Obesity is a risk factor for transformed migraine but not chronic tension-type headache

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Neurology 2006;67;252
DOI 10.1212/01.wnl.0000225052.35019.f9

HIGH LIGHT

Obesity is a risk factor for transformed migraine but not chronic tension-type headache

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Abstract—*Objective:* To assess the influence of the body mass index (BMI) on the prevalence and severity of chronic daily headache (CDH) and its most frequent subtypes, transformed migraine (TM) and chronic tension-type headache (CTTH). *Methods:* The authors gathered information on headache, medical features, height, and weight using a computer-assisted telephone interview. Participants were divided into five categories, based on BMI: underweight (<18.5), normal weight (18.5 to 24.9), overweight (25 to 29.9), obese (30 to 34.9), and morbidly obese (>35). The prevalence and severity of CDH, TM, and CTTH were assessed. Multivariate analyses modeling these diagnoses as a function of BMI were conducted. *Results:* Among 30,215 participants, the prevalence of CDH was 4.1%; 1.3% had TM and 2.8% CTTH. In contrast with the normal weight group (3.9%), the prevalence of CDH was higher in obese (5.0% [odds ratio (OR) = 1.3, 95% CI = 1.1–1.6]) and morbidly obese (6.8% [OR = 1.8, 95% CI = 1.4 to 2.2]). BMI had a strong influence on the prevalence of TM, which ranged from 0.9% of the normal weighted to 1.2% of the overweight (OR = 1.4 [1.1 to 1.8]), 1.6% of the obese (OR = 1.7 [1.2 to 2.43]), and 2.5% of the morbidly obese (OR = 2.2 [1.5 to 3.2]). The effects of the BMI on the prevalence of CTTH were just significant in the morbidly obese group. Adjusted analyses showed that obesity was associated with CDH and TM but not CTTH. *Conclusions:* Chronic daily headache and obesity are associated. Obesity is a stronger risk factor for transformed migraine than for chronic tension-type headache.

NEUROLOGY 2006;67:252–257

In 2000, the National Health and Nutrition Examination Survey indicated that 64% of the adults in the United States had a body mass index (BMI) of 25 or more and were therefore overweight or obese.[1] In 2002, the prevalence of obesity had increased by 16% compared with the period of 1988 to 1994.[1]

Obesity is a risk factor for chronic daily headaches (CDHs),[2,3] headaches occurring 15 or more days per month.[4] The primary CDHs (no underlying cause can be identified) are subdivided in CDH of long duration (>4 hours per day) or short duration.[4] The CDHs of long duration (referred herein as CDH) affect up to 4% of the adults in the United States.[2] The two most frequent subtypes of CDH are transformed migraine (TM) and chronic tension-type headache (CTTH).[2,5] TM develops in migraineurs whose attacks increase in frequency, whereas CTTH evolves from episodic tension-type headache.[6]

A longitudinal population study identified that among individuals with episodic headache, obesity was associated with a fivefold increased annual incidence of new-onset CDH.[3] A large population study also suggested that obesity is associated with the frequency and severity of migraine attacks, although it does not appear to be a risk factor for migraine itself.[7]

To further investigate the relationship of obesity to CDH, we conducted a large population study. We hypothesized that, being a risk factor for migraine frequency and severity, obesity is a stronger risk factor for TM than for CTTH. We also investigated the influence of the BMI on the severity, disability, and clinical features of CDH and its subtypes.

Methods. *Population sample and computer-assisted telephone interview.* This study was conducted in three large metropolitan areas in the United States, from 1997 to 2000. Households were selected using random digit dialing methods, and no less than 10 attempts were made to contact each household. At the time of initial telephone contact, a census of the household was obtained from the person who answered the phone. All age-eligible individuals (>18 years) from the household who agreed to participate were interviewed. Oral informed consent (institutional review board approved) was obtained, and the purpose of the survey was described to the respondents, who were subsequently scheduled for an interview with trained interviewers, using a validated computer-assisted telephone interview (CATI).[8]

In the CATI, participants were first asked if they had at least one headache not due to a head injury, hangover, pregnancy, or an illness such as a cold or flu. They were subsequently asked if they had at least five headaches in the previous year. For those who

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Disclosure: Data collection was conducted without financial support. Data analyses were supported by an unrestricted grant from Ortho-McNeil Neurologics (OMP). M.E.B. and R.B.L. have received prior research support from OMP in excess of $10,000. M.E.B. and R.B.L. have received honoraria in excess of $10,000 from education activities supported by OMP. M.E.B. and R.B.L. are on the migraine advisory board of OMP.

Received December 12, 2005. Accepted in final form March 29, 2006.

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responded positively, they were asked about how many different types of headache they had. Questions were first asked about the most severe self-defined headache type that the respondent had in the last 12 months. If respondents had a second and different self-defined headache, the same questions were also asked about this headache.

The survey also assessed demographic information (age, gender, race, educational level, marital status) and health status (history of several other medical conditions). Respondents were requested to provide their weight and height at the time of the interview. Headache severity and headache-related disability were assessed in a 10-point scale (from no severe/disabling at all to as severe/disabling as it could be). Finally, the questionnaire assessed the amount of over-the-counter, prescribed analgesic medication for headache and prescribed analgesic medication used for other pain conditions used in the prior month and prior 3 months.

Headache status. The following groups were defined based on the headache status: Group 1: Persons with CDH had an average of 15 or more headache days per month, with an average duration of more than 4 hours per day. The classification of CDH is controversial. The most accepted criteria for CDH (Silberstein and Lipton [S-L] criteria) divide it in four groups: TM, CTTH, new daily persistent headache (NDPH), and hemicrania continua (HC).[4] The second edition of the International Classification of Headache Disorders (ICHD-2) defines a disorder analogous to TM, chronic migraine (CM), and presents criteria for the other CDH.[9] Studies show that the criteria for CM are problematic and that the TM definition should be used instead.[10] It is important to emphasize that all subjects with CM also fill criteria for TM.

Our algorithm does not allow the diagnosis of NDPH and HC, but these are rare. Consistently, we subdivided the persons with CDH into those with migraine attacks (herein called TM) and without migraine attacks (CTTH). It is important to emphasize that although CTTH was defined exactly as proposed by the ICHD-2, TM was not defined strictly as proposed by the S-L criteria, owing to limitations in our dataset. Herein we define TM as CDHs associated with at least 12 migraine attacks in the prior year. All of these subjects fill criteria for TM according to the S-L criteria, but not all subjects with TM according to the S-L criteria would be captured by this definition.

Group 2: Controls had no headaches or had fewer than 108 headaches per year and did not fill criteria for migraine. Migraineurs were taken into account for prevalence calculation but were excluded from the control group for comparisons with the CDH group.

Severity and disability. Severity of pain was abstracted from a 10-point pain scale. It was defined as mild in those whose usual pain intensity ranged from 1 to 3. It was moderate in those with usual headache pain ranging from 4 to 7 and severe in those with usual pain ranging from 8 to 10.

Questions on disability assessed how many days, over a 3-month period, the subject missed work or school activities because of their headache.

Analysis. Analyses were performed using Stata (Intercooled Stata 6.0 for Windows, College Station, TX). Data were summarized using frequency counts and descriptive statistics. BMI was calculated according to the following formula: BMI = (weight [lbs]/height^2 [in]) * 703. We defined five categories based on BMI: underweight (<18.5), normal weight (18.5 to 24.9), overweight (25 to 29.9), obese (30 to 34.9), and morbidly obese (>35). The χ^2 test was used to compare proportions. We modeled headache features (frequency of headache, duration of headache, headache-related disability, presence and severity of associated symptoms) as dependent variables, using BMI, use of acute or preventive medication, age, race, socioeconomic status, as dependent variables. Based on the 10-point pain intensity scale, headaches were defined as mild (scored from 1 to 3), moderate (scored from 4 to 7), or severe (scored from 8 to 10). Mild, moderate, or severe disability was defined using similar cut-scores in a 10-point disability scale.

Multivariate logistic regression was used to estimate the odds ratio (OR) for each explanatory variable. Continuous independent variables were evaluated for nonlinearity using squared and higher-order terms. Backwards stepwise maximum-likelihood estimation was used to arrive at a parsimonious model.

Finally, to estimate the differential effects of obesity on CDH and its subtypes, we conducted independent adjusted multivariate models, modeling CDH, TM, and CTTH, as dichotomous variables. The dichotomous variables were defined as follow: 1) CDH vs non-CDH status; 2) TM vs no CDH (no TM and no CTTH) status; 3) CTTH vs no CDH (no TM and no CTTH) status.

Variates in the multivariate models included obesity status (BMI >30 was defined as obesity), use of acute or preventive medication, age, race, socioeconomic status, and other pain syndromes. The goodness of fit of the model was assessed by the –2 log likelihood and the Nagelkerke R^2 term.

Results. Complete CATI headache history, weight, and height were obtained from 30,849 subjects (table 1). Respondents were predominantly women (61.8%) and Caucasian (64.8%). Age ranged from 18 to 89 years (mean = 38.7 years). The majority had completed high school. Most (50.9%) had a normal BMI; 31.1% were overweight, 10.4% were obese, and 4.5% were morbidly obese. A small proportion of the subjects (3.1%) were underweight (table 1).

Crude prevalence of CDH by demographic factors. CDH was diagnosed in 1,243 individuals, yielding a 1-year period prevalence of 4.1%. Table 1 shows the prevalence of CDH according to the demographic features. The crude prevalence of CDH was higher in women than in men (5.0 vs 2.1%, OR = 1.7, 95% CI = 1.5 to 2.0). The prevalence was not significantly different in Caucasians (4.1%) and African American (3.7%). CDH prevalence increased with age (3.2% in those ages 18 to 29 and 4.6% in those age 60 or older) and showed an inverse relationship with level of education (from 8.5% in those with less than 12 years of education to 1.6% in those who graduated from college) (table 1).

Effects of BMI on TM and CTTH. Compared with the normal weight group (3.9%), the prevalence of CDH was significantly higher in obese (5.0% [OR = 1.3, 95% CI = 1.1 to 1.6]) and morbidly obese (6.8% [OR = 1.8, 95% CI = 1.4 to 2.2]) subjects. Underweight (4.0%) and overweight (3.8%) subjects were not significantly different from the normal-weighted group (figure 1).

The prevalence of TM was 1.3%. BMI had a strong influence on the prevalence of TM. The prevalence of TM in the normal weighted was 0.9% and increased to 1.2% of the overweight (OR = 1.4 [1.1 to 1.8]), 1.6% of the obese (OR = 1.7 [1.2 to 2.43]), and 2.5% of the morbidly obese (OR = 2.2 [1.5 to 3.2]). Normal weighted and underweighted did not significantly differ (figure 2).

CTTH had a prevalence of 2.8%. The effects of the BMI on the prevalence of CTTH were far less robust (figure 3). Compared with the normal-weighted group (prevalence of 3%), the prevalence of CTTH was not significantly different in those underweight (2.9%), overweight (2.6%), and obese (3.3%). The prevalence was significantly higher in morbidly obese (4.3% [OR = 1.4, 95% CI 1.1 to 1.9]).

Effects of BMI on headache frequency and attack-related disability. Among those with CDH, we assessed the proportion of subjects with virtually daily headaches (360 to 365 days per year) as a function of the BMI (figure 4). Compared with the normal weight group (36% had daily headaches), a significantly higher proportion of obese (48.7% [OR = 1.5, 95% CI 1.1 to 2.1]) and morbidly obese (51% [OR = 1.7, 95% CI 1.1 to 2.6]) subjects had daily headaches. The proportion of underweight and overweight subjects was not statistically different from that in the normal weight group.

The proportion of subjects that reporting having missed at least 3 days of activity due to headache in the last 3

Table 1 *Prevalence of chronic daily headaches according to demographic features and body mass index*

	Chronic daily headache		Total sample	Prevalence of chronic daily headache, %		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
	n	%	n	%			
Sex							
Male	232	18.7	10,828	35	2.1	1	1
Female	1,011	81.3	20,021	65	5.0	2.1 (1.5–2.7)	1.9 (1.6–2.3)
Age, y							
18–29	214	17.2	6,787	22	3.2	1	1
30–39	294	23.6	7,404	24	4.0	1.2 (1.06–1.5)	1.3 (1.1–1.7)
40–49	357	28.7	8,330	27	4.3	1.4 (1.2–1.6)	1.4 (1.2–1.6)
50–59	236	18.9	5,245	17	4.5	1.4 (1.2–1.7)	1.6 (1.1–1.9)
60+	141	11.3	3,085	10	4.6	1.5 (1.2–1.8)	1.6 (1.3–2.0)
Race							
Caucasian	832	67.5	20,262	65.7	4.1	1	1
African American	332	26.9	8,989	29.1	3.7	0.9 (0.8–1.0)	1.0 (0.8–1.2)
Other	43	3.5	700	2.3	6.1	1.5 (1.1–2.1)	1.6 (1.1–2.1)
Not stated/missing	25	2.1	900	2.9	2.8	0.6 (0.4–1.0)	0.6 (0.4–1.0)
Highest education level							
<12th grade	153	8.3	1,800	5.8	8.5	1	1
High school	357	28.9	8,308	26.9	4.3	0.6 (0.5–0.7)	0.7 (0.3–0.9)
Some college/2 y	345	28.0	7,952	25.7	4.3	0.6 (0.4–0.8)	0.6 (0.4–0.8)
College/4 y	296	24.0	8,010	25.9	3.7	0.5 (0.3–0.75)	0.6 (0.4–0.8)
Graduate school	70	5.7	4,500	14.6	1.6	0.2 (0.1–0.4)	0.3 (0.2–0.4)
Not stated/missing	61	4.9	280	0.9	21.8	4.0 (2.4–6.7)	3.9 (1.2–8.0)
Body mass index							
Underweight (<18.5)	38	3.0	941	3.1	4.0	1.04 (0.7–1.4)	1 (0.5–1.8)
Normal weight (18.5–24.9)	603	48.5	15,501	51.3	3.9	1	1
Overweight (25–29.9)	352	28.3	9,258	30.6	3.8	0.97 (0.85–1.1)	1 (0.9–1.1)
Obese (30–34.9)	156	12.5	3,133	10.4	5.0	1.3 (1.1–1.6)	1.5 (1.2–1.8)
Morbidly obese (>35)	94	7.6	1,382	4.6	6.8	1.8 (1.4–2.2)	2.0 (1.4–2.4)

* Adjusted by use of acute or preventive medication, age, race, socioeconomic status, and depression.

months was significantly higher in overweight, obese, and morbidly obese compared with the normal weight group (table 2).

Finally, we assessed the proportion of subjects reporting severe pain in more than 50% of their attacks (table 2); a significantly higher proportion of CDH subjects who were overweight, obese, and morbidly obese had it compared with the normal weight group, which was not significantly differ from the underweight group.

Adjusted and multivariate analyses. After adjusting by use of acute or preventive medication, age, race, socioeconomic status, and marital status, we found that compared with normal weighted persons with headache, CDH was more prevalent in obese individuals (OR = 1.5, 95% CI 1.2 to 1.8) and morbidly obese (OR = 2.0, 95% CI = 1.4 to 2.4) (table 1) and that underweight and overweight individuals were not statistically different from those with normal weight.

In independent logistic regression models, we further

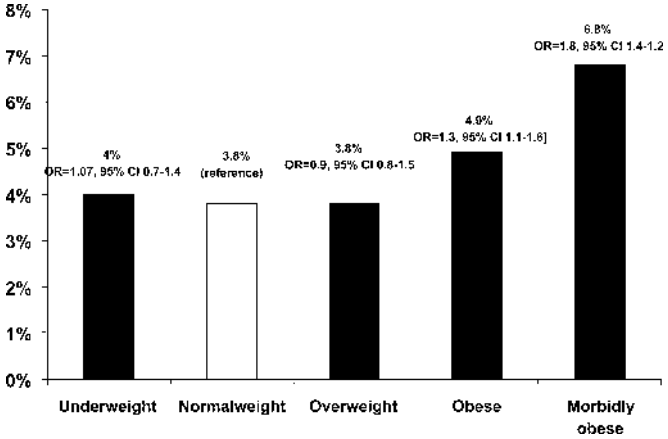

Figure 1. Prevalence of chronic daily headache according to the body mass index.

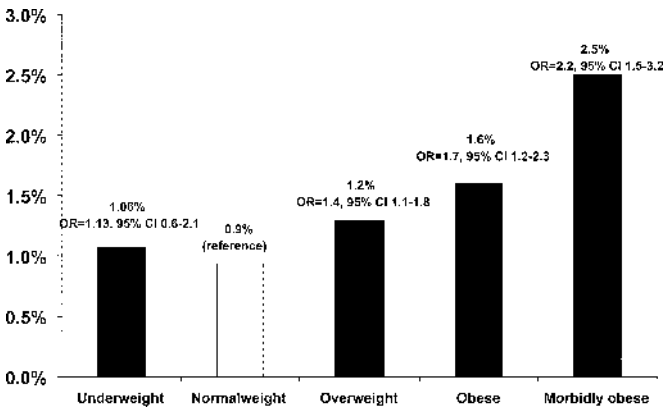

Figure 2. Prevalence of transformed migraine according to the body mass index.

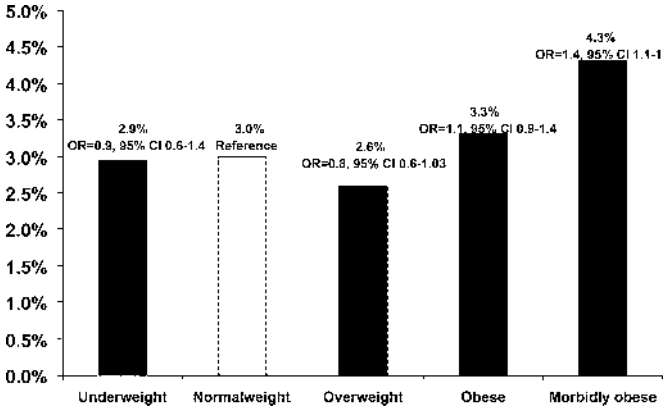

Figure 3. Prevalence of chronic tension-type headache according to the body mass index.

assessed the relationship of the obesity status to a diagnosis of CDH, TM, and CTTH, after adjusting for covariates (gender, age, race, use of headache medications, sleep problems, education status, and depression). Obesity, CDH, TM, and CTTH were independently modeled as dichotomous variables. BMI was associated with a diagnosis of CDH ($p < 0.001$) and a diagnosis of TM ($p < 0.001$), but not with a diagnosis of CTTH.

Among those with CDH, the proportion of subjects with daily headaches ($p < 0.001$), proportion of subjects with severe headaches ($p < 0.01$), and proportion of subjects who missed at least 3 days of activity due to the headaches ($p < 0.01$) were associated with BMI. Similar significant associations were seen for TM. Obesity was associated with the proportion of those with CTTH with daily headaches but not with the proportion of attacks or number of missed days due to the headache.

Discussion. Obesity is associated with CDH in our large population sample. The association is stronger for TM than for CTTH. Obesity is also associated with the frequency of attacks (daily headaches) as well as proportion of subjects with severe pain and frequent disability among those with CDH and TM. Furthermore, CDH prevalence increases with increasing BMI category from normal to overweight, obese, and morbidly obese.

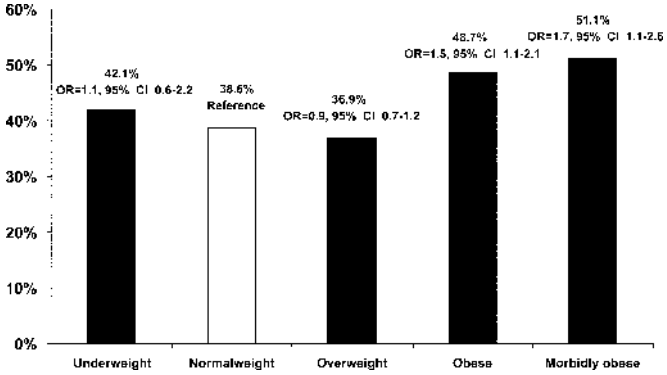

Figure 4. Proportion of subjects with chronic daily headache and headaches every day, according to the body mass index.

Table 2 *Severity and disability of severe headaches in subjects with chronic daily headaches, according to the body mass index*

	n	%*	Odds ratio (95% CI)
Severe headaches			
Underweight	16	42.1	0.9 (0.4–1.8)
Normal	269	44.6	1
Overweight	186	52.8	1.4 (1.1–1.8)
Obese	78	56.4	1.6 (1.2–2.2)
Morbidly obese	55	58.5	1.9 (1.1–2.7)
Attack-related disability in >3 d over 3-mo period			
Underweight	16	42.1	1.2 (0.6–2.3)
Normal	229	38.0	1
Overweight	176	50.0	1.6 (1.3–2.1)
Obese	89	57.1	2.2 (1.5–3.1)
Morbidly obese	57	60.6	2.5 (1.6–3.9)

These associations remain significant after adjusting for other factors.

These findings are compatible with prior results in headache studies. In a study of patients with episodic migraine from this sample, obesity was a risk factor for very frequent headaches (10 to 14 days per month) after adjusting for covariates. BMI was also significantly associated with pain intensity, disability, and exacerbation by physical activity.[7] Finally, in a longitudinal study, obesity was a risk factor for new-onset CDH.[3]

Whereas BMI category had a consistent and increasing relationship with TM prevalence, the relationship between obesity and CTTH is less clear in our data. It is not known if obesity is associated with the frequency and severity of episodic tension-type headache. In the current study, BMI category was not associated with CTTH, with the exception of the morbidly obese group.

Our episodic migraine and CDH studies generate consistent results. Obesity is associated with increased frequency and severity of attacks in patients with episodic migraine.[6] Presumably our findings in episodic migraine reflect a pre-CDH phase. In the current study, BMI category is a risk factor for CDH, reflecting a later stage in the process of chronification. Obese subjects with CDH have more frequent attacks than normal-weighted subjects with CDH.

The interrelationships of headache frequency and obesity are complex and may just be speculated about. Attack frequency, per se, is a risk factor for chronification.[3] Furthermore, frequency and severity of attacks appear to be associated with the risk of trigeminal allodynia, which, in turn, is caused by neuronal sensitization at the level of the trigeminal caudalis.[11,12] Once sensitization develops, response to specific migraine therapy seems to be reduced and the likelihood of attack recurrence increases.[11] In addition, obesity is itself a pro-inflammatory state, as discussed be-

low.[13,14] Obese persons with migraine may have more frequent and severe attacks and may be more likely to develop central sensitization. This would explain why obesity is comorbid with TM and not with migraine.

Obesity may influence headache through several mechanisms. First, obesity is recognized as pro-inflammatory and pro-thrombotic state. Adipocytes secrete a variety of cytokines, including interleukin-6 and tumor necrosis factor-α. Markers of inflammation, including leukocyte count, tumor necrosis factor-α, interleukin-6, and C-reactive protein, are also increased in obesity.[15] Moreover, obesity is associated with an increase in adipose tissue macrophages, which also participate in the inflammatory process through the elaboration of cytokines.[16] This may be particularly important for migraine, which is associated with neurovascular inflammation[17-19] and provides a background that helps to explain the relationship between obesity and TM, the result of migraine progression.

Additionally, plasma calcitonin gene-related peptide (CGRP) levels are elevated in obese individuals, particularly in women, and fat intake may be associated with increased CGRP secretion.[20] After weight loss, CGRP concentrations remain unchanged. Perhaps elevated plasma CGRP levels may constitute a primary phenomenon in obese women and fat intake may be associated with increased CGRP secretion.[20] This may be of importance in migraine, where it is well known that CGRP is an important postsynaptic mediator of the migraine trigeminovascular inflammation,[21] and experimental CGRP inhibitors are effective in the acute treatment of migraine.[22]

Finally, recent data suggest that hypothalamic neuropeptides orexin A and orexin B play a role in nociception, and stimulate the prejunctional release of CGRP from trigeminal neurons.[23,24] It is also demonstrated that orexin A is important in the regulation of energy metabolism in humans and that in obesity the activity of these peptides is disturbed.[25] It may be speculated that the dysmodulation in the orexin pathways may be associated with increased susceptibility to neurogenic inflammation and consequent migraine attacks.

Some cautions are required in assessing our results. Women are overrepresented, probably because interviews were conducted during business hours most of the time. We addressed this issue by stratifying by gender and modeling the data including demographic features. Our results are similar for males and females and cannot be accounted for by selection bias. Second, there may be some misclassification of headache type because patients did not receive in-person neurologic examination. Accordingly, we may have occasionally missed idiopathic intracranial hypertension, a secondary cause of CDH, and this may have happened more frequently in those obese. Given the long duration of CDH and the low frequency of secondary disorders in the population, this effect is likely to be modest. Third, although we modeled our data adjusting for covariates, several potential confounders were not measured. Examples include specific food triggers (obese subjects may be exposed to them more often), exercises (which may have a protective effect), and sleep apnea. Finally and most important, BMI was calculated based on weight and height that were self-reported. Recent research has investigated this particular issue. Differences between self-reported (over the phone) and measured stature, weight, and BMI were investigated for a sample of 3,797 adolescents. It was concluded that, at least for adolescents, self-reports of stature, weight, and BMI are on the average valid representations of their measured counterparts.[26] In adults, the National Health Interview Survey interviewed 68,556 adults, and calculated their BMI using CATI assessments of weight and height that were identical to ours, generating data adopted by health policy makers.[27] CATI with self-reported weight has also been used to assess comorbidity between obesity and other health problems.[28] Nonetheless, it is reasonable to suppose that obese individuals would tend to underestimate their reported weight, creating a bias difficult to assess in our results.

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Neurology 2006;67;252
DOI 10.1212/01.wnl.0000225052.35019.f9