Profiles of Obesity, Weight Gain, and Quality of Life in Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

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• PURPOSE: Obesity and weight gain are known risk factors for idiopathic intracranial hypertension (IIH; or pseudotumor cerebri). The authors examined profiles of body mass index (BMI) and patterns of weight gain associated with IIH. They also examined vision-specific health-related quality of life (HRQOL) in newly diagnosed IIH patients and explored the relative contribution of obesity and weight gain to overall HRQOL in this disorder.

• DESIGN: Matched case-control study.

• METHODS: Female patients with newly diagnosed IIH (n = 34) and other neuro-ophthalmologic disorders (n = 41) were enrolled in a case-control study to assess patterns of self-reported weight gain. The HRQOL was examined using the 25-Item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) and the SF-36 Health Survey (Physical Components Summary and Mental Components Summary [MCS]).

• RESULTS: Higher BMIs were associated with greater risk of IIH (P = .003, logistic regression analysis adjusting for case–control matching), as were higher percentages of weight gain during the year before symptom onset (P = .004). Moderate weight gain (5% to 15%) was associated with a greater risk of IIH among both obese and nonobese patients. Obesity and weight gain influenced the relation between HRQOL and IIH only for subscale scores reflecting mental health (SF-36 MCS). The NEI-VFQ-25 and SF-36 subscale scores were lower in IIH compared with other neuro-ophthalmologic disorders and published norms.

• CONCLUSIONS: Higher levels of weight gain and BMI are associated with greater risk of IIH. Even nonobese patients (BMI <30) are at greater risk for IIH in the setting of moderate weight gain. Vision-specific and overall HRQOL are affected to a greater extent in IIH than in other neuro-ophthalmologic disorders. (Am J Ophthalmol 2007;143:635–641. © 2007 by Elsevier Inc. All rights reserved.)

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH; ALSO known as pseudotumor cerebri) is a well-characterized disorder based on clinical criteria.[1,2] The exact pathophysiologic mechanisms underlying the increased intracranial pressure in IIH have not been established. Although numerous conditions, medications, and lifestyle factors have been implicated as potential risk factors for IIH, the strongest evidence for association exists for obesity and weight gain.[3–12] Incidence and case-control studies have documented IIH to be associated with female gender, obesity, and weight gain. Idiopathic intracranial hypertension has the potential to cause severe or blinding visual loss in up to 25% of patients.[13–15] Furthermore, the prevalence of obesity (body mass index [BMI] ≥30) in the United States has nearly doubled over the past two decades, suggesting that the prevalence of IIH is rising.

Idiopathic intracranial hypertension tends to occur in young women of childbearing age and is likely to have significant effects on health-related quality of life (HRQOL) through its associations with visual loss, headache, weight issues, and depression.[16] Because successful treatment and prevention of recurrence in IIH ideally should incorporate aspects of weight management, risk factor reduction, and quality-of-life outcomes, a more detailed understanding of these disease features is important. The purpose of this study was to determine the profiles of obesity and weight gain associated with IIH and to explore potential risk factors, using a risk factor questionnaire. We also sought to explore the extent to which vision-specific HRQOL is affected in IIH relative to other neuro-ophthalmologic disorders.

See accompanying Editorial on page 683.

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METHODS

• **PATIENTS AND NEURO-OPHTHALMOLOGIC CONTROLS:** This was a case-control study with a matched design, the primary aim of which was to capture data on obesity, patterns and reasons for weight gain, and other commonly implicated medical conditions and medications in patients with IIH and controls with other neuro-ophthalmologic disorders. Neuro-ophthalmologists at seven academic medical centers identified patients for this study. Patients aged 15 to 55 years who satisfied the Modified Dandy Criteria for IIH[1,2] and who had been diagnosed within the previous four weeks were invited to participate by their neuro-ophthalmologist. Control subjects were patients who were evaluated by the same neuro-ophthalmologist within approximately four weeks of the enrolled patient for a new diagnosis; these patients were required not to have IIH. Controls were identified by the neuro-ophthalmologist from among a list of patients seen within four weeks of the IIH patient. As soon as patients and potential controls were identified, contact information was provided to one of the authors (L.J.B.) after the neuro-ophthalmologist obtained permission from the patient. Controls also were matched to patients based on gender and age (±five years). One control subject was matched to each IIH patient; when possible, two control subjects were paired with each case. Because only two men were enrolled in this study, only female patients and controls were included in the final analyses. Institutional review boards at each institution (including the University of Pennsylvania, Children's Hospital of Philadelphia, Emory University, University of Iowa, Baylor College of Medicine, University of Mississippi, and Albert Einstein Medical Center in Philadelphia) approved all study protocols, and telephone and written informed consent were obtained from each study participant. Data were analyzed in accordance with Health Insurance Portability and Accountability Act (HIPAA) guidelines (data were collected before the enactment of HIPAA).

• **RISK FACTOR QUESTIONNAIRE:** The risk factor questionnaire in this study contained 33 items and was designed by study investigators and tested for clarity using 10 volunteers. The questionnaire included open-ended questions regarding prior medication use, prior and current weight, patterns of weight gain, and perceived reasons for weight gain. In addition, there were specific questions related to recent use of tetracycline class antibiotics, pregnancy history, menstrual irregularities, and corticosteroid use.

Questionnaire administration was performed using a telephone interview format. After informed consent was obtained, patients were contacted by an investigator at the University of Pennsylvania (L.J.B.) to confirm the diagnosis of IIH (through medical record review with patient consent) and to establish as closely as possible the date of first onset of symptoms referable to IIH defined as one or more of the following: headache, nausea, vomiting, transient visual obscurations, blurred vision, decreased peripheral vision, diplopia, or pulsatile tinnitus. This date was used as the reference date in the risk factor questionnaire for determining whether weight gain, medication use, or other exposures occurred before onset of IIH. For patients whose IIH was discovered based on optic disk swelling during a routine eye examination (asymptomatic patients), the date of the examination was used as the reference date if no symptoms could be recalled by the patient. For matched controls, the reference date used in the questionnaire was the same as that for the corresponding patient. Because the reference date was ascertained and assigned by a single investigator (a neuro-ophthalmologist), the telephone interviewer was masked to case vs control status and followed a standardized script for each questionnaire.

• **QUALITY OF LIFE ASSESSMENTS:** Vision-specific HRQOL was assessed using the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25).[17–20] The NEI-VFQ-25 consists of 25 items presented in a Likert scale format in which patients are asked to rate the level of severity of particular visual symptoms or difficulty of activities such as reading ordinary print in newspapers or driving. The NEI-VFQ-25 is a short-form version of the 51-item National Eye Institute Visual Function Questionnaire, a vision-specific HRQOL instrument derived from a multicondition focus group process.[17–20] The NEI-VFQ-25 was administered during the telephone interview according to standard instructions. Patients were requested to answer all questions as though they were wearing their usual correction (glasses or contact lenses) for the visual activity specified.

To examine overall aspects of HRQOL, the 36-item Health Status Questionnaire from the Medical Outcomes Study (SF-36), the most widely used generic HRQOL measure, was administered. The reliability and validity of the SF-36 have been established across a variety of conditions, and population norms from patients with a variety of conditions, including visual impairment, are available.[21] Two summary scales for the SF-36, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), were used in this study.

• **STATISTICAL ANALYSES:** Data analyses and calculations were performed using Stata statistical software version 8.0 (Stata Corp, College Station, Texas, USA). Continuous data were summarized using means and standard deviations (or medians and ranges for skewed data). Between-group comparisons for continuous variables were performed using two-sample *t* tests. Logistic regression models were used to examine associations of potential risk factors or exposures with IIH patient vs control status, adjusting for matching between patients and controls.

TABLE. Characteristics of Patients with Idiopathic Intracranial Hypertension and Neuro-ophthalmologic Controls

	Idiopathic Intracranial Hypertension Patients (n = 34)	Neuro-Ophthalmologic Controls (n = 41)
Age (yrs), mean ± SD	32 ± 10	35 ± 9
Time from symptom onset/reference date (mos), median (range)*	5.1 (0.5 to 57)	5.4 (0.3 to 59)
Body mass index at symptom onset/reference date, median (range)†	31.8 (20 to 70)	22.9 (16 to 51)
Percent weight gain in year preceding symptoms/reference date, median (range)‡	7.4% (0 to 43)	1.6% (0 to 19)

SD = standard deviation.

*Reference date for controls was defined as date of onset of disease-related symptoms for matched idiopathic intracranial hypertension patient.

†Body mass index = weight (kg)/height $(m)^2$.

‡Body mass index and percent weight gain were significantly higher in idiopathic intracranial hypertension patients compared with controls ($P < .0001$ for body mass index, $P = .002$ for percent weight gain, Wilcoxon rank-sum test).

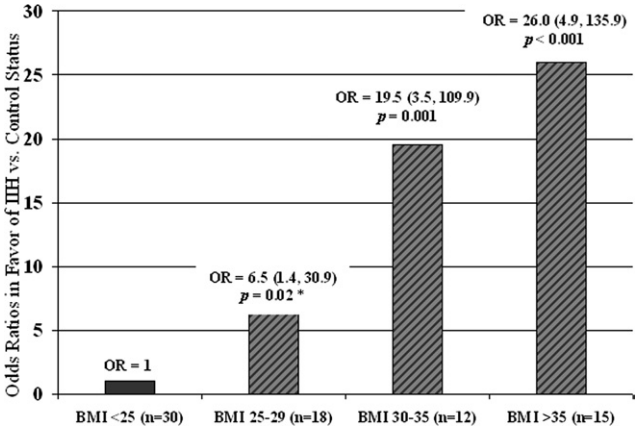

FIGURE 1. Association between body mass index (BMI) and idiopathic intracranial hypertension (IIH) in this study cohort. Bars represent odds ratios (ORs) in favor of IIH vs control status for each BMI category compared with BMI <25. Categories were defined according to published standards: <25 is considered ideal; 25 to 29 is overweight; 30 to 35 is obese, class I; and >35 is obese, class II/III. Higher levels (categories) of BMI were associated with progressively greater risk of IIH ($P < .001$, logistic regression adjusting for case/control matching). *P values for individual BMI category ORs also calculated based on logistic regression models.

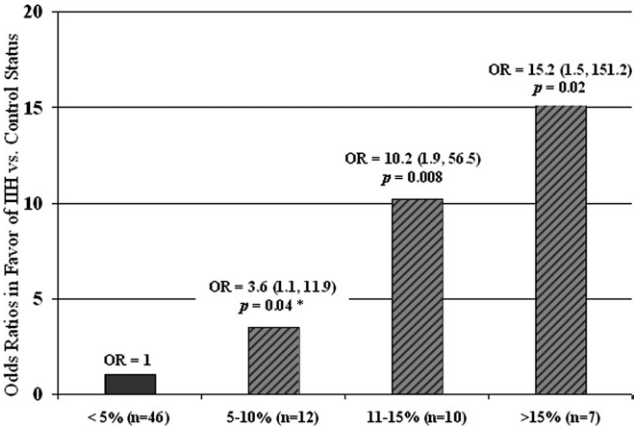

FIGURE 2. Association between percent weight gain and idiopathic intracranial hypertension (IIH). Weight gain was captured as maximum increase in weight over the 12 months before symptom onset (or reference date for matched controls) and calculated as a percentage of the patient's total weight. Bars represent odds ratios (ORs) in favor of IIH vs control status for each weight gain category compared with weight gain <5%. Increments of 5% were chosen as categories because they effectively divided the study cohort into quartiles. Similar to body mass index (BMI), higher levels of percent weight gain were associated with progressively greater risk of IIH ($P = .002$ across weight gain categories, logistic regression models adjusting for case/control matching). *P values for individual weight gain category ORs also calculated based on logistic regression models.

RESULTS

THIRTY-FOUR IIH PATIENTS AND 41 PATIENTS WITH NEURO-ophthalmologic disorders other than IIH (neuro-ophthalmologic controls) participated in the case-control study. Demographic and clinical characteristics are presented in the Table. All IIH patients (and all matched controls) in this cohort were female. Patients and controls were well matched for age and with respect to the time from symptom onset (or reference date for controls) to study enrollment.

Overall, BMI at study enrollment was significantly higher among IIH patients (Table). More detailed analyses of BMI categories, defined according to published standards for obesity (BMI <25, ideal; BMI 25 to 29, overweight; BMI 30 to 35, obese, class I; and BMI >35, obese, class II/III), showed that higher levels of BMI were associated with progressively greater risk of IIH (Figure 1). These results were observed when examining both BMI as a continuous variable and when incorporating BMI category as an ordered categorical variable in models to predict IIH vs control status ($P = .003$, logistic regression adjusting for case–control matching).

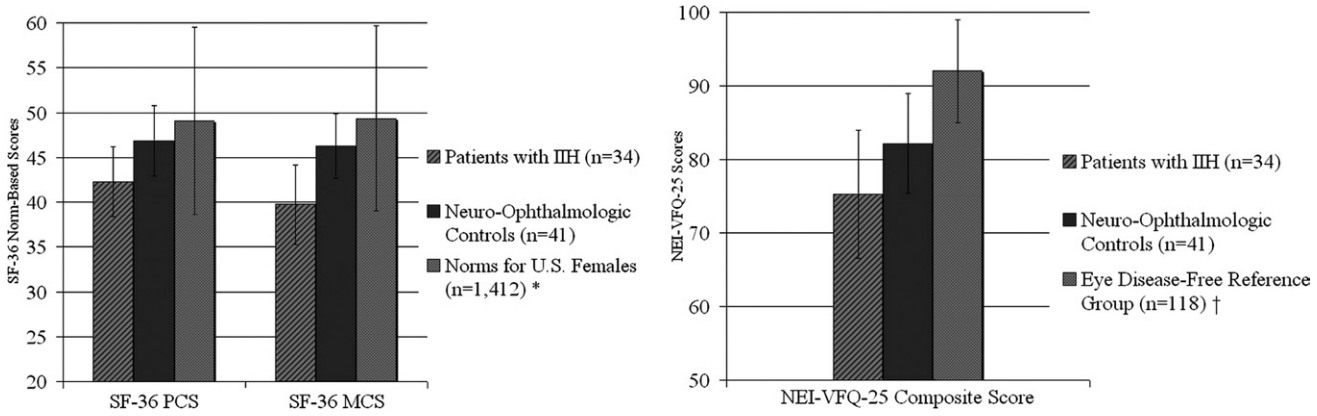

FIGURE 3. Health-related quality of life scores for patients with idiopathic intracranial hypertension (IIH) compared with neuro-ophthalmologic controls and published norms and reference groups. (Left) Mean scores (±standard deviation [SD]) for the 36-item Health Status Questionnaire from the Medical Outcomes Study (SF-36) health survey. Data are reported as summary measures of Physical Components Summary (PCS) and Mental Components Summary (MCS) scores. The SF-36 scores are reported in the standard fashion (norm-based such that the average for the United States population is 50, with a standard deviation of ±10). *Compared with United States norms for females (n = 1,412), IIH patients in this cohort scored significantly lower for both the PCS and MCS ($P < .0001$ for PCS and MCS, two-sample *t* test). Scores were lower in the IIH group compared with neuro-ophthalmologic controls for the MCS and PCS ($P = .10$ for PCS and $P = .02$ for MCS, generalized estimating equation [GEE] models adjusting for case/control matching). (Right) Mean scores (±standard deviation) for the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) for IIH patients vs neuro-ophthalmologic controls and a published eye disease-free reference group. Data are reported as composite scores (unweighted average of all NEI-VFQ-25 items except General Health [one item]). Composite scores range from 0 to 100, with lower scores indicating higher degrees of self-reported visual dysfunction. †Compared with a published eye disease-free reference group (n = 118), IIH patients in this cohort scored significantly lower for the NEI-VFQ-25 composite score ($P < .0001$, two-sample *t* test). Scores were lower in the IIH group compared with neuro-ophthalmologic controls for the NEI-VFQ-25 composite, but these results did not reach statistical significance ($P = .18$, GEE models adjusting for case–control matching).

Neuro-ophthalmologic controls self-reported little weight gain on average (median, 1.6%; range, 0% to 19%) within the 12 months before the reference time, whereas IIH patients reported greater degrees of weight gain (median, 7.4%; range, 0% to 43%; Table). Similar to BMI, higher levels of percent weight gain were associated with progressively greater risk of IIH ($P = .004$ for percent weight gain as a continuous variable; $P = .002$ for categories, logistic regression). The risk of IIH was greatest for patients who reported a maximum weight gain of more than 15% (Figure 2).

Based on clinical observations that patients in whom IIH develops do not always meet criteria for obesity (class I to III) and that some have gained only a moderate amount of body weight (5% to 15%), we explored the potential relationship between moderate weight gain and IIH among patients with low BMI. We found that it was not only the previously obese patients who subsequently gained a moderate amount of weight in whom IIH developed (odds ratio [OR], 3.5; $P = .33$; 95% confidence interval [CI], 0.3 to 42.9). Patients with a BMI of less than 30 (nonobese) who gained a moderate amount of weight also were more likely to develop IIH (OR, 8.5; $P = .004$; 95% CI, 2.0 to 36.6) as compared with patients with a similar BMI who did not gain weight.

Among IIH patients who reported a more than 5% weight gain (n = 21), the most common self-reported reasons for weight gain included pregnancy (57%), reduced activity (52%), increases in food intake (43%), changes in diet (38%), and depression (33%). Although some patients reported more than one reason for weight gain, six patients (29%) described weight gain despite no visible changes in eating habits or activity levels (reasons unknown).

We performed an exploratory analysis to determine if other commonly implicated medications or conditions, such as tetracycline use, were reported with sufficient frequency to comment on their association with IIH. These analyses revealed that use of tetracycline antibiotics within six months before IIH symptom onset (or reference date for controls) was more common among patients vs controls (tetracycline use reported in six of 34 IIH patients [18%] vs one of 41 controls [2%]). Using logistic regression models accounting for weight gain, self-reported use of tetracycline class antibiotics within six months before symptom onset was found to be associated with IIH in this cohort of patients (OR in favor of IIH, 14.4; 95% CI, 1.5 to 136.5; $P = .02$).

Because weight issues and other symptoms, including visual loss, are likely to affect HRQOL in IIH, we examined scores for overall and vision-specific HRQOL in our

study cohort and compared scores of IIH patients with those of neuro-ophthalmologic controls and published norms and reference groups. Compared with United States norms for females (n = 1,412), IIH patients in this cohort scored significantly lower for both the SF-36 PCS and MCS ($P < .0001$, two-sample t test). Differences in SF-36 scores between IIH patients and neuro-ophthalmologic controls approached significance for the PCS ($P = .10$) and were significant for the MCS ($P = .02$, generalized estimating equation models adjusting for case–control matching; Figure 3, Left), suggesting that IIH may have a relatively greater impact on HRQOL compared with other neuro-ophthalmologic disorders.

The SF-36 United States norms for vision impairment (n = 259; mean age, 54 years; vision impairment defined as self-report blindness or other trouble seeing with one or both eyes, even when wearing glasses) were comparable with our IIH cohort for the PCS subscale (41.9 ± 12.5 for United States norms vs 42.2 ± 11.6 for IIH; $P = .88$, two-sample t test). However, for the MCS, IIH patients in this study scored lower than United States vision impairment norms (45.2 ± 12.8 for United States norms for vision impairment vs 39.7 ± 13.2 for IIH; $P = .02$), despite the relatively younger age of the IIH cohort. Neuro-ophthalmologic control MCS scores were similar to the United States norms for vision impairment (46.1 ± 11.5 for controls; $P = .67$). The IIH patient scores also were worse than those of United States norms for back pain and sciatica (n = 519; PCS scores, 43.1 ± 11.6 for norms vs 42.2 ± 11.6 for IIH; $P = .64$; MCS scores, 46.9 ± 11.7 for norms vs 39.7 ± 13.2 for IIH; $P = .0006$).

With respect to vision-specific HRQOL, the NEI-VFQ-25 composite scores were significantly lower in the IIH cohort compared with a published eye disease-free reference group of 118 patients (75 ± 9 vs 92 ± 7; $P = .0004$, t test with unequal variances; Figure 3, Right).[17,20] Patients with other neuro-ophthalmologic disorders in this study (heterogeneous group of diagnoses including migraines, diplopia, eye pain, amaurosis fugax, ptosis, acute zonal occult outer retinopathy, and optic neuropathy) also had significantly lower scores for the NEI-VFQ-25 composite than the published disease-free reference group ($P = .003$, t test with unequal variances). Within domains captured by the NEI-VFQ-25, differences between IIH patients and neuro-ophthalmic controls were greatest for subscales of general health (single item not included in composite score, 35 ± 28 for IIH vs 54 ± 30 for controls) and ocular pain (60 ± 28 for IIH vs 75 ± 27 for controls). Tests of statistical significance were not performed for all individual NEI-VFQ-25 subscale scores because overall composite scores were not significantly different between IIH and control groups. The NEI-VFQ-25 composite scores among IIH patients in this study (75 ± 9) were most similar to those of published reference groups for diabetic retinopathy (NEI-VFQ-25 composite score, 73 ± 22), cataract (78 ± 13), and glaucoma (84 ± 13). Adding BMI and percent weight gain to these models revealed that these variables did not influence the association between IIH and PCS or the NEI-VFQ-25 composite scores, but were independent predictors of MCS scores.

DISCUSSION

ALTHOUGH OBESITY AND WEIGHT GAIN ARE ESTABLISHED risk factors for IIH, results of this study show that increasing levels of BMI and percent weight gain are associated with progressively greater risk of IIH. Analogous to a dose-response effect, these findings not only support the association of obesity and weight gain with IIH, but also suggest a role for underlying mechanisms that could be targeted by preventative or therapeutic interventions. Even relatively small amounts of weight gain, in the 5% to 15% range, increased the risk of IIH compared with a less than 5% weight gain in this cohort. Furthermore, patients whose BMIs were within the nonobese range (BMI <30) were no less at risk for IIH after a moderate degree of weight gain than patients who already were obese. These findings expand the profile of the patient at risk for IIH to those who gain as little as approximately 10 pounds and to individuals who are not classified as overweight or obese before the onset of weight gain. Our results are in agreement with those of previous case control studies[11,22] that have examined obesity and weight gain as overall factors, yet complement these previous observations by further defining the patterns of obesity and weight gain most associated with IIH.

That obesity and weight gain are likely involved in the causal pathway leading to IIH is emphasized by observations of this investigation and others. Although IIH remains an uncommon disorder, recent studies suggest that an increasing incidence of IIH may parallel secular trends for obesity prevalence in the United States over the past 20 years. The fact that only a very small proportion of individuals who gain moderate amounts of weight experience IIH suggests that as-yet unknown factors may be involved in determining IIH risk. Future epidemiologic studies and clinical trials should address further physiologic factors that may be responsible for a link between obesity, weight gain, and IIH.[23,24] For example, recent studies by Subramanian and associates[22] examined the potential role for plasma ghrelin, a hormone involved in regulation of body weight, as well as leptin and insulin in IIH.

Because our findings support an association of tetracycline with IIH, we agree with previous authors[25,26] that tetracycline-class antibiotics should be avoided in patients with known IIH. However, because the degree of association in our study was not highly significant ($P = .02$) in the context of examining multiple potential risk factors, we believe that larger case-control studies, with ascertainment of pharmacy records in addition to self-report, are needed.

Unlike previous investigations, this study explored self-reported reasons for weight gain among patients with IIH. Although reported reasons were similar in the IIH group to those of controls who gained more than 5% of body weight, 29% of IIH patients could not identify one or more specific reasons for their weight gain. Interestingly, in our study, 13 (38%) IIH patients reported less than 5% weight gain, of which 10 (29%) reported no weight gain. This is consistent with a previous study by Giuseffi and associates[11] in which 42% had no weight change. Because weight gain is such an important risk factor for IIH, the fact that so many patients did not report recent weight gain underscores the need to understand better the pathophysiology of the disease.

There is evidence from retrospective studies that even a small degree of weight loss in IIH may lead to improved outcomes with respect to resolution of papilledema.[24] One study found that a 6% reduction in weight was associated with resolution of papilledema. This finding is consistent with our results indicating that weight gains of as little as 5% may increase the risk of IIH. Although the effects of weight loss on visual and other outcomes in IIH have not been demonstrated prospectively in observational studies or clinical trials, results of this study support a relationship between BMI levels, weight gain, and risk of IIH and thus support the inclusion of weight loss plans as one aspect of intervention in the treatment of IIH. Because levels of BMI not only relate to adipose tissue, but also reflect changes in fluid balance or orthostatic edema, associations of BMI and weight gain with IIH observed in this study support the need for future investigations that address these underlying mechanisms.[25] The effectiveness of weight-loss regimens, and whether these are affected by depression and other factors, also will be important to assess in upcoming IIH clinical trials.

Weight issues and other symptoms, including visual loss, are likely to affect HRQOL in IIH. Data from this study, in fact, indicate that IIH affects HRQOL to a degree similar to that of other potentially vision-threatening disorders such as cataracts, diabetic retinopathy, and glaucoma.[20] Both physical and mental aspects of HRQOL were rated as reduced by IIH patients in our cohort, suggesting that a comprehensive and perhaps multidisciplinary approach to this disorder is warranted.

Our results are notable for a relatively large difference between IIH patients and neuro-ophthalmologic controls in the category of ocular pain, and this is consistent with previous findings that 44% of IIH patients experience retrobulbar pain (half of which was related to eye movement).[15] However, the MCS scores of IIH patients also were relatively reduced as compared with United States norms for back pain and sciatica.[17] Although these results suggest that the presence of pain alone may not entirely account for the lower MCS scores in the IIH group, levels of pain severity, which may affect comparability between our IIH cohort and SF-36 back pain and sciatica norms, were not assessed. It will be interesting in future studies to capture pain intensity and frequency to assess comparability of IIH with other conditions.

Obese patients have been shown to have lower HRQOL scores than nonobese controls, and there is a strong association between IIH and obesity. In fact, a study by Kleinschmidt and associates[16] found that a group of controls weight-matched to an IIH group likewise had significantly lower HRQOL scores on the SF-36 than did normal-weight controls. The obese control group likewise showed increased levels of depression and anxiety. However, the patients with IIH had significantly lower subscale scores for social functioning and had lower scores for both depression and anxiety than could be accounted for by obesity alone. These IIH patients also self-reported a much lower level of perceived health as compared with obese patients one year previously, consistent with our findings that IIH patients self-report general health to be lower than matched controls with other neuro-ophthalmologic disorders. To the extent that coping mechanisms may affect perceptions of health and quality of life, assessment tools that capture this aspect of mental health (including the Daily Coping Assessment) will be helpful to include in future investigations of IIH and other neuro-ophthalmic disorders.

In our study, BMI and weight gain did not influence associations between IIH and vision-specific and overall physical HRQOL, but were independent predictors of mental HRQOL. Obesity and weight gain therefore are important factors influencing HRQOL in IIH and in general, yet seem to affect most greatly the mental health aspects of HRQOL. Given the potential for even mild to moderate weight gain to be associated with IIH and the observation that risk of IIH increases with increasing BMI, data from this study support recommendations for weight control and weight loss in this group of patients. Future clinical trials of treatment strategies for IIH should aim to quantify the effects of weight loss on the progression of IIH and should include HRQOL measures among study end points.

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Biosketch

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