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The relation between change in blood pressure and death from cardiovascular disease

Acknowledgements

Abstract

Background: It is well established that high blood pressure (BP) increase the risk of death from cardiovascular diseases (CVD). However, most studies have focused on baseline BP, and relatively few have examined the effects of a change in BP over a period of time.

Design: Population-based prospective cohort study with 11 years of follow-up.

Methods: The study was carried out using data from the population-based Nord-Trøndelag health study (HUNT) linked with the Cause of Death Registry at Statistics Norway. BP measurements from HUNT 1 (1984-96) and HUNT 2 (1995-97) were used to calculate individual change in BP between the surveys. A total of 25,187 women and 22,099 men were followed up on cause of death from baseline in HUNT 2. We used Cox regression to analyze the effect of both relative and absolute changes in BP, separately for men and women, and also stratified by physical activity level.

Results: During follow-up, 2,084 men and 1,854 women had died from CVD. An absolute increase in Systolic BP of ≥40 mmHg was associated with an increase in risk ratio (RR) of 1.1 (95 % confidence interval (CI) 0.9-1.3 and 0.9-1.4) in both men and women, compared to having a stable BP (-4 to +4 mmHg). On the other hand, a decrease in Systolic BP of ≥20 mmHg was associated with an increase in RR of 1.8 (CI 1.5-2.2) and 1.9 (CI 1.5-2.2) for men and women respectively, compared to being stable. For diastolic BP, the largest increase (≥40 mmHg) was associated with a RR of 1.3 (CI 1.1-1.6 and 1.0-1.5) in both men and women compared to a stable BP. Relative changes in BP showed a similar pattern; the strongest effect was observed among people who reduced their BP between the surveys. However, having a high systolic BP (≥140 mmHg) at both surveys resulted in a RR of 1.4 (CI 1.2-1.7) in men and 2.0 in women (CI 1.6-2.5). There were no large differences in the estimated associations when comparing physically active to inactive, although active people who increased their systolic BP with ≥40 mmHg had a RR of 1.5 (CI 1.0-2.4), whereas this was not evident among the inactive.

Conclusion: Overall, a reduced BP was associated with the highest of death, but the risk was also increased among people with the largest increase in BP, and among those who had a stable high blood pressure. There were marginal differences in the association between BP and risk of death being active and inactive persons.

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Introduction

There is a well-established relation between high blood pressure (BP), or hypertension (HT), and cardiovascular disease (CVD) and mortality (Lewington et al., 2002, Chobanian et al., 2003, Graham et al., 2007, Murakami et al., 2008). Studies have shown that the risk of CVD increases progressively and linearly from levels as low as 115 mmHg systolic blood pressure (SBP) and 75 mmHg diastolic blood pressure (DBP), and for every 20 mmHg systolic and 10 mmHg diastolic increase in BP, there was shown a doubling in CVD mortality (Lewington et al., 2002). Similar, but somewhat weaker results have been reported from another study (Murakami et al., 2008). Correspondingly, longitudinal data from the Framingham Heart Study indicated that BP values in the 130-139/85-89 mmHg range are associated with a more than twofold higher risk (RR) of CVD compared with those with BP levels below 120/80 mmHg (Vasan et al., 2001b).

Whether systolic or diastolic BP is the most important determinant of CVD or mortality has been a subject for discussion. Traditionally, DBP has been considered the best predictor, but during the last three decades, the importance of SBP has become clearer (Strandberg & Pitkala, 2003). High SBP reflects an elevation in total peripheral resistance and/or large artery stiffness, whilst the levels of DBP are influenced by arterial or arteriolar alterations in opposite ways. Hence, an increase in peripheral vascular resistance leads to an elevation in SBP, whereas stiffening of large arteries may induce a decrease in DBP (Fang et al., 1995). Normal levels of BP are therefore influenced by the combination of these two vascular alterations, which are both independent risk factors of CVD, who further is argued with that DBP not necessarily reflect cardiovascular risk (Sleight, 1988, Safar, 1989).

Although the effects of high BP have been extensively studied, relatively few studies have examined the effect of changes in BP over time, and the results have been inconclusive (Tervahauta et al., 1994., Witteman et al., 1994, Vartiainen et al., 1994). These studies were limited by small numbers of subjects and end points, focused on either SBP or DBP, and were primarily adjusted for baseline BP only. However, a few studies have been studying the effects of changes in BP over time in large populations. Sesso et al. (2000a) examined this issue, and found that change SBP had no relation with an increase in CVD, but did find a relation between change in DBP and CVD. Benetos et al. (2000) found a relation between BP and CVD concerning an increase in SBT combined with a decrease in DBP, and with an increase in both SBP and DBP together. Thus, the knowledge concerning implications of

longitudinal changes in BP is somewhat sparse, particularly changes in large population groups, and with long follow-up time.

The purpose of this study is to examine the effect of long term changes in BP on risk of death from CVD, and also to examine if physical activity may influence these associations.

Methods

Study Population

In Nord Trøndelag County in Norway, the total adult population aged 20 years and older was invited to participate in the HUNT Study (Health Study of North Trøndelag) between 1984 and 1986. Among the 87,285 individuals who were eligible to participate in the cohort, 77,216 (39,390 women and 37,826 men) (88.4 %) accepted the invitation. They filled in the questionnaire that was included with the invitation, and attended a clinical examination that among other factors included measurements of blood pressure, body height, and body weight using standardized methods. At the clinical examination, the participants received a second questionnaire that was to be filled in and returned from home with a prestamped envelope. Information was collected on a range of health-related subjects, and included, among other items, self-reported leisure-time physical activity, prior or present use of drugs, history of relevant diseases, smoking status, alcohol consumption, and educational attainment.

Approximately a decade later, a second wave of the HUNT studies, the HUNT 2, was executed (1995-1997). Of the 77,216 participants in HUNT 1, 47,286 (25,187 women and 22,099 men) accepted the invitation to also participate in HUNT 2, which had an isolated participation of 65,215 (72.5 %). The procedures in HUNT 2 were largely similar as in HUNT 1, but more extensive information was collected.

In the main analyses, we included the 47,286 participants who participated in both waves of the study. We excluded 698 participants who had suffered from stoke, myocardial infarction or angina pectoris at baseline, in HUNT 2. A total of 46,598 (24,870 women and 21,728 men) participants were included in the preliminary/initial analysis. In the analyses concerning BP-measurements, 174 subjects had missing values in SBP in either HUNT 1 or HUNT 2, and 181 subjects had missing values in DBP in either HUNT 1 or HUNT 2. Further, in supplementary analyses stratified by PA, 16,279 participants had missing/incomplete data, and we also conducted analyses of people who did not use of antihypertensive drugs, and

excluded 8,250 participants who reported former or current use. Finally, a total of 384 participants had missing data on BMI, and were excluded from the fully adjusted analysis.

Blood Pressure (BP)

In HUNT 1, BP was measured to the nearest 2 mm Hg using calibrated mercury manometers with standard cuff size, whereas in HUNT 2, Dinamap (Criticon), with variable cuff-size was used. For more details, see Holmen et al. (1991). In HUNT 1, BP was measured twice, and in HUNT 2, BP was measured three times. In this study, the BP values that were used in the analyses were the second of the two measurements in HUNT 1, and the mean of the second and third measurements in HUNT 2.

We calculated the individual change in BP measurement, from HUNT 1 to HUNT 2; both the relative and absolute change, and for both systolic and diastolic blood pressure. Regarding absolute changes in BP, participants were classified in six categories, as shown in Table 1. In the regression analyses of relative change we used the category number five as reference, whereas in analyses on absolute change, a stable BP defined as -4 to +4 mmHg was used as reference (i.e. category four).

Regarding relative change, we divided BP in to three categories (<120 mmHg, 120-129 mmHg and ≥140 mmHg in SBP, and <80 mmHg, 80-89 mmHg and ≥90 mmHg in DBP) based on measurements from HUNT 1 and HUNT 2. Further, the participants were then classified into nine separate groups (see Table 2), defined by either an increase, decrease or a stable BP between the surveys.

Table 1. Absolute changes in BP from HUNT 1 to HUNT 2 - categories

Category	Systolic Blood Pressure		Diastolic Blood Pressure	
	From	To	From	To
1	≥+40 mmHg	-	≥+20 mmHg	-
2	+20 mmHg	+39 mmHg	+10 mmHg	+19 mmHg
3	+5 mmHg	+19 mmHg	+5 mmHg	+9 mmHg
4	-4 mmHg	+4 mmHg	-4 mmHg	+4 mmHg
5	-19 mmHg	-5 mmHg	-9 mmHg	-5 mmHg
6	≥-20 mmHg	-	≥-10 mmHg	-

Table 2. Relative changes in BP from HUNT 1 to HUNT 2 - categories

Category	Systolic Blood Pressure		Diastolic Blood Pressure	
	HUNT 1	HUNT 2	HUNT 1	HUNT 2
1	<120 mmHg	<120 mmHg	<80 mmHg	<80 mmHg
2	<120 mmHg	120-139 mmHg	<80 mmHg	80-89 mmHg
3	<120 mmHg	≥140 mmHg	<80 mmHg	≥90 mmHg
4	120-139 mmHg	<120 mmHg	80-89 mmHg	<80 mmHg
5	120-139 mmHg	120-139 mmHg	80-89 mmHg	80-89 mmHg
6	120-139 mmHg	≥140 mmHg	80-89 mmHg	≥90 mmHg
7	≥140 mmHg	<120 mmHg	≥90 mmHg	<80 mmHg
8	≥140 mmHg	120-139 mmHg	≥90 mmHg	80-89 mmHg
9	≥140 mmHg	≥140 mmHg	≥90 mmHg	≥90 mmHg

Physical activity (PA)

In the questionnaire at HUNT 2 participants were asked to answer questions concerning their leisure-time PA. They were asked to report their weekly average time spent on either light (no sweat/not out of breath) or hard (sweat/out of breath) physical activity, with four response options (0, <1, 1-2, ≥3). In the present study, we summarized the score of PA and divided it into two categories, active or inactive. In addition, participants who did not report physical activity, or reported only on one of the variables, were categorized as "missing". To satisfy to the term active, the participants had to state an exercise amount inside the two highest categories of "light" activity (equal ≥1 hours/week) <u>and</u> inside the three highest categories of "hard" activity (equal >0 hours/week).

Other variables

The questionnaire in the HUNT 2 study contained information on several potential confounders. The smoking variable used in this study, is a recoded variable which divided the participants in current smokers, former smokers, persons who had never smoked, and subjects with missing data. BMI was calculated from the standard method (weight x height^2), and age was adjusted as a continuous variable. In analysis of active versus inactive persons, sex was adjusted for as a categorical variable.

End points

The mandatory reporting of deaths by physicians and public health officers to the national Cause of Death Registry in Norway constitutes the basis for the coding of underlying cause of death. In this study, the primary end point was deaths caused by CVD (ICD 10, I 00-I 99, ICD 9, I 390- I 459).

Statistical analysis

Person-years were calculated from the date of attendance to the clinical examination during the second period of data collection (HUNT 2, 1995-97) until the date of death, or until the end of follow up, December 31st, 2008, whichever came first. Cox-regression analysis was used to calculate age-adjusted and multivariable adjusted mortality rate ratios (RRs) in different BP-groups, with 95 % confidence intervals (CI), associated with changes in BP (as described earlier).

The analyses were performed separately for men and women in those concerning change in BP, except from analysis stratified according to activity status. In supplementary analyses, we also excluded participants who reported current or former use of BP lowering medication at HUNT 2.

Statistical analyses were conducted with the use of SPSS/PASW software (version 18.0; SPSS/PASW Institute, Chicago, Illinois, USA) and all reported P-values are two-sided.

Ethics

This study was approved by the Regional Committee for Ethical Medical Research (REK). All participants signed an informed consent upon participation in HUNT 2.

Results

The HUNT 2 study was performed in 1995-97, and the follow-up period in this study ended at December 31st, 2008, leaving a total follow-up period of 11.4 years, (530,969 person-years). During the time of follow-up, a total of 2,084 men and 1,854 women had died from CVD.

Table 3. Baseline characteristics according to categories of absolute change in SBP

Systolic BP*	≥ +40	+20 to +39	+5 to +19	-4 to +4	-5 to -19	≥ -20
Men						
Number of persons	935	3,937	7,627	4,549	3,504	1,067
Mean Age, years	65.7±11.0	59.9±12.9	54.4±13.3	52.7±13.3	54.7±14.4	63.9±15.4
Mean BMI, kg/m²	27.3±3.5	27.1±3.3	26.6±3.2	26.4±3.2	26.5±3.6	26.8±3.8
Active, %	24.0	29.0	32.6	34.0	32.5	22.3
Current smokers, %	25.9	28.6	29.7	29.7	30.0	25.7
Women						
Number of persons	1,678	5,584	8,729	4,570	3,180	1,064
Mean Age, years	65.2±12.2	59.6±13.3	54.4±13.7	52.6±14.0	55.6±15.3	67.6±14.1
Mean BMI, kg/m2	27.9±4.6	27.3±4.4	26.4±4.3	25.9±4.3	26.2±4.7	27.9±5.5
Active, %	13.1	19.5	24.4	26.1	22.3	10.6
Current smokers, %	22.1	25.0	30.0	32.0	30.5	18.9

Values are mean ± Standard Deviation (SD). *Values in mmHg.

We examined the association between changes in BP and risk of death from CVD, separately for men and women (table 4 and 5, respectively).

Absolute change in BP and CVD mortality

In the analyses considering absolute change in BP (Table 4), there was no clear association between an increased BP and risk of CVD death; people who increases of their SBP with ≥+40 mmHg had a relative risk (RR) of 1.1 (CI 0.9-1.3) for men, and 1.1 (0.9-1.3) for women compared to those with a stable SBP. However, a decrease in SBP of ≥-20 mmHg was

associated with a significantly higher RR of 1.8 (CI 1.5-2.2) for men, and 1.9 (CI 1.5-2.2) for women.

The effect of an increase in DBP was somewhat stronger than for SBP; men who had a ≥+20 mmHg increase in SBP had a RR of 1.3 (CI 1.1-1.6), whereas the corresponding RR in women was 1.3 (CI 1.0-1.5). On the other hand, a decrease in DBP was not as strongly associated with the risk of CVD death as a decrease in SBP; men who reduced their DBP with ≥-20 mmHg had a RR of 1.4 (CI 1.2-1.6), while women had a RR of 1.2 (CI 1.0-1.4).

Relative change in BP and CVD mortality

Compared with the reference group, who had a SBP of 120-139 mmHg in both surveys, a decrease in SBP from 120-139 to <120 was related to a relative risk (RR) of 1.5 (CI 1.2-2.0) for men, and 2.0 (CI 1.3-3.0) for women. On the other hand, an increase in SBP from 120-139 to ≥140 mmHg was associated with a RR of 1.1 (CI 0.9-1.3) for men, and 1.5 (CI 1.2-1.9) for women. Further, having a stable high SBP of ≥140 mmHg in both surveys was related to a RR of 1.4 (CI 1.2-1.7) for men, and 2.0 (CI 1.6-2.5) for women.

A decrease in SBP from ≥140 to 120-139 mmHg gave a RR of 1.6 (CI 1.3-2.0) for men, and 2.6 (CI 1.9-3.4) for women. The RR increases further when SBP decreases from ≥140 to <120 mmHg, with 2.4 (CI 1.7-3.4) for men, and 4.5 (CI 3.0-6.7) for women. A stable low SBP of <120 mmHg in both surveys was associated with a RR of 0.6 (CI 0.3-1.0) for women, whilst for men, there was no clear difference in risk (RR 1.0; CI 0.7-1.4). Concerning decreases in DBP, the pattern in quite similar to that observed for SBP.

Table 4: *Absolute change in systolic and diastolic blood pressures in relation to the risk of cardiovascular death, during 11.4 years of follow-up, men and women separately*

Variable	**Men**					**Women**				
	Person-years	No. of deaths	Age- adj. RR[a]	Multiadj. RR[b]	95% Confidence Interval	Person-years	No. of deaths	Age- adj. RR[a]	Multiadj. RR[b]	95% Confidence Interval
Systolic Blood Pressure										
≥ +40	10,923	173	1.1	1.1	0.9-1.4	18,317	223	1.1	1.1	0.9-1.3
+20 to +39	9,565	430	0.9	0.9	0.8-1.1	64,704	417	0.9	0.9	0.8-1.1
+5 to +19	43,320	560	0.9	0.9	0.8-1.1	103,332	476	1.0	1.0	0.8-1.2
-4 to +4	87,818	292	1	1	Reference	54,184	219	1	1	Reference
-5 to -19	52,538	350	1.2	1.2	1.0-1.4	36,202	240	1.1	1.1	0.9-1.3
≥ -20	39,194	262	1.9	1.8	1.5-2.2	10,324	267	1.9	1.9	1.5-2.2
Diastolic Blood Pressure										
≥ +20	10,311	132	1.3	1.3	1.1-1.6	13,314	161	1.3	1.3	1.0-1.5
+10 to +19	33,706	226	1.1	1.1	0.9-1.3	41,495	219	0.9	0.9	0.8-1.1
+5 to +9	33,472	226	1.1	1.1	0.9-1.3	41,190	155	0.8	0.8	0.6-0.9
-4 to +4	81,686	514	1	1	Reference	92,445	452	1	1	Reference
-5 to -9	37,598	309	1.1	1.1	0.9-1.3	43,211	249	0.9	0.9	0.7-1.1
≥ -10	45,453	635	1.4	1.4	1.2-1.6	55,357	606	1.2	1.2	1.0-1.4

[a]Adjusted for age (continuous).

[b]Adjusted for age (continuous), sex (men, women), body mass index (continuous), physical activity (active, inactive, missing) and smoking (current, former, never, missing).

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Table 5: *Relative change in systolic and diastolic blood pressures in relation to the risk of cardiovascular death, during 11.4 years of follow-up, men and women separately*

	Men					Women				
Variable	**Person-years**	**No. of deaths**	**Age- adj. RR[a]**	**Multiadj. RR[b]**	**95% Confidence Interval**	**Person-years**	**No. of deaths**	**Age- adj. RR[a]**	**Multiadj. RR[b]**	**95% Confidence Interval**
Systolic Blood Pressure										
<120 to <120	10,992	38	0.9	1.0	0.7-1.4	46,123	15	0.5	0.6	0.3-1.0
<120 to 120-139	20.240	61	0.9	0.9	0.7-1.2	45,165	43	0.9	0.9	0.6-1.3
<120 to ≥140	6,270	52	1.3	1.2	0.9-1.7	13,380	38	1.1	1.2	0.8-1.7
120-139 to <120	12,188	75	1.5	1.5	1.2-2.0	13,914	28	1.9	2.0	1.3-3.0
120-139 to 120-139	65,189	213	1	1	Reference	46,603	93	1	1	Reference
120-139 to ≥140	51,616	403	1.1	1.1	0.9-1.3	51,412	321	1.5	1.5	1.2-1.9
≥140 to <120	1,461	42	2.6	2.4	1.7-3.4	1,378	41	4.6	4.5	3.0-6.7
≥140 to 120-139	15,412	177	1.7	1.6	1.3-2.0	9,056	139	2.6	2.6	1.9-3.4
≥140 to ≥140	58,888	1006	1.4	1.4	1.2-1.7	60,031	1124	2.0	2.0	1.6-2.5
Diastolic Blood Pressure										
<80 to <80	42,258	196	1.1	1.1	0.9-1.4	88,712	186	0.7	0.7	0.6-0.9
<80 to 80-89	21,480	86	0.9	0.9	0.7-1.2	28,260	79	0.8	0.8	0.6-1.1
<80 to ≥90	7,216	67	1.3	1.3	1.0-1.7	9,034	68	1.2	1.2	0.9-1.7
80-89 to <80	34,659	278	1.3	1.2	1.0-1.5	39,673	223	0.9	0.9	0.7-1.1
80-89 to 80-89	37,268	201	1	1	Reference	33,203	193	1	1	Reference
80-89 to ≥90	23,712	218	1.4	1.3	1.1-1.6	22,681	198	1.1	1.0	0.8-1.3
≥90 to <80	11,472	212	1.8	1.8	1.5-2.1	13,877	237	1.6	1.6	1.3-1.9
≥90 to 80-89	25,246	306	1.5	1.5	1.3-1.8	21,589	241	1.1	1.1	0.9-1.4
≥90 to ≥90	38,915	502	1.5	1.5	1.3-1.8	29,982	417	1.3	1.3	1.1-1.5

[a]Adjusted for age (continuous).

[b]Adjusted for age (continuous), sex (men, women), body mass index (continuous), physical activity (active, inactive, missing) and smoking (current, former, never, missing).

Exclusion of persons using BP-medication

We also analyzed the effect of change in BP, after excluding people who had used or were current users of BP-medication or anti-hyperintensive drugs. This leaded to the exclusion of 8,250 participants.

There were only marginal differences compared to the main analyses, were mostly marginal, when concerning relative changes in BP (data not shown), but it could be mentioned that of the few significant differences, decreases in SBP from ≥140 to 120-130 mmHg was associated with a RR of 1.4 (CI 1.1-1.7), and that a stable high SBP of ≥140 to ≥140 mmHg gave a somewhat lower (RR of 1.3, CI 1.1-1.7) among men than in the main analyses.

Stratified analyses according to activity level

We examined the effects of changes in BP (both relative and absolute changes) on death from CVD (see Table 6), stratified according to physical activity level (defined as active or inactive).

Concerning absolute BP, an increase in SBP of ≥+40 mmHg was related to an increase in a RR of 1.56 (CI 1.0-2.4) for active, and only 1.06 (CI 0.8-1.3) for inactive. For active, this is significantly higher than the RR in the main analyses. The RR associated with a decrease in SBP of ≥-20 mmHg, the RR was also higher for active than inactive, with 2.27 (CI 1.4-3.6) versus 1.89 (CI 1.5-2.2). Between these extreme categories, little difference was observed. In comparison, changes in DBP revealed smaller differences between active and inactive. When comparing variables, only slight differences are shown between active and inactive. Similar findings are revealed when comparing absolute changes in DBP for active and inactive with the equivalent changes in the main analyses.

Relative changes in BP showed similar trends as absolute changes; inactive persons have lower RR with a stable low and stable BP, whilst active persons have somewhat lower RR associated with a stable on high and increasing BP. However, differences were in general quite small (data not shown).

Table 6: *Absolute change in systolic and diastolic blood pressures and relative risk if cardiovascular death, stratified by activity level*

Variable	**Active**				**Inactive**			
	Person-years	No. of deaths	Multiadj. RR[a]	95% Confidence Interval	Person-years	No. of deaths	Multiadj. RR[a]	95% Confidence Interval
Systolic Blood Pressure								
≥ *+40*	5,100	37	1.5	1.0-2.4	10,890	161	1.0	0.8-1.3
+20 to +39	26,690	87	1.1	0.8-1.6	42,249	356	0.9	0.7-1.0
+5 to +19	56,129	107	1.1	0.7-1.5	73,402	441	0.9	0.8-1.1
-4 to +4	33,392	47	1	Reference	38,949	230	1	Reference
-5 to -19	22,246	48	1.1	0.7-1.7	27,639	255	1.2	1.0-1.4
≥ *-20*	3,978	30	2.2	1.4-3.6	8,493	263	1.8	1.5-2.2
Diastolic Blood Pressure								
≥ *+20*	5,456	22	1.3	1.1-1.5	8,723	108	1.4	1.1-1.7
+10 to +19	20,680	47	1.1	0.9-1.3	28,496	171	0.9	0.7-1.1
+5 to +9	20,909	44	0.9	0.8-1.1	27,943	145	0.9	0.7-1.1
-4 to +4	52,017	100	1	Reference	65,205	410	1	Reference
-5 to -9	22,794	50	1.0	0.8-1.1	30,651	253	1.0	0.9-1.2
≥ *-10*	25,679	93	1.2	1.1-1.4	40,582	619	1.4	1.2-1.6

[a]Adjusted for age (continuous), sex (men, women), body mass index (continuous), and smoking (current, former, never, missing).

Discussion

Main results

In this prospective study we found that an absolute decrease in BP, especially systolic BP, was associated with a higher risk of CVD death than having a stable BP, and that an only a large increase in BP was associated with an increased risk. Relative changes showed a similar pattern, including that having a stable high BP was associated with an increased risk of death from CVD. When considering the effect of a decrease in BP, one should be aware that the size of the most extreme category (from ≥140 to <120 mmHg SBP) is very small, and that a possible explanation to the results might be that the subjects in this group might suffer from various illnesses that could both affect BP and risk of death. In addition, the results show the largest decreases among the oldest. Analyses with excluded BP-medication users only lead to small differences from the main analyses.

When comparing active with inactive, there were only minor differences, but an absolute decrease in both SBP and DBP seems to be somewhat more strongly related to death from CVD for inactive than active. Furthermore, an increase in SBP was associated with a higher risk among active, but not among inactive.

Strengths and limitations

The population in this study consists of the majority of the adult population in a stable homogenous population in Norway. The participants come from a county that is mainly rural and relatively scattered where income is dominated by agriculture, small industries, education and small-scale trade, and the population is considered fairly representative for Norway as a whole.

Information on BP, PA and other factors was only assessed at baseline, and updated measurements during follow-up were not available. The questionnaires may have been filled out somewhat subjectively. Also, the assessments of PA and smoking took place only once, and before the start of the follow-up. Thus, in this study individual changes in PA and smoking, might be subject for possible misclassification, due to the extensive period of time from baseline to the end of follow-up. In addition, the variable concerning whether or not the participants should be classified as active or inactive, have most likely been somewhat to "strict", due to the fact that one third of the participants turned out to have missing values.

Instead of demanding reporting of participation in both light and hard activity, reporting one of them would probably have been sufficient. Hence, the results from the analyses between active and inactive could therefore be subject to selection bias.

Another possible bias that might have influenced the results in this study is the fact that BP has been measured somewhat differently in HUNT 1 than in HUNT 2. In HUNT 1, BP was only measured twice, whilst in HUNT 2 it was measured three times. When excluding the first measurements, we only had one and two measurements, respectively, as basis to calculate the mean BP. Pickering et al. (2005) suggests a minimum of two measurements, and an additional one or two measurements if there is a >5 mmHg difference between the first and second measurements. Also, at HUNT 1, a standard cuff size was used on all participants, irrespective of arm circumference, and this could lead to an overestimation of the actual blood pressure in some participants. Thus, the results could have influenced the results, and underestimated the association related to BP increase, due to the potential confounding of "undercuffing" (Manning et al., 1983). In addition, numerous variables might confound BP-measurements (Pickering et al., 2005).

Comparison with other studies

To the author`s knowledge, no study has performed similar analyses on relative change in BP, but studies concerning absolute changes in BP does exist in a reasonable consent. Benetos et al. (2000) examined combined changes in SBP and DBP, and found that an increase in SBP combined with a decrease in DBP is associated with a substantially higher risk of CVM. Contradictory to our results, Benetos et al. (2000) found an increase in cardiovascular mortality rates and RR when comparing increases with decreases or stable SBP and DBP, respectively. In addition, a general increase in SBP tended to have a slightly higher RR than in DBP. Vasan et al. (2001b) also found a linear increase in risk of CVD related to increase in BP over a time-period of 4 years, and found SBP to be the major determinant.

Sesso et al. (2000a) performed a study on absolute changes (over 2 years) in SBP and DBP and death from CVD, and found a small increase in risk when SBP increased or decreased with between 3 and 6 mmHg (not significant). All reductions in DBP lead to a RR increase of 1.13 to 1.16, similar with our findings on decreases of ≥20 mmHg. Subjects who have an increase in DBP may retain some CVD benefit from their lower initial DBP, and subjects with decreases in DBP may retain some CVD risk from their initial DBP. Further, Sesso et al.

(2000a) found that only the current SBP level, regardless of prior pattern in change, may be necessary in determining the risk of CVD. One should take notice of that the short follow-up time of only two years in his study may have contributed to these findings. However, the Framingham Heart study did not find any associations between 12-year changes in BP a subsequent risk of CVD (Woodbury et al., 1981) even though they had a substantial longer follow-up period. This leads to the question of whether or not changes in BP matters particularly when it comes to risk prediction, and whether or not the length of follow-up should be considered as a major variable in such studies?

Sesso et al. (2000a) also performed an analysis with all BP-medication users excluded, but found no association for changes in SBP, and an inverse association for changes in DBP. However, there were substantially fewer cases of death from CVD overall, in agreement with the present study.

Benetos et al. (2001) found that the role of DBP on death from CVD is determined by gender and SBT level. For men, the hazard levels were highest on <90 an >110 mmHg, and for women at >100 mmHg (4 times higher for men overall). Franklin et al. (1999) showed that SBP is a stronger predictor for coronary heart disease than DBP. Port et al. (2003) states that a possible causation might be that SBP increases steadily with age, but at different rates in men and women. Furthermore, Benetos et al. (2000) also found a higher risk of death from CVD, but only in men and especially those with high SBP. This somewhat contradictory to our study, that found relatively similar risks of death from CVD when comparing both SBP and DBP, and men and women. However, the size of the categories in SBP is double the size of those in DBP (i.e. the largest variable in absolute change in SBP include values of ≥40 mmHg, whilst the largest variable in absolute change in DBP include values of ≥20 mmHg). For instance, Sesso et al. (2000a) used DBP values that were approximately two thirds the size of the SBP values. Thus, the difference of variable sizes in SBP versus DBP should be considered subject for discussion.

Previous research on change in BP and risk of CVD has mainly focused on controlling for the baseline level of BP. Sesso et al. (2000a) support this analyzing strategy, highlighting the importance of primary prevention to maintain or reduce current BP levels. Our study supports this approach when concerning prevention of both increases and decreases in BP, and emphasizes the importance of the cause of increases and decreases in BP have on risk prediction. Hence, BP changes should not only be considered as a causation, but also as an

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effect of lifestyle changes. Sesso et al. (2000a) also indicate that studies based on baseline BP measurements, could be expected to demonstrate a positive association between changes in BP and risk of CVD mainly because changes in BP determinate subsequent BP, which in turn predicts the risk of CVD. An important consideration in all longitudinal studies is that one must expect a certain increase in SBP due to the fact that people age, especially with a follow-up period of more than 10 years.

Possible mechanisms

Arterial BP is determined by cardiac output and total peripheral resistance. Any factor which raises cardiac output or total peripheral resistance will lead to a raise in BP. Raised total peripheral vascular resistance is the hallmark of essential HT and the major determinant of systemic hyperintensive vascular disease (Mayet & Hughes, 2003). DBP are influenced by arterial or arteriolar alterations in opposite ways; an increase in peripheral vascular resistance leads to an elevation in DBP, whereas stiffening of large arteries may contribute to a decrease in DBP. Hence, the stiffening of arteries is a classic pattern for an increase in SBP combined with a decrease in DBP (Fang et al., 1995, Nichols & O`Rourke, 1998). However, relatively little is known about arteriolar changes in human hypertension (Mayet & Hughes, 2003).

Wasan et al. (2001a) states that even though numerous investigators have reported CVD risks associated with elevated BP, and contrary to the present study, few have presented the absolute and relative risks of CVD according to the BP categories used in clinical practice. Further, Benetos et al. (2000) suggests that SBP and DBP may not be specific or sensitive enough to identify groups of subjects that already are at high risk owing to BP values, even if they are generally correlated to cardiovascular risk. This is supported by Vasan et al. (2001a), who underscore the need for additional research to determine whether persons with high-normal BP who are at risk for CVD, such as elderly persons, diabetics, or persons with multiple risk factors, will benefit from BP lowering.

Conclusion

In summary, we found that an absolute decrease in BP, especially systolic BP, was associated with a higher risk of CVD death than having a stable BP, and that an only a large increase in BP was associated with an increased risk. Relative changes showed a similar pattern, and also that having a stable high BP was associated with an increased risk of death from CVD. There

were no large differences in these associations between participants who were physically active versus those reporting to be inactive. It is likely that the increased risk of CVD death associated with a BP reduction could be due to reverse causation. The results suggest that maintaining a stable blood pressure within the normal range should be emphasized.

References

Benetos A., Thomas, F., Safar, M., Bean K., & Guize, L. (2001) Should Diastolic and Systolic Blood Pressure Be Considered for Cardiovascular Risk Evaluation: A Study in Middle-Aged Men and Women. *J Am Coll Cardiol*; 37:163-8.

Benetos A., Zureik, M., Morcet, J., Thomas, F., Bean, K., Safar, M., & Ducimeterière, P. (2000) A Decrease in Diastolic Blood Pressure Combined With an Increase in Systolic Blood Pressure Is Associated With a Higher Cardiovascular Mortality in Men. *J Am Coll Cardiol*; 35: 673-80.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo Jr, J. L., Jones D. L., Materson, B. J., Oparil, S., Wright Jr, J. T., & Roccella E. J. (2003). Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). *Hypertension*, 42:1206.

Fang, J., Madhavan, S., Cohen, H., & Alderman, M.H. (1995). Measures of blood pressure and myocardial infarction in treated hyperintensive patients. *J Hypertens*; 13: 413-9.

Franklin, S.S., Kahn, S.A., Wong, N.D., Larson, M.G., Levy, D. (1999). Is pulse pressure useful in predicting risk for coronary heart disease? *Circulation*; 100; 354-60.

Graham, I., Atar, D., Borch-Johnsen, K., Boysen, G., Burell, G., Cifkova, R., Dallongeville, J., De Backer, G., Ebrahim, S., Gjelsvik, B., Herrmann-Lingen, C., Hoes, A., Humphries, S., Knapton, M., Perk, J., Priori1, S. G., Pyorala1, K., Reiner, Z., Ruilope, L., Sans-Menendez, S., Scholte op Reimer, W., Weissberg, P., Wood, D., Yarnell, J., Zamorano, J. L. (2007). European guidelines on cardiovascular disease prevention in clinical practice: executive summary Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *European Heart Journal;* 28, 2375–2414

Holmen, J., Forsen, L., Hjort, P.F., Midthjell, K., Waaler, H.T., & Bjørndal, A.(1991). Detecting hypertension: screening versus case finding in Norway. *BMJ*; 302: 219-222.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., & Collins, R. (2002). Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Prospective Studies Collaboration. *Lancet*; 360:1903-13

Manning, D.M., Kuchirka, C., & Dasdupta, I. (1983). Miscuffing: inappropriate blood pressure cuff application. *Circulation*; 68; 763-766.

Mayet, J. & Hughes, A. (2003). Cardiac and vascular pathophysiology in hypertension. *Heart*; 89: 1104-1109.

Murakami, Y., Hozawa, A., Okamura, T., Ueshima, H. (2008). Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension*; 51(6):1483-91

**Nichols, W.W. & O`Rourke, M.F.** (1998). *McDonald`s blood flow in arteries: theoretical, experimental and clinical principles*, 4th ed. London: Edvard Arnold.

Nusselder, W. J., Franco, O. H., Peeters, A., & Mackenbach, J. P. (2009) Living healthier for longer: Comparative effects of three heart healthy behaviors on life expectancy with and without cardiovascular disease. *BMC Public Health*; 9:487.

Pickering, T.G., Hall, J.E., Appel, L.A., Falkner, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S.G., & Roccella, E.J. (2005). Recommendations for Blood Pressure Measurement in Humans and Experimental Animals: Part 1: Blood Pressure Measurement in Humans: A Statement for Professionals From the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*; 111; 697-716.

Port, S., Demer, L., Jennrich, R., Walter, D. & Garfinkel, A. (2003). Systolic blood pressure and mortality. *Lancet*; 355; 175-180.

Safar, M.E. (1989). Pulse pressure in clinical hypertension: clinical and therapeutical implications. *J Hypertens*; 7: 769-76.

Sesso, H.D., Spampfer, M.J., Rosner, B., Gaziano, J.M., & Hennekens, C.H. (2000) (a). Two-Year Changes in Blood Pressure and Subsequent Risk of Cardiovascular Disease in Men. *Circulation*; 102; 307-312.

Sesso, H.D., Spampfer, M.J., Rosner, B., Hennekens, C.H., Gaziano, J.M., Manson, J.E. & Glynn, R.J. (2000) (b). Systolic and Diastolic Blood Pressure, Pulse Pressure, and Mean Arterial Pressure as Predictors of Cardiovascular Disease in Men. *Hypertension*; 36; 801-807.

Sleight, P. (1988). Blood pressures, hearts, and U-shaped curves (letter). *Lancet*; 1: 235.

Strandberg TE, Pitkala K. (2003). What is the most important component of blood pressure: systolic, diastolic or pulse pressure? *Curr Opin Nephrol Hypertens*; May; 12(3):293-7

Tervahauta M, Pekkanen J, Enlund H., & Nissinen, H. (1994). Change in blood pressure and 5-year risk of coronary heart disease among elderly men: the Finnish cohorts of the Seven Countries Study. *J Hypertens*; 12: 1183–1189.

Vartiainen E, Puska P, Pekkanen J, Tuomilehto, J., & Jousilahti, P. (1994). Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *BMJ*; 309: 23–27.

Vasan, R. S., Larson, M. G., Leip, E. P., Evans, J.C., O`Donnel, C.J., Kannel, W.B., & Levy, D. (2001) (a) Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*; 345; 18: 1291-97.

Vasan, R. S., Larson, M. G., Leip, E. P., Kannel, W. B., Levy, D. (2001) (b) Assessment of frequency of progression to hypertension in nonhypertensive participants in the Framingham Heart Study: a cohort study. *Lancet*; 358: 1682–86

Witteman JC, Grobbee DE, Valkenburg HA, van Hemert, A.M., Stijnen, T., Burger, H., & Hofman, A. (1994). J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet*; 343: 504 –507.

Woodbury, M.A., Manton, K.G., & Stallard, E. (1981). A dynamic analysis of chronic disease development: a study of sex specific changes in coronary heart disease incidence and risk factors in Framingham. *Int J Epidemiol*; 10; 355-366.