Appendix 3

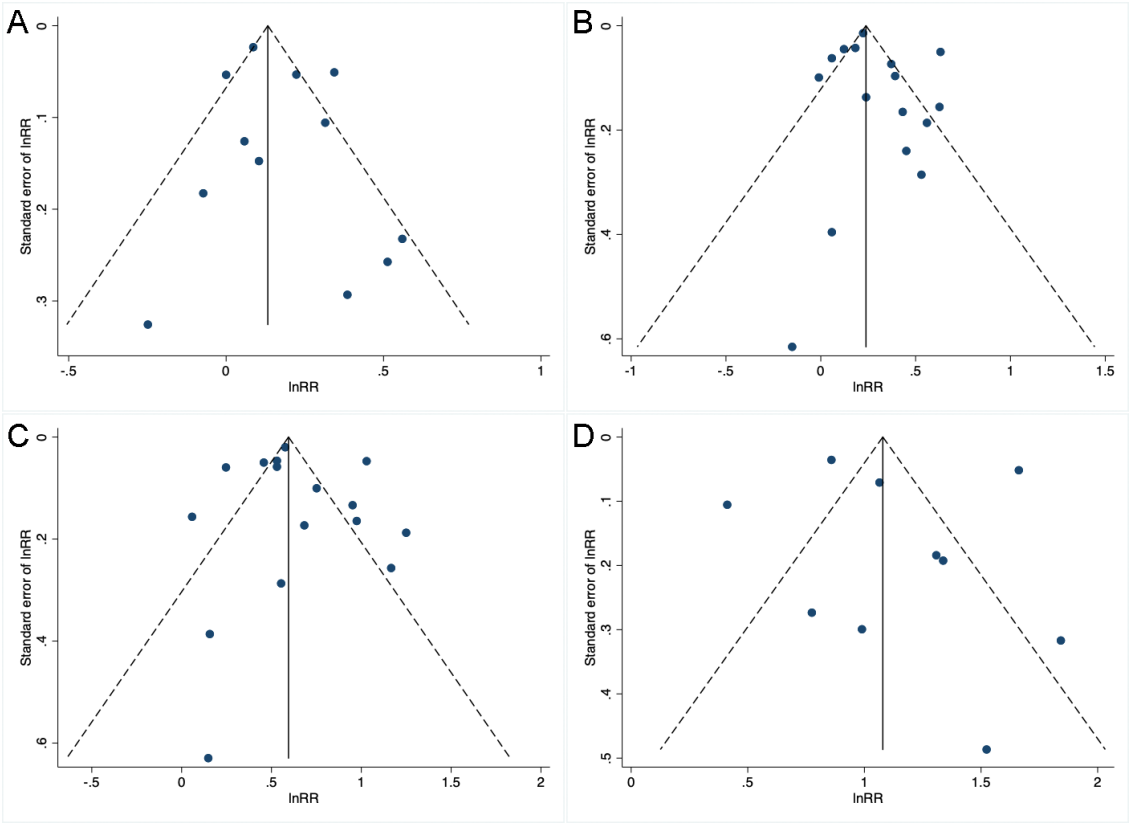

Figure S1. Funnel plots for the outcome of cardiovascular events. A. Funnel plot for cardiovascular events comparing normal BP and optimal BP (Egger's test for funnel plot asymmetry; p=0.38). B. Funnel plot for cardiovascular events comparing high normal BP and optimal BP (Egger's test for funnel plot asymmetry; p=0.39). C. Funnel plot for cardiovascular events comparing grade 1 hypertension and optimal BP (Egger's test for funnel plot asymmetry; p=0.65). D. Funnel plot for cardiovascular events comparing grade 2 hypertension and optimal BP (Egger's test for funnel plot asymmetry; p=0.78). BP, blood pressure.

Table S1 GRADE summary of findings for the associations of increased blood pressure and individual study outcomes.

Optimal compared to normal BP

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Optimal	Corresponding risk Normal			
Cardiovascular events	Study population		RR 1.19 (1.08 to 1.31)	2365285 (12 studies)	⊕⊕⊕⊖ moderate[1,2,3]
	40 per 1000	48 per 1000 (43 to 52)			
Coronary heart disease	Study population		RR 1.09 (0.99 to 1.21)	1577243 (10 studies)	⊕⊕⊕⊖ moderate[1,2,3]
	20 per 1000	22 per 1000 (20 to 24)			
Stroke	Study population		RR 1.14 (1.03 to 1.27)	1574119 (9 studies)	⊕⊕⊕⊖ moderate[1,2,3,4]
	20 per 1000	23 per 1000 (21 to 25)			
All-cause mortality	Study population		RR 0.95 (0.93 to 0.97)	753687 (6 studies)	⊕⊕⊖⊖ low[1,2,4,5]
	100 per 1000	95 per 1000 (93 to 97)			

Optimal compared to high normal BP

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Optimal	Corresponding risk High normal			
	Study population				

Cardiovascular events	40 per 1000	54 per 1000 (49 to 60)	RR 1.35 (1.22 to 1.49)	2954416 (16 studies)	⊕⊕⊕⊖ moderate[1,2,3]
Coronary heart disease	Study population		RR 1.25 (1.18 to 1.34)	2439595 (14 studies)	⊕⊕⊕⊖ moderate[1,2,3]
	20 per 1000	25 per 1000 (24 to 27)			
Stroke	Study population		RR 1.27 (1.15 to 1.39)	2435892 (13 studies)	⊕⊕⊕⊖ moderate[1,2,3]
	20 per 1000	25 per 1000 (23 to 28)			
All-cause mortality	Study population		RR 1.07 (0.98 to 1.17)	517983 (8 studies)	⊕⊕⊖⊖ low[1,2,4,5]
	100 per 1000	107 per 1000 (98 to 117)			
Optimal compared to Grade 1 hypertension					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Optimal	Corresponding risk Grade 1 hypertension			
Cardiovascular events	Study population		RR 1.92 (1.68 to 2.19)	2182273 (16 studies)	⊕⊕⊕⊕ high[2,3]
	40 per 1000	77 per 1000 (67 to 88)			
Coronary heart disease	Study population		RR 1.65 (1.48 to 1.84)	1688116 (14 studies)	⊕⊕⊕⊖ moderate[1,2,3]
	20 per 1000	33 per 1000 (30 to 37)			
Stroke	Study population				

	20 per 1000	38 per 1000 (31 to 46)	RR 1.89 (1.56 to 2.28)	1683223 (13 studies)	⊕⊕⊕⊖ moderate[1,2,3]
All-cause mortality	Study population		RR 1.42 (1.18 to 1.71)	481964 (8 studies)	⊕⊕⊖⊖ low[2,4]
	100 per 1000	142 per 1000 (118 to 171)			

Optimal compared to Grade 2 hypertension

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Optimal	Grade 2 hypertension			
Cardiovascular events	Study population		RR 3.15 (2.31 to 4.29)	178652 (10 studies)	⊕⊕⊕⊕ high[2,3,6]
	40 per 1000	126 per 1000 (92 to 172)			
Coronary heart disease	Study population		RR 2.27 (1.86 to 2.78)	136659 (8 studies)	⊕⊕⊕⊕ high[2,3,4,6]
	20 per 1000	45 per 1000 (37 to 56)			
Stroke	Study population		RR 2.87 (2.07 to 3.96)	134715 (7 studies)	⊕⊕⊕⊖ moderate[1,2,3,4]
	20 per 1000	57 per 1000 (41 to 79)			
All-cause mortality	Study population		RR 2.01 (1.38 to 2.93)	14450 (5 studies)	⊕⊕⊕⊕ high[2,4,6,7]
	100 per 1000	201 per 1000 (138 to 293)			

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group

and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] The risks associated with the observed blood pressure category were inconsistent among the included studies.

[2] Information on antihypertensive treatments was limited and thus its effect on outcome risks could not be totally eliminated.

[3] The associated risks increased across blood pressure categories.

[4] The number of included studies was less than 10 and thus the assessment of publication bias was not recommended in this situation.

[5] The risk of all-cause mortality associated with high blood pressure increased from the level above 140/90 mmHg.

[6] The risk associated with grade 2 hypertension was consistent and robust across studies.

[7] The risk of all-cause mortality associated with high blood pressure increased in a dose-responsive manner when the BP was above the level of 140/90 mm Hg.

Table S2. Sensitivity and heterogeneity analysis of pooled relative risks of cardiovascular events across BP categories.

	Normal BP			High normal BP			Grade 1 hypertension			Grade 2 hypertension		
	RR(95%CI)	f	I-squared	RR(95%CI)	f	I-squared	RR(95%CI)	f	I-squared	RR(95%CI)	f	I-squared
Overall studies	1.19 (1.08 to 1.31)	11	74.1%	1.36 (1.22 to 1.49)	15	85.6%	1.92 (1.68 to 2.19)	15	91.5%	3.15 (2.31 to 4.29)	9	95.8%
Excluding studies with high risk of bias	1.19 (1.08 to 1.31)	11	74.1%	1.35 (1.22 to 1.49)	14	86.5%	1.93 (1.69 to 2.20)	14	92.0%	3.08 (2.24 to 4.24)	8	96.3%
Excluding studies with all male participants	1.14 (1.03 to 1.27)	6	57.8%	1.36 (1.21 to 1.53)	8	65.9%	2.03 (1.72 to 2.39)	8	84.6%	3.71 (2.29 to 6.02)	3	82.3%
Excluding studies with only military members	1.18 (1.06 to 1.33)	10	74.5%	1.38 (1.24 to 1.53)	14	85.3%	1.94 (1.68 to 2.24)	14	92.0%	3.15 (2.31 to 4.29)	9	95.8%
Excluding studies of retrospective design	1.19 (1.04 to 1.36)	9	71.8%	1.38 (1.17 to 1.64)	12	87.2%	1.94 (1.57 to 2.41)	12	92.9%	3.20 (2.21 to 4.64)	8	96.3%
Excluding studies with nonequivalent outcomes	1.18 (1.06 to 1.30)	10	75.2%	1.35 (1.20 to 1.51)	13	86.9%	1.87 (1.61,2.17)	13	92.0%	3.20 (2.21 to 4.64)	8	96.3%
Limiting studies reporting some levels of adjustment	1.17 (1.05 to 1.32)	9	76.6%	1.39 (1.22 to 1.58)	11	88.0%	1.92 (1.62 to 2.29)	11	93.4%	3.02 (1.98 to 4.58)	7	97.2%
Limiting studies using only mercury monitor for BP measurements	1.22 (0.91 to 1.64)	3	66.4%	1.80 (1.63 to 1.99)	5	3.9%	2.40 (1.92 to 3.01)	5	53.5%	4.12 (3.11 to 5.46)	5	67.8%
Limiting studies involving only untreated participants	1.12 (0.97 to 1.29)	5	51.9%	1.24 (1.09 to 1.41)	5	32.6%	1.76 (1.33 to 2.32)	5	77.0%	2.75 (1.82 to 4.15)	2	55.8%

Abbreviation: RR, relative risk; CI, confidence interval; f, degrees of freedom; BP, blood pressure. BMI, body mass index.