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Migraine and Obesity: Epidemiology, Possible Mechanisms, and the Potential Role of Weight Loss Treatment

Dale S. Bond, Ph.D.[1], **Julie Roth, M.D.**[2], **Justin M. Nash, Ph.D.**[3], and **Rena R. Wing, Ph.D.**[1]

[1] Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University/The Miriam Hospital Weight Control and Diabetes Research Center, Providence RI

[2] Department of Neurology, The Warren Alpert Medical School of Brown University/Rhode Island Hospital, Providence RI

[3] Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University/The Miriam Hospital, Centers for Behavioral and Preventive Medicine, Providence RI

Abstract

Migraine and obesity are two public health problems of enormous scope that are responsible for significant quality of life impairment and financial cost. Recent research suggests that these disorders may be directly related, with obesity exacerbating migraine in the form of greater headache frequency and severity, or possibly increasing the risk for having migraine. The relationship between migraine and obesity may be explained through a variety of physiological, psychological, and behavioral mechanisms, many of which are affected by weight loss. Given that weight loss might be a viable approach for alleviating migraine in obese individuals, randomized controlled trials are needed to test the effect of weight loss interventions in obese migraineurs. Large-scale weight loss trials have shown that behavioral interventions, in particular, can produce sustained weight losses and related cardiovascular improvements in patients who are diverse in body weight, age, and ethnicity. Consequently, these interventions may provide a useful treatment model for showing whether weight loss reduces headache frequency and severity in obese migraineurs, and offering further insight into pathways through which weight loss might exert an effect.

Keywords

migraine; obesity; mechanisms; weight loss

Introduction

Migraine and obesity represent two major public health problems. Both disorders are prevalent, particularly in the United States where 12% of individuals are migraineurs and one-third of persons are obese.[1–2] Migraine and obesity also exact a considerable toll on health. Both conditions are independent risk factors for cardiovascular disease[3–4], comorbid with pain-related and psychiatric conditions[5–7], and associated with quality of life impairment.[8–9] Finally, migraine and obesity both impose a large economic burden on society. Health care costs attributable to migraine are estimated to exceed $11 billion

Address correspondence to: Dale S. Bond, Ph.D., Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University/The Miriam Hospital, Weight Control and Diabetes Research Center, 196 Richmond Street, Providence RI, 02903, Tel: 401-793-8940, Fax: 401-793-8944; dbond@lifespan.org.

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annually[10], whereas productivity losses caused by migraine cost American employers $13 billion per year.[11] Obesity is projected to account for $147 billion in health care costs[12], with indirect costs contributing an additional $65 billion to the total economic burden.[13]

Recent research suggests that migraine and obesity may be directly linked. Obesity is related to higher frequency and severity of headache attacks among individuals who have migraine.[14–16] There is also some evidence to suggest that obesity is associated with migraine prevalence.[17–18] These findings recently gave rise to the notion that weight management strategies should be incorporated within a migraine treatment plan for patients who are obese.[19] In this article, we describe the symptoms, epidemiology, and pathophysiology of migraine. We then review studies that have examined the epidemiological association between migraine and obesity followed by a discussion of possible mechanisms that may link the two disorders. Finally, we explore the potential role of weight loss in treatment of migraine and potential mechanisms through which weight loss may alleviate headache attacks.

Migraine: symptomatology, epidemiology and disability, and pathophysiology

Symptomatology

Migraine is a neurological disorder involving episodes of head pain that are frequently throbbing, unilateral and severe. According to the International Headache Society (IHS)[20], attacks typically last 4 to 72 hours and are often accompanied by nausea, vomiting, or sensitivity to light, sound, or movement. Approximately one-third of migraineurs have attacks that are preceded or accompanied by anaura, characterized by transient focal neurological symptoms that are most often visual but may also involve disturbances in sensory, speech and motor functioning.

Epidemiology and disability

Migraine prevalence is highest in individuals aged 25–55 years, typically the most economically productive period in peoples' lives.[1] In the United States, one-year prevalence of migraine is 18% in women, a rate that is three times that of men.[9] Globally, migraine is most prevalent in the Americas and Europe and least prevalent in Africa and Asia.[1, 21] A similar race pattern is observed in the United States where whites have higher rates than African Americans and Asian-Americans, suggesting race-related differences in genetic vulnerability to migraine.[22] Population-based data also suggest that low socioeconomic status contributes to elevated risk for migraine.[9]

Migraine is not only common, but disabling. In the United States, an estimated 28 million adults have severe migraine headaches. Thirty-one percent of migraineurs experience ≥3 severe headaches per month and over half (54%) report that their headaches cause severe impairment or necessitate bed rest.[23] Migraine is estimated to cause 112 million bedridden days per year, a figure which corresponds to 300,000 people staying in bed every 24 hours because of headaches.[11, 21] Several studies also suggest that migraine-related disability causes substantial disruption to family life in terms of postponement of household work, withdrawal from social and family activities, and adverse effects on relationships at home and at work.[24]

Pathophysiology

While genetic factors are likely involved in susceptibility to migraine[25], the events that initiate migraine attacks are not well understood. Cortical spreading depression (CSD), described as a self-propagating wave of neuronal depolarization that spreads over the cortex

(particularly the occipital region), is believed to underlie the migraine aura and trigger headaches via stimulation of the trigeminal nerve.[26–29]

Specifically, CSD is proposed to stimulate release of substances from the brain and blood vessels including ions and neurotransmitters such as glutamate and nitrous oxide. These substances activate the trigeminal innervations of meningeal nociceptors to release several neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, and neurokinin A, all of which induce vasodilation and leakage of plasma proteins, leading to neurogenic inflammation and employment of macrophages and mast cells.[26–29] Simultaneously, modulation of both central pain processing pathways, in the thalamus, gray matter of the midbrain, and hypothalamus, as well as vascular and autonomic function occurs via serotonin and catecholamines.[29] The throbbing quality of the pain of migraine is associated with activation of pain-sensitive structures along the cerebral vasculature, augmented by the effect of vasoactive intestinal peptide (VIP) on the extracerebral vasculature. Nausea and other autonomic symptoms are associated with central and peripheral autonomic activation, while photophobia and phonophobia, and perhaps allodynia are attributed to sensitizing of central pain processing pathways.[28] The clinical picture of migraine is thus represented as a culmination of autonomic and nociceptive peripheral and central nervous system dysfunction, coupled with sterile “neurogenic” inflammation, and neuropeptide dysregulation.

Epidemiological Relationship between Migraine and Obesity

Research is more consistent in supporting the link between obesity and migraine frequency and severity than it is between obesity and migraine prevalence. The relationship between migraine and obesity was first evaluated in a clinic-based study that showed obese patients were 3 times as likely as age-matched normal-weight controls to have migraine.[30] Several large cross-sectional studies have since investigated this relationship in population-based samples (see Table 1). Bigal et al.[14] evaluated 30,215 participants with headache history, 3,719 of whom had migraine. Obesity was not associated with increased prevalence of migraine, but was related to headache attack frequency. Reporting of frequent headaches (10–14 headache d/mo) increased from 4.4% in the normal weight group to 13.4% in the obese group and 20.7% in the severely obese group. Additionally, migraineurs in the severely obese group were nearly twice as likely to report experiencing severe headache pain, compared to those in the normal weight group. Finally, headache disability and clinical features of migraine (photophobia, phonophobia) were also shown to increase with BMI category.

Bigal and colleagues[16] subsequently reported findings that further supported the relationship between obesity and migraine frequency. In this study, 18,968 of 162,576 (11.7%) individuals aged 12 years and older screened positive for migraine. Among these individuals, the occurrence of very frequent headaches was significantly higher in the obese (8.2%) and morbidly obese (10.4%) groups, compared to the normal-weight group (6.5%). Additionally, the percentage of participants with some headache disability was higher in the obese (38.4%) and morbidly obese (40.9%) groups, relative to the normal-weight group (32.0%).

Consistent with the findings of Bigal et al.[14], several recent studies have found no relationship between obesity and increased prevalence of migraine. Keith and colleagues employed 11 different datasets to examine the association between BMI and headache or migraine in more than 200,000 women.[31] Findings showed that obese women had increased risk for headache, but not specifically migraine. Mattson[32] evaluated the relationship between BMI and migraine in 684 women aged 40–74 years. Results showed that neither

migraine prevalence nor frequency, severity and duration of headache attacks varied as a function of obesity status. Finally, Winter and colleagues[33] assessed the relationship between BMI and migraine in 63,467 Women's Health Study participants aged ≥ 45 years. Findings showed that migraine prevalence was higher in those with a BMI ≥ 35, although this association disappeared after adjustment for cardiovascular factors and postmenopausal status. However, increasing BMI among migraineurs was associated with more frequent headaches and clinical features.

By contrast, two studies conducted in National Health and Nutrition Examination Survey (NHANES) participants have shown an association between obesity and migraine prevalence. Participants were considered to have migraine if they answered "yes" to having severe headaches or migraines during the past 3 months. In the first study, Ford et al.[17] evaluated 7,601 participants and found that those who were underweight (<18.5) or obese (BMI ≥ 30) were at higher risk for having severe headaches or migraine compared to those who were normal weight. In the second study, Peterlin et al.[18] examined the relationship between severe headaches or migraine and both total (based on BMI) and abdominal (based on waist circumference) obesity in nearly 22,000 participants. In men and women aged 20–55 years, higher prevalence was associated with both total and abdominal obesity. However, in women older than 55 years, migraine prevalence was reduced in those with abdominal obesity.

The reasons for inconsistency in findings regarding the relationship between BMI and migraine prevalence are not entirely clear, but several methodological differences may underlie this variation. Whereas some of the studies used measured height and weight[17–18, 32], others relied on self-reported height and weight[14, 16, 31, 33] which may be problematic given that obese migraineurs have been shown to underreport their weight.[34] There have also been a variety of methods used to define and diagnose migraine, thus creating difficulty in interpreting and comparing findings across studies. Finally, some studies were conducted exclusively in women of peri-and post-menopausal age who have lower migraine rates than women in their reproductive years.[35]

Based on the studies above, there appears to be a relationship between obesity and migraine, particularly in women during their reproductive years. While there is stronger evidence to suggest that obesity exacerbates migraine, it is less clear whether obesity increases risk for having migraine. Additional population studies that use direct measures of obesity and standardized IHS criteria to diagnose migraine are needed to better address this important clinical and research question.

Possible mechanisms underlying the relationship between migraine and obesity

Several potential mechanisms may help to explain the linkage between migraine and obesity. These mechanisms can be classified into three groups: 1) physiological, 2) psychological, and 3) behavioral.

Physiological mechanisms

The relationship between migraine and obesity might be explained in part by common inflammatory mediators. Neurogenic inflammation resulting from activation of the trigeminal vascular system figures predominantly in the pain of migraine. Stimulation of trigeminal ganglion nociceptors induces the release of proinflammatory substances, most notably CGRP and substance P.[26, 28–29] In obese individuals, CGRP levels are elevated and show further increases after fat intake.[36] Similarly, substance P has been identified in adipose tissue and may contribute to enlargement of fat depots and thus the pro-

inflammatory milieu that occurs with obesity.[37] Further, levels of inflammatory adipocytokines, including tumor necrosis factor (TNF)-α and interleukin (IL-6), that increase with higher levels of adiposity[38] are elevated at the onset of migraine attacks.[39] Finally, levels of C-reactive protein (CRP)which increase during systemic inflammation are elevated in both migraineurs and obese individuals.[40–41] Thus, the inflammatory state that exists with obesity may exacerbate the inflammatory response in migraine, possibly contributing to headaches that are more frequent or severe.[42]

Various neurotransmitters and peptides directed by the hypothalamus in regulation of eating behavior also play a role in migraine pathophysiology. For example, the neurotransmitter serotonin binds to receptors (5-HT_{1A}, $5HT_{1B}$, 5-HT_{2A}, and $5HT_{2C}$) involved in control of energy intake with the 5-HT_{1B} and 5-HT_{2C} receptors signaling satiety.[43] Except for transient rises in serotonin levels during headache attacks, migraine is postulated to involve chronically low serotoninergic activity[43], which could contribute to increased caloric intake and weight gain.[44–45] Serotonin further affects eating behavior via various neuropeptides, including orexin-A. Along with its roles in appetite and feeding, orexin-A is also associated with reward, arousal, stimulation of spontaneous physical activity, and modulation of glucose levels.[46–48] Moreover, obese women have been shown to have lower plasma levels of orexin-A compared to controls[49], which holds particular relevance for migraine as orexin-A deficiency is postulated to promote inflammation in the trigeminal system.[42] This notion is further supported by research using rat models that shows injection of orexin-A reduces perception of painful stimuli[50] and inhibits neurogenic vasodilation and release of CGRP from trigeminal neurons.[51] Interestingly, another orexigenic connection between migraine and obesity may be sleep dysregulation. Both disorders are common co-morbid conditions in patients with narcolepsy[52–53], a sleep disorder characterized by orexin-A deficiency.[54]

Adipocytokines such as adiponectin and leptin that regulate body weight through effects on metabolism and appetite may promote inflammatory processes underlying migraine and obesity. For example, low adiponectin levels are shown to coincide with a proinflammatory environment marked by elevated levels of TNF-α, IL-6, and CRP, and have been implicated in both obesity and migraine.[55–56] Similarly, leptin may induce release of cytokines[57] and contribute to heightened pain sensitivity.[58] Elevated leptin concentrations occurring with obesity are also associated with increased susceptibility to chronic inflammatory/autoimmune diseases.[59] However, less is known about the role of leptin in migraine. A recent study found lower leptin levels in episodic migraineurs compared to controls, although this difference did not persist after adjusting for the migraineurs' lower fat mass.[60] Consequently, further studies are needed to directly examine whether increased leptin levels in obese migraineurs contributes to alterations in cytokines and exacerbation of headache activity.

Finally, sympathetic dysregulation plays a role in both migraine and obesity.[61–62] Migraineurs are shown to have sympathetic hypofunction during asymptomatic periods and sympathetic hyperfunction during attack periods.[62] Similarly, obesity is related to sympathetic hyperstimulation as well as reduced serotonin tone.[42, 61] Consequently, it has been postulated that as a result of sympathetic hypofunction, obese migraineurs may have difficulty in adapting to the elevated sympathetic tone associated with obesity, thus making them susceptible to an increased number of attacks.[42]

Psychological mechanisms

Certain psychological factors and conditions may provide insight into the migraine-obesity relationship. For example, psychological stress affects both migraine and obesity. Stress can promote migraine onset in predisposed individuals[63], precipitate or aggravate headache attacks in those who already have migraine[64], and increase risk for transformation of

episodic to chronic migraine.[65] These effects are presumed to be the product of biochemical changes inherent to the physiological stress response that can increase sensitivity of the trigeminal system, promote neurogenic inflammation and reduce pain threshold.[66] Additionally, the experience of migraine itself can be a stressor and through maladaptive coping strategies such as medication overuse may increase headache frequency.[67] Similarly, studies have shown associations between psychological stress and increased risk of obesity and weight gain[68–70], that may be mediated by dysregulation of the hypothalamic-pituitary-adrenal axis[71], greater preference for high calorie, palatable foods[72], and reduced control over food intake.[72] As previously described, such disturbances in hypothalamic function and eating regulation are thought to modulate the migraine-obesity relationship.

Certain psychiatric disorders related to obesity, including major depression and anxiety disorders, are also risk factors for developing migraine and experiencing frequent, disabling attacks.[6–7] Tietjen et al.[73] recently examined the effects of anxiety and depression on the relationship between migraine and obesity in 721 migraineurs (88% female, 30% obese) from 8 different headache treatment centers. Findings showed that depression and anxiety were most common in the obese migraineurs. Additionally, both depression and anxiety in this group were associated with higher headache frequency and disability, suggesting that these disorders may modify the relationship between obesity and migraine.

Behavioral Mechanisms

Behavioral risk factors represent another area of overlap between migraine and obesity. For example, disturbances in sleep behavior, particularly short sleep duration, are more common in migraineurs than in non-migraineurs[74], are a common trigger factor for migraine attacks[75], and are associated with increased headache frequency and severity.[76] Short sleep duration also appears to play a role in weight gain and obesity, particularly in children and young adults.[77] Obstructive sleep apnea, a common complication of obesity, is also associated with transformation of episodic to chronic migraine.[78] Thus, it is possible that sleep disturbances in migraineurs may be compounded by obesity, thereby increasing risk for more frequent and/or severe attacks.

Certain dietary habits are important in both migraine and obesity. For example, skipping breakfast has shown to be associated with increased risk of migraine[79] as well as weight gain[80] and obesity.[81] Similarly, irregular meal frequency is associated with migraine[82] and is shown to increase energy intake[83], possibly contributing to weight gain and obesity. Consumption of a high-fat diet, which is a major contributor to weight gain and obesity[84], has also been shown in migraineurs.[85] Further, particular consequences of a high-fat diet including elevated blood pressure and cholesterol levels may increase risk for having migraine and migraine progression.[86]

Low physical activity may be another factor contributing to the co-occurrence of migraine and obesity. Research has shown that low physical activity levels are associated with obesity status[87], as well as higher migraine prevalence and more frequent migraine attacks.[88–89]

Why weight loss might be effective for alleviating headaches in obese migraineurs

Given that weight loss affects many of the physiological, psychological, and behavioral mechanisms proposed to link migraine and obesity, it may well prove to be a means of reducing headache frequency and severity in obese migraineurs. With respect to physiological mechanisms, weight loss could prevent or decrease the severity of migraine attacks by altering central nervous signaling pathways via increases in orexin A[90], and through inflammatory pathways mediated in part by increases in adiponectin and decreases

in leptin.[91–92] Associated reductions in inflammatory cytokines[93], CRP[94], and sympathetic tone[95] may also play a role in altering the central and peripheral inflammatory cascades that lead to the pain of migraines.

Additionally, weight-loss related improvements in psychological factors including mood[96] and stress-coping ability[97] could help to alleviate migraine.[42, 67, 73] Similarly, enhancement of sleep quality and disturbances that may occur with weight loss could reduce headache frequency and severity.[98–99] Decreases in fat consumption and increases in physical activity are strongly correlated with weight loss[100–101], and both behaviors have shown to be associated with reduction in headache frequency and severity.[85, 102] Finally, weight loss may impact migraine in obese individuals via improvements in conditions that are comorbid to both disorders, such as hypertension and hyperlipidemia[86, 103], depression[73, 96], diabetes[104–105], and sleep apnea.[78, 106]

Weight loss and headache

Despite these plausible mechanisms linking obesity and migraine, few studies have examined the impact of weight loss on headache, and none have studied whether weight loss improves migraine in obese adults. Sugerman et al.[107] examined the effects of bariatric surgery on idiopathic intracranial hypertension, an obesity-related disease of which severe, persistent headaches is a symptom. Weight loss at 4-months post-surgery was associated with resolution of headaches in all but 1 of 19 female patients; in addition, headaches recurred in 2 patients who had subsequent weight regain.

More recently, Hershey et al.[108] examined the effect of weight and weight change on various headache parameters in 913 pediatric headache sufferers (71% of whom who had migraine). Body mass index (BMI) percentile was positively associated with headache frequency at the initial visit. Greater decreases in BMI were associated with greater reductions in headache frequency at 3-and 6-months follow-up for children who were initially overweight or obese, but not for those who were normal weight.

While it is difficult to draw any substantive conclusions from the studies above, the epidemiological and mechanistic links between migraine and obesity suggest that weight loss may be a viable treatment approach for alleviating headaches. In order to properly test the effects of weight loss on migraine, randomized controlled trials involving interventions that can effectively and reliably produce weight loss in obese individuals are needed.

Rationale for conducting randomized trials of behavioral weight loss interventions in obese migraineurs

There is strong justification for conducting randomized trials of behavioral weight loss interventions in obese migraineurs. Behavioral interventions have been demonstrated to be the most effective treatment for mild to moderate obesity, resulting in an average weight loss of 10 kg or approximately 10% of starting weight after 6 months of treatment.[109] Moreover, large randomized controlled trials such as the Diabetes Prevention Program (DPP) and Look AHEAD (Action for Health in Diabetes) have demonstrated that significant weight losses achieved through behavioral intervention can be maintained to produce long-term reductions in cardiovascular disease risk and diabetes incidence in patients of different ages, weights, and ethnicities.[103, 110] DPP and Look AHEAD also provide strong examples of how behavioral treatment length, format, and components can be standardized and administered across multiple sites. Finally, changes in eating and activity habits, body weight, and disease risk factors that occur during behavioral interventions affect many of the previously discussed mechanisms proposed to link migraine and obesity.

Conclusion

Migraine is a prevalent and debilitating disorder. Evidence indicates a possible link between migraine and obesity, with the latter either exacerbating headache activity in current migraineurs or possibly increasing the risk for having migraine. A wide array of physiological, psychological, and behavioral mechanisms may contribute to the co-occurrence of these disorders, the majority of which can be effectively targeted with weight loss. Therefore, conduct of randomized controlled trials to evaluate the effects of weight loss on migraineis warranted. Behavioral weight loss interventions, in particular, may provide a useful treatment model for showing whether modest weight loss reduces headache frequency and severity in obese migraineurs as well as enhancing understanding of different mechanisms through which weight loss might impact migraine.

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References

1. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. Neurol Clin. 2009; 27:321–34. [PubMed: 19289218]
2. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010; 303:235–41. [PubMed: 20071471]
3. Pi-Sunyer X. The medical risks of obesity. Postgrad Med. 2009; 121:21–33. [PubMed: 19940414]
4. Bigal ME, Kurth T, Santanello N, Buse D, Golden W, Robbins M, Lipton RB. Migraine and cardiovascular disease: a population-based study. Neurology. 2010; 74:628–35. [PubMed: 20147658]
5. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009; 9:88. [PubMed: 19320986]
6. Kalaydjian A, Merikangas K. Physical and mental comorbidity of headache in a nationally representative sample of US adults. Psychosom Med. 2008; 70:773–80. [PubMed: 18725426]
7. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry. 2006; 63:824–30. [PubMed: 16818872]
8. Fontaine KR, Barofsky I. Obesity and health-related quality of life. Obes Rev. 2001; 2:173–82. [PubMed: 12120102]
9. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001; 41:646–57. [PubMed: 11554952]
10. Hawkins K, Wang S, Rupnow M. Direct cost burden among insured US employees with migraine. Headache. 2008; 48:553–63. [PubMed: 18070057]
11. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. Arch Intern Med. 1999; 159:813–8. [PubMed: 10219926]
12. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff (Millwood). 2009; 28:w822–31. [PubMed: 19635784]
13. Trogdon JG, Finkelstein EA, Hylands T, Dellea PS, Kamal-Bahl SJ. Indirect costs of obesity: a review of the current literature. Obes Rev. 2008; 9:489–500. [PubMed: 18331420]
14. Bigal ME, Liberman JN, Lipton RB. Obesity and migraine: a population study. Neurology. 2006; 66:545–50. [PubMed: 16354886]
15. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic tension-type headache. Neurology. 2006; 67:252–7. [PubMed: 16864817]

16. Bigal ME, Tsang A, Loder E, Serrano D, Reed ML, Lipton RB. Body mass index and episodic headaches: a population-based study. Arch Intern Med. 2007; 167:1964–70. [PubMed: 17923596]
17. Ford ES, Li C, Pearson WS, Zhao G, Strine TW, Mokdad AH. Body mass index and headaches: findings from a national sample of US adults. Cephalalgia. 2008; 28:1270–6. [PubMed: 18727641]
18. Peterlin BL, Rosso AL, Rapoport AM, Scher AI. Obesity and Migraine: The Effect of Age, Gender and Adipose Tissue Distribution. Headache. 2010; 50:52–62. [PubMed: 19496830]
19. Nicholson R, Bigal M. Screening and behavioral management: obesity and weight management. Headache. 2008; 48:51–7. [PubMed: 18184286]
20. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004; 24 (Suppl 1):9–160. [PubMed: 14979299]
21. Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. Lancet Neurol. 2008; 7:354–61. [PubMed: 18339350]
22. Stewart WF, Lipton RB, Liberman J. Variation in migraine prevalence by race. Neurology. 1996; 47:52–9. [PubMed: 8710124]
23. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007; 68:343–9. [PubMed: 17261680]
24. Lipton RB, Bigal ME, Kolodner K, Stewart WF, Liberman JN, Steiner TJ. The family impact of migraine: population-based studies in the USA and UK. Cephalalgia. 2003; 23:429–40. [PubMed: 12807522]
25. Russell MB. Is migraine a genetic illness? The various forms of migraine share a common genetic cause. Neurol Sci. 2008; 29 (Suppl 1):S52–4. [PubMed: 18545897]
26. Dalkara T, Zervas NT, Moskowitz MA. From spreading depression to the trigeminovascular system. Neurol Sci. 2006; 27 (Suppl 2):S86–90. [PubMed: 16688636]
27. Moskowitz MA. Pathophysiology of headache--past and present. Headache. 2007; 47 (Suppl 1):S58–63. [PubMed: 17425711]
28. Silberstein SD. Migraine pathophysiology and its clinical implications. Cephalalgia. 2004; 24 (Suppl 2):2–7. [PubMed: 15595988]
29. D'Andrea G, Leon A. Pathogenesis of migraine: from neurotransmitters to neuromodulators and beyond. Neurol Sci. 2010; 31 (Suppl 1):S1–7. [PubMed: 20464574]
30. Peres MF, Lerario DD, Garrido AB, Zukerman E. Primary headaches in obese patients. Arq Neuropsiquiatr. 2005; 63:931–3. [PubMed: 16400407]
31. Keith SW, Wang C, Fontaine KR, Cowan CD, Allison DB. BMI and headache among women: results from 11 epidemiologic datasets. Obesity (Silver Spring). 2008; 16:377–83. [PubMed: 18239647]
32. Mattsson P. Migraine headache and obesity in women aged 40–74 years: a population-based study. Cephalalgia. 2007; 27:877–80. [PubMed: 17635528]
33. Winter AC, Berger K, Buring JE, Kurth T. Body mass index, migraine, migraine frequency and migraine features in women. Cephalalgia. 2009; 29:269–78. [PubMed: 19143772]
34. Katsnelson MJ, Peterlin BL, Rosso AL, Alexander GM, Erwin KL. Self-reported vs measured body mass indices in migraineurs. Headache. 2009; 49:663–8. [PubMed: 19472442]
35. Lipton RB, Bigal ME. The epidemiology of migraine. Am J Med. 2005; 118 (Suppl 1):3S–10S. [PubMed: 15841882]
36. Zelissen PM, Koppeschaar HP, Lips CJ, Hackeng WH. Calcitonin gene-related peptide in human obesity. Peptides. 1991; 12:861–3. [PubMed: 1788147]
37. Karagiannides I, Pothoulakis C. Substance P, obesity, and gut inflammation. Curr Opin Endocrinol Diabetes Obes. 2009; 16:47–52. [PubMed: 19104238]
38. Ferroni P, Basili S, Falco A, Davi G. Inflammation, insulin resistance, and obesity. Curr Atheroscler Rep. 2004; 6:424–31. [PubMed: 15485587]
39. Perini F, D'Andrea G, Galloni E, Pignatelli F, Billo G, Alba S, Bussone G, Toso V. Plasma cytokine levels in migraineurs and controls. Headache. 2005; 45:926–31. [PubMed: 15985111]
40. Vanmolkot FH, de Hoon JN. Increased C-reactive protein in young adult patients with migraine. Cephalalgia. 2007; 27:843–6. [PubMed: 17668468]

41. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999; 282:2131–5. [PubMed: 10591334]
42. Bigal ME, Lipton RB, Holland PR, Goadsby PJ. Obesity, migraine, and chronic migraine: possible mechanisms of interaction. Neurology. 2007; 68:1851–61. [PubMed: 17515549]
43. Alstadhaug KB. Migraine and the hypothalamus. Cephalalgia. 2009; 29:809–17. [PubMed: 19604254]
44. Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs: effects on appetite expression and use for the treatment of obesity. Drugs. 2007; 67:27–55. [PubMed: 17209663]
45. Peterlin BL, Rapoport AM, Kurth T. Migraine and Obesity: Epidemiology, Mechanisms, and Implications. Headache. 2010; 50:631–648. [PubMed: 19845784]
46. Kotz CM, Wang C, Teske JA, Thorpe AJ, Novak CM, Kiwaki K, et al. Orexin A mediation of time spent moving in rats: neural mechanisms. Neuroscience. 2006; 142:29–36. [PubMed: 16809007]
47. Tsuneki H, Wada T, Sasaoka T. Role of orexin in the regulation of glucose homeostasis. Acta Physiol (Oxf). 2009
48. Matsuki T, Sakurai T. Orexins and orexin receptors: from molecules to integrative physiology. Results Probl Cell Differ. 2008; 46:27–55. [PubMed: 18204827]
49. Baranowska B, Wolinska-Witort E, Martynska L, Chmielowska M, Baranowska-Bik A. Plasma orexin A, orexin B, leptin, neuropeptide Y (NPY) and insulin in obese women. Neuro Endocrinol Lett. 2005; 26:293–6. [PubMed: 16135994]
50. Watson SL, Watson CJ, Baghdoyan HA, Lydic R. Thermal Nociception is Decreased by Hypocretin-1 and an Adenosine A(1) Receptor Agonist Microinjected into the Pontine Reticular Formation of Sprague Dawley Rat. J Pain. 2009
51. Holland PR, Akerman S, Goadsby PJ. Orexin 1 receptor activation attenuates neurogenic dural vasodilation in an animal model of trigeminovascular nociception. J Pharmacol Exp Ther. 2005; 315:1380–5. [PubMed: 16160082]
52. Dahmen N, Bierbrauer J, Kasten M. Increased prevalence of obesity in narcoleptic patients and relatives. Eur Arch Psychiatry Clin Neurosci. 2001; 251:85–9. [PubMed: 11407443]
53. Dahmen N, Kasten M, Wieczorek S, Gencik M, Epplen JT, Ullrich B. Increased frequency of migraine in narcoleptic patients: a confirmatory study. Cephalalgia. 2003; 23:14–9. [PubMed: 12534574]
54. Wurtman RJ. Narcolepsy and the hypocretins. Metabolism. 2006; 55:S36–9. [PubMed: 16979425]
55. Antoniades C, Antonopoulos AS, Tousoulis D, Stefanadis C. Adiponectin: from obesity to cardiovascular disease. Obes Rev. 2009; 10:269–79. [PubMed: 19389061]
56. Peterlin BL, Bigal ME, Tepper SJ, Urakaze M, Sheftell FD, Rapoport AM. Migraine and adiponectin: is there a connection? Cephalalgia. 2007; 27:435–46. [PubMed: 17448181]
57. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD, Diehl AM. Leptin regulates proinflammatory immune responses. FASEB J. 1998; 12:57–65. [PubMed: 9438411]
58. Maeda T, Kiguchi N, Kobayashi Y, Ikuta T, Ozaki M, Kishioka S. Leptin derived from adipocytes in injured peripheral nerves facilitates development of neuropathic pain via macrophage stimulation. Proc Natl Acad Sci U S A. 2009; 106:13076–81. [PubMed: 19620723]
59. Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul. 2009; 43:157–68. [PubMed: 19908934]
60. Guldiken B, Guldiken S, Demir M, Turgut N, Tugrul A. Low leptin levels in migraine: a case control study. Headache. 2008; 48:1103–7. [PubMed: 18547265]
61. Lambert GW, Straznicky NE, Lambert EA, Dixon JB, Schlaich MP. Sympathetic nervous activation in obesity and the metabolic syndrome-Causes, consequences and therapeutic implications. Pharmacol Ther. 2010
62. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache. 2004; 44:53–64. [PubMed: 14979884]
63. De Benedittis G, Lorenzetti A, Pieri A. The role of stressful life events in the onset of chronic primary headache. Pain. 1990; 40:65–75. [PubMed: 2339018]

64. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia. 1992; 12:221–8. discussion 186. [PubMed: 1525797]
65. Houle T, Nash JM. Stress and headache chronification. Headache. 2008; 48:40–4. [PubMed: 18184284]
66. Sauro KM, Becker WJ. The stress and migraine interaction. Headache. 2009; 49:1378–86. [PubMed: 19619238]
67. Nash JM, Thebarge RW. Understanding psychological stress, its biological processes, and impact on primary headache. Headache. 2006; 46:1377–86. [PubMed: 17040334]
68. Elfhag K, Rossner S. Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. Obes Rev. 2005; 6:67–85. [PubMed: 15655039]
69. Block JP, He Y, Zaslavsky AM, Ding L, Ayanian JZ. Psychosocial stress and change in weight among US adults. Am J Epidemiol. 2009; 170:181–92. [PubMed: 19465744]
70. Pyykkonen AJ, Raikkonen K, Tuomi T, Eriksson JG, Groop L, Isomaa B. Stressful life events and the metabolic syndrome: the prevalence, prediction and prevention of diabetes (PPP)-Botnia Study. Diabetes Care. 2010; 33:378–84. [PubMed: 19880581]
71. Bose M, Olivan B, Laferrere B. Stress and obesity: the role of the hypothalamic-pituitary-adrenal axis in metabolic disease. Curr Opin Endocrinol Diabetes Obes. 2009; 16:340–6. [PubMed: 19584720]
72. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. Nutrition. 2007; 23:887–94. [PubMed: 17869482]
73. Tietjen GE, Peterlin BL, Brandes JL, Hafeez F, Hutchinson S, Martin VT, et al. Depression and anxiety: effect on the migraine-obesity relationship. Headache. 2007; 47:866–75. [PubMed: 17578537]
74. Odegard SS, Engstrom M, Sand T, Stovner LJ, Zwart JA, Hagen K. Associations between sleep disturbance and primary headaches: the third Nord-Trondelag Health Study. J Headache Pain. 2010
75. Fukui PT, Goncalves TR, Strabelli CG, Lucchino NM, Matos FC, Santos JP, et al. Trigger factors in migraine patients. Arq Neuropsiquiatr. 2008; 66:494–9. [PubMed: 18813707]
76. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. Headache. 2005; 45:904–10. [PubMed: 15985108]
77. Nielsen LS, Danielsen KV, Sorensen TI. Short sleep duration as a possible cause of obesity: critical analysis of the epidemiological evidence. Obes Rev. 2010
78. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. Pain. 2003; 106:81–9. [PubMed: 14581114]
79. Molarius A, Tegelberg A, Ohrvik J. Socio-economic factors, lifestyle, and headache disorders-a population-based study in Sweden. Headache. 2008; 48:1426–37. [PubMed: 18624712]
80. Niemeier HM, Raynor HA, Lloyd-Richardson EE, Rogers ML, Wing RR. Fast food consumption and breakfast skipping: predictors of weight gain from adolescence to adulthood in a nationally representative sample. J Adolesc Health. 2006; 39:842–9. [PubMed: 17116514]
81. Marin-Guerrero AC, Gutierrez-Fisac JL, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. Eating behaviours and obesity in the adult population of Spain. Br J Nutr. 2008; 100:1142–8. [PubMed: 18377684]
82. Nazari F, Safavi M, Mahmudi M. Migraine and Its Relation with Lifestyle in Women. Pain Pract. 2010
83. Farshchi HR, Taylor MA, Macdonald IA. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. Am J Clin Nutr. 2005; 81:16–24. [PubMed: 15640455]
84. Astrup A, Ryan L, Grunwald GK, Storgaard M, Saris W, Melanson E, Hill JO. The role of dietary fat in body fatness: evidence from a preliminary meta-analysis of ad libitum low-fat dietary intervention studies. Br J Nutr. 2000; 83 (Suppl 1):S25–32. [PubMed: 10889789]
85. Bic Z, Blix GG, Hopp HP, Leslie FM, Schell MJ. The influence of a low-fat diet on incidence and severity of migraine headaches. J Womens Health Gend Based Med. 1999; 8:623–30. [PubMed: 10839648]

86. Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. Neurology. 2005; 64:614–20. [PubMed: 15728281]
87. Bond DS, Jakicic JM, Vithiananthan S, Thomas JG, Leahey TM, Sax HC, Pohl D, Roye GD, Ryder BA, Wing RR. Objective quantification of physical activity in bariatric surgery candidates and normal-weight controls. Surg Obes Relat Dis. 2010; 6:72–8. [PubMed: 19837009]
88. Queiroz LP, Peres MF, Piovesan EJ, Kowacs F, Ciciarelli MC, Souza JA, et al. A nationwide population-based study of migraine in Brazil. Cephalalgia. 2009; 29:642–9. [PubMed: 19187337]
89. Varkey E, Hagen K, Zwart JA, Linde M. Physical activity and headache: results from the Nord-Trondelag Health Study (HUNT). Cephalalgia. 2008; 28:1292–7. [PubMed: 18771495]
90. Bronsky J, Nedvidkova J, Zamrazilova H, Pechova M, Chada M, Kotaska K, Nevoral J, Prusa R. Dynamic changes of orexin A and leptin in obese children during body weight reduction. Physiol Res. 2007; 56:89–96. [PubMed: 16497092]
91. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Guigliano D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA. 2003; 289:1799–804. [PubMed: 12684358]
92. Williams KV, Mullen M, Lang W, Considine RV, Wing RR. Weight loss and leptin changes in individuals with type 2 diabetes. Obes Res. 1999; 7:155–63. [PubMed: 10102252]
93. Forsythe LK, Wallace JM, Livingstone MB. Obesity and inflammation: the effects of weight loss. Nutr Res Rev. 2008; 21:117–33. [PubMed: 19087366]
94. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a systematic review. Arch Intern Med. 2007; 167:31–9. [PubMed: 17210875]
95. Straznicky NE, Lambert EA, Nestel PJ, McGrane MT, Dawood T, Schlaich MP, Masuo K, Eikelis N, de Courten B, Mariani JA, Esler MD, Socratous F, Chopra R, Sari CI, Paul E, Lambert GW. Sympathetic neural adaptation to hypocaloric diet with or without exercise training in obese metabolic syndrome subjects. Diabetes. 2010; 59:71–9. [PubMed: 19833893]
96. Williamson DA, Rejeski J, Lang W, Van Dorsten B, Fabricatore AN, Toledo K. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. Arch Intern Med. 2009; 169:163–71. [PubMed: 19171813]
97. Westenhoefer J, von Falck B, Stellfeldt A, Fintelmann S. Behavioural correlates of successful weight reduction over 3 y. Results from the Lean Habits Study. Int J Obes Relat Metab Disord. 2004; 28:334–5. [PubMed: 14647175]
98. Chaput JP, Drapeau V, Hetherington M, Lemieux S, Provencher V, Tremblay A. Psychobiological impact of a progressive weight loss program in obese men. Physiol Behav. 2005; 86:224–32. [PubMed: 16112692]
99. Calhoun AH, Ford S. Behavioral sleep modification may revert transformed migraine to episodic migraine. Headache. 2007; 47:1178–83. [PubMed: 17883522]
100. Raynor HA, Jeffery RW, Tate DF, Wing RR. Relationship between changes in food group variety, dietary intake, and weight during obesity treatment. Int J Obes Relat Metab Disord. 2004; 28:813–20. [PubMed: 15037882]
101. Wadden TA, West DS, Neiberg RH, Wing RR, Ryan DH, Johnson KC, Foreyt JP, Hill JO, Trence DL, Vitolins MZ. One-year weight losses in the Look AHEAD study: factors associated with success. Obesity (Silver Spring). 2009; 17:713–22. [PubMed: 19180071]
102. Narin SO, Pinar L, Erbas D, Ozturk V, Idiman F. The effects of exercise and exercise-related changes in blood nitric oxide level on migraine headache. Clin Rehabil. 2003; 17:624–30. [PubMed: 12971707]
103. The Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007; 30:1374–83. [PubMed: 17363746]
104. Guldiken B, Guldiken S, Taskiran B, Koc G, Turgut N, Kabayel L, et al. Migraine in metabolic syndrome. Neurologist. 2009; 15:55–8. [PubMed: 19276782]
105. Albu JB, Heilbronn LK, Kelley DE, Smith SR, Azuma K, Berk ES, Pi-Sunyer FX, Ravussin E. Metabolic changes following a 1-year diet and exercise intervention in patients with type 2 diabetes. Diabetes. 2010; 59:627–33. [PubMed: 20028945]

106. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, Wadden TA, Kelley D, Wing RR, Pi-Sunyer FX, Reboussin D, Kuna ST. Sleep AHEAD research group. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med. 2009; 169:1619–26. [PubMed: 19786682]

107. Sugerman HJ, Felton WL 3rd, Sismanis A, Kellum JM, DeMaria EJ, Sugerman EL. Gastric surgery for pseudotumor cerebri associated with severe obesity. Ann Surg. 1999; 229:634–40. discussion 40–2. [PubMed: 10235521]

108. Hershey AD, Powers SW, Nelson TD, Kabbouche MA, Winner P, Yonker M, Linder SL, Bicknese A, Sowel MK, McClintock W. Obesity in the pediatric headache population: a multicenter study. Headache. 2009; 49:170–7. [PubMed: 18783447]

109. Levy RL, Finch EA, Crowell MD, Talley NJ, Jeffery RW. Behavioral intervention for the treatment of obesity: strategies and effectiveness data. Am J Gastroenterol. 2007; 102:2314–21. [PubMed: 17561967]

110. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393–403. [PubMed: 11832527]

Table 1

Migraine and Obesity: Findings from Population-Based Studies

Ref	Sample Characteristics			Migraine Prevalence by Weight (BMI) Category		Migraine and Obesity Findings	
	N	Age M and/ or range	Female (%)	Category	(%)	Prevalence	Frequency and Severity
Bigal et al.[15]	30,215	38.7 (18–89)	65	Underweight (<18.5) Normal weight (18.5–24.9) Overweight (25.0–25.9) Obese (30.0–34.9) Morbidly obese (≥ 35.0)	15.8 13.2 11.2 11.8 14.0	• Migraine prevalence was not related to obesity	• Migraineurs who were overweight(OR = 1.3), obese (OR = 2.9) and morbidly obese (OR = 5.7) were at increased risk for having high headache frequency (10–15 headache d/mos.) compared to those who were normal-weight. • Migraineurs who were overweight (1.25), obese (1.31), and morbidly obese (1.9) were at increased risk for having severe headaches compared to those who were normal-weight.
Bigal et al.[16]	162,576	≥ 12	NA	NA	NA	NA	• Migraineurs who were obese (1.3) and morbidly obese (1.7) were at increased risk for experiencing frequent migraine headaches (10–15 headache d/mos.) compared to those who were normal weight.
Ford et al.[17]	7,601	≥ 20	48	Underweight (<18.) Normal weight (18.5–24.9) Overweight (25.0–25.9) Obese (30.0–34.9)	34.0 18.9 20.7 25.9	• Participants who were underweight (OR = 2.1) and obese (OR = 1.4) were at increased risk for having severe headaches or migraine compared with normal-weight participants.	NA
Keith et al.[31]	220,370	16–94	100	NA	NA	• Migraine prevalence was not related to obesity.	NA
Mattson et al.[32]	684	54 (40–74)	100	Non-obese (< 30) Obese (≥ 30)	19.9 16.9	• Migraine prevalence was not related to obesity.	• Migraine frequency and severity was not related to obesity.
Peterlin et al.[18]	21,783	≥ 20	51	≤ 55 years old Non-obese (< 30) Obese (≥ 30) > 55 years old Non-obese (< 30) Obese (≥ 30)	22.9 28.4 NA NA	• In men and women 55 years of age, total obesity (based on BMI) and abdominal obesity (based on waist circumference) were	NA

Ref	Sample Characteristics			Migraine Prevalence by Weight (BMI) Category		Migraine and Obesity Findings	
	N	Age M and/ or range	Female (%)	Category	(%)	Prevalence	Frequency and Severity
						associated with higher migraine prevalence. In women > 55 years of age, abdominal obesity was associated with lower prevalence of migraine.	
Winter et al.[33]	63,467	54 (≥ 45)	100	Under/normal-weight (<23.0) Normal weight (23.0–24.9) Overweight I (25.0–26.9) Overweight II (27.0–29.9) Obese (30.0–34.9) Severely obese (≥ 35.0)	13.8 14.4 15.2 14.3 14.5 16.4	• Obesity was not associated with active migraine or prior history of migraine.	• Migraineurs who were under/ normal-weight (2.1) and severely obese (3.1) were at increased risk for having daily migraine compared to those with the lowest associated risk (overweight II, migraine frequency < 6/yr)