An Intensive Behavioral Weight Loss Intervention and Hot Flushes in Women

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Background: Higher body mass index is associated with worse hot flushes during menopause but the effect of weight loss on flushing is unclear.

Methods: Self-administered questionnaires were used to assess bothersome hot flushes in a 6-month randomized controlled trial of an intensive behavioral weight loss program (intervention) vs a structured health education program (control) in 338 women who were overweight or obese and had urinary incontinence. Weight, body mass index, abdominal circumference, physical activity, calorie intake, blood pressure, and physical and mental functioning were assessed at baseline and at 6 months. Repeated-measures proportional odds models examined intervention effects on bothersome hot flushes and potential mediating factors.

Results: Approximately half of participants (n=154) were at least slightly bothered by hot flushes at baseline. Among these women, the intervention was associated with greater improvement in bothersome flushes vs control (odds ratio [OR] for improvement by 1 Likert category, 2.25; 95% confidence interval [CI], 1.20-4.21). Reductions in weight (OR, 1.32; 95% CI, 1.08-1.61; per 5-kg decrease), body mass index (1.17; 1.05-1.30; per 1-point decrease), and abdominal circumference (1.32; 1.07-1.64; per 5-cm decrease) were each associated with improvement in flushing, but changes in physical activity, calorie intake, blood pressure, and physical and mental functioning were not related. The effect of the intervention on flushing was modestly diminished after adjustment for multiple potential mediators (OR, 1.92; 95% CI, 0.95-3.89).

Conclusion: Among women who were overweight or obese and had bothersome hot flushes, an intensive behavioral weight loss intervention resulted in improvement in flushing relative to control.

Trial Registration: clinicaltrials.gov Identifier: NCT00091988

Arch Intern Med. 2010;170(13):1161-1167
associated with significant improvement in bothersome hot flushes compared with the control program. We also examined whether changes in weight, BMI, abdominal circumference, physical activity, calorie intake, blood pressure, and overall physical or mental functioning were associated with improvement in bothersome hot flushes in this population.

METHODS

PRISE PARTICIPANTS

PRISE was a randomized controlled trial that evaluated the effect of a 6-month intensive lifestyle and behavior change intervention vs a structured health education program to promote weight loss in 338 women who were overweight or obese and had urinary incontinence. Characteristics of the study sample, inclusion and exclusion criteria, sample size calculations, and interventions have been previously reported. Briefly, women had to be at least 30 years of age, have a BMI of 25 to 50, and report in a voiding diary at least 10 episodes of incontinence per week to be eligible. Women were excluded if they reported any condition that would prevent them from safely participating in an intensive diet and exercise program without medical supervision and if they had undergone medical therapy for incontinence or weight loss in the previous month.

Participants were recruited from the local community at the Miriam Hospital in Providence, Rhode Island, and the University of Alabama at Birmingham and randomly allocated in a 2:1 ratio to the lifestyle and behavior change program (intervention;n=226) or the structured education program (control; n=112). Although participants were aware of their treatment assignment, research personnel collecting outcomes data were masked to treatment. All participants gave informed consent to participate in the study, and the institutional review boards at both clinical sites and the coordinating center approved all study procedures.

INTERVENTIONS

Participants in the intensive intervention group were assigned to a lifestyle and behavior change program modeled after the Diabetes Prevention Program and Look AHEAD (Action for Health in Diabetes) trials, which were designed to produce significant improvement in bothersome hot flushes in this population.

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OUTCOME MEASURES

Bothersome hot flushes and other menopausal symptoms were assessed at baseline and at 6 months using questionnaire measures originally developed for the Breast Cancer Prevention Trial and administered in subsequent prevention and hormone therapy trials involving middle-aged and older women. Specifically, participants were asked to indicate how bothersome hot flushes or hot flashes had been in the past month, using a 5-point Likert scale with the response categories not at all, slightly, moderately, quite a bit, and extremely.

Other demographic and clinical characteristics were assessed using self-administered questionnaires at baseline and at 6 months. Physical activity was assessed using the validated Paffenbarger physical activity questionnaire, which provides an estimate of the average kilocalories of energy expended per week based on participant self-report about walking, stair climbing, and medium-intensity and heavy-intensity physical activity. Dietary calorie intake was assessed using the validated Block food frequency questionnaire, which estimates average daily diet and nutrient intake based on participant self-report of usual eating habits during the past 6 months. Overall physical and mental functioning was assessed using the physical and mental summary components of the 36-item Short Form Health Survey (SF-36) functioning scales, scored from 0 to 100, with higher scores indicating better overall functioning.

Participants were weighed at baseline and at 6 months using digital scales (Tanita BWB 800; Tanita Corporation of America Inc, Arlington Heights, Illinois), and height was measured using wall-mounted stadiometers. Abdominal circumference was measured after voiding using a tape measure (Gullick II Tape Measure model 67020; Creative Engineering Inc, Plymouth, Massachusetts). Heart rate and blood pressure were measured with the patient in the sitting position (Dinamap Monitor Pro 10; GE Healthcare, Buckinghamshire, England), following standardized protocols.

STATISTICAL ANALYSES

All analyses were restricted to participants who reported being at least slightly bothered by hot flushes at baseline and thus had the potential to show improvement during the trial. Among these participants, the baseline characteristics of women randomized to the intervention vs control group were compared by mixed linear regression for normally distributed continuous variables, ranked mixed linear regression for nonnormally distributed continuous variables, and proportional odds regression for categorical variables, using generalized estimating equations. All models controlled for clinical site and accounted for clustering of outcomes among women participating in the same behavior change or health education sessions. Subsequent analyses of intervention effects were adjusted for any characteristics that were unequally distributed between the intervention vs control group at baseline.

Among participants reporting bothersome hot flushes at baseline, the effects of the intervention vs control program on weight, BMI, abdominal circumference, physical activity, calorie intake, blood pressure, and overall physical and mental functioning during 6 months were examined using mixed linear regression for normally distributed continuous variables and ranked mixed linear regression for nonnormally distributed continuous variables, again controlling for clinical site and accounting for clustering of outcomes among women participating in the same behavior change or health education sessions. Intervention effects on self-reported hot flushes during 6 months were then examined using repeated-measures proportional odds regression, using all available data from any study visit, after checking that there were no major violations of the proportional odds assumption. Repeated-measures regression was chosen to ensure efficient use of information about time-dependent covariates and to minimize loss of information.
resulting from loss to follow-up. Odds ratios (ORs) in these models were scaled to reflect improvement in hot-flush bothersomeness by 1 Likert category (eg, from quite a bit to moderately or moderately to slightly bothersome). To address possible bias introduced by the use of oral or transdermal estrogen use or selective serotonin reuptake inhibitor medication use, intervention effect models were run with and without adjustment for estrogen and selective serotonin reuptake inhibitor use at baseline and at 6 months.

Next, associations between change in weight, BMI, abdominal circumference, physical activity, calorie intake, blood pressure, and overall physical and mental functioning and change in hot flushes during 6 months were examined using repeated-measures proportional odds regression, combining data from the intervention and control groups. Finally, to assess for possible mediation of intervention effects by change in these variables, additional repeated-measures proportional odds models were developed to compare the effects of the intervention vs control program on hot flushes while adjusting for improvement in weight, BMI, abdominal circumference, physical activity, calorie intake, blood pressure, and overall functioning. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 338 participants in PRIDE, 226 were randomized to the intensive weight loss intervention and 112 to the control group (Figure 1). Approximately half of participants in each group (99 in the intervention and 55 in the control group) reported being at least slightly bothered by flushing at baseline and were eligible for our analyses. Of these 154 participants, 141 (91.6%) provided data on hot flushes at 6 months. Self-reported hot-flush bothersomeness was not associated with frequency of urinary incontinence at baseline (OR, 0.99; 95% confidence interval [CI], 0.91-1.08).

The mean (SD) age of participants with baseline hot flushes was 53 (8) years (Table 1). Eighty-nine of 147 participants (60.5%) reported no menstrual period in the past year, and 19 (12.3%) reported using oral or transdermal estrogen. Just more than half (n=79) indicated that they were at least moderately bothered and 13 (8.4%) indicated that they were extremely bothered by flushing at baseline. Compared with control individuals, women randomized to the intervention reported slightly greater...
physical activity at baseline but did not differ significantly with regard to other characteristics, including hot flushes (Table 1).

Among women reporting hot flushes at baseline, those randomized to the intervention group were significantly more likely to remain in the study and contribute hot-flush data at 6 months compared with controls (96 of 99 women [96.9%] in the intervention group vs 45 of 55 controls [81.8%]; \( P = .001 \)). Women who were missing hot-flush data at 6 months reported being less physically active at baseline than women with complete data (mean [SD] kilocalories per week, 3662 [423] vs 7941 [1011]; \( P = .08 \)) but did not differ significantly with respect to other characteristics, such as mean weight (98 vs 96 kg; \( P = .11 \)), BMI (38 vs 36; \( P = .25 \)), abdominal circumference (114 vs 108 cm; \( P = .25 \)), caloric intake (2226 vs 2013 kcal; \( P = .99 \)), systolic blood pressure (128 vs 129 mm Hg; \( P = .16 \)), diastolic blood pressure (73 vs 72 mm Hg; \( P = .98 \)), SF-36 physical component score (49 vs 48; \( P = .81 \)) and mental functioning scores (49 vs 49; \( P = .52 \)), and self-reported hot flushes (49% vs 38% with at least moderately bothersome symptoms; \( P = .61 \)).

Among women who were at least slightly bothered by flushing at baseline, the intensive lifestyle intervention was associated with significantly greater decreases in weight, BMI, abdominal circumference, and systolic and diastolic blood pressure relative to the control group (Table 2). No statistically significant effect of the intervention on self-reported physical activity, total caloric intake, or overall physical or mental functioning was observed.

After 6 months, 65 of 141 participants (46.1%) with baseline hot flushes reported improvement in flushing by at least 1 category of bothersomeness, 53 (37.6%) reported no change, and 23 (16.3%) reported worsening by at least 1 category (Figure 2). In repeated-measures proportional odds regression, the intensive intervention was associated with more than a 2-fold increased odds of improvement in flushing by 1 category of bothersomeness relative to the control group (OR, 2.23; 95% CI, 1.19-4.15; \( P = .01 \)). This effect was not diminished after adjustment for baseline differences in self-reported physical activity between intervention groups (adjusted OR, 2.25; 95% CI, 1.20-4.21; \( P = .01 \)), after adjustment for use of oral or transdermal estrogen at any visit (2.06; 1.09-3.89; \( P = .03 \)), or after adjustment for use of selective serotonin reuptake inhibitor medications at any visit (2.24; 1.19-4.23; \( P = .01 \)).

In aggregate analyses of all women reporting bothersome hot flushes at baseline, decrease in weight, decrease in BMI, and decrease in abdominal circumference were each associated with improvement in self-reported hot flushes during 6 months (Table 3). No significant associations between changes in physical activity, caloric intake, blood pressure, or overall self-reported physical and mental functioning and change in flushing bothersomeness were observed.

The effect of the intensive intervention on bothersome hot flushes was modestly decreased and no longer statistically significant after adjustment for improvement in weight (adjusted OR for improvement in flushing by 1 category of bothersomeness, 1.92; 95% CI, 0.94-3.92). Similarly, modest decreases in intervention effects were noted after adjustment for BMI (adjusted OR, 1.88; 95% CI, 0.93-3.81) or abdominal circumference (1.88; 0.95-3.70). After cumulative adjustment for change in all potential mediating variables (ie, BMI, abdominal circumference, physical activity, caloric intake, blood pres-
sure, and physical and mental functioning; weight was excluded because of collinearity with BMI), the effect of the intensive intervention on flushing remained modestly decreased and nonsignificant (OR, 1.92; 95% CI, 0.95-3.89).

COMMENT

In this randomized controlled trial of an intensive behavioral weight loss intervention vs a structured health education program in women who were overweight or obese and had urinary incontinence, women with bothersome hot flushes who were randomized to the intensive intervention reported significantly greater improvement in flushing bothersomeness after 6 months compared with controls. Improvements in weight, BMI, and abdominal circumference (but not self-reported physical activity, calorie intake, overall physical and mental functioning, or measured blood pressure) were associated with improvement in bothersome hot flushes in this population. The effect of the intensive intervention on bothersome hot flushes was partly but not completely explained by improvements in weight, BMI, and abdominal circumference.

Multiple observational studies have documented that women with a higher BMI report more frequent or severe hot flushes during menopause, but the mechanisms underlying this association are poorly understood. Women who are overweight or obese are known to have higher circulating estrogen levels as a result of adipocyte-based aromatization of estrone and conversion of androstenedione to estrone, which might be expected to decrease rather than increase the severity of their menopausal symptoms. Recently proposed explanations for the observed association between BMI and hot flushes have included greater insulation against heat loss owing to increased peripheral fat, abnormal sympathetic neural activity associated with increased visceral fat, and alterations in leptin and other cytokines expressed by adipocytes that affect thermoregulatory function. Alternatively, women who are overweight or obese may differ in psychological or social factors that affect their subjective experience of and willingness to report symptoms such as hot flushes.

Our findings indicate that women who are overweight or obese and experience bothersome hot flushes may also experience improvement in these symptoms after pursuing behavioral weight loss strategies; however, improvements in weight or body composition may not be the only mediators of this effect. Given that the behavioral intervention in PRIDE could not be masked, 1 possible explanation for the apparent incomplete mediation of the intervention effect by weight loss is that participants’ reporting of their symptoms at 6 months was influenced by knowledge of their treatment assignment. It is notable, however, that women randomized to the intensive intervention did not report greater improvement in other quality-of-life outcomes, such as physical or mental functioning as measured by the SF-36, compared with controls, even though these were also self-reported outcomes with the potential to be influenced by knowledge of treatment assignment. Furthermore, because the primary outcome of the PRIDE trial was change in frequency of urinary incontinence rather than improvement in menopausal symptoms, participants were given no special counseling about hot flushes and had no particular reason to expect that their flushing symptoms would be influenced by the study intervention.

Several previous studies of physical activity interventions have reported conflicting effects on menopausal symptoms, with one nonrandomized trial suggesting that physical activity is protective against hot flushes, another randomized trial suggesting that physical activity may worsen hot flushes, and other studies reporting no effect on flushing. Prior interventional studies were not confined to women with hot flushes at baseline, however, and detection of intervention effects tended to be limited by the low prevalence of baseline symptoms. In our study, we did not find that increased self-reported physical activity was associated with either improvement or worsening in bothersome flushing among women who were symptomatic at baseline, and change in physical activity did not explain intervention effects. Physical activity may be overestimated when assessed by self-report, however, and it is possible that more objective or precise quantification may have yielded a different pattern of associations with flushing symptoms.

Limited previous research has explored the role of calorie consumption and other dietary factors in influencing women’s experience of hot flushes. Although we did not find an association between total calorie intake and self-reported bothersome hot flushes in our study,
it is possible that the effects of the PRIDE intervention on hot flushes may be mediated by changes in consumption of specific nutrient components or the timing of meals, and further research involving more detailed analysis of dietary habits may be helpful in addressing this issue. Several other limitations of this research should be noted. First, participants in PRIDE had urinary incontinence at baseline, which may limit the generalizability of our findings to women without incontinence. Urinary incontinence is associated with decreased overall health and depression in women, which have the potential to influence the perceived bothersomeness of other health-related symptoms. To date, however, epidemiologic research has not supported an association between incontinence and menopause in women, and in the PRIDE population itself, we found no evidence that women with more bothersome hot flushes had more severe or frequent incontinence at baseline.

Second, hot flushes were assessed by a single self-report measure emphasizing the bothersomeness of symptoms during the past month, which may be vulnerable to memory and reporting biases and which may reflect not only the frequency of symptoms but also the effect of symptoms on women’s sense of well-being. Additional research using more detailed self-report measures of flushing frequency, such as hot-flush symptom diaries, may be helpful in confirming these findings and in assessing for possible differential effects on flushing frequency vs bothersomeness.

Finally, a greater proportion of women were lost to follow-up in the control than in the intervention group. If women who were lost to follow-up experienced greater improvement in hot flushes than those who remained in the study, this could result in overestimation of the main intervention effect on flushing in these analyses. Nevertheless, participants who drop out of weight management trials are often those who experience less improvement in weight or associated symptoms, and thus we might expect the greater loss to follow-up in the control group to bias our results toward the null.

From a clinical perspective, our findings suggest that women who are overweight or obese and have bothersome hot flushes may be counseled that behavioral weight loss efforts may decrease the burden of their symptoms. Some hot flushes may be counseled that behavioral weight loss efforts may decrease the burden of their symptoms. It should also evaluate whether women’s perceptions of self-management success while attempting to change their lifestyle or lose weight may modify their experience of these symptoms.

Accepted for Publication: January 12, 2010.
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Author Contributions: Drs Huang, Subak, West, and Grady 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. Study concept and design: Huang, Subak, Wing, West, and Grady. Acquisition of data: Wing, Macer, and Grady. Analysis and interpretation of data: Huang, Subak, West, Hernandez, and Grady. Drafting of the manuscript: Huang and Macer. Critical revision of the manuscript for important intellectual content: Huang, Subak, Wing, West, Hernandez, and Grady. Statistical analysis: Hernandez. Obtained funding: Subak, Wing, West, and Grady. Administrative, technical, and material support: Subak, West, and Macer. Study supervision: Huang, Subak, West, and Grady.

Financial Disclosure: Dr Huang reports receiving grant support from Pfizer Inc and Bionovo Inc to conduct research unrelated to hot flushes. Dr Subak has served on an advisory board and receives grant support from Pfizer Inc to conduct research unrelated to hot flushes. Dr Grady has received grant support from Berlex Inc, Eli Lilly and Company, and Bionovo Inc for research related to hot flushes and/or other menopausal symptoms and has been paid as a consultant to lead a Data and Safety Monitoring Board for Organon International Inc.

Funding/Support: This research was supported by the National Institute of Diabetes and Digestive and Kidney Diseases and the Office of Research on Women’s Health (grants U01 DK067860, U01 DK067861, U01 DK067862, K24 DK068389, and K24 DK080775), as well as the National Center for Research Resources (grant KL2RR024130), a component of the Clinical and Translational Science Award for Medical Research at the National Institutes of Health.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the views of the National Institutes of Health. Project officers from the National Institute of Diabetes and Digestive and Kidney Diseases were members of the Program to Reduce Incontinence by Diet and Exercise steering committee overseeing the conduct of the Program to Reduce Incontinence by Diet and Exercise study, collection of the data, and approval of manuscripts using the data.

Previous Presentation: This study was presented at the national meeting of the Society of General Internal Medicine; May 14, 2009; Miami, Florida.

Additional Contributions: We acknowledge the contributions made by the Program to Reduce Incontinence by Diet and Exercise investigators, staff, consultants, and Data and Safety Monitoring Board, who were compensated for their effort: the University of Alabama at Birmingham: Frank Franklin, MD, PhD (principal investigator), Holly E. Richter, PhD, MD (co-investigator), Kathryn L. Burgio, PhD (co-investigator), Leslie Abdo, BSN, RN, CCRN, Charlotte Bragg, MS, RD, LD, Kathy Carter, RN, BSN, Juan Dunlap, Stacey Gilbert, MPH, Sara Hannum, BS, Anne Hubbell, MS, RD, LD, Karen Marshall, BS, Lisa Pair, CRNP, Penny Pierce, RN, BSN, Clara Smith, MS, RD, Sue Thompson, RN, Janet Turman, BA, and Audrey Wrenn, MAEd. The Miriam Hospital: Rena Wing, PhD (principal investigator), Amy Gorin, PhD (co-investigator), Deborah Myers, MD (co-investigator), Tammy Monk, MS, Rheanna Ata, BA, Megan Butryn, PhD, Pamela Coward, MEd, RD, Linda Gay, MS, RD, CDE, Jacki Hecht, MSN, RN, Anita Lepore-Ally, RN, Heather Niemeier, PhD, Yael Nillini, BA, Angela Pinto, PhD, Deborah Ranslow-Robles, Natalie Robinson, MS, RD, Deborah Sepinwall, PhD, Margaret E. Hahn, MSN, RNP,
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