

# Influence of Weight Reduction on Blood Pressure

## A Meta-Analysis of Randomized Controlled Trials

Judith E. Neter, Bianca E. Stam, Frans J. Kok, Diederick E. Grobbee, Johanna M. Geleijnse

**Abstract**—Increased body weight is a strong risk factor for hypertension. A meta-analysis of randomized controlled trials was performed to estimate the effect of weight reduction on blood pressure overall and in population subgroups. Twenty-five randomized, controlled trials (comprising 34 strata) published between 1966 and 2002 with a total of 4874 participants were included. A random-effects model was used to account for heterogeneity among trials. A net weight reduction of  $-5.1$  kg (95% confidence interval [CI],  $-6.03$  to  $-4.25$ ) by means of energy restriction, increased physical activity, or both reduced systolic blood pressure by  $-4.44$  mm Hg (95% CI,  $-5.93$  to  $-2.95$ ) and diastolic blood pressure by  $-3.57$  mm Hg (95% CI,  $-4.88$  to  $-2.25$ ). Blood pressure reductions were  $-1.05$  mm Hg (95% CI,  $-1.43$  to  $-0.66$ ) systolic and  $-0.92$  mm Hg (95% CI,  $-1.28$  to  $-0.55$ ) diastolic when expressed per kilogram of weight loss. As expected, significantly larger blood pressure reductions were observed in populations with an average weight loss  $>5$  kg than in populations with less weight loss, both for systolic ( $-6.63$  mm Hg [95% CI,  $-8.43$  to  $-4.82$ ] vs  $-2.70$  mm Hg [95% CI,  $-4.59$  to  $-0.81$ ]) and diastolic ( $-5.12$  mm Hg [95% CI,  $-6.48$  to  $-3.75$ ] vs  $-2.01$  mm Hg [95% CI,  $-3.47$  to  $-0.54$ ]) blood pressure. The effect on diastolic blood pressure was significantly larger in populations taking antihypertensive drugs than in untreated populations ( $-5.31$  mm Hg [95% CI,  $-6.64$  to  $-3.99$ ] vs  $-2.91$  mm Hg [95% CI,  $-3.66$  to  $-2.16$ ]). This meta-analysis clearly shows that weight loss is important for the prevention and treatment of hypertension. (*Hypertension*. 2003;42:878-884.)

**Key Words:** obesity ■ body weight ■ blood pressure ■ hypertension, obesity ■ meta-analysis ■ clinical trials

Hypertension is an established risk factor for cardiovascular diseases and is common among obese subjects.<sup>1</sup> In Western societies, the prevalence of obesity is increasing, which is likely to increase the burden of hypertension and consequently, of cardiovascular mortality.<sup>2</sup> From 1960 to 2000, the prevalence of obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) for American adults aged 20 to 74 years increased from 13.4% to 30.9%. In 2000, the prevalence of overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) for American adults was 64.5%.<sup>3</sup> Weight loss has been proposed as an effective, nonpharmacologic means for the primary prevention of hypertension.<sup>4</sup> An early meta-analysis by Staessen et al<sup>5</sup> in 1988 showed a reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of  $-2.4$  and  $-1.5$  mm Hg per kilogram weight loss, respectively.

Targeted weight loss interventions in population subgroups might be more effective for the prevention of hypertension than a general-population approach because of interindividual differences in BP and body weight. In the present meta-analysis of 25 randomized controlled trials (RCTs), both the overall and subgroup effects of body weight reduction on BP were assessed. This stratified meta-analysis could strengthen the scientific basis for weight control as an important ingre-

dent of hypertension control programs in the community and in individual patients.

## Methods

### Selection of Studies

Systematic literature searches in electronic databases (Cab Abstract, Current Contents, FSTA, and MEDLINE Advanced) were conducted for RCTs of weight reduction and BP by using the search phrase (overweight OR weight reduction OR obes\* OR weight OR diet\*) AND (hypertension OR blood pressure) AND (trial OR intervention OR random\* OR study) as title words or MeSH terms. Article reference lists were examined for additional articles.

Trials that fulfilled the following criteria were eligible for meta-analysis: (1) an RCT design, (2) published after 1966, (3) conducted in humans, (4) written in English, and (5) nonpharmacologic reduction of body weight. A total of 97 articles was identified, of which 72 were excluded on the basis of the predefined criteria (literature list of excluded trials is available from the authors); ie, they did not fulfill the inclusion criteria ( $n=21$ ), the intervention period was  $<8$  weeks ( $n=2$ ), there were co-interventions from which the effect of weight loss could not be separated ( $n=28$ ), inappropriate or missing BP data ( $n=5$ ), study objective was not weight reduction ( $n=4$ ), or overlapping data with other publication(s) ( $n=12$ ). Figure 1 shows the number of studies that were identified and excluded at different stages of the selection process. A total of 25 trials<sup>6-30</sup> proved eligible for this meta-analysis.

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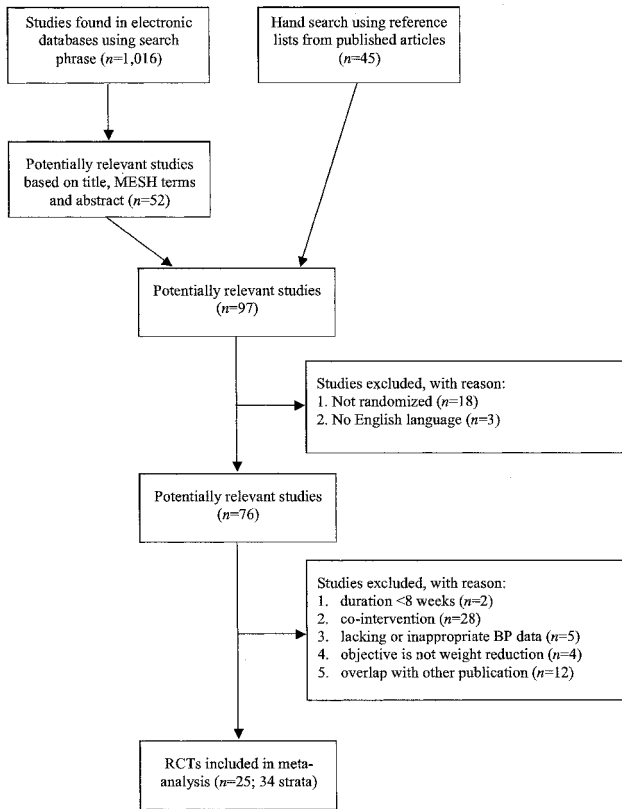
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**Figure 1.** Selection of RCTs for meta-analysis of weight reduction and BP.

### Data Abstraction

Original articles were retrieved for data abstraction. Two investigators (J.E.N., B.E.S.) independently collected data on population characteristics, study design, and treatment effect on a standard form. For trials in which BP and body weight measurements were recorded at several points in time,<sup>6–14</sup> data were abstracted for the intervention period during which the maximal BP effect was achieved. If intermediate measurements were not reported, then the total intervention period was used.<sup>15–30</sup> Different types of weight intervention could have been examined within the same trial, ie, energy restriction, increased physical activity, or the combined intervention. When this was the case, these interventions were analyzed as separate strata. For 2 trials, the authors were contacted to obtain missing data.<sup>15,25</sup> For 1 trial, in which the age of the trial population was not reported, the mean age of other trial populations combined (ie, 46 years) was imputed in the data analysis.<sup>28</sup>

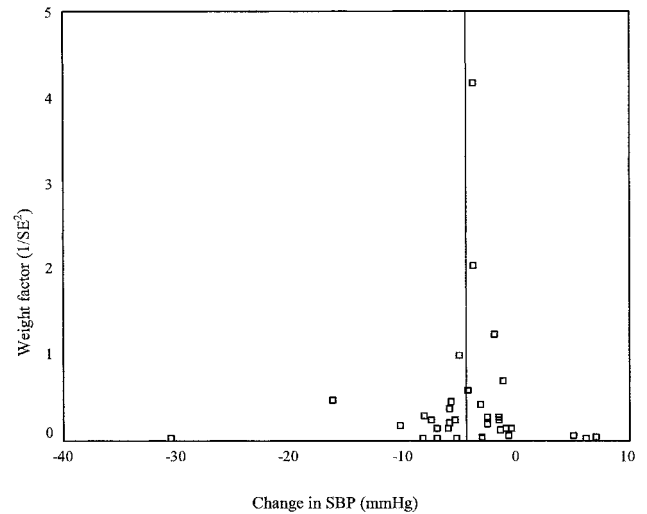
### Quantitative Data Synthesis

Changes in BP from baseline in the control group were subtracted from changes in the intervention group to obtain the net BP effect of weight reduction. SEs of the treatment effect were also abstracted. If not reported, SEs were derived from SDs or SEs for BP effects within groups, confidence intervals (CIs), test statistics, or probability values. For estimations of SE, a correlation of 0.5 between the variances at baseline and at follow-up within each group was assumed, according to Follmann et al,<sup>31</sup> as follows:

$$SE = \sqrt{\{(SE_{\text{baseline}})^2 + (SE_{\text{follow-up}})^2 - (2 \times 0.5 \times SE_{\text{baseline}} \times SE_{\text{follow-up}})\}}$$

In one article,<sup>26</sup> variance measures were not presented, so SE was predicted from all other trials by means of linear regression by using the trial sample size as the independent variable.

A random-effects model was chosen for meta-analysis to account for heterogeneity in BP effect among trials. An advanced statistical technique for meta-analysis of continuous outcomes was applied that



**Figure 2.** Funnel plot to explore publication bias in 25 RCTs of weight reduction and BP. Open squares represent individual trials (or trial strata); net change in SBP is plotted against the reciprocal of its variance (weight factor). The funnel plot was roughly symmetrical about the mean-effect size (vertical line), except for the outlying study by Reisin et al.<sup>27</sup>

takes into account both within- and between-study variation (SAS PROC MIXED).<sup>32</sup> The weight factor by which BP effects were weighted was  $1/(SE^2 + \tau^2)$ , where  $\tau$  is the between-study variation.

To examine the effect modification of BP response to weight loss, meta-analyses were performed in predefined strata of mean age ( $\leq 45$  vs  $> 45$  years), gender ( $< 50\%$  vs  $\geq 50\%$  females), type of intervention (energy restriction vs increased physical activity vs combined intervention), race (white vs black vs Asian), initial BMI ( $< 30$  vs  $\geq 30$  kg/m<sup>2</sup>), antihypertensive treatment (no vs yes; coded as “yes” if 1 or more subjects were being treated with antihypertensive drugs), weight loss ( $\leq 5$  vs  $> 5$  kg), and baseline hypertensive status (yes vs no; based on initial BP level only, ie,  $< 140/90$  vs  $\geq 140/90$  mm Hg). Stratified meta-analyses were repeated with a multivariate model to adjust for potential confounders, ie, mean age, gender (percent females), initial BP, change in body weight of trial populations, and duration of intervention.

A funnel plot of SBP effect against the weight factor was visually examined for potential publication bias (Figure 2). The funnel plot was roughly symmetrical about the mean-effect size line, except for the outlying study by Reisin et al.<sup>27</sup> For this reason, meta-analyses were also performed after exclusion of this study.

## Results

### Overview of Trials

The population and study characteristics of trials of weight reduction and BP are presented in Table 1. The analysis was based on 25 parallel trials published between 1978 and 2002, comprising 34 strata with a total of 4874 subjects. The duration of intervention until the maximal BP effect (or, if not reported the overall BP effect) was achieved varied between 8 and 260 weeks. Most studies (82%) included both men and women. The mean age of trial populations ranged from 37 to 66 years. Half of the populations were hypertensive (on the basis of initial BP cutoff level of 140/90 mm Hg), and 24% of the populations were taking antihypertensive medication. Mean total duration was 66.6 weeks, and mean duration until the maximal BP effect was achieved was 35.3 weeks. The overall percentage of subjects in RCTs who dropped out after randomization was small (4.8%).

TABLE 1. Population and Study Characteristics of RCTs of Weight Reduction and BP

Study*	Year	N†	Duration, wk‡	Age, y	Females, %	Race	Drug Treated§	Intervention	BMI, kg/m <sup>2</sup>	Body Weight, kg		SBP, mm Hg		DBP, mm Hg	
										Initial	Change	Initial	Change (SE)	Initial	Change (SE)
Anderssen et al <sup>15a</sup>	1995	95	52	45	10	W	No	EN	29.0	91.5	-5.1	131.0	-5.9 (2.20)	87.3	-2.7 (1.64)
Anderssen et al <sup>15b</sup>	1995	92	52	45	10	W	No	PA	28.5	89.5	-2.0	130.5	-1.6 (2.02)	88.2	-2.0 (1.64)
Anderssen et al <sup>15c</sup>	1995	108	52	45	10	W	No	EN, PA	28.5	89.8	-6.7	130.6	-5.4 (2.02)	87.6	-4.5 (1.58)
Andersson et al <sup>16</sup>	1991	18	17	53	100	W	No	EN	29.4	80.9	-6.0	144.5	-7.0 (6.08)	93.0	-8.0 (4.48)
Anonymous <sup>6</sup>	1990	233	156 (26)	39	33	W, B	No	EN	28.5	85.4	-5.8	125.0	-5.1 (1.00)	83.2	-2.8 (1.00)
Anonymous <sup>7</sup>	1997	1099	208 (26)	43	34	W, B	No	EN, PA	31.0	93.5	-4.5	127.4	-3.8 (0.49)	85.9	-2.7 (0.39)
Ard et al <sup>17</sup>	2000	44	8	40	96	B	Yes	EN, PA	37.8	101.4	-6.7	123.6	-4.3 (1.31)	79.3	-2.5 (1.13)
Blumenthal et al <sup>18a</sup>	2000	68	26	48	57	W, B	No	EN, PA	32.3	93.5	-8.6	143.0	-8.3 (5.86)	93.6	-7.0 (3.15)
Blumenthal et al <sup>18b</sup>	2000	66	26	47	51	W, B	No	PA	32.7	95.0	-2.5	139.9	-5.3 (5.87)	93.8	-5.7 (3.00)
Blumenthal et al <sup>18c</sup>	2000	90	26	48	58	W, B	No	EN	32.4	94.3	-6.1	140.4	-3.0 (4.93)	93.4	-1.3 (2.74)
Croft et al <sup>9</sup>	1986	130	52 (26)	48	48	...	No	EN	...	84.5	-6.3	161.0	-7.0 (2.58)	97.0	-6.0 (1.47)
Fagerberg et al <sup>9</sup>	1984	30	20 (12)	51	0	W	No	EN	30.8	97.5	-8.6	152.6	6.2 (5.57)	101.0	-0.5 (2.89)
Fortmann et al <sup>19a</sup>	1988	73	52	44	0	...	No	EN	29.5	93.4	-7.4	119.0	-1.6 (1.90)	79.5	-3.0 (1.90)
Fortmann et al <sup>19b</sup>	1988	77	52	44	0	...	No	PA	29.2	94.5	-5.1	121.1	-2.5 (1.90)	78.5	-1.5 (1.90)
Gordon et al <sup>20</sup>	1997	33	12	49	69	...	No	EN	33.8	96.6	-6.1	145.0	-2.6 (2.24)	95.4	-2.0 (1.58)
Haynes et al <sup>21</sup>	1984	51	26	47	33	...	No	EN	...	91.9	-3.3	134.5	5.0 (3.94)	90.1	1.5 (1.11)
He et al <sup>10</sup>	2000	95	364 (78)	43	47	W, B	No	EN, PA	28.9	85.1	-3.5	122.3	-5.8 (1.47)	84.3	-3.2 (1.12)
Jalkanen et al <sup>22</sup>	1991	49	52	49	50	W	Yes	EN	30.5	82.9	-4.0	153.5	7.0 (4.68)	101.5	0.0 (2.34)
Lalonde et al <sup>23a</sup>	2002	19	12	46	74	...	Yes	PA	28.8	79.0	-3.7	134.3	-3.1 (5.80)	84.6	0.0 (3.76)
Lalonde et al <sup>23b</sup>	2002	22	12	46	55	...	Yes	PA	28.4	77.7	-1.2	130.6	-0.7 (4.00)	83.3	0.4 (3.05)
Langford et al <sup>24</sup>	1991	180	26	48	51	W, B	No	EN	...	87.7	-3.7	143.9	-1.2 (1.19)	93.9	-0.8 (1.47)
MacMahon et al <sup>11</sup>	1985	38	25 (21)	41	24	...	No	EN	32.9	95.9	-7.9	150.0	-5.9 (1.64)	100.1	-6.7 (1.86)
Masuo et al <sup>25a</sup>	2002	40	24	37	0	A	No	PA	27.5	82.7	-4.1	154.0	-1.0 (2.64)	101.5	-4.0 (2.45)
Masuo et al <sup>25b</sup>	2002	40	24	37	0	A	No	EN	27.6	83.3	-1.4	152.0	-6.0 (2.64)	100.0	-5.0 (2.64)
Oberman et al <sup>26</sup>	1990	163	26	49	45	W, B	No	EN	30.4	88.0	-3.5	143.4	-1.4 (2.75)	93.3	-1.3 (1.95)
Reisin et al <sup>27</sup>	1978	83	26	47	37	...	Yes	EN	...	83.5	-9.1	171.4	-30.5 (6.01)	111.6	-20.8 (2.50)
Singh et al <sup>28</sup>	1990	206	13	46	21	A	Yes	EN	...	66.7	-11.9	154.2	-16.3 (1.46)	99.5	-12.0 (0.86)
Singh et al <sup>29</sup>	1995	217	16	47	22	A	Yes	EN	24.6	66.7	-2.8	153.7	-7.5 (2.01)	100.1	-6.5 (1.59)
Stamler et al <sup>30</sup>	1989	194	260	38	13	W, B	No	EN	...	84.3	-2.7	122.2	-2.0 (0.90)	82.2	-1.9 (0.80)
Stevens et al <sup>12</sup>	1993	538	78 (26)	43	32	W, B	No	EN, PA	29.5	89.8	-5.6	124.4	-3.8 (0.70)	83.8	-2.5 (0.60)
Whelton et al <sup>13</sup>	1998	488	156 (13)	66	48	W, B	Yes	EN, PA	28.9	81.1	-1.9	128.0	-3.2 (1.53)	71.3	-0.3 (0.94)
Wing et al <sup>14a</sup>	1998	67	104 (26)	45	79	...	No	EN	36.0	98.5	-7.6	115.3	-8.2 (1.83)	73.5	-4.0 (2.42)
Wing et al <sup>14b</sup>	1998	65	104 (26)	46	80	...	No	PA	36.0	98.3	-0.6	115.2	-0.4 (2.55)	73.8	0.5 (3.78)
Wing et al <sup>14c</sup>	1998	63	104 (26)	46	79	...	No	EN, PA	35.9	98.1	-8.8	117.0	-10.3 (2.34)	74.4	-4.7 (2.52)

W indicates white; B, black; A, Asian; EN, energy restriction; and PA, increased physical activity.

\*a, b, and c suffixes denote different strata from the same study.

†No. of subjects who completed the trial.

‡Total follow-up period is in weeks; duration until maximal BP effect is given in parentheses for trials for which these data were available.<sup>6-14</sup>

§Coded yes if trial population included 1 or more subjects on antihypertensive drug treatment.

||Maximal change or, if not available, change for total follow-up period.

¶Either the population belonged to a race category other than black, white, or Asian or information on race was not provided in the article.

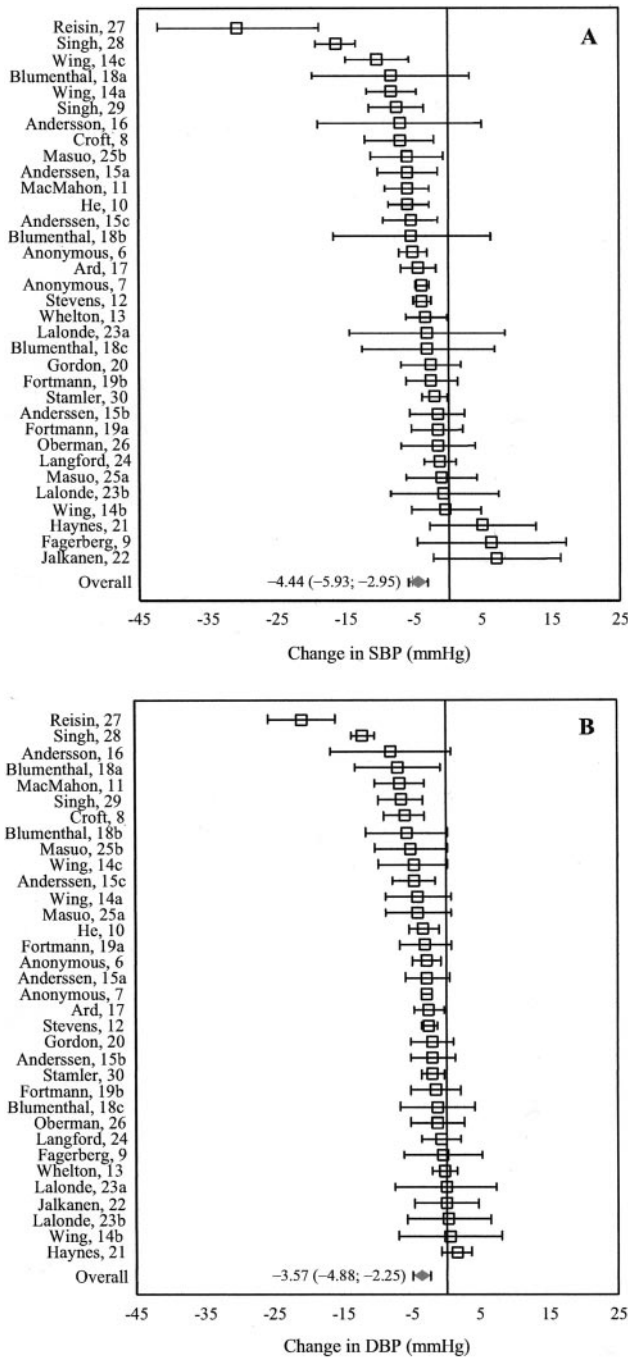
#Initial BMI of the study population could not be derived from the article.

## Changes in Body Weight

Mean initial body weight and BMI were 88.3 kg and 30.7 kg/m<sup>2</sup>, respectively. Mean net change in body weight of the population was -5.8% of initial body weight, ie, -5.1 kg (95% CI, -6.03 to -4.25), ranging from -0.6 to -11.9 kg. Average weight reductions in the energy restriction, increased physical activity, and combined intervention subgroups were -6.7 kg (95% CI, -8.27 to -5.11), -3.1 kg (95% CI, -4.54 to -1.75), and -6.2 kg (95% CI, -7.87 to -4.55), respectively.

## Changes in BP

Forest plots for net changes in SBP and DBP due to weight reduction, with 95% CIs, are presented in Figure 3. An average net weight reduction of -5.1 kg by means of energy restriction, increased physical activity, or the combined intervention was associated with a significant reduction in SBP of -4.44 mm Hg (95% CI, -5.93 to -2.95) and a significant reduction in DBP of -3.57 mm Hg (95% CI, -4.88 to -2.25). When expressed per kilogram of weight loss, reductions in SBP and DBP were -1.05 mm Hg (95% CI, -1.43



**Figure 3.** BP effects in RCTs of weight reduction and BP. Open squares represent average net changes in SBP (Forest plot A) and DBP (Forest plot B) in individual trials (or trial strata), with 95% CIs; pooled estimates from meta-analysis are depicted as gray diamonds; a, b, and c suffixes denote different strata from the same trial.

to  $-0.66$ ) and  $-0.92$  mm Hg (95% CI,  $-1.28$  to  $-0.55$ ), respectively. Exclusion of the outlying study by Reisin et al<sup>27</sup> caused a small attenuation of the overall estimates, ie,  $-4.17$  mm Hg (95% CI,  $-5.55$  to  $-2.80$ ) for SBP and  $-3.12$  mm Hg (95% CI,  $-4.17$  to  $-2.07$ ) for DBP.

**BP Response in Subgroups**

Findings from stratified meta-analyses are presented in Table 2. In the stratified meta-analysis, larger BP reductions were

observed in populations with an average weight loss  $>5$  kg than in populations with less weight loss, both for SBP ( $-6.24$  mm Hg [95% CI,  $-8.06$  to  $-4.41$ ] vs  $-2.44$  mm Hg [95% CI,  $-4.38$  to  $-0.49$ ]) and DBP ( $-4.97$  mm Hg [95% CI,  $-6.62$  to  $-3.31$ ] vs  $-1.97$  mm Hg [95% CI,  $-3.71$  to  $-0.21$ ]). BP reductions were also larger in populations who were taking antihypertensive medication than in untreated populations, both for SBP ( $-7.00$  mm Hg [95% CI,  $-10.02$  to  $-3.98$ ] vs  $-3.77$  mm Hg [95% CI,  $-5.33$  to  $-2.22$ ]) and DBP ( $-5.49$  mm Hg [95% CI,  $-8.06$  to  $-2.93$ ] vs  $-2.97$  mm Hg [95% CI,  $-4.39$  to  $-1.55$ ]). When subgroups were compared on the basis of initial BP level ( $<140/90$  mm Hg vs  $\geq 140/90$  mm Hg), there was no difference in SBP response, but reductions in DBP were approximately twice as large in hypertensives, although this difference was not statistically significant ( $-4.92$  [95% CI,  $-6.73$  to  $-3.12$ ] vs  $-2.35$  [95% CI,  $-4.05$  to  $-0.65$ ]). Weight loss caused larger BP reductions in Asian than in white or black populations, both for SBP and DBP, but findings must be interpreted with caution because of limited statistical power. Age, initial BMI, gender (percent females), and type of intervention did not significantly influence SBP and DBP response to weight loss in unadjusted analyses (Table 2).

Excluding the study of Reisin et al<sup>27</sup> yielded a smaller contrast in BP response between treated and untreated populations, ie,  $-5.87$  mm Hg (95% CI,  $-8.79$  to  $-2.94$ ) versus  $-3.79$  mm Hg [95% CI,  $-5.25$  to  $-2.32$ ] for SBP and  $-3.90$  mm Hg (95% CI,  $-6.10$  to  $-1.70$ ) versus  $-2.90$  mm Hg (95% CI,  $-4.06$  to  $-1.74$ ) for DBP.

Findings from multivariate stratified analyses were consistent with univariate results (Table 2), except for strongly increased BP estimates for intervention with physical activity ( $-4.74$  mm Hg [95% CI,  $-7.60$  to  $-1.88$ ] for SBP and  $-4.65$  mm Hg [95% CI,  $-6.84$  to  $-2.45$ ] for DBP), which resulted from correction for the amount of weight reduction.

**Discussion**

This meta-analysis of 25 RCTs comprising 4874 participants from different ethnic populations showed a BP reduction of  $-4.4/-3.6$  mm Hg for an  $\approx 5$ -kg weight loss by means of energy restriction, physical activity, or both. Larger BP reductions were achieved in populations that included subjects taking antihypertensive drugs.

Our meta-analysis was based on trials with an RCT design, which have high internal validity. For trials in which BP measurements were repeatedly recorded during follow-up, data were abstracted at the time point when the maximal effect of weight reduction on BP was achieved (32% of the strata). In most of these RCTs, the maximal effect was reached before the end of the trial. A likely explanation is lack of compliance during long-term intervention.

A previous meta-analysis of 12 trials by Staessen et al,<sup>5</sup> published in 1988, showed a BP reduction of  $-2.4/-1.5$  mm Hg per kilogram weight loss, which is substantially larger than our estimate ( $-1.1/-0.9$  mm Hg per kg). However, half of the studies in the meta-analysis by Staessen et al<sup>5</sup> were not randomized, and only 2 trials overlapped with our study, which might explain this discrepancy. The results of our subgroup analysis by hypertensive status are not consis-

**TABLE 2. Changes in SBP and DBP in 25 RCTs of Weight Reduction and BP, Overall and in Subgroups**

Stratum	No. of Strata*	SBP, mm Hg†		DBP, mm Hg†	
		Unadjusted	Adjusted‡	Unadjusted	Adjusted‡
Overall	34	-4.44 (-5.93; -2.95)	-4.78 (-5.76; -3.80)	-3.57 (-4.88; -2.25)	-3.56 (-4.31; -2.81)
Age					
≤45 years	15	-4.19 (-6.19; -2.20)	-4.74 (-6.35; -3.12)	-3.17 (-5.04; -1.31)	-3.69 (-4.96; -2.43)
>45 years	19	-4.74 (-6.95; -2.52)	-4.80 (-6.48; -3.13)	-3.94 (-5.76; -2.12)	-3.43 (-4.63; -2.23)
Gender					
<50% females	21	-4.75 (-6.54; -2.97)	-5.05 (-6.10; -3.99)	-4.04 (-5.61; -2.48)	-3.89 (-4.66; -3.12)
≥50% females	13	-3.74 (-6.40; -1.07)	-3.91 (-5.69; -2.13)	-2.53 (-4.82; -0.24)	-2.50 (-3.93; -1.08)
Hypertension§					
No	17	-4.08 (-6.01; -2.16)	-4.46 (-5.71; -3.21)	-2.35 (-4.05; -0.65)	-2.62 (-3.83; -1.42)
Yes	17	-4.95 (-7.25; -2.64)	-4.73 (-6.40; -3.06)	-4.92 (-6.73; -3.12)	-4.36 (-5.72; -3.00)
Race					
White	14	-3.19 (-4.79; -1.59)	...	-2.50 (-3.00; -1.99)	...
Black	4	-4.67 (-8.86; -0.49)	...	-3.08 (-4.92; -1.23)	...
Asian	4	-8.77 (-11.91; -5.64)	...	-9.81 (-11.17; -8.44)	...
Intervention					
Energy restriction	19	-4.93 (-6.84; -3.02)	-4.33 (-5.70; -2.97)	-4.25 (-5.95; -2.55)	-2.84 (-3.80; -1.87)
Physical activity	8	-1.73 (-5.14; 1.69)	-4.74 (-7.60; -1.88)	-1.93 (-5.07; 1.22)	-4.65 (-6.84; -2.45)
Combined intervention	7	-5.15 (-7.78; -2.51)	-5.66 (-7.52; -3.81)	-3.12 (-5.60; -0.64)	-4.44 (-5.68; -3.19)
Initial BMI					
<30 kg/m <sup>2</sup>	15	-4.14 (-4.95; -3.33)	-4.59 (-5.70; -3.49)	-2.61 (-3.29; -1.93)	-3.11 (-4.01; -2.21)
≥30 kg/m <sup>2</sup>	13	-4.09 (-4.87; -3.31)	-4.05 (-5.06; -3.05)	-2.75 (-3.39; -2.11)	-2.77 (-3.50; -2.04)
Weight reduction					
≤5 kg	16	-2.44 (-4.38; -0.49)	-2.70 (-4.59; -0.81)	-1.97 (-3.71; -0.21)	-2.01 (-3.47; -0.54)
>5 kg	18	-6.24 (-8.06; -4.41)	-6.63 (-8.43; -4.82)	-4.97 (-6.62; -3.31)	-5.12 (-6.48; -3.75)
Antihypertensive drugs¶					
No	26	-3.77 (-5.33; -2.22)	-4.11 (-5.23; -3.00)	-2.97 (-4.39; -1.55)	-2.91 (-3.66; -2.16)
Yes	8	-7.00 (-10.02; -3.98)	-6.70 (-8.71; -4.69)	-5.49 (-8.06; -2.93)	-5.31 (-6.64; -3.99)

\*No. of strata in subgroup analyses may not total 34 because of missing data.

†BP changes were obtained from a random-effects model, with 95% CI end points in parentheses.

‡Adjusted for age, gender (% females), initial BP, change in body weight, and duration.

§Based on initial BP level (<140/90 mm Hg vs ≥140 mm Hg), not on use of antihypertensive medication.

||Races other than black, white, and Asian were not considered in subgroup analysis because of small numbers; power for multivariate analysis in strata of race was insufficient.

¶Coded "yes" if trial population included one or more subjects on antihypertensive drug treatment.

tent with the meta-analysis of 8 RCTs by Ebrahim and Smith,<sup>33</sup> in which the BP response was larger in hypertensive populations (-5.2/-5.2 mm Hg) than in normotensive populations (-2.8/-2.3 mm Hg). However, hypertension in our analysis was defined on the basis of BP level only and not on use of antihypertensive medication, which accounts for part of this difference. The Cochrane review by Mulrow et al<sup>34</sup> showed that modest weight loss in the range of 3% to 9% of initial body weight was roughly associated with a 3-mm Hg reduction in BP in overweight, hypertensive persons, which is smaller than in our study. Mulrow et al<sup>34</sup> did not perform pooling of trials because of marked heterogeneity in study designs, entry criteria, and outcome measurement. Most of the 18 trials in their meta-analysis included combined interventions (eg, weight reduction plus sodium restriction), from which the effect of body weight reduction could not be separated.

A meta-analysis of aerobic exercise and BP by Whelton et al<sup>35</sup> showed that BP was significantly reduced even in trials in which overall weight loss was minimal. This suggests that exercise reduces BP independently of changes in body weight. In our multivariate analysis, which was standardized for the amount of weight loss, the effect on DBP was larger when body weight was reduced by physical activity compared with energy restriction. This confirms the idea that physical activity also reduces BP by mechanisms unrelated to weight loss.

Although the exact mechanism of the relation between hypertension and obesity and the effect of weight loss on BP is unknown, there are several plausible biologic pathways.<sup>1</sup> The renin-angiotensin-aldosterone system is overactivated in obese subjects, and renin activity and aldosterone concentrations are higher than in lean subjects.<sup>36-38</sup> Furthermore, activity of the sympathetic nervous system is increased in

hypertensive, obese subjects, which could induce obesity-related renal effects.<sup>38–40</sup> Alternatively, there might be inhibition of the natriuretic peptides system, of which the functional effects are vasodilatation and natriuresis.<sup>38,41,42</sup> Decreased insulin sensitivity and hyperinsulinemia as part of the metabolic syndrome might also form an essential link between obesity and hypertension, although this interrelation is still not fully understood.<sup>43</sup>

Additional studies are needed to investigate the long-term effects of weight reduction on BP. It is also important to examine whether weight loss has a persistent beneficial effect on cardiovascular risk, even after regaining weight. Data on weight reduction and BP in children and adolescents are scanty. Trials in this field are clearly warranted because of the increasing prevalence of obesity and hypertension at younger ages, which is becoming a major medical problem and a threat to public health.<sup>44</sup>

In conclusion, the results from this meta-analysis provide unequivocal evidence that weight loss makes an important contribution to the treatment of hypertension, especially in subjects taking antihypertensive medication. Prevention of weight gain is likely to have a large impact on the burden of hypertension and consequently, cardiovascular diseases in the general population.

## Perspectives

This meta-analysis of 25 RCTs showed reductions in SBP and DBP of  $\approx 1$  mm Hg for each kilogram of weight loss. In particular, subjects on antihypertensive drug treatment might benefit from weight reduction. This study provides unequivocal evidence that lifestyle modifications to reduce body weight should be a major component in the treatment of hypertension. The prevalence of overweight in Western societies has strongly increased in the past decades. Weight control in the population is of the utmost importance to prevent an increase in the prevalence of hypertension and consequently, of cardiovascular morbidity and mortality.

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