

Stress Reduction in the Secondary Prevention of Cardiovascular Disease

Randomized, Controlled Trial of Transcendental Meditation and Health Education in Blacks

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Background—Blacks have disproportionately high rates of cardiovascular disease. Psychosocial stress may contribute to this disparity. Previous trials on stress reduction with the Transcendental Meditation (TM) program have reported improvements in cardiovascular disease risk factors, surrogate end points, and mortality in blacks and other populations.

Methods and Results—This was a randomized, controlled trial of 201 black men and women with coronary heart disease who were randomized to the TM program or health education. The primary end point was the composite of all-cause mortality, myocardial infarction, or stroke. Secondary end points included the composite of cardiovascular mortality, revascularizations, and cardiovascular hospitalizations; blood pressure; psychosocial stress factors; and lifestyle behaviors. During an average follow-up of 5.4 years, there was a 48% risk reduction in the primary end point in the TM group (hazard ratio, 0.52; 95% confidence interval, 0.29–0.92; $P=0.025$). The TM group also showed a 24% risk reduction in the secondary end point (hazard ratio, 0.76; 95% confidence interval, 0.51–0.1.13; $P=0.17$). There were reductions of 4.9 mm Hg in systolic blood pressure (95% confidence interval –8.3 to –1.5 mm Hg; $P=0.01$) and anger expression ($P<0.05$ for all scales). Adherence was associated with survival.

Conclusions—A selected mind–body intervention, the TM program, significantly reduced risk for mortality, myocardial infarction, and stroke in coronary heart disease patients. These changes were associated with lower blood pressure and psychosocial stress factors. Therefore, this practice may be clinically useful in the secondary prevention of cardiovascular disease.

Clinical Trial Registration—URL: www.clinicaltrials.gov Unique identifier: NCT01299935. (*Circ Cardiovasc Qual Outcomes*. 2012;5:750-758.)

Key Words: cardiovascular disease ■ integrative medicine ■ health status disparities ■ complementary therapies ■ meditation ■ mind–body therapies ■ stress

Cardiovascular disease (CVD) is the leading cause of death in the United States and the world.^{1,2} Blacks suffer from disproportionately high rates of CVD morbidity and mortality.^{1,3} Substantial evidence indicates that psychosocial stress contributes to the onset and progression of CVD.^{4–8} The attributable risk associated with psychosocial stress factors across diverse populations is similar to traditional CVD risk factors.⁸ Psychological distress factors, including depression, anger, hostility, and anxiety, predict CVD clinical events.^{9–11} The disparity in CVD in blacks may be related to disproportionate levels of psychosocial and environmental stress.^{12–16} Randomized,

controlled trials of stress reduction using the Transcendental Meditation (TM) program have reported decreases in CVD risk factors, surrogate end points, and mortality in blacks and the general population.^{17–24} The overall objective of this trial was to evaluate the effects of practice of the TM program in the secondary prevention of CVD in blacks.

Methods

Study Design

The trial was conducted between March 1998 and July 2007 in 2 phases. The first phase was from March 1998 to April 2003. After a hiatus in

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funding, the second phase was conducted from March 2004 to July 2007. All phase 1 subjects were invited to participate in phase 2. Subjects provided written informed consent separately for each of the 2 phases.

The clinical site was the Department of Medicine, Medical College of Wisconsin, Milwaukee, and the administrative and data coordinating center was the Institute for Natural Medicine and Prevention, Maharishi University of Management, Fairfield, Iowa. The institutional review boards of both institutions approved the protocol. The trial was monitored by an independent data and safety monitoring board.

Participants

Eligible patients were black men and women with angiographic evidence of at least 1 coronary artery with >50% stenosis. Exclusion criteria were acute myocardial infarction (MI), stroke, or coronary revascularization within the previous 3 months, chronic heart failure with ejection fraction <20%, cognitive impairment, and noncardiac life-threatening illness. Subjects continued usual medical care throughout the study.

Subjects were identified from the African American Heart Health Registry of the Medical College of Wisconsin and other databases of Milwaukee area hospitals. Each patient's physician gave permission for study participation.

Procedure

Subjects were randomly assigned to either the TM or health education (HE) arms using a stratified block design. The strata were sex (male/female), age (above and below median for each cohort), and lipid-lowering medication (yes/no). Stratification factors were based on previous literature indicating that these are strong predictors of cardiovascular clinical events—fatal and nonfatal.^{25,26} Random allocation was performed by the study biostatistician who concealed the allocation schedule and conveyed the assignments to the study coordinator. Investigators, data collectors, and data management staff were blinded to group assignment. Intervention groups met separately to

minimize contamination. Because double blinding in behavioral trials is generally not feasible, this was a single-blinded trial.²⁷

Subjects were assessed at baseline, month 3 and every 6 months after baseline for clinical events, blood pressure (BP), body mass index (BMI), and adherence. Lifestyle behaviors (diet, exercise, and substance use) and psychosocial distress factors were assessed annually.

Outcomes

The primary end point was the time-to-first event of the composite of all-cause mortality, nonfatal MI, or nonfatal stroke. The secondary clinical end point was time-to-first event for the composite of cardiovascular mortality, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for ischemic heart disease-non-MI or heart failure. Additional secondary, intermediate end points included BP, smoking, alcohol, BMI, diet, exercise, and psychological distress.

Mortality and cause of death were determined from death certificates and the National Death Index.^{28,29} At semiannual study visits, participants reported hospitalizations. Nonfatal events were confirmed from hospital discharge summaries. All clinical end points were adjudicated by a blinded, independent reviewer who applied standardized and validated criteria.³⁰

Three successive BP measurements were taken with a mercury sphygmomanometer in the seated position. BMI was calculated as weight/height². Dietary patterns were assessed with the Block Dietary Food Consumption Questionnaire.³¹ Smoking and alcohol use were determined from weekly recall questionnaires.³² A modified Minnesota Leisure Time Physical Activity Questionnaire was used for exercise.³³ Psychological distress factors were assessed with the CES-D Scale for depression,^{34,35} the Cook-Medley Hostility Inventory composite score for hostility,^{36,37} and the Anger Expression scale for anger-in, anger-out, anger-control, and total anger.³⁸

Expectation of treatment benefits was assessed by questionnaire at baseline in a subset of 71 subjects. Regularity of home practice for both groups was determined by questionnaire at each posttesting session. Practice of at least once a day was considered regular. Attendance at group instructional and follow-up meetings was recorded.

Interventions

The TM program was used as a mind–body intervention for its effects on physiological correlates of stress and related CVD outcomes because of its standardization, reproducibility, and validity.^{23,24,39–41} It is the principal mind–body technique of Maharishi Ayurveda, a comprehensive traditional system of natural medicine.^{42,43} The TM technique is described as a simple, natural, effortless procedure that is practiced 20 minutes twice a day while sitting comfortably with eyes closed.^{40,44,45} During the practice, it is reported that ordinary thinking processes settle down, and a distinctive wakeful hypometabolic state characterized by neural coherence and physiological rest is gained.^{46–48} Standard teaching materials and format were used.⁴⁰ The TM technique was taught in a 7-step course of instruction comprising six 1.5- to 2-hour individual and group meetings taught by an instructor certified by Maharishi Foundation USA.⁴⁰ Thereafter, follow-up and maintenance meetings were held weekly for the first month, biweekly for the following 2 months, and monthly thereafter for the remainder of phases 1 and 2.

The control intervention was a cardiovascular health education program designed to match the format of the experimental intervention for instructional time, instructor attention, participant expectancy, social support, and other nonspecific factors.^{27,49} The content was based on standard, published materials.^{50,51} The instructors were professional health educators. The HE subjects were advised to spend at least 20 minutes a day at home practicing heart-healthy behaviors, eg, exercise, healthy meal preparation, and nonspecific relaxation. Care was taken to separate both intervention groups to minimize contact and communication.

Statistical Analysis

Baseline comparisons of group data for continuous variables were assessed with *t* tests for independent variables. Dichotomous variables were compared using the Fisher exact test.

WHAT IS KNOWN

- Psychosocial stress is associated with the onset and progression of cardiovascular disease in blacks and the general population.
- Stress reduction with the Transcendental Meditation program has previously been shown to beneficially affect cardiovascular risk factors, eg, hypertension, psychological stress, substance abuse, insulin resistance, myocardial ischemia, left ventricular mass and carotid atherosclerosis.

WHAT THE STUDY ADDS

- This randomized, controlled trial found that adding stress-reducing Transcendental Meditation to usual care in patients with coronary heart disease resulted in a 48% reduction in the risk for cardiovascular clinical events, that is, mortality, myocardial infarction, and stroke during >5 years of follow-up.
- Potential mechanisms for the observed differences in survival include lower blood pressure and anger scores. There was evidence for dose–response effect between regularity of meditation practice and longer survival.
- The Transcendental Meditation program may be useful in the secondary prevention of cardiovascular disease.

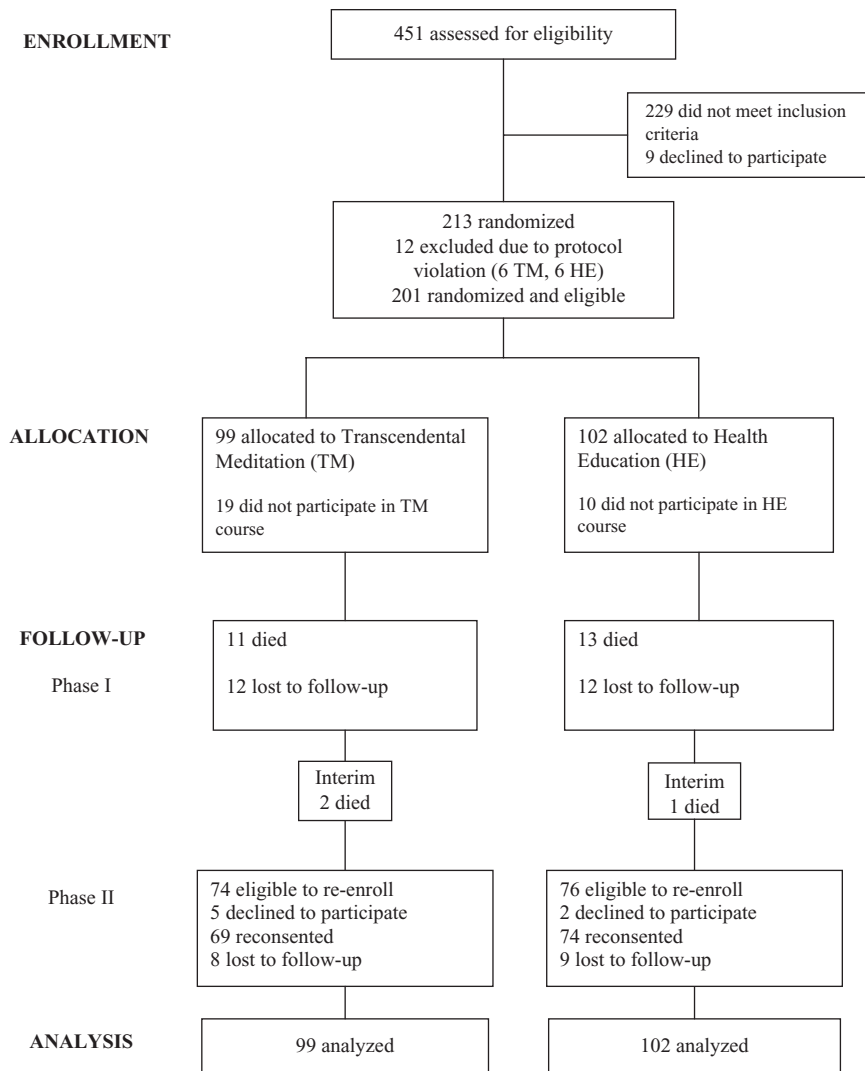


Figure 1. Participant flow diagram.

Survival curves were estimated by the Kaplan-Meier product limit method using time-to-first event. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazard model. Event data from phases 1 and 2 for all subjects were included in the survival analyses with time to event censored at the end of the subjects' follow-up. That is, subjects who enrolled in phase 1 were followed through completion of phase 1. Subjects who reconsented and reenrolled in phase 2 were followed through completion of phase 2, including the interim/hiatus period. Mortality data were collected from public records for all subjects regardless of reenrollment status and confirmed with death certificates.^{28,29} Multivariate models covaried for the stratification factors of age, sex, and lipid-lowering medication status because this is recommended to improve the precision and power of the analyses.^{52,53}

The primary survival analysis comprised the study periods during which subjects were consented and enrolled (either phase 1 only or phase 1 through 2). Reenrollment in phase 2 of the study was examined as an additional grouping factor in the analyses of baseline characteristics and as a time-dependent covariate in the survival analyses. The validity of the proportional hazards assumption was tested by assessing the joint significance of the reenrollment variable, the treatment variable, and their interaction. A second, independent analysis of the survival data was conducted by Dr Bruce Barton, Department of Quantitative Health Sciences, University of Massachusetts Medical School.

Changes in intermediate outcomes were analyzed using a repeated measures mixed model. Subject differences were modeled as random

effects. Other independent variables were fixed effects. Time was modeled as a continuous linear trend. Baseline level of the outcome, age, sex, and lipid-lowering medication were covariates. The model was fit over all available data points by restricted maximum likelihood estimation.

All primary and secondary outcomes were analyzed using the intention-to-treat principle. Power calculations were based on the approach of Proschan and Hunsberger for conditional power.⁵⁴ The power calculation for phase 1 estimated that with 374 subjects, there was 80% power to detect a 36% risk reduction in the composite of cardiovascular mortality, nonfatal MI, nonfatal stroke, coronary artery bypass graft surgery, percutaneous coronary intervention, and hospitalizations for heart failure and ischemic heart disease (non-MI). At the completion of phase 1, 201 subjects had been recruited (Figure 1). With review and approval of the data and safety monitoring board, a single interim analysis determined that with 201 subjects and an additional 5 years of follow-up to accrue the required number of events, the trial had 80% power to detect a 50% risk reduction in the data and safety monitoring board-approved end point of all-cause mortality, nonfatal MI, and nonfatal stroke.

Results

There were 201 participants who met eligibility criteria, provided informed consent, and were randomized to either TM

Table 1. Demographic and Baseline Characteristics by Treatment Group†

Characteristic	Mean (SD)		P
	TM (n=99)†	HE (n=102)†	
Female participants	41.4	44.1	0.70
Age, y	59.9 (10.7)	58.4 (10.5)	0.30
Lipid-lowering medication	59.6	60.8	0.86
ACE inhibitors	43.4%	45.1%	0.81
Angiotensin receptor agonists	7.1%	6.9%	0.95
β-blockers	2.0%	2.0%	0.98
Calcium channel blockers	34.3%	36.3%	0.77
Diuretics	43.4%	46.1%	0.71
Aspirin	41.4%	31.4%	0.14
Married	32.7	26.5	0.34
Education, y	11.3 (2.7)	9.9 (3.6)	0.003**
Household income, \$	16 979 (17 807)	14 194 (15 023)	0.25
Income <\$10 000	48.5	47.1	0.84
Weight, kg	93.1 (19.4)	92.6 (24.0)	0.87
BMI	32.2 (6.8)	32.7 (7.4)	0.56
Stenosed arteries, No.	1.8 (0.9)	1.8 (0.9)	0.91
Systolic blood pressure, mm Hg	133.0 (18.7)	131.5 (18.0)	0.57
Diastolic blood pressure, mm Hg	77.5 (12.3)	76.8 (11.4)	0.68
Hypertensive (BP >140/90 mm Hg)	39.4	35.3	0.55
Heart rate, bpm	72.0 (10.1)	72.2 (9.6)	0.89
Currently smoke	38.4	43.1	0.49
Consume alcohol	30.3	28.4	0.77
Use illicit drugs	4.0	4.9	0.77
Moderate or vigorous physical activity, h/d	4.4 (4.0)	4.9 (4.0)	0.41
Anger expression	26.0 (11.9)	28.5 (11.3)	0.14
CMHI	15.2 (5.1)	15.9 (5.3)	0.38
CESD	13.8 (9.9)	17.8 (11.7)	0.01**
Treatment expectancy	3.5 (0.9)	3.7 (0.9)	0.36

TM indicates Transcendental Meditation program; HE, health education control group; ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CMHI, Cook-Medley Hostility Inventory composite score^{37,38}; and CESD, Center for Epidemiological Studies Depression Scale.^{35,36}

†For continuous variables, data are expressed as mean (SD) values; for dichotomous variables, data are expressed as percentage of patients.

(n=99) or HE (n=102) in phase 1 (Figure 1). The rate of non-participation in the treatment groups was 19 of 99 or 19% in the TM group and 10 of 102 or 10% in the HE group, a nonsignificant difference ($P=0.07$, Fishers exact test). At the beginning of phase 2, 143 subjects were reenrolled in the second phase. Fifty-eight subjects from phase 1 did not participate in phase 2 because of death, attrition, or lack of informed consent. Of these, 25 or nearly half, had primary outcome events during phase 1.

As shown in Table 1, the groups were generally similar at baseline; 42% were women; mean age was 59 years; half of the participants reported incomes of <\$10 000/year. Significant baseline differences were education level and CESD score. No significant interactions were found on any of the baseline variables between treatment group and phase 2 reenrollment.

Randomized subjects were observed for a maximum of 9.3 years and a mean of 5.4±2.4 years (TM group = 5.3±2.3 years, HE group = 5.4±2.5 years). There were 52 primary end point events. Of these, 20 events occurred in the TM group and 32 in the HE group (Table 2). Figure 2 shows the survival curves for the primary end point of mortality, MI, and stroke. Table 3 presents the results of the survival analyses. In the primary analysis, the adjusted HR for the TM group compared with the HE group was 0.52 (95% CI, 0.29–0.92; $P=0.025$). The stratification factors of age, sex, and lipid-lowering medications used as covariates were jointly significant as predictors of time to event ($P=0.0003$, for the individual covariates: $P=0.0003$, $P=0.057$, and $P=0.03$, respectively). The test for violation of the proportional hazards assumption was not significant.

In secondary and sensitivity analyses, adjustment for baseline education and CESD score in addition to the stratification

Table 2. Components of Primary and Secondary Clinical Event End Points

End Point	Number of Events		
	TM	HE	Both
Primary end point*			
All-cause mortality	17	24	41
Nonfatal MI	1	4	5
Nonfatal stroke	2	4	6
Total	20	32	52
Secondary end point*			
CVD mortality	4	5	9
Nonfatal MI	0	2	2
Nonfatal stroke	2	4	6
Revascularization (CABG, PCI)	17	15	32
Hospitalization for CHD	12	18	30
Hospitalization for CHF	9	10	19
Total	44	54	98

TM indicates Transcendental Meditation program; HE, health education control group; MI, myocardial infarction; CVD, cardiovascular disease; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; CHD, coronary heart disease; and CHF, congestive heart failure.

*The counts of events refer to first events, and therefore the counts of primary and secondary events in each category may differ.

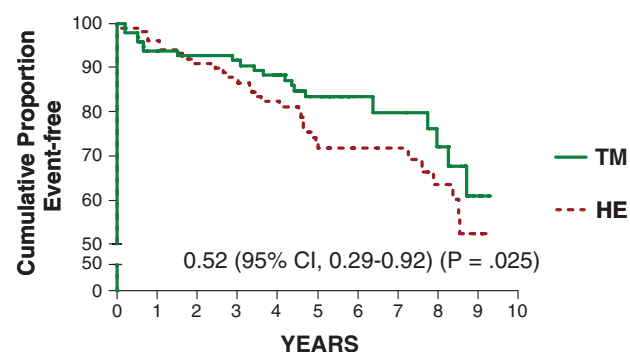


Figure 2. Kaplan-Meier survival curves of primary end point (all-cause mortality, nonfatal MI, or nonfatal stroke). HE indicates the health education intervention; TM, the Transcendental Meditation program.

factors showed a similar result (HR, 0.54; 95% CI, 0.30–0.98; $P=0.04$). Eleven additional deaths occurred during the hiatus period and phase 2 in subjects whose enrollment terminated at the end of phase 1 (7 in TM group and 4 in HE group). Nonfatal events were not available for these subjects because their consent and enrollment had terminated although their fatal events were available from public records.^{28,29} Including these fatal events in non-reenrolled subjects, there were 27 primary end point events in the TM group and 36 in the HE group. The adjusted HR for the TM group compared with the HE group was 0.57 (95% CI, 0.34–0.96; $P=0.03$).

There were 98 secondary end point events. Of these, 44 occurred in the TM group and 54 in the HE group (Table 2). As shown in Table 3, the adjusted HR for the TM group compared with the HE group was 0.76 (95% CI, 0.51–1.13;

Table 3. Results of Survival Analyses

	Hazard Ratio (95% Confidence Interval)	<i>P</i>
Primary end point		
Unadjusted	0.64 (0.37–1.12)	0.12
Adjusted for stratification variables (age, sex, lipid-lowering medications)—primary analysis	0.52 (0.29–0.92)	0.025
Adjusted for stratification variables + education, baseline CESD	0.54 (0.30–0.98)	0.04
Including events in non-reenrolled subjects during hiatus and phase 2 adjusted for stratification variables	0.57 (0.34–0.96)	0.03
Secondary end point		
Unadjusted	0.77 (0.52–1.15)	0.21
Adjusted for stratification variables (age, sex, lipid-lowering medications)	0.76 (0.51–1.13)	0.17
Adjusted for stratification variables + education, baseline CESD	0.82 (0.54–1.24)	0.36

CESD indicates Center for Epidemiological Studies Depression Scale.^{35,36}

$P=0.17$). With additional adjustment for education and CESD score, the HR was 0.82 (95% CI, 0.54–1.24; $P=0.36$).

Independent analysis of the primary and secondary survival data confirmed identical results (Dr Bruce Barton, University of Massachusetts Medical School).

Table 4 shows changes in the intermediate outcomes averaged during the trial. There was a significant net difference of -4.9 mm Hg in systolic BP in the TM group compared with HE group (95% CI, -8.3 to -1.5 mm Hg; $P=0.01$). For diastolic BP, there was a net difference of -1.6 mm Hg (95% CI, -3.4 to 0.3 mm Hg; $P=0.27$). There were no significant between-group changes in BMI, physical activity, alcohol use, smoking, or diet. There were significant improvements in anger-in, anger-control, and total anger ($P=0.02$, $P=0.02$, and $P=0.03$), respectively for the TM vs HE group. There were no significant changes in anger-out, depression, or hostility for the TM versus HE groups. There were significant group by time interactions for anger-in ($P=0.002$) and total anger ($P=0.01$), although not for anger-control or other intermediate outcomes.

Experimental subjects practiced the TM technique an average of 8.5 times per week. Control subjects practiced healthy lifestyle activities an average of 8.6 times per week. Attendance at follow-up meetings averaged during 5.4 years was 48% for each group. There were no significant differences in home practice or meeting attendance for either group in phase 1 compared with phase 2.

In the high-adherence subgroup of subjects who were regular in home practice ($n=141$), the HR was 0.34 (95% CI, 0.16–0.69; $P=0.003$). The interaction between treatment and adherence (high versus low) showed a statistical trend ($P=0.08$). Cox regression analysis within the TM group indicated that frequency of home practice was inversely associated with primary clinical events ($P=0.04$). On average, subjects attended 70% of all semiannual testing visits.

Table 4. Changes in Intermediate Outcomes During 5.4-Year Average Follow-Up

Outcome (TM/HE No.)	TM Group Change, Mean (SE)	HE Group Change, Mean (SE)	Net Difference (TM–HE)	P
Systolic BP, mm Hg (86/97)	0.022 (1.264)	4.883 (1.184)	–4.861	0.01
Diastolic BP, mm Hg (86/97)	–3.433 (0.683)	–1.877 (0.643)	–1.556	0.27
HR, bpm (86/97)	0.518 (0.541)	–0.145 (0.509)	0.663	0.01
BMI, kg/m ² (86/97)	–0.070 (0.274)	–0.144 (0.258)	0.074	0.94
Exercise, h/d (81/88)	0.454 (0.327)	0.440 (0.316)	0.014	0.13
Alcohol, drinks/wk (80/90)	–2.494 (0.424)	–3.109 (0.400)	0.615	0.46
Cigarettes, No./d (84/93)	–0.637 (0.324)	–0.027 (0.309)	–0.610	0.16
Anger-in (85/94)	–1.826 (0.399)	–1.618 (0.378)	–0.209	0.02
Anger-out (85/94)	0.266 (0.338)	–0.156 (0.321)	0.422	0.87
Anger-control (85/94)	–0.267 (0.290)	–1.344 (0.277)	1.077	0.02
Total anger (85/94)	–1.171 (0.750)	–0.531 (0.712)	–0.640	0.03
Depression (85/93)	–0.252 (0.713)	0.686 (0.680)	–0.938	0.20
Hostility (84/92)	–0.703 (0.346)	–0.621 (0.330)	–0.082	0.53

TM indicates Transcendental Meditation program; HE, health education control group; BP, blood pressure; HR, heart rate; and BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Discussion

This randomized, controlled trial on the secondary prevention of CVD in a high-risk population extends previous trials reporting that mind–body intervention with the TM program reduced CVD risk factors, surrogate end points, and mortality.^{17–24,39,55,56} In this trial, the TM program was associated with 48% risk reduction in the composite of mortality, nonfatal MI, and nonfatal stroke in black men and women with coronary heart disease during an average of 5.4 years follow-up. These results were confirmed by independent data analysis. Concurrently, there were improvements in BP and psychosocial distress factors, particularly anger. Regularity of TM practice was associated with increased survival.

The effects of active intervention were stable and reliable during the trial. The 2 treatment groups did not differ in characteristics between phases 1 and 2, indicating that there was no evidence of selective attrition. Adherence to the interventions was similar in both phases. Although there were between-group baseline differences on education and depression, adjusting for these differences did not substantially affect the primary outcome.

The average BP reduction of 5 mm Hg is similar to that found in meta-analyses of shorter term trials of the TM program.^{17,18} Reduction in systolic BP may be 1 physiological mechanism for reduced clinical events in this trial because this magnitude of reduction has been associated with 15% reduction in cardiovascular clinical events.⁵⁷ The improvements in anger expression and control may also have contributed to enhanced survival, because anger has been associated with CVD clinical events in coronary heart disease patients.¹⁰ There was a nonsignificant reduction in smoking in the TM group. It is possible that other mechanisms not evaluated in this study contributed to the reduced risk in the TM group. Previous studies have reported reductions in sympathetic nervous system tone, hypothalamic-pituitary-adrenal axis activation, insulin resistance, left ventricular mass, myocardial ischemia, carotid atherosclerosis, and heart failure.^{19–21,58–60}

Central nervous system integration has been proposed as a neurophysiologic basis for these physiologic effects.^{61,62}

There was some evidence of a dose–response relationship between practice of the TM program and survival. There was a significant association between regularity of home practice and survival. Further, the subgroup of subjects who were regular in their TM practice had a 66% risk reduction compared with the overall sample risk reduction of 48%.

To our knowledge, this is the first randomized, controlled trial to demonstrate a reduction in the risk for mortality, MI, and stroke with the individual practice of a relatively simple mind–body intervention, particularly in a high-risk racial/ethnic population.⁶³ Previous randomized trials of stress reduction methods in patients with coronary heart disease typically used group-based psychosocial counseling methods with complex multimodal interventions, lacked attention controls, and resulted in heterogeneous outcomes.^{63–68} This is also the first prospectively designed and conducted randomized, controlled trial to evaluate effects on CVD clinical events of a nonpharmacologic, lifestyle modification approach for hypertension.⁶⁹

There were limitations to this study. The sample size did not allow for sufficiently powered analyses of single clinical end points. The 24% risk reduction in the secondary composite end point of CVD mortality, MI, stroke, coronary revascularization, and CVD hospitalization did not reach statistical significance ($P=0.17$). This may have been related to variability in the use of revascularization procedures and hospitalizations in the community. The reduction in depression in the meditation group was not significant, perhaps, because depression was already low in this group at baseline, which may have contributed to lack of further reduction in one or both groups. Hostility scores were relatively low in both groups at baseline. There were no significant differences between groups in change in BMI, exercise, or alcohol consumption, although in both study groups there were apparent (within group) improvements in exercise and alcohol consumption. As noted earlier, there was a nonsignificant reduction in cigarette smoking in the stress reduction group. The sample was limited to

a single racial/ethnic sample. However, previous studies have reported improvements in CVD outcomes with the TM program in general population samples, suggesting that this finding is generalizable.^{17–20,39}

Another limitation was the variable length of time of subject participation and the heterogeneity of outcome data for subjects who did not reenroll in phase 2. However, when all available data, that is, mortality from non-reenrolling subjects was included in a sensitivity analysis of the primary end point, the results were similar to the main analysis in treatment effect and significance level. The unadjusted results of the primary end point analysis showed a nonsignificant statistical trend ($P=0.12$). However, the HR adjusted for covariates of age, sex, and antihypertensive medications was significant ($P=0.025$). According to Pocock et al⁵² and Consolidated Standards of Reporting Trials (CONSORT) recommendations, adjusted analyses frequently improve the precision of the estimate of the treatment effect.⁷⁰ Furthermore, because these factors were used in the stratified randomization procedure, it is recommended to adjust for stratification factors to achieve the most efficient treatment comparison.^{52,53} This is particularly relevant when the adjustment factors predict the outcome, as they did in this trial.⁵²

The proportion of cardiovascular deaths in the present trial was lower than national averages.¹ This may have been because of the sample size or method of collecting causes of death from death certificates. The accuracy of death certificate data for cause of death has been seriously questioned.^{71,72} There was a nonsignificantly higher nonparticipation rate in the TM group compared with HE controls. Because the analysis was based on intention to treat, the higher nonparticipation rate in the TM group may have led to a more conservative estimate of the treatment effect.

This trial did not address the effects of other mind–body, meditation-type interventions on clinical events. Although several meta-analyses and comparative studies suggest a distinctive effect of the TM program,^{18,48,73} it remains for future comparative effectiveness trials to address differential effects of mind–body interventions on CVD clinical events.

Conclusions

This randomized, controlled trial found that a selected mind–body, stress reduction intervention, the TM program, significantly reduced risk for mortality, MI, and stroke in black men and women with coronary heart disease. These changes in clinical events were associated with lower BP and psychosocial distress. Thus, the TM program may be a clinically useful behavioral intervention in the secondary prevention of CVD in this and perhaps other high-risk populations.

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Disclosures

Dr Schneider has served as an investigator on research grants from the National Institutes of Health and US Department of Defense and is a consultant to Maharishi Foundation USA, a nonprofit educational organization. Dr Grim's spouse is president and sole owner of Shared Care Research and Education Consulting. Dr Rainforth has served as an investigator on research grants from the National Institutes of Health and US Department of Defense and his spouse is an independent contractor to Maharishi Foundation, USA. Dr Nidich has served as an investigator on research grants from the National Institutes of Health, US Department of Defense and David Lynch Foundation and his spouse is an independent contractor to Maharishi Foundation, USA. Dr Gaylord-King has served as an investigator on research grants from the National Institutes of Health, US Department of Defense and GMDO, a nonprofit organization. Dr Salerno has served as an investigator on research grants from the National Institutes of Health and US Department of Defense. The other authors report no conflicts.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220.
2. Mackay J, Mensah GA, Mendis S, Greenlund K. *The Atlas of Heart Disease and Stroke, 2004, World Health Statistics*. Geneva, Switzerland: World Health Organization; 2009.
3. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB. State of disparities in cardiovascular health in the United States. *Circulation*. 2005;111:1233–1241.
4. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol*. 2008;51:1237–1246.
5. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol*. 2005;45:637–651.
6. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. 2007;370:1089–1100.
7. Bairey Merz CN, Dwyer J, Nordstrom CK, Walton KG, Salerno JW, Schneider RH. Psychosocial stress and cardiovascular disease: pathophysiological links. *Behav Med*. 2002;27:141–147.
8. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
9. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66:802–813.
10. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *J Am Coll Cardiol*. 2009;53:936–946.
11. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol*. 2010;56:38–46.

12. Wyatt SB, Williams DR, Calvin R, Henderson FC, Walker ER, Winters K. Racism and cardiovascular disease in African Americans. *Am J Med Sci*. 2003;325:315–331.
13. Clark R, Anderson NB, Clark VR, Williams DR. Racism as a stressor for African Americans. A biopsychosocial model. *Am Psychol*. 1999;54:805–816.
14. Roberts CB, Vines AI, Kaufman JS, James SA. Cross-sectional association between perceived discrimination and hypertension in African-American men and women: the Pitt County Study. *Am J Epidemiol*. 2008;167:624–632.
15. Whitfield KE, Weidner G, Clark R, Anderson NB. Sociodemographic diversity and behavioral medicine. *J Consult Clin Psychol*. 2002;70:463–481.
16. Barnes V, Schneider R, Alexander C, Staggars F. Stress, stress reduction, and hypertension in African Americans: an updated review. *J Natl Med Assoc*. 1997;89:464–476.
17. Anderson JW, Liu C, Kryscio RJ. Blood pressure response to Transcendental Meditation a meta-analysis. *Am J Hypertens*. 2008;21:310–316.
18. Rainforth MV, Schneider RH, Nidich SI, Gaylord-King C, Salerno JW, Anderson JW. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. *Curr Hypertens Rep*. 2007;9:520–528.
19. Paul-Labrador M, Polk D, Dwyer JH, Velasquez I, Nidich S, Rainforth M, Schneider R, Merz CN. Effects of a randomized controlled trial of Transcendental Meditation on components of the metabolic syndrome in subjects with coronary heart disease. *Arch Intern Med*. 2006;166:1218–1224.
20. Zamarrá JW, Schneider RH, Besseghini I, Robinson DK, Salerno JW. Usefulness of the Transcendental Meditation program in the treatment of patients with coronary artery disease. *Am J Cardiol*. 1996;78:77–80.
21. Castillo-Richmond A, Schneider RH, Alexander CN, Cook R, Myers H, Nidich S, Haney C, Rainforth M, Salerno J. Effects of stress reduction on carotid atherosclerosis in hypertensive African Americans. *Stroke*. 2000;31:568–573.
22. Schneider RH, Alexander CN, Staggars F, Rainforth M, Salerno JW, Hartz A, Arndt S, Barnes VA, Nidich SI. Long-term effects of stress reduction on mortality in persons > or = 55 years of age with systemic hypertension. *Am J Cardiol*. 2005;95:1060–1064.
23. Walton KG, Schneider RH, Nidich S. Review of controlled research on the Transcendental Meditation program and cardiovascular disease. Risk factors, morbidity, and mortality. *Cardiol Rev*. 2004;12:262–266.
24. Barnes VA, Orme-Johnson DW. Prevention and treatment of cardiovascular disease in adolescents and adults through the Transcendental Meditation program: A research review update. *Curr Hypertens Rev*. 2012;8:227–242.
25. D'Agostino RB Sr, Vasán RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
26. National Cholesterol Education Program. *Classification, Prevalence, Detection, Evaluation. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*. Washington, D.C.: National Institutes of Health-National Heart, Lung, and Blood Institute; 1993:I-1–I-21.
27. Powell LH, Calvin JE Jr, Mendes de Leon CF, Richardson D, Grady KL, Flynn KJ, Rucker-Whitaker CS, Janssen I, Kravitz G, Eaton C; Heart Failure Adherence and Retention Trial Investigators. The Heart Failure Adherence and Retention Trial (HART): design and rationale. *Am Heart J*. 2008;156:452–460.
28. Edlavitch SA, Baxter J. Comparability of mortality follow-up before and after the National Death Index. *Am J Epidemiol*. 1988;127:1164–1178.
29. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. *Am J Epidemiol*. 1984;119:837–839.
30. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) *JAMA*. 2002;288:2981–2997.
31. Boucher B, Cotterchio M, Kreiger N, Nadalin V, Block T, Block G. Validity and reliability of the Block98 food-frequency questionnaire in a sample of Canadian women. *Public Health Nutr*. 2006;9:84–93.
32. Elmer PJ, Grimm R Jr, Laing B, Grandits G, Svendsen K, Van Heel N, Betz E, Raines J, Link M, Stamler J. Lifestyle intervention: results of the Treatment of Mild Hypertension Study (TOMHS). *Prev Med*. 1995;24:378–388.
33. Folsom AR, Caspersen CJ, Taylor HL, Jacobs DR Jr, Luepker RV, Gomez-Marin O, Gillum RF, Blackburn H. Leisure time physical activity and its relationship to coronary risk factors in a population-based sample. The Minnesota Heart Survey. *Am J Epidemiol*. 1985;121:570–579.
34. Radloff L. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;3:385–401.
35. Long Foley K, Reed PS, Mutran EJ, DeVellis RF. Measurement adequacy of the CES-D among a sample of older African-Americans. *Psychiatry Res*. 2002;109:61–69.
36. Barefoot JC, Dodge KA, Peterson BL, Dahlstrom WG, Williams RB Jr. The Cook-Medley hostility scale: item content and ability to predict survival. *Psychosom Med*. 1989;51:46–57.
37. Nabi H, Singh-Manoux A, Ferrie JE, Marmot MG, Melchior M, Kivimäki M. Hostility and depressive mood: results from the Whitehall II prospective cohort study. *Psychol Med*. 2010;40:405–413.
38. Spielberger C, Sydeman S, Owen A, Marsh B. Measuring anxiety and anger with the State-Trait Anxiety Inventory (STAI) and the State-Trait Anger Expression Inventory (STAXI). In: Maruish M, ed. *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment*. Mahwah, NJ: Lawrence Erlbaum Associates; 1999:1507.
39. Alexander CN, Langer EJ, Newman RI, Chandler HM, Davies JL. Transcendental Meditation mindfulness, and longevity: an experimental study with the elderly. *J Pers Soc Psychol*. 1989;57:950–964.
40. Roth R. *Maharishi Mahesh Yogi's Transcendental Meditation*. Washington, DC: Primus; 2002.
41. Walton KG, Schneider RH, Salerno JW, Nidich SI. Psychosocial stress and cardiovascular disease. Part 3: Clinical and policy implications of research on the Transcendental Meditation program. *Behav Med*. 2005;30:173–183.
42. Schneider RH, Alexander CN, Salerno JW, Robinson DK Jr, Fields JZ, Nidich SI. Disease prevention and health promotion in the aging with a traditional system of natural medicine: Maharishi Vedic Medicine. *J Aging Health*. 2002;14:57–78.
43. Sharma H, Clark C. *Ayurvedic Healing: Contemporary Maharishi Ayurveda Medicine and Science*. London, UK: Singing Dragon Publications, 2012.
44. Rosenthal N. *Transcendence: Healing and Transformation Through Transcendental Meditation*. New York, NY: Penguin-Tarcher; 2011.
45. Travis F. Transcendental Meditation technique. In: Craighead W, Nemeroff C, eds. *The Corsini Encyclopedia of Psychology and Behavioral Science*. New York, NY: John Wiley and Sons; 2001:1705–1706.
46. Jevning R, Wallace RK, Beidebach M. The physiology of meditation: a review. A wakeful hypometabolic integrated response. *Neurosci Biobehav Rev*. 1992;16:415–424.
47. Travis F, Shear J. Focused attention, open monitoring and automatic self-transcending: Categories to organize meditations from Vedic, Buddhist and Chinese traditions. *Conscious Cogn*. 2010;19:1110–1118.
48. Walton KG, Schneider RH, Nidich SI, Salerno JW, Nordstrom CK, Bairey Merz CN. Psychosocial stress and cardiovascular disease Part 2: effectiveness of the Transcendental Meditation program in treatment and prevention. *Behav Med*. 2002;28:106–123.
49. Windsor R, Baranowski T, Clark N, Cutter G. *Evaluation of Health Promotion, Health Education and Disease Prevention Programs*. Mountainview, CA: Mayfield Publishing Co; 1994.
50. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
51. Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report. *Circulation*. 2002;106:3143–3421.
52. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med*. 2002;21:2917–2930.
53. Committee for Proprietary Medicinal Products. *Points to Consider on Adjustment for Baseline Covariates 2863/2899*. London, UK: The European Agency for the Evaluation of Medicinal Products; 2003.
54. Proschian MA, Hunsberger SA. Designed extension of studies based on conditional power. *Biometrics*. 1995;51:1315–1324.
55. Alexander CN, Schneider RH, Staggars F, Sheppard W, Clayborne BM, Rainforth M, Salerno J, Kondwani K, Smith S, Walton KG, Egan B. Trial

- of stress reduction for hypertension in older African Americans. II. Sex and risk subgroup analysis. *Hypertension*. 1996;28:228–237.
56. Schneider RH, Alexander CN, Staggars F, Orme-Johnson DW, Rainforth M, Salerno JW, Sheppard W, Castillo-Richmond A, Barnes VA, Nidich SI. A randomized controlled trial of stress reduction in African Americans treated for hypertension for over one year. *Am J Hypertens*. 2005;18:88–98.
 57. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
 58. Mills PJ, Schneider RH, Hill D, Walton KG, Wallace RK. Beta-adrenergic receptor sensitivity in subjects practicing Transcendental Meditation. *J Psychosom Res*. 1990;34:29–33.
 59. Barnes VA, Kapuku GK, Treiber FA. Impact of Transcendental Meditation on left ventricular mass in African American adolescents. *Evid Based Complement Alternat Med*. 2012;2012:923153.
 60. Jayadevappa R, Johnson JC, Bloom BS, Nidich S, Desai S, Chhatre S, Raziano DB, Schneider R. Effectiveness of Transcendental Meditation on functional capacity and quality of life of African Americans with congestive heart failure: a randomized control study. *Ethn Dis*. 2007;17:72–77.
 61. Travis F, Wallace RK. Autonomic and EEG patterns during eyes-closed rest and Transcendental Meditation practice: the basis for a neural model of TM practice. *Conscious Cogn*. 1999;8:302–318.
 62. Travis F, Haaga DA, Hagelin J, Tanner M, Nidich S, Gaylord-King C, Grosswald S, Rainforth M, Schneider RH. Effects of Transcendental Meditation practice on brain functioning and stress reactivity in college students. *Int J Psychophysiol*. 2009;71:170–176.
 63. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol*. 2009;169:1158–1165.
 64. Friedman M, Thoresen CE, Gill JJ, Ulmer D, Powell LH, Price VA, Brown B, Thompson L, Rabin DD, Breall WS Alteration of type A behavior and its effect on cardiac recurrences in post myocardial infarction patients: summary results of the recurrent coronary prevention project. *Am Heart J*. 1986;112:653–665.
 65. Jones DA, West RR. Psychological rehabilitation after myocardial infarction: multicentre randomised controlled trial. *BMJ*. 1996;313:1517–1521.
 66. Writing Committee for the ENRICH Investigators. Effects of treating depression and low level social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease (ENRICH) patients randomized trial. *JAMA*. 2003;289:3106–3116.
 67. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svärdsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). *Arch Intern Med*. 2011;171:134–140.
 68. Orth-Gomér K, Schneiderman N, Wang HX, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circ Cardiovasc Qual Outcomes*. 2009;2:25–32.
 69. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ*. 2007;334:885–888.
 70. Keech A, Gebski V, Pike R, eds. *Interpreting and Reporting Clinical Trials: A Guide to the CONSORT Statement and the Principles of Randomized Controlled Trials*. Sydney, Australia: Australasian Medical Publishing Co; 2007:27
 71. Smith Sehdev AE, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. *Arch Intern Med*. 2001;161:277–284.
 72. Ravakhah K. Death certificates are not reliable: revivification of the autopsy. *South Med J*. 2006;99:728–733.
 73. Orme-Johnson DW, Walton KG. All approaches to preventing or reversing effects of stress are not the same. *Am J Health Promot*. 1998;12:297–299.

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