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Can weight loss improve migraine headaches in obese women? Rationale and design of the WHAM randomized controlled trial

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Abstract

Background—Research demonstrates a link between migraine and obesity. Obesity increases the risk of frequent migraines and is associated with migraine prevalence among reproductive-aged women. These findings are substantiated by several plausible mechanisms and emerging evidence of migraine improvements after surgical and non-surgical weight loss. However, no previous study has examined the effect of weight loss on migraine within a treatment-controlled framework. The WHAM trial is a RCT to test the efficacy of behavioral weight loss as a treatment for migraine.

Study design—Overweight/obese women (n=140; BMI=25.0–49.9 kg/m²) who meet international diagnostic criteria for migraine and record ≥ 3 migraines and 4–20 migraine days using a smartphone-based headache diary during a 4-week baseline period, will be randomly assigned to 4 months of either group-based behavioral weight loss (intervention) or migraine education (control). Intervention participants will be taught strategies to increase physical activity and consume fewer calories in order to lose weight. Control participants will receive general education on migraine symptoms/triggers and various treatment approaches. Both groups will use smartphones to record their headaches for 4 weeks at baseline, after the 16-week treatment period, and at the end of a 16-week follow-up period. Changes in weight and other potential physiological (inflammation), psychological (depression), and behavioral (diet and physical activity) mediators of the intervention effect will also be assessed.

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Conclusion—The WHAM trial will evaluate the efficacy of a standardized behavioral weight loss intervention for reducing migraine frequency, and the extent to which weight loss and other potential mediators account for intervention effects.

Keywords

migraine; headache; obesity; weight loss; randomized controlled trial

Introduction

1.1. The epidemiology and burden of migraine

Migraine is a neurovascular disorder involving recurrent headaches that are typically throbbing, unilateral and severe. Headaches last 4–72 hours and are frequently accompanied by nausea, vomiting, or sensitivity to light, sound, or movement. One-third of migraineurs also experience an aura, a transient focal neurological phenomenon involving visual, sensory, speech or motor disturbances that precede or accompany a headache [1]. Migraine afflicts 12% of Americans and three times more women (17.1%) than men (5.6%) [2]. Most migraineurs experience headaches that cause substantial or severe disability, causing disruption to occupational, family, and social activities [2–3]. Migraine also exacts a heavy societal toll, with costs of treatment and reduced productivity exceeding \$24 billion/year [4–5].

1.2. Migraine and obesity: epidemiology, mechanisms, and implications for weight loss treatment

Epidemiological research has identified several conditions related to migraine, including obesity. In one of the first studies to examine this association, Bigal et al. found that the proportion of migraineurs with 10–14 headache days increased from 4.4% in the normal weight group to 5.8% in the overweight group, 13.6% in the obese group, and 20.7% in the severely obese group [6]. Subsequent population-based studies have produced similar findings and also shown that obesity increases risk for progression to chronic migraine (> 15 headache days/month) [7–8].

Additionally, several studies [6, 9–12], but not all [6, 13–15], suggest that obesity is associated with higher prevalence of episodic migraine (> 15 headache days/month). Reasons for these discrepant findings are unclear, although studies with positive findings have tended to rely on measured versus self-reported height and weight and include reproductive-aged women who have higher migraine rates than women of perimenopausal and postmenopausal age [16].

Several putative mechanisms substantiate the epidemiologic association between migraine and obesity, one being common inflammatory processes [17–19]. Obesity may intensify the neurovascular inflammatory response in migraine and contribute to increased headache frequency via secretion of inflammatory cytokines. An elevated inflammatory response and higher headache frequency may also promote sensitization of central neurons to noxious and non-noxious stimuli, increasing risk for migraine progression [17–19]. Psychological conditions that are comorbid to migraine and obesity such as depression may also increase risk of frequent migraines [20]. Furthermore, migraine and obesity share several behavioral risk factors, such as low physical activity and a high-fat, high-calorie diet [19].

Despite strong empirical support for a migraine-obesity link, evidence for weight loss as a treatment for migraine is only just emerging. In two recent studies, headache frequency and severity were significantly decreased in migraineurs after weight loss induced by bariatric surgery [21–22]. However, both studies included small samples and lacked a control group,

limiting generalizability and the ability to rule out regression towards the mean, participant expectancy effects and other methodological artifacts as a contributor to migraine improvements. In another non-controlled trial involving adolescent migraineurs, significant reductions in headache frequency and related parameters including acute medication usage were observed after 6 months of behavioral weight loss, and maintained through 12 months [23]. Given these promising, albeit preliminary findings, there is a need for larger, controlled trials to determine the effect of weight loss on migraine.

The Women's Health and Migraine (WHAM) study is designed to test the efficacy of a standardized behavioral weight loss intervention versus a migraine education control condition in overweight/obese female migraineurs. Behavioral weight loss interventions focused on improving diet and physical activity consistently produce weight losses of 8–10 kg at 6 months, which reduces the risk of diabetes and improves cardiovascular disease risk factors. However, the WHAM trial is the first to evaluate the impact of weight loss on migraine within a treatment-controlled framework and the first to assess potential mechanisms linking weight loss to reductions in headache frequency. This trial also includes an innovative electronic headache diary that allows for real-time reporting of headache activity via smartphone, which promotes compliance and may reduce bias traditionally associated with diaries.

1.3. Aims of the WHAM trial

The WHAM trial is a single-site randomized controlled trial (RCT) sponsored by the National Institute of Neurological Disorders and Stroke comparing the effects of a 16-week standardized behavioral weight loss intervention and a migraine education control condition on migraine headache frequency and related parameters in obese (BMI = 25.0–49.9 kg/m²) female migraineurs aged 18 to 50 years. Both groups will use smartphones to record their headaches for 4 weeks at a time at baseline, after the 16-week treatment period, and at the end of a 16-week non-intervention, follow-up period. Weight and other potential physiological (inflammation), psychological (depression), and behavioral (diet and physical activity) intervention mediators will be assessed at pre-treatment and at the end of treatment prior to the post-treatment headache diary in order to allow for tests of prospective effects on migraine days (Figure 1 illustrates and provides a rationale for the hypothesized mediation pathways). The aims of this study are as follows:

1.3.a. Primary aim—To examine whether intervention participants record greater reductions in the number of migraine days per 4-week period from baseline to post-treatment than control participants.

1.3.b. Secondary aims

1. To examine whether weight losses at the end of treatment mediate differences between the intervention and control groups in reduction of migraine days at post-treatment.
2. To examine whether intervention group participants maintain greater reductions in the relative frequency of migraine days at the end of the 16-week non-intervention follow-up period compared to control group participants.

1.3.c. Exploratory aims

1. To examine whether changes in diet and physical activity at the end of treatment mediate differences between the intervention and control groups in reduction of migraine day relative frequency, independently of weight loss, at post-treatment.

2. To examine whether weight loss-related changes in inflammatory markers and depression at the end of treatment mediate differences between the intervention and control groups in reduction of migraine days at post-treatment.

2. Research design and methods

Figure 2 illustrates the WHAM study design. One hundred and forty overweight/obese females who screen positive for migraine and complete the baseline assessment that includes a 4-week smartphone-based headache diary and measurement of the hypothesized weight, inflammation, diet, physical activity, and depression intervention mediators, will be randomly assigned to 16 consecutive weeks of either behavioral weight loss intervention or migraine education control in a 1:1 ratio. Randomization procedures will be performed by the study statistician using randomly permuted blocks of 2–5 simultaneously for participants in each cohort. Intervention group participants will receive a standard behavioral weight loss program that is modeled after the DPP and Look AHEAD trials [24–27]. Control group participants will receive general education on migraine symptoms, triggers, and both pharmacological and non-pharmacological treatment approaches. After the 16-week treatment period, participants in both groups will complete the post-treatment assessment involving another 4 weeks of smartphone-based headache monitoring and measurement of the hypothesized intervention mediators. Finally, participants will undergo a 16-week follow-up assessment involving measurement of weight and another 4-week smartphone-based headache diary. All of the above measures will be administered by an assessor blinded to group assignment. This protocol was approved by the Institutional Review Board at The Rhode Island Hospital in Providence, Rhode Island.

2.1. Participant eligibility

A total of 140 females will be recruited to participate in this study. Eligibility will be limited to individuals who: (a) have migraine with or without aura, as confirmed by the study neurologist; (b) record at least 3 individual migraine headache episodes and between 4 and 20 migraine headache days during the 4-week baseline headache monitoring period; (c) are between the ages of 18 and 50; and (d) have a body mass index (BMI) between 25.0 and 49.9 kg/m². This study will only include reproductive-aged females given that migraine disproportionately affects females and most commonly during their childbearing years [2]. Additionally, positive associations between migraine and obesity have been consistently observed in premenopausal females [9, 12], but not in perimenopausal or postmenopausal women [9–10, 15]. An upper BMI limit of 49.9 was chosen because individuals with a BMI 50 are more likely to have medical comorbidities, experience physical limitations that may limit exercise participation, and require greater medical supervision and different weight loss approaches (medications, liquid formula, or bariatric surgery) [28]. To allow continued access to standard of care treatment, individuals who have been on a stable regimen of preventive and/or abortive migraine medications for at least 2 months prior to study entry and do not intend to change this regimen while the study is ongoing will be permitted to enroll in the trial. This decision also applies to medications used for depression and oral contraception. Participants who have remaining unmet treatment needs or want to pursue new or different pharmacological options at the conclusion of the study will be referred to an appropriate medical provider. All participants will provide written informed consent at the initial study orientation.

2.2. Study recruitment

Participants will be recruited through a variety of methods and sources including: advertisements in local newspapers and magazines; postings on the Internet, the Lifespan hospital network (available to employees and the public), social media outlets, and e-mail listserves; direct mailing of study brochures to the target demographic; and solicited

referrals from primary care and neurology clinics. Advertisements will be targeted to overweight women who have migraine and want to learn about different behavioral approaches to achieving migraine relief.

2.3. Migraine screening procedures

The process of establishing a valid diagnosis of migraine with or without aura will be divided into 3 phases. First, trained research staff will conduct a telephone screening interview with individuals who contact the research center in response to study advertisements. The interview will consist of validated questions that conform to International Headache Society (IHS) migraine criteria [1] and are designed to obtain information about migraine frequency, severity, related disability and other clinical features. Next, individuals who screen positive over the telephone and meet other eligibility criteria will be invited to a study orientation during which they will undergo a confirmatory diagnostic evaluation by the study board-certified neurologist. Last, participants who receive a positive migraine diagnosis from the neurologist will receive a smartphone and instructions on how to use this device to record their headache activity for the next 28 consecutive days (see Section 2.6.a. for a more detailed description of the features and advantages of the smartphone-based headache diary. See Figure 3 for examples of smartphone-based headache diary forms). At the conclusion of this monitoring period, participants will attend an individual visit at which their diary responses will be reviewed to confirm fulfillment of migraine frequency eligibility criteria (i.e. 3 individual migraine episodes and 4–20 migraine days per 28 days). These data will also serve as a baseline measure of headache frequency and other related migraine parameters. Participants with incomplete data or who do not meet migraine frequency criteria will be declared ineligible.

2.4. Interventions

2.4.a. Behavioral Weight Loss Intervention Group—The intervention approach employed in the WHAM trial has been modeled after The Diabetes Prevention Program (DPP), and Look AHEAD multi-center clinical trials [25, 27]. DPP tested whether a behavioral weight loss or pharmacological treatment could prevent or delay the onset of Type 2 diabetes [27]. Look AHEAD compared the effects of behavioral weight loss treatment to a diabetes education and support control condition on incidence of cardiovascular disease among overweight individuals with diabetes [25]. Both trials were successful in producing 7 kg weight losses at the end of 16 weeks and reducing risk of diabetes and improving CVD risk factors, respectively [24, 26]. Although behavioral weight loss interventions are typically delivered over 24 weeks, the decision was made to implement a 16-week intervention given our initial pilot work showing that migraine headache days were reduced on average by $61.6\% \pm 31.4\%$ (8.0 ± 2.4 to 3.3 ± 2.7 migraine days) in 8 obese female migraineurs after a 16-week behavioral weight loss intervention (unpublished data). Moreover, maximum weight losses with standard behavioral treatments are usually achieved between 16 and 24 weeks.

Participants will receive an intensive group-based behavioral weight loss program involving 16 consecutive weekly meetings in which they will receive intervention goals and strategies to limit fat and caloric intake and to increase home-based structured exercise. The groups will be led by a multidisciplinary team of Master's level registered dietitians, exercise physiologists, and behavioral therapists. The intervention strategies employed in the WHAM trial have been widely tested and refined, and are detailed below.

Weight loss goals: Participants will be encouraged to lose 1 to 2 pounds per week and to achieve a weight loss of at least 7% of initial body weight. Several strategies will be used to assist participants in achieving the intervention weight loss goal including encouraging daily

self-monitoring of body weight, conducting private weigh-ins prior to each weekly group session, and providing weight graphs that chart participants' current weight in relation to the intervention weight loss goal.

Diet: Participants will be placed on a standard calorie and fat restricted diet with goals of 1200–1500 kcal/day and fat gram goals of 33–42 grams/day (25% calories from fat) if pre-treatment weight is < 200 pounds (if pre-treatment weight ≥ 200 pounds, participants will be prescribed 1500–1800 kcal/day and 42–50 fat grams/day). This approach is standard in behavioral weight loss interventions and is consistent with American Heart Association and American Diabetes Association guidelines [25, 27]. Diet-related intervention lesson content will focus on eating and dietary strategies to limit calories and fat, including approaches to fast food, restaurant, and holiday eating. To aid in meeting of calorie and fat goals, participants will receive sample meal plans, a fat/calorie guidebook, and instructions to self-monitor their daily calorie and fat intake daily in food diaries. Food diaries will be reviewed each week by the interventionist who will provide written feedback to participants.

Exercise: The intervention will also include an exercise component given that the combination of diet and exercise has been shown to be the most effective non-surgical strategy for producing weight loss [29–30]. Participants will be given a structured exercise goal that gradually progresses to 250 weekly minutes of moderate-to-vigorous intensity exercise (50 minutes, 5 days/week) that is accumulated in bouts ≥ 10 minutes in duration. This level of exercise is consistent with current physical activity guidelines for achieving clinically significant and long-term weight loss [31]. Participants will also be given strategies to limit time spent in sedentary behaviors and increase their lifestyle activities, including provision of a pedometer and accompanying daily step goal that progresses to 6,000 steps/day above baseline [32]. To counter the burden and barriers inherent to supervised exercise protocols, participants will be instructed to engage in home-based exercise [33], primarily in the form of brisk walking [34–35].

Behavior therapy: Standard behavioral strategies will be employed to assist in the modification of eating and exercise habits. The strategies include stimulus control [36], problem-solving [37], social support [38], goal-setting [39], and relapse prevention [40]. In addition, participants will be instructed to engage in daily self-monitoring of their body weight and eating and activity behaviors [41].

2.4.b. Migraine Education Control Group—This condition is designed to be matched for treatment contact with the behavioral weight loss intervention and provide didactic information on migraine headaches and both standard and alternative treatment approaches. Participants will attend 16 consecutive weeks of group lectures involving topics and content which include migraine information and didactic information on evidence-based migraine self-management strategies. The first 4 sessions will be devoted to a variety of topics including migraine symptoms and pathophysiology, migraine triggers, risk factors for progression to chronic migraine, migraine issues specific to women, and standard abortive and preventive pharmacological treatment options. Subsequent sessions will focus on standard and alternative non-pharmacological approaches to migraine prevention and treatment including: stress management and relaxation techniques; healthy eating and awareness of dietary triggers; physical activity; sleep hygiene; and alternative and complementary therapies such as yoga and acupuncture. Participants in this condition will not receive behavioral weight loss strategies including weekly weigh-ins, self-monitoring materials and behavioral goals and prescriptions with individually-tailored feedback and reinforcement. Additionally, participants will not receive specific goals/prescriptions, practice opportunities, or any other materials to assist them in adopting or changing

headache management behaviors. For example, relaxation strategies such as progressive muscle relaxation and deep breathing will be described in general terms by the therapist but participants will not have the opportunity to practice these techniques in session nor will they be given prescriptions or materials to encourage practice outside of the session.

The rationale for choosing the above described control condition was based on several factors. To make causal inferences about the effects of behavioral weight loss on migraines, it was essential to select a credible attention control intervention that delivered equivalent therapist contact but none of the key active intervention components, thereby yielding similar high study adherence rates but minimal or no weight loss. This decision is supported by previous large weight loss trials including Look AHEAD and PRIDE that have shown that participants assigned to educational control conditions achieve markedly smaller weight losses (0.7%–1.6% vs. 8.0%–8.6% of initial body weight) yet have similar high rates of study completion (86%–95% vs. 97%–98%) versus those assigned to behavioral weight loss intervention [42–43]. While consideration was given to conducting a comparative effectiveness trial (e.g., behavioral weight loss vs. a standard behavioral migraine treatment) or a component analysis (e.g., diet vs. diet plus exercise), it was decided that it was necessary to first establish proof of concept before evaluating whether behavioral weight loss is efficacious relative to another established behavioral treatment or which components of the behavioral weight loss intervention may be most important for migraine management.

2.5. Treatment fidelity

Several methods will be employed to ensure that the behavioral weight loss and migraine education control interventions are implemented as designed. Detailed patient and therapist manuals will be created that all clinical staff will be required to read and review. Weekly supervision sessions will be held with all of the clinical staff. All intervention and control group sessions will be audio recorded, and an independent rater blinded to group assignment will each review a random sample of 20% of the session tapes to verify that the protocols are being implemented correctly and behavioral strategies for weight loss or migraine management are not being prescribed to the control group. Therapists will also be required to complete weekly checklists indicating that they delivered the designated intervention components.

2.6. Participant adherence and retention

The goal of this trial is to have at least 90% of participants complete the post-treatment assessment (i.e. primary endpoint). To achieve this goal, we will stress the importance of attending every session and completing all assessments during the informed consent process. Participants' completion of the intensive pre-treatment assessment including entering information about their headache activity into the smartphone diary for 28 consecutive days will serve as a behavioral run-in period to identify committed participants. Compliance with the smartphone-based diary will be assessed remotely on a daily basis. Participants who fail to complete the diary or provide incomplete information will be contacted immediately by study staff to collect the missing data. If participants do not respond to these efforts, they will be declared ineligible.

Participant attendance at group sessions will be monitored and we will aim to achieve levels of 80% attendance in the behavioral weight loss intervention and migraine education control groups during the 16-week treatment period. When participants miss a group meeting, they will be asked to attend a brief make-up visit before the next weekly group meeting. At the make-up visit, content that was missed during the previous week will be reviewed, and reasons for missed visits and solutions to attendance barriers will be discussed. We will monitor the progress of the behavioral weight loss intervention participants towards

achievement of the 7% weight loss goal and compliance with self-monitoring diet and physical activity.

Adherence to study medication requirements will be determined via a “brown bag medication review” which will enable clinical staff to see medications that participants are currently taking and inquire about any changes in usage patterns. This procedure will be conducted at each assessment point and at the end of each month during the intervention period. Participants who report that they have started taking new medications or changed the types of medications they were taking at study entry will be terminated from the study.

All participants will complete an inventory at the end of the 16-week treatment period that assesses changes in behaviors for both weight control (e.g., diet and exercise) and headache management (e.g., monitoring headache triggers, practicing relaxation techniques) to identify control participants who initiate weight loss efforts and intervention participants who adopt headache management behaviors that do not overlap with those used for weight control (i.e. ‘unplanned crossover’).

Several methods will be used to promote participant completion of the different assessment measures. To facilitate compliance with daily completion of the smartphone headache diary, an accompanying web-based application will be employed that allows for immediate transfer of participants’ real-time data to a private server and sending of intelligent prompts to participants when a complete diary entry has not been received. For in-clinic assessments, participants will be sent reminders and called the day before each of their assessment visits and be given a cash honorarium following each of the post-treatment and follow-up assessments.

2.7. Assessment components

As shown in Figure 2, participants will record their headache activity and use of acute medications for 28 days at a time using a smartphone-based headache diary at baseline, at the end of the 16-week treatment period (post-treatment), and the end of a 16-week non-intervention follow-up period. Weight will be assessed prior to completion of the smartphone-based headache diary at pre-treatment, at the end of treatment as a potential mediator of intervention effect on number of migraine days, and at the end of the 16-week follow-up period. Exploratory mediators (inflammatory biomarkers, depression, dietary fat intake, and physical activity) will be assessed during baseline and at the end of treatment. Other headache parameters, anthropometric characteristics, and cardiometabolic, psychological and behavioral factors will also be assessed at these time points. All measures will be administered by the same blinded assessor at each time point. Participants will receive a cash honorarium at the end of the post-treatment period and at the end of the follow-up period for completion of all assessment components.

2.7.a. Migraine headache activity and related parameters—The primary outcome in this study will be mean change from pre- to post-treatment in the number of migraine headache days in a 28-day period measured via smartphone and an accompanying web-based headache diary application. Participants will also use this device to record the severity and duration of their headaches, various clinical features (i.e. photophobia, phonophobia, nausea, aversion to physical activity), related level of disability, and acute medication usage.

Gold-standard pencil-and-paper measures of headache disability (i.e. Migraine Disability Assessment [44] and Headache Impact Test-6 [45–46]) will also be administered to participants. The validated Allodynia Symptom Checklist [47] will be used to measure changes in severity and presence of allodynia (i.e. pain in response to a stimulus that does not normally provoke pain), as this phenomenon has shown to be related to BMI in

migraineurs [48]. The Headache Management Self-Efficacy Scale [49] will be used to measure changes in participants' degree of confidence in their ability to manage and prevent headache pain, with the hypothesis that this variable will underlie migraine frequency changes to a greater extent in participants assigned to migraine education control versus those assigned to behavioral weight loss intervention. This construct has previously been shown to be an important mediator of the effects of behavioral headache treatments [50].

2.7.b. Weight and other anthropometric characteristics—Participants' weight will be measured to the nearest 0.1 kg using a calibrated digital scale and height in millimeters using a wall-mounted stadiometer. BMI will be calculated from these measures. Waist circumference, a correlate of chronic pain and migraine [9, 51], will be measured at the midpoint between the highest point of the iliac crest and the lower part of the costal margin at the mid-axillary line.

2.7.c. Inflammatory biomarkers and cardiometabolic risk factors—Peripheral blood samples will be collected from an antecubital vein of each participant, after fasting, to examine changes in the two inflammatory biomarkers of interest, high-sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6). Levels of CRP will be determined via latex-enhanced immunoturbidimetry, with a lower limit of detection of 0.02 mg/l. IL-6 in serum samples will be examined using a solid phase sandwich enzyme-linked immunosorbent assay technique and concentrations will be determined spectrophotometrically.

Total cholesterol, high-density lipoprotein, and triglycerides will also be examined via serum. Additionally, fasting concentrations of glucose and insulin will be analyzed and these data will be used to compute HOMA-IR as a measure of insulin sensitivity. Finally, systolic and diastolic blood pressure will be measured.

2.7.d. Depression and other psychological factors—The Centers for Epidemiologic Studies-Depression Scale [52] will be used to assess changes in the frequency of depressive mood and symptoms during the previous 7 days. Participants' levels of anxiety and stress will be assessed via the Generalized Anxiety Disorder Scale [53–54] and the Perceived Stress Scale [55], respectively. Higher levels of anxiety symptoms are associated with both migraine and obesity, and may moderate the association between these disorders [20]. Psychological stress precipitates and exacerbates migraine headache and is associated with weight gain and obesity [56–59].

2.7.e. Physical activity, dietary fat intake, and other behavioral factors—The SenseWear Mini Armband (SWA; Body Media, Inc., Pittsburgh, PA) will be used to objectively assess amount of time spent performing different intensities of physical activity. The SWA is a wireless multi-sensor monitor worn on the upper arm over the left triceps muscle that simultaneously integrates motion data from a triaxial accelerometer and physiological metrics from skin temperature, galvanic skin response, and heat flux sensors to provide minute-by-minute estimates of energy expenditure. Data are processed with proprietary software algorithms that match each recorded minute of data with an activity class (e.g., walking, running, rest). Each activity class has a linear regression model that enables mapping of values from motion and physiologic sensors to energy expenditure. The SWA has been shown to accurately estimate energy expenditure when evaluated against doubly labeled water or indirect calorimetry [60–61]. The primary variables of interest will be average daily minutes of moderate-to-vigorous physical activity accumulated overall and in bouts of at least 10 minutes. Participants will wear the device for 7 consecutive days at each of the different assessment time points.

Participants will complete three 24-hour dietary recalls collected via telephone by a blinded assessor at baseline and after the 16-week treatment period to assess changes in percentage of calories consumed from fat, other diet components (i.e. total calories and percentage of calories from carbohydrates and protein), eating patterns (e.g., eating time and frequency), and common dietary triggers for migraine. This method is highly correlated with independently observed food intake [62–63].

Sleep quality and duration will be measured subjectively via the Pittsburgh Sleep Quality Index (PSQI) [64]. Obstructive sleep apnea (OSA) and poor sleep quality is common in obese individuals and is a risk factor for migraine progression [65–66]. Moreover, OSA is shown to improve after behavioral weight loss intervention and treatment of OSA in migraineurs reduces headache frequency [67–68]. Although polysomnographic testing is the gold standard method for diagnosing OSA, use of this cost- and time-intensive procedure to detect post-intervention changes in OSA is outside the scope of this trial. Consequently, we will rely on subjective methods [i.e. PSQI and inquiring about use of Continuous Positive Airway Pressure (CPAP)] to detect changes in OSA among participants who report having this condition at baseline.

2.8. Statistical analysis, sample size, and power estimates

2.8.a. Analytic Plan—Our Primary Aim revolves around changes in the relative frequency of migraine days from baseline to post-treatment, and comparison of these changes across the behavioral weight loss intervention and migraine education control arms. Each study subject will contribute two counts of migraine days (corresponding to the 4-week baseline and post-treatment monitoring periods respectively) assumed to be distributed as conditionally independent Poisson variables, given a common multiplicative frailty term that captures the effect of time-invariant subject characteristics, such as gender and race [69]. Such models can be estimated via Proc PHREG of SAS/STAT V9.2 [70], using the equivalence between the conditional Poisson likelihood and the Cox partial likelihood noted by Xu and colleagues [71]. Further, an offset term will be used to account for differences in exposure time across study periods.

Secondary Aim 1 focuses on the extent to which end-of-treatment weight loss (wk 16) mediates group effects on post-treatment change in migraine counts (wks 17–20), assuming the latter are found to be statistically significant in Primary Aim 1. The mediation hypothesis will be tested using the Baron & Kenny approach [72], which requires that we also establish the statistical significance of the associations between a) group assignment and end-of-treatment weight loss; and b) end-of-treatment weight loss and post-treatment reduction in migraine days, controlling for group assignment. If control for end-of-treatment weight loss leads to (c) attenuation of group differences in post-treatment reduction in migraine days, then mediation is said to be complete, else only partial mediation holds. Significance of the indirect path will be evaluated using the product of coefficients along this path [73]. Since the sampling distribution of this product shows considerable skewness and kurtosis, interval estimation will be based upon bias-corrected and accelerated (BCA) bootstrap confidence intervals [74–75]. Another quantity of interest is the proportion of the treatment assignment effect mediated via the weight-loss pathway. Its bootstrap distribution will be carefully examined, with narrower confidence intervals reported as necessary to minimize the impact of outliers arising from occasional near-zero denominator terms (e.g., we may report intervals having coverage 80%–90% instead of the usual 95%).

Long-term maintenance of treatment effects (Secondary Aim 2) will be studied as for Primary Aim 1, with counts of migraine days during the final 4 weeks of the 16-week follow-up period replacing counts over the 4 weeks following the 16-week treatment period.

As shown in Figure 1B, Exploratory Aim 1 seeks to estimate the direct effects of changes in diet and physical activity at end-of-treatment (week 16) on post-treatment change in migraine counts (wks 17–20), over and above any indirect effects of these two putative mediators via induced weight change at end-of-treatment (wk 16). Estimation of such direct effects requires the fitting of a multivariate mediation model, with changes in dietary measures, physical activity, and weight as mediators, and treatment group as the independent variable. For implementation details, we refer the reader to Napolitano et al. [76], which describes a successful implementation of this model in a physical activity context.

As also shown in Figure 1B, Exploratory Aim 2 seeks to estimate the weight-loss related changes in inflammatory markers and depression at end-of-treatment mediate subsequent group differences in reduction of migraine days at post-treatment. Since we are only interested in the effect of changes in inflammatory markers and depression that are induced by weight loss, we will fit a bivariate mediation model in which 16-wk weight loss will be the independent variable, 16-wk changes in inflammatory markers and depression will be the putative mediators, and number of migraine days during wks 17–20 will be the dependent variable.

2.8.b. Power Calculations—Power calculations for our Primary Aim will be based on an equal number of migraine days across study arms ($\lambda_{01} = \lambda_{00} = 10$) during the 4-week pre-tx period. Following treatment, these rates are expected to diverge, dropping by 50% in the treatment arm ($\lambda_{11} = 5$) and by 20% in the control arm ($\lambda_{10} = 8$). As a result, the within-subject period effect is given by $RR_1 = 0.50$ in the treatment arm and by $RR_0 = 0.80$ in the control arm, for a net treatment effect of $RRR = RR_1/RR_0 = 5/8$. Power for testing $H_0: RRR = 1$ vs. $H_a: RRR < 1$ using conditional Poisson regression is estimated at 80% assuming $N = 63$ subjects per group after attrition. Since attrition is unlikely to exceed 10% of initial study enrollment, we will recruit $N = 140$ subjects ($N = 70$ per arm) at baseline. To the extent that such attrition is spread evenly throughout the follow-up period, we should be able to include partial information on subjects dropping out between weeks 17–20 to further increase precision of our estimates

2.9. Discussion

The WHAM trial is the first to test the efficacy of behavioral weight loss as a treatment for migraine in obese women, a population at elevated risk for having migraine and experiencing frequent migraine headaches [6–11]. Additionally, this study has several important strengths and innovations that seek to advance study of behavioral treatments for migraine. The behavioral weight loss intervention will be compared to a migraine education control intervention that provides the same amount of therapist attention, but none of the active intervention strategies (self-monitoring, goals with individually-tailored feedback and reinforcement, etc.) used to produce weight loss and expected improvements in migraine headaches. Our inclusion of an attention control versus a wait-list or usual care control condition will enable us to test whether the behavioral weight loss intervention produces improvements in migraine headaches above and beyond nonspecific influences such as therapist attention or positive expectations, thereby strengthening causal inference [77].

We will conduct a formal test of mediation to determine whether the active intervention produced the expected reduction in number of migraine days via changes in body weight. Additionally, we will test putative physiological (inflammation), psychological (depression), and behavioral (diet and physical activity) mediators in an exploratory analysis [17–19]. In additional exploratory analyses, we will attempt to evaluate even more complex mediation pathways such as whether the influence of weight loss on reduction in migraine frequency is

mediated in part through increases in headache management self-efficacy [49–50] or whether weight loss-related changes in inflammation and migraine frequency are mediated in part through reduction in allodynia [47–48]. The primary and exploratory mediation analyses will advance understanding of the relationships among migraine, obesity, weight loss, and different putative mechanisms as well as inform future weight loss approaches to treating migraine.

We will use novel, state-of-the art measures to assess both migraine headaches and certain mediators underlying intervention efficacy. While recent studies have used PalmPilot handheld computers for real-time assessment of migraine headaches and related parameters [78–80], this technology requires manual downloading of headache recordings. In the current study, assessment of headache frequency and related parameters will be accomplished via a smartphone-based electronic diary. Prior to randomization, and during the post-treatment and follow-up assessment periods, participant will be asked to report their headache activity daily for 28 days by completing a series of Web-based forms that are accessed via a smartphone provided by the study. This type of electronic headache diary has several potential advantages compared to traditional paper diaries. Paper diaries are often completed retrospectively, which introduces inaccuracy due to simple forgetting and well known cognitive biases [81–82]. In addition, the adaptive nature of the electronic assessment has the potential to reduce participant burden while simultaneously providing more detailed information on headache activity [83]. Responses to the questions that are asked early in the daily assessment of headache activity are automatically used to determine which questions participants receive later in the assessment. For example, participants who indicate that they did not use medication to treat a headache are not asked follow-up questions about their medication use. This approach makes the daily diary more efficient [83]. Other potential advantages of the electronic diary include ease of use (e.g., no need to carry bulky paper forms), immediate transmission of data to the investigative team so (no loss of data if the device is lost), fewer errors (the electronic diary forms automatically check for common errors and prompt the patient to make a correction). Disadvantages include increased cost, a need for technical expertise and resources to implement the electronic diary, a need to train participants in the use of the electronic diary. It is also important to note that all types of diaries rely on the potentially inaccurate assumption of the accuracy of self-report [81]. However, there is currently no known method of objective headache assessment.

Similarly, although physical activity is an established correlate of migraine frequency and severity, previous studies have examined free-living physical activity using retrospective self-report measures which are highly susceptible to bias [84–87]. The present study will be the first to use an objective measure of physical activity in migraineurs that employs accelerometry technology in combination with physiological parameters to provide estimates of energy expenditure and time spent performing different intensities of physical activity. This study will also be the first to assess diet and eating patterns in migraineurs using a multi-call 24 hour dietary recall procedure that is considered the gold standard method and is highly correlated with independently observed food intake [62–63].

Finally, in addition to being able to test whether migraine headaches are improved after short-term weight loss, this study will also provide the opportunity to examine the extent to which migraine improvements are sustained during a 4-month non-intervention, weight maintenance period. Finding that migraine improvements are better sustained in participants who are more successful at maintaining their weight loss would provide additional evidence of the influence of weight and weight change on migraine. Furthermore, evidence of these effects would justify future studies that incorporate a longer-term follow-up.

2.10. Conclusions

The WHAM study promises to have significant implications for research and clinical practice. It is the first RCT to examine whether weight loss improves migraine headaches and provides an empirical framework for the recent clinical recommendation that behavioral weight loss strategies be incorporated with a treatment plan for obese migraineurs [88]. Findings from this study may aid clinicians in motivating obese migraineurs to lose weight which will lead to health improvements and potential reductions in headache frequency, severity and related disability. The WHAM trial will also provide important novel data that will enhance understanding of putative mechanisms of change in migraine headache activity with weight loss. Finally, because migraine and obesity are two health problems of enormous scope, findings from the WHAM trial will have considerable relevance for public health.

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Fig. 1. Hypothesized mediational pathways through which the behavioral weight loss intervention contributes to reduction in frequency of migraine headaches

A. Primary mediator: weight loss

We will test the hypothesis that greater weight loss mediates differences in reduction of migraine days between the behavioral weight loss (BWL) intervention and migraine education (ME) control groups, as depicted in Figure 1A above. Weight loss is identified as the primary mediator based on epidemiological research that demonstrates a relationship between obesity and increased migraine frequency [6–8] and recent observational data indicating significant reductions in migraine frequency after both surgical and behavioral weight loss interventions [20–22].

B. Exploratory mediators: Changes in inflammation, depression, and physical activity and dietary patterns.

In exploratory mediational analyses depicted above in Figure 1B, we will first examine whether more favorable changes in physical activity and/or diet, adjusting for weight loss, mediate differences in reduction of migraine days between the BWL intervention and ME control groups. Physical activity and diet were identified as mediators given that increases in physical activity and decreases in caloric intake are primary targets of BWL interventions and are strong predictors of treatment success [89–91]. Moreover both behaviors are related to reductions in migraine frequency and severity [92–94]. We will next examine whether greater weight-loss associated reductions in inflammatory biomarkers and/or depression account for differences in reduction of migraine days between the BWL intervention and ME control groups. Inflammation was selected as a mediator because systemic inflammation is a pathophysiological process shared by migraine and obesity [17, 19], obesity-related inflammation is thought to contribute to higher migraine frequency via increased neurovascular inflammation and central sensitization [17], and reductions in inflammation as evidenced by lowered levels of C-reactive protein (CRP) and proinflammatory cytokines such as interleukin-6 (IL-6) occur after BWL interventions [95–96]. Depression was chosen as a mediator because depression is comorbid to both obesity and migraine, increases risk for high headache frequency in obese migraineurs, and is reduced after BWL intervention [20, 97–98].

Fig. 2. Study design and timeline of study assessments and interventions

Participants will be randomized to receive behavioral weight loss intervention or migraine education for 16 weeks. Participants will complete a 4-week electronic migraine headache diary at pre- and post-treatment and after a 16-week non-intervention, weight maintenance period. Hypothesized mediators of the intervention effect including weight, inflammation, depression, and physical activity and dietary habits will be assessed prior to completion of the electronic headache diary at pre- and post-treatment. Weight will also be assessed at 16-week follow-up.

WHAM
Women's Health and Migraine

Headache Diary Instructions

Complete a headache diary entry every day before you go to sleep, even if you did not have a headache.

- If you did not have a headache, you will only complete question #1.
- If you did experience a headache, please answer the following questions about your **most** severe headache of the day.
- Please report on all headache activity and medications taken **since you last completed a diary entry** on the previous day. This includes headache activity that occurred on the previous day after you completed your diary entry.

[Begin Survey](#)

Pain Severity

A. Please rate your pain by checking the one number that best describes your headache pain at its **worst** during the last 24 hours.

No pain 6 Pain as bad as you can imagine

B. Please rate your pain by checking the one number that best describes your headache pain at its **least** in the last 24 hours.

No pain 4 Pain as bad as you can imagine

[Continue](#)

Did the headache change with activity, such as walking stairs? [Worse](#)

Did you suffer from nausea? [Mild](#)

Were you bothered by light? [No](#)

Were you bothered by sound? [Moderate](#)

Did you take any medications to treat your headache today? [Yes](#)

[Continue](#)

Figure 3.
Example smartphone-based headache diary forms