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Can weight loss improve migraine headaches in obese women? Rationale and design of the Women's Health and Migraine (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 an 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/m^2) 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.

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.

1. 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 h and are frequently accompanied by nausea, vomiting, or sensitivity to light, sound, or movement.

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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 ($\geq$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/m^2) 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 (Fig. 1 illustrates and provides a rationale for the hypothesized mediation pathways). The aims of this study are as follows:

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.

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.

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.