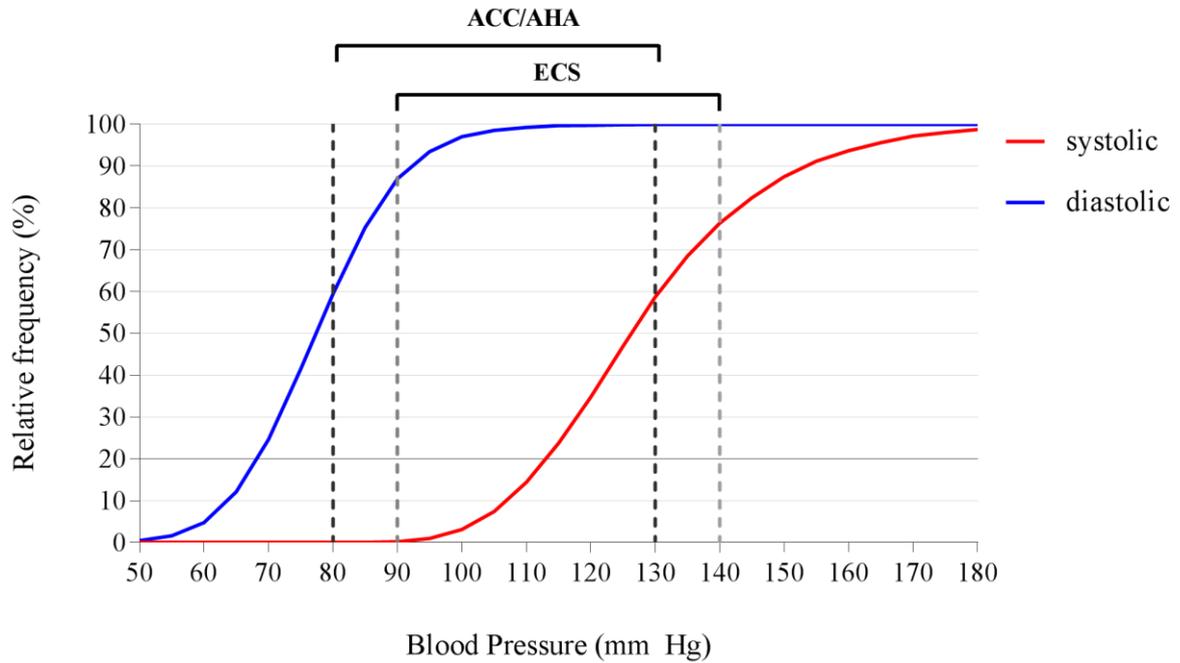
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Central Illustration: Departure from the current ECS to the ACC/AHA hypertension cut-off has increased hypertension prevalence, while capturing a population with substantially lower CVD risk.



- **ECS** = European Society of Cardiology;
hypertension defined as ≥ 140 systolic or ≥ 90 diastolic
- **ACC/AHA** = American College of Cardiology & American Heart Association;
hypertension defined as 130-139 mm Hg systolic or 80-89 mm Hg diastolic

Figure 1. Prevalence of S1 and S2 hypertension in men (n=5,982) and women (n=5,621) of the MONICA/KORA study, by age group.

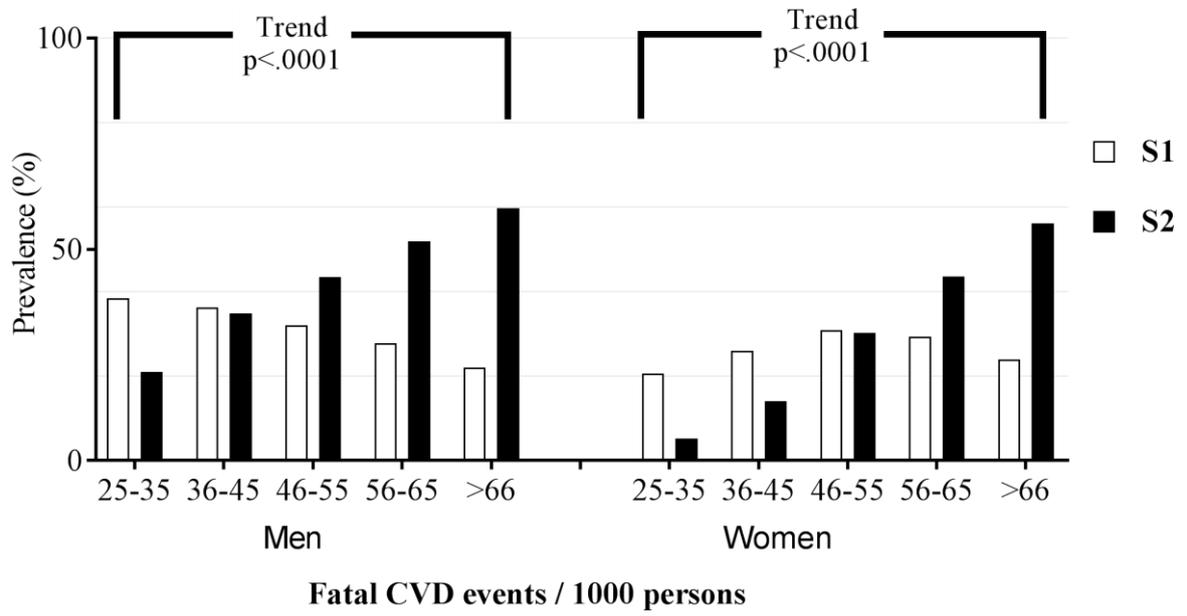


Figure 2. Prevalence of non-treated S2 hypertension participants by age group in the MONICA/KORA cohort (n=2,971).

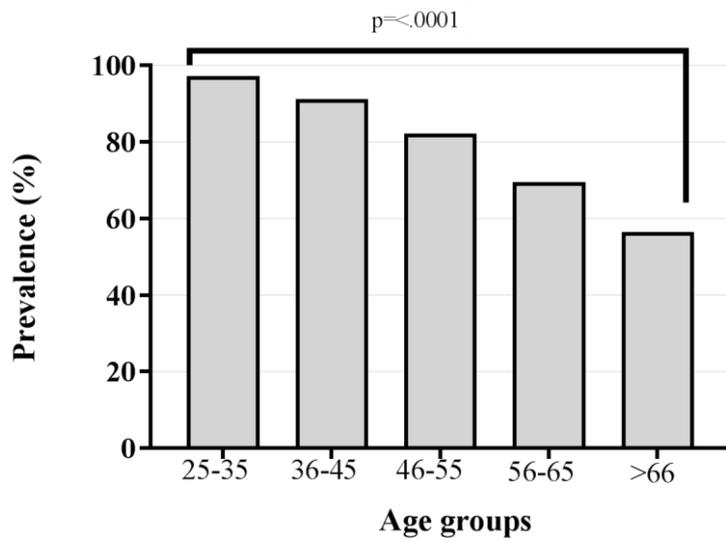


Figure 3. Adjusted CVD-specific mortality per 1000 persons with S2 and S1 hypertension in the MONICA/KORA study (N=11,603)

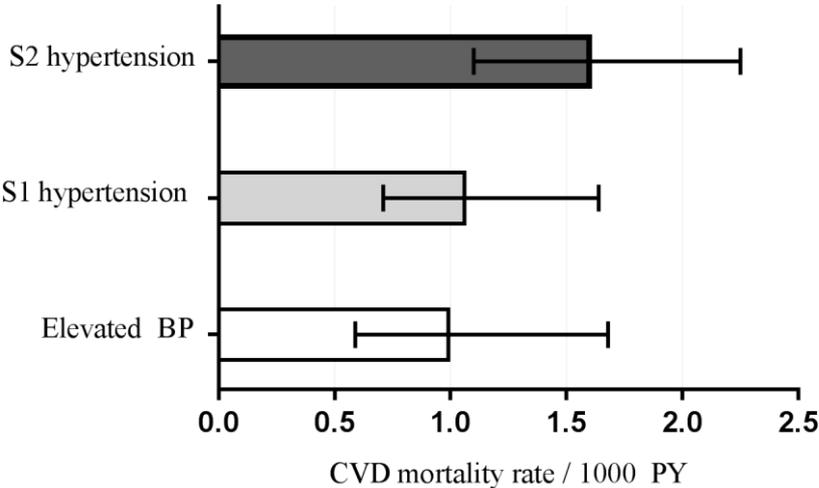


Table 1. Baseline characteristics of CVD risk factors grouped by BP categories of the 2017 ACC/AHA Guideline in adults between 25-74 years old (N=11,603)

| | | Normal BP | Elevated BP | Stage 1 hypertension | Stage 2 hypertension | <i>p</i> |
|-----------------------------|---------------|------------------|--------------------|-----------------------------|-----------------------------|----------|
| | | ≤120/80 | 120-129/<80 | 129-139/80-89 | ≥140/>90 | |
| Total (n,%) | | 2857 (24.62) | 1429(12.32) | 3403 (29.33) | 3914 (33.73) | <.0001 |
| Age (mean years, SD) | 47.25 (±13.3) | 41.18 (±11.7) | 45.12 (±13.8) | 46.44 (±12.8) | 53.32 (±12.2) | <.0001 |
| Men | 5982 (51.6) | 872 (30.5) | 758 (53.0) | 1919 (56.4) | 2433 (62.2) | <.0001 |
| Women | 5621 (48.4) | 1985 (69.5) | 671 (50.0) | 1484 (43.6) | 1481 (37.8) | <.0001 |
| Smoking | 2807 (24.2) | 747 (26.2) | 389 (27.2) | 826 (24.3) | 845 (21.6) | <.0001 |
| Hyperchol ¹ | 4687 (40.4) | 775 (27.1) | 478 (33.5) | 1364 (40.1) | 2070 (52.9) | <.0001 |
| Obesity ² | 2123 (18.3) | 216 (7.6) | 160 (11.2) | 605 (17.8) | 1142 (29.2) | <.0001 |
| Physical inactivity | 6698 (57.8) | 1509 (52.8) | 775 (54.2) | 1911 (56.2) | 2503 (64.0) | <.0001 |
| Type 2 Diabetes | 422 (3.6) | 26 (0.91) | 38 (2.7) | 113 (3.3) | 245 (6.3) | <.0001 |
| Depressed mood | 4251 (36.6) | 1125 (39.4) | 520 (36.4) | 1201 (35.3) | 1405 (35.9) | .01 |
| High CVD Risk ³ | 1616 (13.9) | 210 (6.9) | 118 (9.5) | 460 (13.5) | 828 (21.2) | <.0001 |
| History of CVD ⁴ | 961 (8.3) | 151 (5.3) | 108 (7.6) | 238 (7.0) | 464 (11.9) | <.0001 |
| Antihypertensive Medication | 1535 (13.2) | 130 (4.6) | 123 (8.6) | 339 (10.0) | 943 (24.1) | <.0001 |

¹Hypercholesterolemia: total cholesterol ≥ 240 mg/dL, ²obesity: BMI ³ 30 kg/m², ³high CVD risk: 3 or more CVD risk factors present,

⁴history of CVD: presents prevalent myocardial infarction, heart failure, angina or stroke

Table 2. Hazard Ratios (HR, 95% CI) of fatal CVD events in S2 hypertension ($\geq 140/90$ mmHg) (n=3,914), S1 hypertension (130-139 mmHg systolic/80-89 mmHg diastolic) (n=3,403) and combined S2 and S1 hypertension (n=7,317) in comparison to normal BP (n=2,857).

| Variable | Model 1 | Model 2 | Model 3 | Model 4 |
|-------------------------------|---------------------------|---------------------------|--------------------------|--------------------------|
| S2 vs. normal BP | 1.85 (1.26-2.71)** | 1.71 (1.16-2.51)** | 1.53 (1.04-2.27)* | 1.54 (1.04-2.28)* |
| Smoking | - | 2.18 (1.64-2.89)*** | 2.11 (1.60-2.78)*** | 2.11 (1.59-2.80)*** |
| Physical inactivity | - | 1.23 (0.93-1.63) | 1.25(0.95-1.64) | 1.21 (0.96-1.59) |
| Obesity ¹ | - | 1.55 (1.20-2.00)*** | 1.44 (1.12-1.87)** | 1.47 (0.14-1.91)** |
| Hypercholesterol ² | - | - | 1.22 (0.95-1.56) | 1.22 (0.95-1.57) |
| Type 2 Diabetes | - | - | 2.67 (1.96-3.62)*** | 2.60 (1.92-3.54)*** |
| Depressed Mood | - | - | - | 1.34 (1.05-1.71)* |
| S1 vs. normal BP | 1.10 (0.72-1.67) | 1.08 (0.71-1.65) | 0.95 (0.62-1.46) | 0.93 (0.61-1.44) |
| Smoking | - | 2.29 (1.48-3.56)*** | 2.29 (1.47-3.56)*** | 2.28 (1.46-3.56)*** |
| Physical inactivity | - | 1.67 (1.07-2.59)* | 1.64 (1.06-2.55)* | 1.61 (1.09-2.39)* |
| Obesity ¹ | - | 1.59 (1.04-2.44)* | 1.46 (0.95-2.25) | 1.48 (0.96-2.28) |
| Hypercholesterol ² | - | - | 1.59(1.08-2.36)* | 1.61 (1.09-2.39)* |
| Type 2 Diabetes | - | - | 3.32(1.99-5.57)*** | 3.10 (1.83-5.26)*** |
| Depressed Mood | - | - | - | 1.29 (0.87-1.91) |
| S1+S2 vs. normal BP | 1.56 (1.08-2.26)* | 1.46 (1.01-2.11)* | 1.30 (0.89-1.89) | 1.29(0.89-1.89) |
| Smoking | - | 2.26 (1.78-2.87)*** | 2.19 (1.73-2.79)*** | 2.19 (1.73-2.79)*** |
| Physical inactivity | - | 1.33(1.05-1.65)* | 1.34 (1.06-1.69)* | 1.31 (1.03-1.65)* |
| Obesity ¹ | - | 1.61 (1.30-2.00)*** | 1.49 (1.20-1.86)*** | 1.52 (1.22-1.89)*** |
| Hypercholesterol ² | - | - | 1.36 (1.10-1.68)** | 1.36 (1.10-1.68)** |
| Type 2 Diabetes | - | - | 2.82 (2.12-3.67)*** | 2.73 (2.10-3.55)*** |
| Depressed Mood | - | - | - | 1.29 (1.05-1.60)* |

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

¹obesity: BMI ≥ 30 kg/m, ²Hypercholesterolemia: total cholesterol ≥ 240 mg/dL

Model 1: crude model (adjusted for age, sex and survey)

Model 2: adjusted for age, sex, survey and lifestyle factors

Model 3: adjusted for age, sex, survey and lifestyle and somatic factors

Model 4: adjusted for age, sex, survey, lifestyle factors, somatic factors and depressed mood