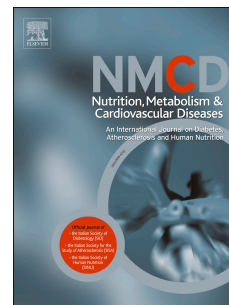


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The Combined effect of blood pressure and C-reactive protein with the risk of mortality from coronary heart and cardiovascular diseases

A brief title: Combined effect of systolic blood pressure, CRP and Mortality

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Abstract

Background and aims: Both blood pressure and C-reactive protein (CRP) are individually associated with cardiovascular mortality risk. However, the combined effect of systolic blood pressure (SBP) and CRP on coronary heart disease (CHD) and cardiovascular disease (CVD) mortality risk, has not been studied.

Methods and Results: We evaluated the joint impact of SBP and CRP and the risk of mortality in the Kuopio Ischemic Heart Disease prospective cohort study of 1622 men aged 42-61 years at recruitment with no history of CVD. SBP and CRP were measured. SBP was categorized as low and high (cut-off 135 mmHg) and CRP as low and high (cut-off 1.54 mg/L) based on ROC curves. Multivariable adjusted hazard ratios (HRs) with confidence intervals (CI) were calculated.

During a median follow-up of 28 years, 196 cases of CHD and 320 cases of CVD deaths occurred. Elevated SBP (>135 mmHg) combined with elevated (CRP >1.54mg/L) were associated with CHD and CVD mortality (HR 3.41, 95% CI, 2.20–5.28, $p<0.001$) and (HR 2.93, 95% CI, 2.11–4.06, $p<0.001$) respectively after adjustment for age, examination year, smoking, alcohol consumption, BMI, Type 2 diabetes, energy expenditure, total cholesterol, serum HDL cholesterol, antihypertensive medication and use of aspirin.

Conclusion: The combined effect of both high systolic blood pressure and high CRP is associated with increased risk of future CHD and CVD mortality as compared with both low SBP and low CRP levels in general male Caucasian population.

Key words: C-reactive protein, men, systolic blood pressure, mortality

HIGHLIGHTS

- Little is known about the combined effect of systolic blood pressure (SBP) and CRP on mortality
- The combined effect of raised SBP and CRP is associated with increased risk of mortality from cardiovascular causes
- The combined effect of both the factors should be considered while initiating therapy

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Introduction

Inflammation plays an important role in the progression and development of cardiovascular disease (CVD) (1). The commonly used inflammation marker C-reactive protein (CRP) is an acute-phase protein produced in response to infection, tissue injury caused by infection and inflammation. However, evidence shows that CRP levels may contribute to an increased risk of CVD (2, 3, 4, 5, 6). It is known that inflammation plays a role in the development of hypertension (7). Hypertension is an established risk factor for CVD morbidity and mortality, and almost 50% of the CVD events attributed to it. Furthermore, CRP predicts CVD risk beyond the other known CVD risk factors (8, 9, 10, 11, 12). CRP, is also known to be associated with cardiovascular events such as myocardial infarction, stroke, coronary events, cardiovascular events and mortality after premature coronary event coronary events (9, 10, 11, 12). Among hypertensive patients higher CRP levels have been observed (7-9). Increased CRP levels reduce nitric oxide production in endothelial cells (13, 14) leading to vasoconstriction and increased production of endothelin (15, 16). It has been suggested that hypertension may be in part an inflammatory disorder. CRP has been associated with myocardial infarction, stroke, coronary events, cardiovascular events and mortality after premature coronary event in both men and women (9, 10, 11, 12, 17, 18, 19). Hence the aim of our prospective population-based study was to study the combined effect of elevated blood pressure and CRP as risk predictors for CHD and CVD mortality in general male population.

Study Population

The Kuopio Ischemic Heart Disease (KIHD) risk factor study, a population-based prospective cohort study designed to study risk factors for atherosclerotic cardiovascular outcomes in a population-based sample of men from eastern Finland. The study population was a representative sample of men living in the city of Kuopio and its surrounding rural areas who were 42–61 years of age at baseline examinations performed from March 1984 through December 1989. 2682 eligible men participated in the study. The present analysis are based on 1622 participants with no history of CVD and had complete data on relevant covariates, and mortality. The study was approved by the Research Ethics Committee of the University of Eastern Finland, and each participant provided written informed consent. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Classification of mortality events

Statistics Finland annually links the date and underlying, immediate, and intermediate causes of death to KIHD subjects. The classification of death bases on the International Classification of Diseases (ICD) developed by the World Health Organization.

Cardiovascular deaths refer to ICD-10 codes I00–I99 and ICD-9 codes 390–459. Non-cardiovascular deaths refer to all other causes of death. In this study, we classified deaths according to the underlying cause. Cardiovascular disease deaths included deaths from causes other than coronary heart disease deaths and included cerebrovascular causes, and peripheral vascular diseases. CHD deaths included both stable and unstable angina, myocardial infarction and all other heart conditions diseases. Coronary heart disease deaths were based on diagnosis based on symptoms, ECG findings, cardiac enzyme elevations and autopsy findings due to cardiac reasons.

Assessment of risk markers

An experienced nurse measured blood pressure using a sphygmomanometer (Hawksley, United Kingdom) in a seated position in a quiet room from 8:00 to 10:00 am (20). The BP protocol used was 15 minutes of supine rest with BP measured at minutes 5, 10, and 15; standing at rest with 1 BP reading taken after 1 minute; and 10 minutes of seated rest with BP measured at minutes 5 and 10 (20). The mean of these 6 values were used as mean BP at rest. Hypertension at rest was defined as hypertension confirmed by current use of antihypertensive medication and/or SBP >140 mmHg and/or DBP >90 mmHg.

Physical examination was performed at the baseline visit together with blood samples taken, and self-administered questionnaires collected. Body weight and height were also measured. Body mass index (BMI) was estimated as weight in kilograms divided by the square of height in meters. Blood samples were taken between 8 and 10 a.m. after an overnight fast. In addition, participants were asked to abstain from alcohol consumption for at least 3 days and smoking for at least 12 h prior to blood collection. Serum samples were stored frozen at -80°C before measurements of lipids and biochemical analytes. Serum CRP measurements were made with an immunometric assay (21) (Immulite High Sensitivity CRP Assay; DPC, Los Angeles, CA, USA). Fasting plasma glucose (FPG) was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany). For the assessments of alcohol consumption, smoking, baseline health conditions, medication history, socioeconomic status, and education; participants completed self-administered health, cardiovascular diseases in family and lifestyle questionnaires (21, 22). The energy expenditure of physical activity was assessed using the validated KIHD 12-month leisure- time physical activity questionnaire.

Statistical analysis

We examined SBP and CRP and the other risk factors for CHD and CVD mortality by using Cox proportional hazard modeling. To investigate the joint associations of SBP and CRP, with mortality risk, the values of SBP and CRP, were divided into two categories of low/high. Low SBP (≤ 135 mmHg) and low CRP (≤ 1.54 mg/L) were used as a reference category. These cut-off values were based on ROC curves and they were chosen according to the Youden's index that refers to the maximum sum of sensitivity and specificity - 1. Three sets of covariates were used: Model (1) consisted of age and examination year; Model (2) consisted of Model 1 with the smoking, alcohol consumption, BMI, Type 2 diabetes, energy expenditure, total cholesterol, serum HDL cholesterol, antihypertensive medication and use of aspirin.; and Model (3) consisted of Model 2 together with education, socio-economic status, and history of cardiovascular diseases in the family. We also tested high DBP as a risk factor for CHD and CVD mortality but omitted it from the models because, based on preliminary analyses, SBP was approximately a 1.5-times stronger predictor. Relative hazards were adjusted for risk factors and estimated as antilogarithms of coefficients from multivariable models. All tests for statistical significance were defined as p-values of < 0.05 and were 2-sided. Spearman's correlation was used for biomarkers and selected characteristics. The Kaplan-Meier method was used to calculate the cumulative hazard of mortality according to SBP and CRP cut-off levels (Figures 1 and 2). Statistical analysis was performed by using IBM SPSS software, version 27 for Windows (IBM, Armonk, NY).

Results

During a median follow-up of 28 years, 196 CHD and 320 CVD deaths occurred. Baseline characteristics of subjects in different groups are shown in Table 1. Mean age was 52 years, while SBP was 134 mmHg and mean serum CRP levels were 2.2 mg/L, respectively. Men in the reference group (SBP \leq 135 mmHg and CRP \leq 1.54 mg/L) were younger, had lower BMI, consumed less of alcohol, had fewer cases of type 2 diabetes, and fewer men were smokers or on antihypertensive medication, and had lower case of cardiovascular disease in family but had higher education and socioeconomic statuses. Men with high SBP combined with high CRP ($>$ 135 mmHg and $>$ CRP of $>$ 1.54 mg/L) were older, had higher BMI, consumed more of alcohol, had higher total cholesterol and lower HDL cholesterol, had more cases of type 2 diabetes, used more of antihypertensive and aspirin medication and had higher case of cardiovascular disease in family but had lower education status as compared to other groups.

Systolic blood pressure, C-reactive protein and coronary heart disease mortality

In our study, elevated SBP combined with elevated CRP were associated with CHD risk. In an age and examination year adjusted model, when we compared the high SBP combined with high CRP ($>$ 135 mmHg and $>$ 1.54 mg/L) with combined low levels of SBP combined with low CPR (\leq 135 mmHg, \leq 1.54 mg/L reference group) 4.67-fold hazard (95% CI 3.11–7.01, $p<$ 0.001) resulted. Compared to alone high SBP ($>$ 135 mmHg) or high CRP ($>$ 1.54 mg/L), the combination of high SBP and high CRP was approximately two times stronger predictor of CHD, respective HRs for alone high SBP and alone high CRP were 2.21 and 2.29. Statistically significant results were also observed in the group of high SBP ($>$ 135 mmHg) or high CRP ($>$ 1.54 mg/L), (HR, 2.42, 95% CI, 1.65–3.54, $p<$ 0.001). After further adjustment for alcohol consumption, BMI, energy expenditure during exercise, serum total

cholesterol, serum HDL-cholesterol, type 2 diabetes, smoking, antihypertension medication and aspirin the hazard ratio remained statistically significant (HR, 3.41, 95% CI, 2.20–5.28, $p < 0.001$). Further adjustment for socio-economic status, years of education and history of cardiovascular disease in family (Table 2a) the results hardly changed (HR, 3.39, 95% CI, 2.19–5.25, $p < 0.001$). Again, statistically significant results were also observed in the group of high SBP (>135 mmHg) or high CRP (>1.54 mg/L), (HR, 2.24, 95% CI, 1.51–3.31, $p < 0.001$).

Increase in systolic blood pressure, C-reactive protein and coronary heart disease mortality

Furthermore, we also wanted to investigate the role of increase SBP in general population when CRP was below 10mg/L and clinically insignificant as a risk factor for CHD mortality. Subjects, $n=1573$, were divided into groups depending upon their SBP levels. Men with a mean SBP of 123 mmHg (range 93–135 mmHg) together with mean CRP of 0.76 mg/L (range 0.10–1.54 mg/L) was the reference group. Among men with mean SBP of 149 mmHg (range 135–203 mmHg) and mean CRP of 3.18 mg/L (range 1.55–9.87 mg/L) the HR for CHD was 3.54-fold (95% CI, 2.28–5.51, $p < 0.001$) as compared to the reference group after adjustment for all conventional risk factors comparable to Model 3.

Systolic blood pressure, C-reactive protein and cardiovascular disease mortality

In this study, elevated SBP combined with elevated CRP were associated with CVD mortality risk. In an age and examination year adjusted model, when we compared the high SBP combined with high CRP (>135 mmHg and >1.54 mg/L) with combined low levels of SBP combined with low CRP (≤ 135 mmHg, ≤ 1.54 mg/L reference group) 3.57-fold hazard (95%

CI, 2.64–4.83, $p < 0.001$) resulted. Compared to alone high SBP (>135 mmHg) or high CRP (>1.54 mg/L), the combination of high SBP and high CRP was nearly two times stronger predictor of CVD, respective HRs for alone high SBP and alone high CRP were 2.01 and 1.96. After further adjustment for alcohol consumption, BMI, energy expenditure during exercise, serum total cholesterol, serum HDL-cholesterol, type 2 diabetes, smoking, antihypertension medication and aspirin the risk remained statistically significant (HR, 2.93, 95% CI, 2.11–4.96, $p < 0.001$). Further adjustment socio-economic status, years of education and history cardiovascular disease in family (Table 2b) the results slightly attenuated (HR, 2.91, 95% CI, 2.10–4.04, $p < 0.001$). Statistically significant results were also observed in the group of high SBP (>135 mmHg) or high CRP (>1.54 mg/L), (HR, 1.81, 95% CI, 1.35–2.41, $p < 0.001$).

Increase in systolic blood pressure, C-reactive protein and cardiovascular disease mortality

Furthermore, we also wanted to investigate the role of increase SBP in general population when CRP was below 10mg/L and clinically insignificant as a risk factor for CVD mortality. Subjects, $n=1573$, were divided into groups depending on their SBP. Men with a mean SBP of 123 mmHg (range 93–135 mm Hg) together with mean CRP of 0.76 mg/L (range 0.10–1.54 mg/L) was the reference group. Among men with mean SBP of 149 mmHg (range 135–203 mmHg) and mean CRP of 3.18 mg/L (range 1.55–9.87 mg/L) the hazard for CVD was 3.01-fold (95% CI, 2.16–4.20, $p < 0.001$) as compared to the reference group after adjustment for all conventional risk factors comparable to Model 3.

Discussion

Among middle-aged men with history of no apparent CVD at baseline, the combined effect of increased SBP and CRP is associated with a substantially increased risk of CHD and CVD mortality compared with low SBP and low CRP in a population-based sample of men.

Studies have revealed that CRP is higher among subjects with elevated blood pressure (7-9).

Inflammation plays an important role in the progression and development of cardiovascular diseases (1). CRP an actively used marker in clinical practice, produced in response to infection, inflammation, and tissue injury. However, increasing evidence suggests that the CRP level may contribute to an increased risk of CVD (2, 3, 4, 5, 6).

Furthermore, inflammation has also been shown to play a role in the development of hypertension (23, 24). It is also known that hypertension predisposes to LVH, which in turn increases the frequency of malignant ventricular arrhythmias (25, 26). Hypertension is known to be the major risk factor for CHD, CVD morbidity and mortality, raised blood pressure is a major burden for both diseases and global mortality. The prevalence of high blood pressure and the number of people effected worldwide are expected to increase over the coming decades (27). Therefore, preventive strategies are needed, and hence the management of hypertension must be optimized. Decreased coronary vasodilatory reserve may cause hypertensive subjects to be more prone and susceptible to ischemic effects of epicardial coronary narrowing (26). The myocardium in hypertensives is more susceptible to arrhythmias, which suggests the possibility that arrhythmic death is the mechanism heightening the mortality risk compared to the more stable myocardium of a normotensive comparison group.

On the basis other studies, a meta-analysis of CRP individuals free of cardiovascular disease at baseline, the risk conferred by increased CRP was comparable to that of increased systolic

blood pressure, total cholesterol, or non-high-density lipoprotein cholesterol after mutually adjusting for these measures (28).

CRP has been reported to decrease production of nitric oxide by endothelial cells (13-14) and thus might indirectly promote vasoconstriction, platelet activation, leukocyte adherence, oxidation, and thrombosis (15, 16). CRP has also been shown to have pro-atherosclerotic properties by upregulating angiotensin type-1 receptor expression (14, 15), affecting the renin-angiotensin system and contributing to the development of hypertension. All these changes indicate progression of atherosclerosis and endothelial dysfunction with structure and functional changes in the endothelium finally leading to the development of hypertension (14, 15, 16). These findings are consistent with cross-sectional associations for both CRP and IL-6, intercellular adhesion molecule 1, and tumor necrosis factor α with hypertension (15, 16, 29). Due to the public health burden of elevated blood pressure and its global impact, a healthy life style and prevention of hypertension appears to be an important population-level tool to prevent the risk of mortality (30, 31,). Smoking and socioeconomic status are important risk factors in mortality. **Lower socioeconomic status is coupled with financial difficulties, unemployment, psychosocial stress, unhealthy habits, health obstacles, lack of social support, and insufficient cohesion leading to premature death (32). Smoking is a leading cause of morbidity and mortality in the world. It is a leading readily preventable factor. The risks of cardiovascular disease, respiratory disease, and cancer are increased in smokers and, as a consequence, smokers are more likely than non-smokers to die prematurely (33).**

The strengths and limitations of our study merit mentioning. The strengths include its prospective population-based design, long and complete follow-up period. Our representative sample makes it possible to generalize the observed results to male Caucasian populations, these results need to be studied in different populations including women. Furthermore, we

only had baseline assessments of CRP and blood pressure, without knowledge of how these markers changed over time which may have underestimated the observed associations. The assessment of baseline clinical conditions by self-administered questionnaires is a limitation of the study. Though many potential confounders were measured and carefully adjusted to ensure the validity of our key findings, there was still be a potential for residual confounding owing to unmeasured risk factors.

In conclusion, our results suggests that the combined effect of high systolic blood pressure and CRP is associated with an increased risk of both CHD and CVD mortality. Further studies are needed to replicate these associations and study the pathways underlying the findings.

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Table 1. Baseline characteristics of middle-aged men with no history of cardiovascular diseases excluding hypertension. Values indicate mean \pm SD unless otherwise informed.

Variable	All subjects	SBP \leq 135 mmHg CRP \leq 1.54 mg/L	SBP $>$ 135 mmHg or CRP $>$ 1.54 mg/L	SBP $>$ 135 mmHg CRP $>$ 1.54 mg/L	P-value Between groups
n	1622	619	700	303	
CVD events (n)	320	75	146	99	
CHD events (n)	196	37	95	64	
Age	52 \pm 5.4	51 \pm 5.6	52 \pm 5.4	53 \pm 5.1	<0.001
Year of examination	1987 \pm 1.7	1987 \pm 1.6	1987 \pm 1.7	1987 \pm 1.7	0.864
Years of education	9.0 \pm 3.6	9.4 \pm 3.8	8.8 \pm 3.5	8.7 \pm 3.4	0.006
Socioeconomic status, higher values indicate lower status	12 \pm 5.1	11 \pm 5.1	12 \pm 5.0	12 \pm 5.0	0.002
BMI	27 \pm 3.5	25 \pm 2.9	27 \pm 3.2	28 \pm 4.2	<0.001
Alcohol consumption (g week ⁻¹)	74 \pm 119	61 \pm 102	75 \pm 124	100 \pm 136	<0.001
LTPA (kcal day ⁻¹)	137 \pm 160	147 \pm 169	127 \pm 147	140 \pm 169	0.070
Serum total cholesterol (mmol l ⁻¹)	5.9 \pm 1.0	5.8 \pm 1.0	5.8 \pm 1.1	6.0 \pm 1.0	0.001
HDL-cholesterol (mmol l ⁻¹)	1.3 \pm 0.3	1.3 \pm 0.3	1.3 \pm 0.3	1.2 \pm 0.3	<0.001
CRP (mg l ⁻¹)	2.2 \pm 4.3	0.8 \pm 0.4	2.4 \pm 3.8	4.8 \pm 7.5	<0.001
SBP (mmHg)	134 \pm 16	123 \pm 8.0	137 \pm 17	149 \pm 12	<0.001
DBP (mmHg)	89 \pm 10	83 \pm 7.5	91 \pm 10	97 \pm 9.0	<0.001
Diabetes (% of yes: FPG $>$ 6.9 mmol l ⁻¹ or medication)	4.3	1.8	4.4	9.2	<0.001
Smoker (% of yes: smoked less than a month ago)	31	26	31	38	0.001
Uses drugs for hypertension (% of yes)	11	6.3	12	20	<0.001
Uses acetylsalicylic acid (% of yes)	5.4	5.2	4.4	8.3	0.046
CVD in family (% of yes).	78	75	80	81	0.031

Table 2a. Hazard ratios for Coronary Heart Disease Death among Men with Systolic blood pressure combined with C-reactive protein.

	Hazards ratio	95 % Confidence Interval		P-value
SBP combined with CRP				
SBP >135 mmHg or CRP >1.54 mg/L	2.24	1.51	3.31	<0.001
SBP >135 mmHg and CRP >1.54 mg/L	3.39	2.19	5.25	<0.001
Age, years	1.11	1.07	1.15	<0.001
Year of examination	0.96	0.87	1.05	0.339
Body mass index kg/m²	1.04	1.00	1.08	0.069
Alcohol consumption, an increase of 10 grams/week	1.01	1.00	1.02	0.088
Energy expenditure, an increase of 100 kcal/day	1.00	1.00	1.10	0.353
Serum total cholesterol, mmol/l	1.07	0.94	1.22	0.324
Serum HDLcholesterol, mmol/l	0.85	0.51	1.41	0.521
Type 2 diabetes mellitus	2.35	1.46	3.77	<0.001
Cigarette smoker	1.64	1.20	2.25	0.002
Use of anti-hypertensive medication	1.36	0.92	2.03	0.127
Use of acetylsalicylic acid	1.01	0.51	1.99	0.979
Years of education	1.02	0.96	1.08	0.539
Socioeconomic status, higher values indicate lower status	1.06	1.01	1.10	0.010
Cardiovascular diseases in family	0.73	0.53	1.02	0.067

Table 2b. Hazard ratios for Cardiovascular Disease Death among Men with Systolic blood pressure combined with C-reactive protein.

	Hazards ratio	95 % Confidence Interval		P-value
SBP combined with CRP				
SBP >135 mmHg or CRP >1.54 mg/L	1.81	1.35	2.41	<0.001
SBP >135 mmHg and CRP >1.54 mg/L	2.91	2.10	4.04	<0.001
Age, years	1.11	1.08	1.14	<0.001
Year of examination	0.98	0.91	1.05	0.580
Body mass index kg/m²	1.03	0.99	1.06	0.129
Alcohol consumption, an increase of 10 grams/week	1.01	1.00	1.02	0.032
Energy expenditure, an increase of 100 kcal/day	1.00	1.00	1.10	0.167
Serum total cholesterol, mmol/l	1.03	0.92	1.14	0.614
Serum HDLcholesterol, mmol/l	1.14	0.77	1.69	0.501
Type 2 diabetes mellitus	1.84	1.21	2.78	0.004
Cigarette smoker	1.73	1.36	2.22	<0.001
Use of anti-hypertensive medication	1.38	1.00	1.91	0.048
Use of acetylsalicylic acid	0.91	0.53	1.57	0.738
Years of education	0.99	0.94	1.04	0.603
Socioeconomic status, higher values indicate lower status	1.04	1.00	1.07	0.025
Cardiovascular diseases in family	0.73	0.57	0.95	0.017

Figure 1. Cumulative hazard of coronary heart disease (CHD) mortality adjusted for age and the year of examination among the middle-aged men (n = 1622) with no history of cardiovascular diseases. High systolic blood pressure (SBP) denotes >135 mmHg and high C-reactive protein (CRP) denotes >1.54 mg/l.

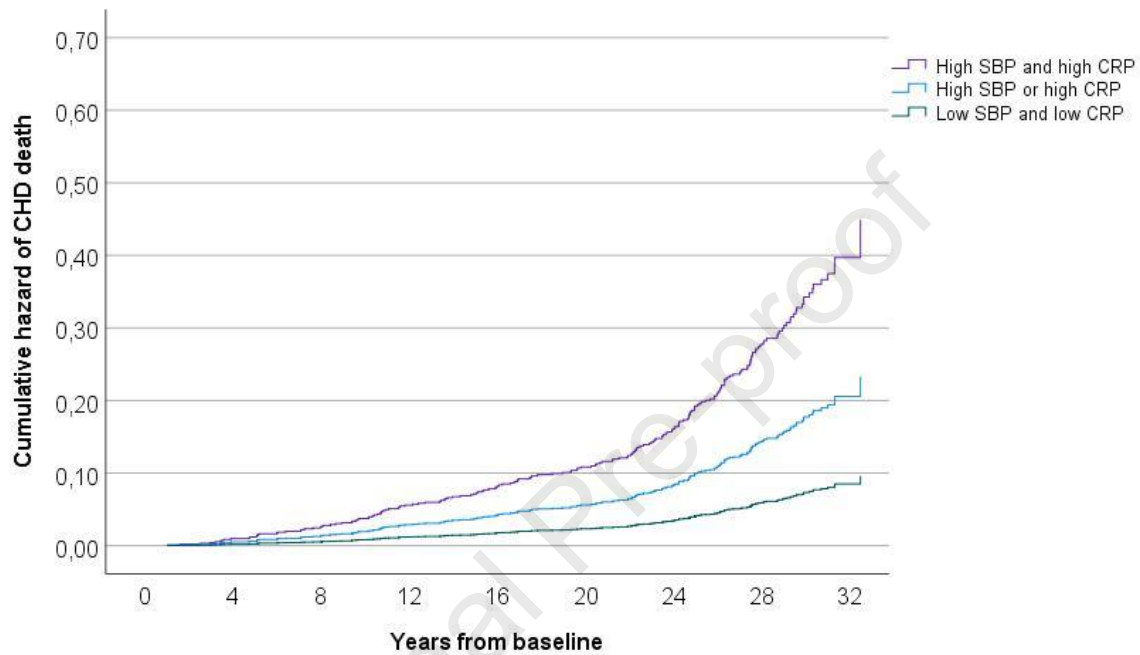
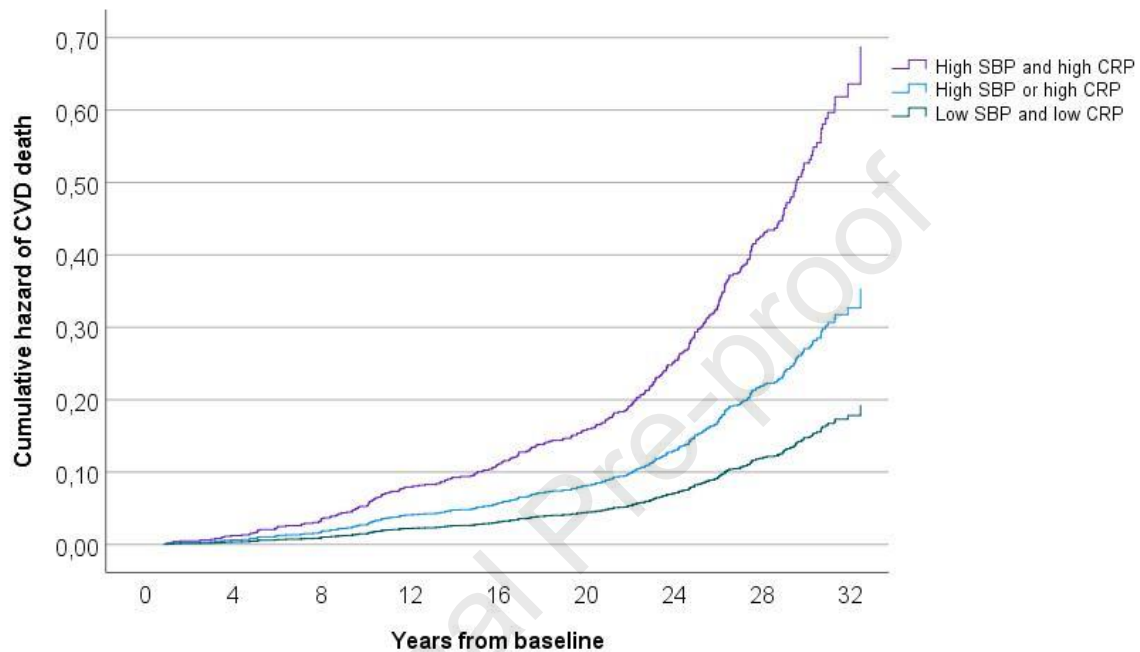


Figure 2. Cumulative hazard of cardiovascular disease (CVD) death adjusted for age and the year of examination among the middle-aged men (n = 1622) with no history of cardiovascular diseases. High systolic blood pressure (SBP) denotes >135 mmHg and high C-reactive protein (CRP) denotes >1.54 mg/l.



HIGHLIGHTS

- Little is known about the combined effect of systolic blood pressure and CRP on mortality
- The combined effect of raised SBP and CRP is associated with increased risk of mortality
- The combined effect of both the factors should be considered while initiating therapy

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