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Effect of Vitamin D Supplementation on Blood Pressure in African-Americans

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Abstract

African-Americans have significantly higher rates of hypertension than whites, and lower circulating levels of 25-hydroxyvitamin D. There are few data about the effect of vitamin D3 (cholecalciferol) supplementation on blood pressure in African-Americans. During two winter periods from 2008–2010, 283 African-Americans (median age, 51 years) were randomized into a four-arm, double-blind trial for three months of placebo, 1,000, 2,000, or 4,000 international units of cholecalciferol per day. At baseline, three months, and six months, systolic and diastolic pressure and 25-hydroxyvitamin D were measured. The 3-month follow-up was completed in 250

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Conflicts of interest and disclosures

None of the authors have a financial or other conflict of interest with respect to the content of this manuscript. The authors of this manuscript had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analyses were performed by an author (DLH), whose affiliations are listed.

(88%) participants. The difference in systolic pressure between baseline and 3 months was +1.7 mmHg for those receiving placebo, −0.66 mmHg for 1,000 units/day, −3.4 mmHg for 2,000 units/day, and −4.0 mmHg for 4,000 units/day of cholecalciferol (−1.4 mmHg for each additional 1000 units/day of cholecalciferol; p=0.04). For each 1 ng/mL increase in plasma 25-hydroxyvitamin D, there was a significant 0.2 mmHg reduction in systolic pressure (p = 0.02). There was no effect of cholecalciferol supplementation on diastolic pressure (p=0.37). Within an unselected population of African-Americans, three months of oral vitamin D3 supplementation significantly, yet modestly, lowered systolic pressure. Future trials of vitamin D supplementation on blood pressure are needed to confirm these promising results, particularly among African-Americans, a population for whom vitamin D deficiency may play a more specific mechanistic role in the pathogenesis of hypertension.

Keywords

Blood pressure; Hypertension; African Americans; Randomized controlled trial; Vitamin D

Introduction

African-Americans in the US have significantly higher rates of hypertension and cardiovascular disease than whites, and lower circulating levels of 25-hydroxyvitamin D (25[OH]D).[1] In prospective studies, lower levels of 25(OH)D are independently associated with a higher risk of developing hypertension.[2–4] Thus, the greater prevalence of vitamin D deficiency among African-Americans may explain a substantial proportion of the racial disparity in blood pressure (BP).[5] Several trials evaluating the effects of vitamin D supplementation on BP have been conducted with inconsistent results.[6–9] However, none of these trials enrolled a sufficient number of black participants to examine the effects of supplementation in this population.

If vitamin D supplementation lowered BP among African-Americans, its widespread use could have major public health benefits. Thus, we examined the influence of vitamin D supplementation in an exclusively black population within a randomized, double-blind, placebo-controlled trial.

Methods

Study Design

This is a prospective, randomized, double-blind, placebo-controlled clinical trial of oral cholecalciferol (vitamin D3) in a healthy Black population (ClinicalTrials.gov: NCT00585637). The primary goal of the trial was to examine the effect of daily supplementation of 1,000 international units (IU) of vitamin D3, 2,000 IU of vitamin D3, and 4,000 IU of vitamin D3, and placebo on plasma 25(OH)D levels. Participants were drawn from Open Doors to Health (ODH), a community-based colorectal cancer prevention study conducted in 12 public housing communities in the Boston metropolitan area.[10] We also recruited participants from community and faith-based organizations and a refer-a-friend program. All participants provided written informed consent; the project was approved by the Institutional Review Board of Harvard School of Public Health. All procedures followed were in accord with institutional guidelines.

Recruitment and randomization

Participants in ODH were invited to participate if they were ages 30–80 years, understood written and spoken English, self-identified as Black or African American,[11–14] and had

permission from their primary care doctors. Participants were enrolled during the winter months in order to minimize the effects of sun exposure on vitamin D levels. We excluded individuals who had pre-existing disorders of calcium metabolism and parathyroid function, type I diabetes, sarcoidosis, active malignancy (other than non-melanoma skin cancer), or active thyroid disease. We also excluded those with cognitive impairment or who planned a vacation or extended travel to a sunny region during the supplementation phase of the study. Those taking vitamin D containing supplements were enrolled if they agreed to discontinue these medications for 6 months prior to enrollment and during the study.

A total of 328 participants were enrolled into the parent trial during the winters of three consecutive years, from 2007–2010 (Figure S1). In year 2 of the study, we amended the original protocol to include BP measurements as an additional endpoint. Thus, to assess the effects of vitamin D supplementation on BP, we did not include the 45 participants enrolled in year 1 in whom we did not measure BP, leaving 283 participants enrolled in years 2 and 3 for this analysis (2008–2010).

Treatments

Participants were randomly assigned in a 1:1:1:1 ratio to one of three doses of cholecalciferol (vitamin D3): 1,000 IU; 2,000 IU; and 4,000 IU, or placebo (Pharmavite LLC, Mission Hill, CA). All capsules also contained 200 mg of calcium. All capsules were indistinguishable, and both participants and research staff were blinded to treatment assignment. Study medications were initiated during early winter (November or December), and were taken orally once daily for three months (completed in February or March).

Endpoints and Follow-up

The primary endpoints of the study were the changes in systolic and diastolic BP (SBP and DBP) from baseline to the 3 month follow-up (at the end of randomized treatment). BP was also measured at the 6 month follow-up, three months after treatment was discontinued. At each follow-up assessment, trained study personnel obtained three BP readings at 5 minute intervals with participants in the seated position and feet flat on the floor. BP was determined with the OMRON HEM-907 device (Omron Healthcare Inc, Bannockburn, Il). This device has been validated,[15–17] and has been used in previous clinical trials.[18, 19] The BP at each assessment was defined as the mean of the second and third readings.

Participants attended study visits at baseline, three months (at the end of randomized treatment), and six months (3 months after treatment discontinuation). At each study visit, a blood specimen was collected; height and weight were measured, and a brief questionnaire was administered. This questionnaire was designed to ascertain socioeconomic and demographic factors, medical information, use of non-study medications, dietary intake of vitamin D-containing foods, use of supplements, physical activity, and smoking.

Compliance and Safety

We monitored adherence and compliance with biweekly telephone calls, monthly visits, electronic pill dispenser systems, and pill counts. To assess for toxicity, we informed participants of the potential for hypercalcemia, educated them on the warning signs and symptoms, and asked participants to call if he or she experienced any such signs or symptoms. We also screened for these problems during biweekly phone calls. Any concerning findings were noted and reported to the study physician, who made a determination about relatedness to vitamin D supplementation and the need for treatment discontinuation and further evaluation.

Plasma Vitamin D Levels

Blood samples collected at baseline, three months, and six months were separated, and plasma was stored in liquid nitrogen in the Dana-Farber Cancer Institute Clinical Research Laboratory (Boston, MA). After completion of the study, all plasma samples were sent as a single batch to the laboratory of Dr. Bruce Hollis (Medical University of South Carolina, Charleston, SC), where 25(OH)D concentrations were measured using the Diasorin radioimmunoassay.[20] All laboratory personnel were blinded to treatment assignment. Masked quality control samples were also assayed; the mean coefficient of variation of 25(OH)D measurements was 9%.

Statistical Analysis

The trial was designed with a statistical power of 80% to detect differences in plasma 25(OH)D level of 5.3 ng/mL between treatment groups. Based on this planned sample size and accounting for exclusion of the 45 participants who already completed the study prior to modification of the protocol to include BP measurements, we estimated that the trial would have 80% power to detect a decrease in systolic BP (SBP) of 4.1 mmHg per 1000 IU/day of vitamin D3 supplementation, and 90% power to detect a 4.7 mmHg decrease in SBP. Differences in the baseline characteristics of participants across the four treatment groups were compared using the Kruskal-Wallis test for continuous variables and a chi-square test for categorical comparisons.

The primary endpoints were 3-month change in SBP at the end of treatment (i.e. SBP at 3 months minus SBP at baseline) and 3-month change in diastolic BP (DBP) at the end of treatment (i.e. DBP at 3 months minus DBP at baseline). For our primary analysis, we used linear regression with the dose of vitamin D3 (per 1000 IU/day) as the independent variable and the 3-month change in SBP (or 3-month change in DBP) as the dependent variables.

We performed a number of *a priori* secondary analyses. First, we analyzed the change in SBP and DBP according to the change in plasma 25(OH)D levels. Second, we analyzed the primary endpoint after excluding individuals who were taking antihypertensive medications at baseline. Third, we analyzed the effect of any vitamin D supplementation (all three treatment groups combined) compared with placebo on SBP and DBP. Fourth, we analyzed the persistence of treatment effects by examining the change in BP from the baseline to the 6 month exam, three months after treatment was discontinued.

We also performed three *post-hoc* secondary analyses. Because a previous meta-analysis found that the effect of vitamin D supplementation on BP was greater in those individuals with higher baseline BP,[21] we analyzed the primary endpoint after stratifying by baseline SBP (< 120 mmHg, ≥ 120 mmHg). In addition, we determined the effect of vitamin D supplementation according to whether or not participants were vitamin D deficient at baseline (plasma 25[OH]D < 20 ng/mL, ≥ 20 ng/mL). We tested whether the effect of cholecalciferol on BP was significantly different according to baseline SBP and plasma 25(OH)D by constructing interaction terms and including these terms in our linear regression models. We also performed a *post-hoc* secondary analysis in which we reanalyzed the effect of vitamin D supplementation on SBP and DBP after adjusting for baseline SBP and DBP, respectively.

Results

Participant characteristics

The current analysis is comprised of the 283 participants who were enrolled and randomized following the inclusion of BP as an additional endpoint (Figure S1). The compliance rate

with randomized therapy in the entire cohort was 96.6%. The 3-month follow-up was completed in 250 of these 283 participants (88%). These 250 individuals who had available BP measurements at baseline and at the end of treatment at 3 months were included in our primary analysis. Participants who did not have available BP measurements at 3-months were evenly distributed across the treatment groups.

The majority of participants reported being non-Hispanic black; 6.7% reported Hispanic ethnicity. The median age of the entire cohort was 51 years (interquartile range [IQR], 44–59 years), and the median body mass index was 31.0 kg/m^2 (IQR, 26.7–36.2 kg/m^2). The median BP was 122/78 mmHg, and 41.7% of participants were taking antihypertensive medications. Baseline characteristics according to randomized treatment assignment are displayed in Table 1. There were no statistically significant differences in any of the participant characteristics across the four groups. However, there did appear to be a non-significantly higher baseline SBP among those assigned 4000 IU/day as compared with those assigned placebo.

Effect of Supplementation on 25(OH)D Levels

The effect of the various doses of cholecalciferol supplementation on 25(OH)D levels after 3 months, as well as the persistence of the effect 3 months after cessation of supplements, is depicted in Figure S2 (panel A). At 3 months, median 25(OH)D levels rose to 45.9, 34.8, and 29.7 ng/mL, respectively, in participants assigned to 4000, 2000, and 1000 IU/day. By 6 months, median levels fell to 31.2, 27.0, and 21.2 ng/mL, respectively, in participants assigned to 4000, 2000, and 1000 IU/day. However, 25(OH)D levels at 6 months remained higher than the baseline levels.

Primary Analysis

The primary efficacy analyses of vitamin D3 supplementation on SBP and DBP are shown in Table 2. For each additional 1000 IU/day of cholecalciferol, SBP was significantly decreased by 1.4 mmHg (p=0.04). There was no effect of cholecalciferol supplementation on DBP, which fell by 0.5 mmHg for each additional 1000 IU/day (p=0.37).

A priori Secondary Analyses

The change in plasma 25(OH)D levels associated with vitamin D3 supplementation was also associated with change in systolic but not diastolic BP. For each 1 ng/mL greater increase in 25(OH)D level between baseline and 3 months, there was a significant 0.2 mmHg reduction in SBP (p = 0.02). In addition, for each 1 ng/mL greater increase in 25(OH)D level between baseline and 6 months, there was a significant 0.2 mmHg decrease in SBP (p = 0.05).

We repeated our primary analysis after excluding those 118 individuals who were taking antihypertensive medications. Among the remaining 132 participants, each additional 1000 IU/day of cholecalciferol supplementation was associated with a decrease in SBP that was similar in magnitude to the whole population (1.2 mmHg); however, this result was not statistically significant (p=0.24), possibly owing to the restricted sample size.

We also examined the effect of any dose of cholecalciferol supplementation (ie, all three treatment groups combined) on 3 month change in BP compared with placebo. In these analyses, cholecalciferol supplementation at any dose lowered SBP by 4.4 mmHg, an effect which approached statistical significance (p = 0.07).

To assess if the effect of vitamin D3 supplementation persisted after discontinuation of supplementation, we examined the change in BP at the 6 month exam, three months after study treatment was discontinued. We did not observe any significant effect of randomized

treatment on either SBP or DBP at the 6 month exam in comparison with the baseline exam (Figure S2, panels B and C). For each 1000 IU/day additional cholecalciferol supplementation, the 6 month SBP was decreased by 0.4 mmHg (p=0.56) and DBP was decreased by 0.2 mmHg (p=0.75).

Post-hoc Secondary Analyses

We repeated our primary analysis after stratifying by baseline SBP (< 120 mmHg, ≥ 120 mmHg) and baseline plasma 25(OH)D (< 20 ng/mL, ≥ 20 ng/mL). The effect of cholecalciferol on BP was identical among those whose baseline SBP < 120 mmHg or ≥ 120 mmHg. In contrast, the effect of each additional 1000 IU/day of cholecalciferol on SBP was larger among those whose baseline plasma 25(OH)D was < 20 ng/mL (a 2.2 mmHg decrease, p=0.03) than among those whose baseline plasma 25(OH)D was ≥ 20 ng/mL (a 0.4 mmHg decrease, p=0.66). However, these effects were not statistically different from each other (p-interaction = 0.33).

We observed a clinically but not statistically significant difference in baseline systolic blood pressure among the treatment groups (Table 1). Thus, we repeated our primary analysis after adjusting for baseline blood pressure. In these models, each 1000 IU/day additional cholecalciferol dose nonsignificantly lowered systolic pressure by 0.7 mmHg (p = 0.29).

Discussion

To our knowledge, this is the largest randomized, double-blind, placebo-controlled trial examining the effects of cholecalciferol supplementation among black individuals. On an intent-to-treat basis, supplementation with cholecalciferol for 3 months significantly lowered SBP, though no effect on DBP was observed. In addition, a greater increase in plasma 25(OH)D level in response to supplementation was significantly associated with a larger decrease in SBP. The magnitude of the effect was greater with higher doses of cholecalciferol, but overall was clinically modest (a 1.4 mmHg decrease in SBP for every 1000 IU/day given).

Our findings suggest that, among African-Americans, vitamin D supplementation may play a role in lowering BP. However, these conclusions are tempered by our observation that the baseline SBP was greatest among participants treated with the highest dose of cholecalciferol, raising the possibility that the effect of cholecalciferol could have been due, in part, to regression to the mean. However, all three groups treated with cholecalciferol had declines in SBP (Figure S2, panel B) and there was a significant decrease in SBP associated with increasing 25(OH)D levels in response to supplementation.

To date, more than ten trials have evaluated the effect of vitamin D therapy on BP,[22–37] four of which were designed specifically to evaluate BP as a primary endpoint.[31, 32, 36, 37] Of these four trials, our results are supported by a placebo-controlled trial which showed that daily intake of 800 IU of cholecalciferol significantly reduced SBP by 7mmHg after 8 weeks of treatment among 148 individuals.[32] In contrast, a single dose of cholecalciferol 100,000 IU did not lower BP after five weeks in a placebo-controlled trial of 189 individuals with vitamin D deficiency.[31] This trial was limited by its short duration, relatively small sample size, and modest 7 ng/mL rise in 25(OH)D levels in response to supplementation.[31]

The largest trial (Women's Health Initiative, n=36,282) was designed to evaluate fracture and cancer risk in a population of largely vitamin D insufficient women, cholecalciferol (400 IU/daily) with calcium was not associated with changes in BP or incident hypertension after 7 years of follow-up.[29] However, the dose of cholecalciferol used was low and not

expected to significantly raise 25(OH)D levels,[38–40] the rate of medication non-compliance was high, and 60% of women assigned to placebo also consumed supplemental vitamin D.

Three meta-analyses combining most of these prior trials failed to observe an overall lowering of BP associated with vitamin D supplementation.[6–9] However, vitamin D supplementation was associated with significant decreases in BP in meta-analyses limited to trials comprised of only hypertensive individuals or to trials using higher doses of vitamin D (>1000 IU/daily).[67]

A major limitation of these prior studies was the limited representation by black individuals. Compared with Caucasians, African-Americans have lower circulating 25(OH)D levels and a higher prevalence of vitamin D deficiency. Moreover, elevated BP among African-Americans is believed to be more strongly mediated by inappropriately elevated activity of the renin-angiotensin system (RAS),[41, 42] which is known to be associated with hypertension and cardiovascular disease.[43–45] The most well-supported mechanism by which vitamin D may affect BP is its role as a negative regulator of the RAS.[46] The development of vitamin D receptor (VDR) null mice has facilitated numerous experiments illuminating the relationship between vitamin D, the RAS, and hypertension.[47] VDR null mice, for example, have significant elevations in renin activity and circulating plasma angiotensin II concentrations,[46] and have hypertension and cardiac hypertrophy that is attenuated when RAS antagonists are administered. Recently, human mechanistic studies have shown that lower levels of $1,25(OH)_2D$ and 25(OH)D are associated with higher plasma renin and angiotensin II concentrations,[48–50] and that lower 25(OH)D levels are associated with higher tissue RAS activity in both the kidney,[51] and in the peripheral vasculature.[52] Although our study did not directly evaluate the RAS, the relatively greater importance of RAS activation among African-Americans may partly explain our observation that vitamin D supplementation lowers BP in this population, a finding which has not been consistently seen in studies that primarily enrolled whites.

Our study has several strengths. First, to our knowledge, this is the first randomized, double-blind, placebo-controlled trial to examine the specific effect of vitamin D supplementation on BP among African-Americans. Second, we used a range of cholecalciferol doses that were sufficient to raise plasma 25(OH)D levels to normal among a population that was largely vitamin D deficient or insufficient at baseline. Third, participants were treated only during the winter months to minimize the influence of seasonal variations on circulating 25(OH)D levels. Last, our compliance with study medications was >95% and ascertainment of BP was performed in a standardized format with a research quality device.

Our study also has several limitations. First, despite randomization, the treatment groups were imbalanced with respect to baseline SBP. The effect of supplementation on change in systolic pressure was attenuated, and no longer significant, after adjusting for baseline systolic pressure. This raises the concern that the significant blood pressure lowering effect that we observed may have been partly explained by regression to the mean; on the other hand, the direction of the effect is toward a benefit from vitamin D supplementation, and the lack of significance could be due to limited power. In addition, we did observe significant decreases in SBP with increasing plasma 25(OH)D levels, supporting a true causal association. Second, although we designed our intervention for three months to minimize the influence of major seasonal variation in 25(OH)D levels, it is possible that a longer duration of treatment may be required to fully assess the effect of supplementation on BP. Third, about 40% of the participants in our study were taking antihypertensive medications at baseline, which could potentially mask the effects of supplementation. However, this would tend to attenuate our observed associations. Moreover, our results were similar among those

who did and did not take antihypertensive medications. Finally, our study did not evaluate the mechanisms that may underlie the effects of vitamin D supplementation.

Perspectives

In this randomized, placebo-controlled trial, cholecalciferol supplementation significantly lowered SBP in African-Americans. If confirmed, our results may also partly inform future therapeutic strategies among African-Americans for whom vitamin D deficiency may play a more specific mechanistic role in the pathogenesis of hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Novelty and significance

What is new?

- Although various randomized trials have examined whether or not vitamin D supplementation can lower blood pressure in predominantly white populations, this had ***not*** been tested in African-Americans.

What is Relevant?

- Low levels of 25(OH)D are consistently associated with increased blood pressure or a higher risk of developing hypertension.
- If this association was causal, vitamin D deficiency may in part explain the discrepant hypertension risk among blacks in the United States.

Summary

- We found that, compared with placebo, vitamin D supplementation modestly but significantly reduced systolic blood pressure. In addition, greater increases in 25(OH)D levels during the study period produced larger reductions in systolic blood pressure.
- If confirmed, these results may inform future therapeutic strategies to reduce blood pressure or prevent hypertension among African-Americans.

Table 1

Baseline characteristics

Characteristic	Vitamin D dose (IU/day)					
	All	**Placebo**	**1000**	**2000**	**4000**	**p-value**
Number	283	72	68	73	70	
			Median (IQR)			
25(OH)D, ng/mL	15.7 (10.7–23.4)	16.3 (11.3–23.9)	16.3 (11.0–23.0)	14.5 (9.9–22.9)	15.6 (11.0–22.9)	0.86
SBP, mmHg	122 (112–136)	120 (108–135)	123 (112–136)	121 (110–134)	128 (118–140)	0.07
DBP, mmHg	78 (71–86)	78 (71–84)	80 (70–88)	75 (71–84)	78 (71–87)	0.47
Age, years	51 (44–59)	51 (44–59)	51 (43–59)	50 (43–57)	51 (46–60)	0.86
BMI, kg/m^2	31.0 (26.7–36.2)	31.1 (26.5–35.7)	30.8 (27.6–37.7)	30.5 (26.0–36.9)	31.2 (27.7–35.7)	0.82
			N (%)			
Female	185 (65.4)	46 (63.4)	50 (73.5)	46 (63.0)	43 (61.4)	0.43
Hispanic	19 (6.7)	3 (4.2)	7 (10.3)	4 (5.5)	5 (7.1)	0.53
Work status						0.76
Employed	106 (37.5)	26 (36.1)	26 (38.2)	29 (39.7)	25 (35.7)	
Retired	41 (14.5)	12 (16.7)	10 (14.7)	9 (12.3)	10 (14.3)	
Education beyond high school	122 (43.3)	29 (40.2)	31 (46.3)	33 (45.2)	29 (41.4)	0.13
Married	89 (31.4)	20 (27.8)	25 (36.8)	23 (31.5)	21 (30.0)	0.71
Smoking status						0.68
Current	88 (31.1)	24 (33.3)	25 (36.8)	21 (28.8)	18 (25.7)	
Past	69 (24.4)	17 (23.6)	14(20.6)	22 (30.1)	16 (22.9)	
Takes multivitamins *	52 (18.4)	8 (11.1)	15 (22.1)	11 (15.1)	18 (25.7)	0.10
Takes vitamin D supplements *	21 (7.4)	8 (11.1)	5 (7.4)	2 (2.7)	6 (8.6)	0.23
History of hypertension	141 (49.8)	35 (48.6)	35 (51.5)	36 (49.3)	35 (50.0)	0.99
Takes antihypertensive medication	118 (41.7)	34 (47.2)	29 (42.6)	27 (37.0)	28 (40.0)	0.71
Takes OCPs (if female)	16 (8.6)	3 (6.5)	3 (6.0)	4 (8.7)	6 (14.0)	0.55
Menopausal (if female)	106 (57.3)	30 (65.2)	26 (52.0)	23 (50.0)	27 (62.8)	0.33

* These supplements were stopped prior to randomization.

Definitions 25(OH)D, plasma 25-hydroxyvitamin D level; OCP, oral contraceptive pill; SBP and DBP, systolic and diastolic blood pressure, BMI, body mass index.

Table 2

Effect of Vitamin D Supplementation on Blood Pressure during the Treatment Period (Baseline to 3 months)

Parameter	Vitamin D dose (IU/day)				Entire study population (all doses)	
	Placebo	1000	2000	4000		
N (at baseline)	72	68	73	70	283	
N (at 3 months)	64	56	65	65	250	
N (difference)	64	56	65	65	250	
	Within-group changes in BP				3 month change in BP per 1000 IU/day	p-value
Baseline SBP, mean (SE)	122.2 (2.2)	124.7 (2.1)	122.8 (2.0)	130.4 (2.4)		
3 month SBP, mean (SE)	124.9 (2.4)	122.5 (2.0)	120.0 (2.4)	126.6 (2.6)	− 1.4 (0.7)	0.04
Difference SBP, mean (SE)	1.7 (2.1)	−0.66 (2.1)	−3.4 (2.0)	−4.0 (2.1)		
Baseline DBP, mean (SE)	78.0 (1.3)	79.8 (1.3)	77.6 (1.4)	79.8 (1.6)		
3 month DBP, mean (SE)	78.9 (1.8)	78.0 (1.6)	76.0 (1.8)	78.0 (1.6)	− 0.5 (0.5)	0.37
Difference DBP, mean (SE)	0.7 (1.6)	−2.5 (1.6)	−1.8 (1.4)	−1.8 (1.50)		