The Journal of Headache and Pain

RESEARCH

Open Access

Inverse association of obesity with bout periodicity in episodic cluster headache: a multicenter cross-sectional study

Byung-Su Kim[1], Mi Ji Lee[2], Byung-Kun Kim[3], Jong-Hee Sohn[4], Tae-Jin Song[5], Min Kyung Chu[6], Soo-Kyoung Kim[7], Jeong Wook Park[8], Heui-Soo Moon[9], Pil-Wook Chung[9] and Soo-Jin Cho[10*]

Abstract

Background Cluster headache (CH) is the most painful headache disorder. Despite a large body of evidence on obesity's negative influence on migraine, its impact on cluster headache disease activity remains unexplored. We aimed to determine whether body mass index (BMI) and obesity are associated with lifetime bout occurrence and annual bout frequency in patients with episodic cluster headache (ECH).

Methods The Korean Cluster Headache Registry (KCHR) is a prospective, multicenter registry of consecutive patients with CH over 4 years. This cross-sectional study included 316 eligible patients with ECH, with ≥ 2 years of duration of CH disease and ≥ 2 times of lifetime bout occurrence. Obesity was determined using the Asia-Pacific classification (obese: BMI ≥ 25.0 kg/m^2). Bout frequency was defined as an average annual number of bout occurrence: number of lifetime bout occurrence divided by total duration of CH disease. The main outcomes included odds ratios (ORs) of BMI and obesity for quartiles of lifetime bout occurrence and annual bout frequency by performing ordinal logistic regression analysis.

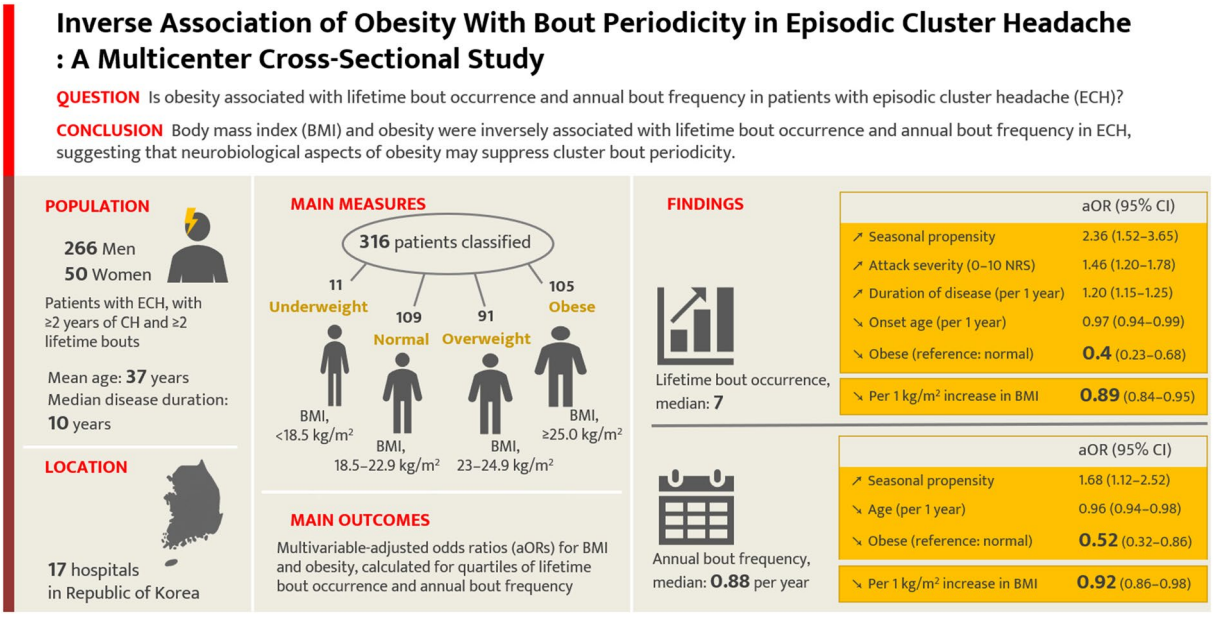
Results The mean (SD) age of the patients was 37 (9.7); 50 (15.8%) were female. The mean (SD) BMI was 23.9 (3.2) kg/m^2; 105 (33.2%) were obese. The median (interquartile range) duration of CH disease was 10 (6–16) years; lifetime bout occurrence was 7 (4–12); and annual bout frequency was 0.88 (0.5–1.10). In multivariable adjusted models, OR of BMI (per 1 kg/m^2) and the obese group for lifetime bout occurrence were 0.89; 95% CI, 0.84–0.95 and 0.40; 95% CI, 0.23–0.68. Age, BMI, and seasonal propensity were associated factors for annual bout frequency. After multivariable adjustment, BMI and obesity were inversely associated with annual bout frequency (BMI per 1 kg/m^2 OR: 0.92; 95% CI: 0.86–0.98 and obese OR: 0.52; 95% CI: 0.32–0.86).

Conclusions BMI and obesity were inversely associated with lifetime bout occurrence and annual bout frequency in ECH, suggesting that neurobiological aspects of obesity may suppress cluster bout periodicity.

*Correspondence:
Soo-Jin Cho
dowonc@naver.com

Full list of author information is available at the end of the article

Graphical Abstract



Keywords Cluster headache, Headache, Body mass index, Obesity, Obesity paradox

Introduction

Cluster headache (CH) is the most painful primary headache disorder, characterized by short, unilateral, intense headache attacks lasting 15 to 180 min, accompanied by ipsilateral cranial autonomic symptoms and restlessness [1–3]. CH attacks can arise up to eight times per day during cluster periods, which persist for several weeks to months (bouts). Following the presence of attack-free remissions between bouts, this disorder is classified as episodic CH (ECH) or chronic CH, with ECH accounting for 75 to 90% [1, 2, 4]. The typical disease history of ECH comprises of recurrent bouts and remission periods over the course of the disease [1, 2, 5, 6].

Obesity is a complex metabolic disease with a steadily rising prevalence [7]. It is associated with an increased risk of serious comorbidities, including type 2 diabetes mellitus, cardiovascular disease, certain cancers, and psychiatric disorders [8]. In headache disorders, previous literature indicates that obesity is associated with a higher incidence of migraine and more severe characteristics (greater severe intensity, higher frequency, and increased risk of migraine chronification) [9]. A population study has shown a dose-response relationship between body mass index (BMI) and migraine headache days [10]. Unlike migraine, very little is known about the association between obesity and CH.

The disease course and activity in patients with CH can vary widely, with lifetime bout occurrence based on cluster bout periodicity influenced by alternating bouts and remission periods. Due to the devastating nature of CH, more frequent bout occurrences can negatively impact the quality of life [11, 12]. However, evidence on determinants of cluster bout periodicity is limited. Therefore, we tested the hypothesis that increasing BMI and obesity may independently influence bout occurrence and annual bout frequency in ECH.

Methods

Study design and patients

This cross-sectional study utilized the Korean Cluster Headache Registry (KCHR) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The KCHR is a prospective, multicenter registry that includes patients with consecutive CH aged ≥ 19 years across Korea. Patients were enrolled over 4 years (September 2016–December 2020) from 15 university hospitals (nine tertiary and six secondary referral centers) and two secondary referral general hospitals. The KCHR protocol has been published previously [12–14]. This study was reviewed and approved by the institutional review boards (IRBs) at each hospital and complied with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients understood the study objectives and provided written informed consent.

KCHR investigators experienced board-certified neurologists specializing in headache disorders and carefully evaluated all patients. CH diagnosis was based on patient history and clinical presentation, using the third edition,

beta version (ICHD-3β), and the third edition (ICHD-3) of the International Classification of Headache Disorders (ICHD) [13]. Of the enrolled patients, only patients meeting ICHD-3 criteria for CH were included in this study. CH subtype was classified according to ICHD-3. Patients without remission within 1 year of their first CH episode or those not followed for more than 1 year were classified as "first CH" and not categorized as episodic CH (ECH) or chronic CH (CCH).

Eligibility criteria for this study were as follows: (1) ECH, (2) a duration of CH disease ≥ 2 years, and 3) ≥ 2 lifetime bout occurrences. Patients were excluded if their diagnosis did not meet the ICHD-3 criteria for ECH (e.g., CCH, probable CH, or first CH) if the duration of CH disease was < 2 years, lifetime bout occurrence was < 2, or the patient had missing data.

Data collection and measurements

At baseline enrollment, data on headache diagnosis, demographics, social habits, CH disease history, headache characteristics, psychiatric status, suicidal ideation and attempts, and headache impact were collected prospectively through in-person interviews by KCHR investigators using structured questionnaires.

For BMI measurement, body height and weight were measured at the first visit to the headache clinic or center by an experienced nurse or staff, with participants wearing thin clothing and no shoes. BMI was calculated as weight in kilograms divided by height in square meters. Patients were classified according to the Asian-Pacific BMI classification: underweight (< 18.5 kg/m^2), normal weight (18.5–23 kg/m^2), overweight (23–25 kg/m^2), and obese (≥ 25 kg/m^2) [15].

The 12-item Allodynia Symptom Checklist assessed cutaneous allodynia during CH pain attacks [16]. Anxiety and depression were evaluated using the Korean versions of the Generalized Anxiety Disorder 7-item scale and the Patient Health Questionnaire 9-item scale [17]. Suicidal ideation and attempts were assessed with two lucid questions: "Have you ever thought that it was better to die?" and "Have you ever attempted suicide?." Headache impact was measured using the 6-item Headache Impact Test [18].

Bout frequency was defined as the average annual number of bout occurrences, calculated by dividing lifetime bout occurrence by the total duration of CH disease [6].

Statistical analysis

To test the study hypothesis, BMI, a key obesity variable, was modeled as a continuous variable (per 1 kg/m^2) and in quartiles. To determine linear trends, we treated the number of BMI quartiles as a continuous variable in each model. Likewise, lifetime bout occurrence and bout frequency, being non-normally distributed, were classified into quartiles. Continuous variables are presented as mean ± standard deviation or median with interquartile range, while categorical variables are presented as counts (percentages). Statistical significance of intergroup differences was assessed using the one-way ANOVA or Kruskal–Wallis tests for continuous variables and Chi-square or linear-by-linear association tests for categorical variables.

Ordinal logistic regression analysis was performed to estimate linear association between BMI (continuous and the quartiles), obesity, and the quartiles of bout occurrence and frequency. The results of the univariable analyses are given odds ratios (ORs) and 95% confidence intervals (CIs), comparing the obesity category to the normal weight category as the reference. All covariates with *P*-values < 0.05 in the univariable analyses were considered potential variables and were entered into the multivariable-adjusted models. In addition, binary logistic regression analyses were performed to determine whether BMI and obesity were associated with sensible cut-off values of lifetime bout occurrence (≥ 10 times) and frequency (≥ 1 bouts per year). The associations between obesity, lifetime bout occurrence, and bout frequency were tested in the context interaction between prespecified subgroups (age: <40 years vs. ≥40 years, sex: female vs. male, current smoking: yes vs. no, alcohol drinking: yes vs. no, onset age of CH disease: <30 years vs. ≥30 years, duration of CH disease: <10 years vs. ≥10 years, coexisting migraine: yes vs. no, diurnal rhythmicity: yes vs. no, and seasonal propensity: yes vs. no).

All statistical analyses were performed using Statistical Package for the Social Sciences (version 18.0, SPSS Inc., Chicago, IL. USA). All tested *P*-values were two-tailed, with $P < 0.05$ considered significant.

Results

Characteristics of study patients

Over 4 years, 459 consecutive patients with CH were prospectively recruited (Additional Fig. 1). Of these, 161 patients were excluded based on the following criteria: (1) CH classification (chronic CH, $n = 19$; probable CH, $n = 45$; first CH, $n = 58$), (2) CH disease duration < 2 years ($n = 94$), (3) lifetime bout occurrence < 2 times ($n = 83$), and (4) missing data ($n = 14$). Ultimately, 316 eligible patients were included in the analysis. The mean (standard deviation [SD]) age was 37 (9.7) years; 50 (15.8%) were female. The mean (SD) BMI was 23.9 (3.2) kg/m^2; 105 (33.2%) were obese. The median (interquartile range [IQR]) duration of CH disease was 10 (6–16) years; lifetime bout occurrence was 7 (4–12); and annual bout frequency was 0.88 (0.5–1.10).

Demographics, disease history, and clinical characteristics were compared across the obesity groups (Table 1).

Table 1 Demographics, disease history, and clinical characteristics stratified by obesity in patients with episodic cluster headache

	All patients (*N* = 316)	Obesity by BMI (kg/m^2) category				*P*
		Underweight BMI, < 18.5 (*N* = 11)	Normal weight BMI, 18.5–22.9 (*N* = 109)	Overweight BMI, 23.0–24.9 (*N* = 91)	Obese BMI ≥ 25.0 (*N* = 105)	
Demographics and social habits						
Age, yr	37 ± 9.7	34.4 ± 9.5	36.9 ± 10.1	36.5 ± 9.6	37.8 ± 9.4	0.633
Female sex, no. (%)	50 (15.8)	5 (45.5)	31 (28.4)	8 (8.8)	6 (5.7)	< 0.001
Current smoking, no. (%)	143 (45.3)	5 (45.5)	47 (43.1)	36 (39.6)	55 (52.4)	0.315
Alcohol drinking, no. (%)	182 (57.6)	3 (27.3)	64 (58.7)	54 (59.3)	61 (58.1)	0.229
Disease history and status						
Onset age of CH disease, yr	25.8 ± 9.7	22.5 ± 8.6	25.2 ± 9.8	25.3 ± 9.4	27 ± 9.8	0.324
Duration of CH disease, yr	10 (6–16)	12 (9–15)	10 (5–16.5)	10 (6–15)	9 (6–16)	0.875
Lifetime bout occurrence	7 (4–12)	14 (4–20)	10 (5–12)	7 (3–11)	6 (3–10)	0.006
Bout frequency (no. of bouts per year)	0.88 (0.5–1.1)	1 (0.6–1.1)	1 (0.6–1.2)	0.9 (0.4–1)	0.6 (0.4–1)	0.007
Coexisting migraine, no. (%)	40 (12.7)	4 (36.4)	20 (18.3)	10 (11)	6 (5.7)	0.004
Disease characteristics						
Duration of bout, week	4 (4–8)	4 (2–8)	4 (3–8)	4 (4–6)	6 (4–8)	0.193
Attack severity (0–10 NRS)	9 (8–10)	9 (9–10)	9 (8–10)	9 (8–10)	9 (8–10)	0.993
Attack frequency per day	1.1 (1–2)	1.5 (1–3)	1 (1–2)	1.1 (1–2)	1.5 (1–2.7)	0.738
Attack duration, mins	90 (60–120)	120 (60–180)	90 (60–120)	90 (60–120)	90 (60–120)	0.38
Diurnal rhythmicity, no. (%)	199 (63)	8 (72.7)	66 (60.6)	59 (64.8)	66 (62.9)	0.835
Seasonal propensity, no. (%)	171 (54.1)	7 (63.6)	65 (59.6)	45 (49.5)	54 (51.4)	0.417
ASC-12 score	0 (0–2)	2 (0–4)	0 (0–2)	0 (0–0)	0 (0–2)	0.049
Psychiatric status and headache impact						
GAD-7 score	7 (3–12)	9 (1–16)	7 (3–12)	6 (3–11)	8 (3–13)	0.453
PHQ-9 score	6 (3–11)	12 (5–16)	6 (3–12)	5 (2–10)	7 (3–11)	0.023
Suicidal ideation, no. (%)	77 (24.4)	1 (9.1)	30 (27.5)	17 (18.7)	29 (27.6)	0.243
Suicidal attempt, no. (%)	3 (0.9)	1 (9.1)	1 (0.9)	0 (0)	1 (1)	0.259
HIT-6 score	70 (65–76)	69 (66–74)	70 (65–76)	69 (63–76)	72 (66–78)	0.366

Data are presented with mean ± standard deviation, median with interquartile range, or number (percentage)

Abbreviations: CH Cluster headache; NRS, Numeric Rating Scale, ASC, the Allodynia Symptom Checklist; GAD-7, the Generalized Anxiety Disorder 7-item scale; PHQ-9, the Patient Health Questionnaire 9-item scale; HIT-6, the 6-item Headache Impact Test

In the obese group, proportions of females, coexisting migraine, total lifetime bout occurrence, and bout frequency were significantly lower. Similar results were observed across groups stratified by the BMI quartiles (Additional Table 1).

Distribution of BMI and obesity across the quartiles of lifetime bout occurrence and annual bout frequency

A shift toward lower BMI quartiles was observed in the upper quartiles of lifetime bout occurrence and frequency ($P = 0.022$ and $P = 0.004$, respectively) (Fig. 1A). For obesity, a clear shift for normal weight with the upper quartiles of lifetime bout occurrence and frequency was observed ($P = 0.021$ and $P = 0.002$, respectively) (Fig. 1B).

Association of BMI with lifetime bout occurrence and annual bout frequency

Higher BMI was inversely associated with lifetime bout occurrence ≥ 10, with an OR of 0.86 (95% CI: 0.80–0.93) and with quartiles of lifetime bout occurrence, with an OR of 0.90 (95% CI: 0.85–0.96) per unit increase in BMI (Table 2). After adjusting for potential covariates, these associations remained significant, with multivariable-adjusted ORs (aORs) of 0.83 (95% CI: 0.76–0.91) and 0.89 (95% CI: 0.84–0.95), respectively (Additional Tables 2 and 3). Compared to the 1st BMI quartile, the aORs for the 4th quartile with lifetime bout occurrence ≥ 10 and the quartiles of lifetime bout occurrence were 0.37 (95% CI: 0.21–0.66) and 0.39 (95% CI: 0.21–0.72), respectively. In addition, BMI quartiles showed a dose-response relationship with both lifetime bout occurrence ≥ 10 and the quartiles of lifetime bout occurrence ($P < 0.001$ and $P < 0.002$, respectively).

For bout frequency, the ORs per unit increase in BMI for bout frequency ≥ 1 and bout frequency quartiles were 0.89 (95% CI: 0.82–0.96) and 0.90 (95% CI: 0.85–0.96), respectively (Table 2). In multivariable-adjusted models, these inverse associations persisted with an aOR of 0.90 (95% CI: 0.83–0.97) and an OR of 0.92 (95% CI: 0.83–0.97) (Additional Tables 4 and 5). The highest BMI quartile had the strongest inverse association with bout frequency ≥ 1 (aOR: 0.4; 95% CI: 0.83–0.97) and with bout

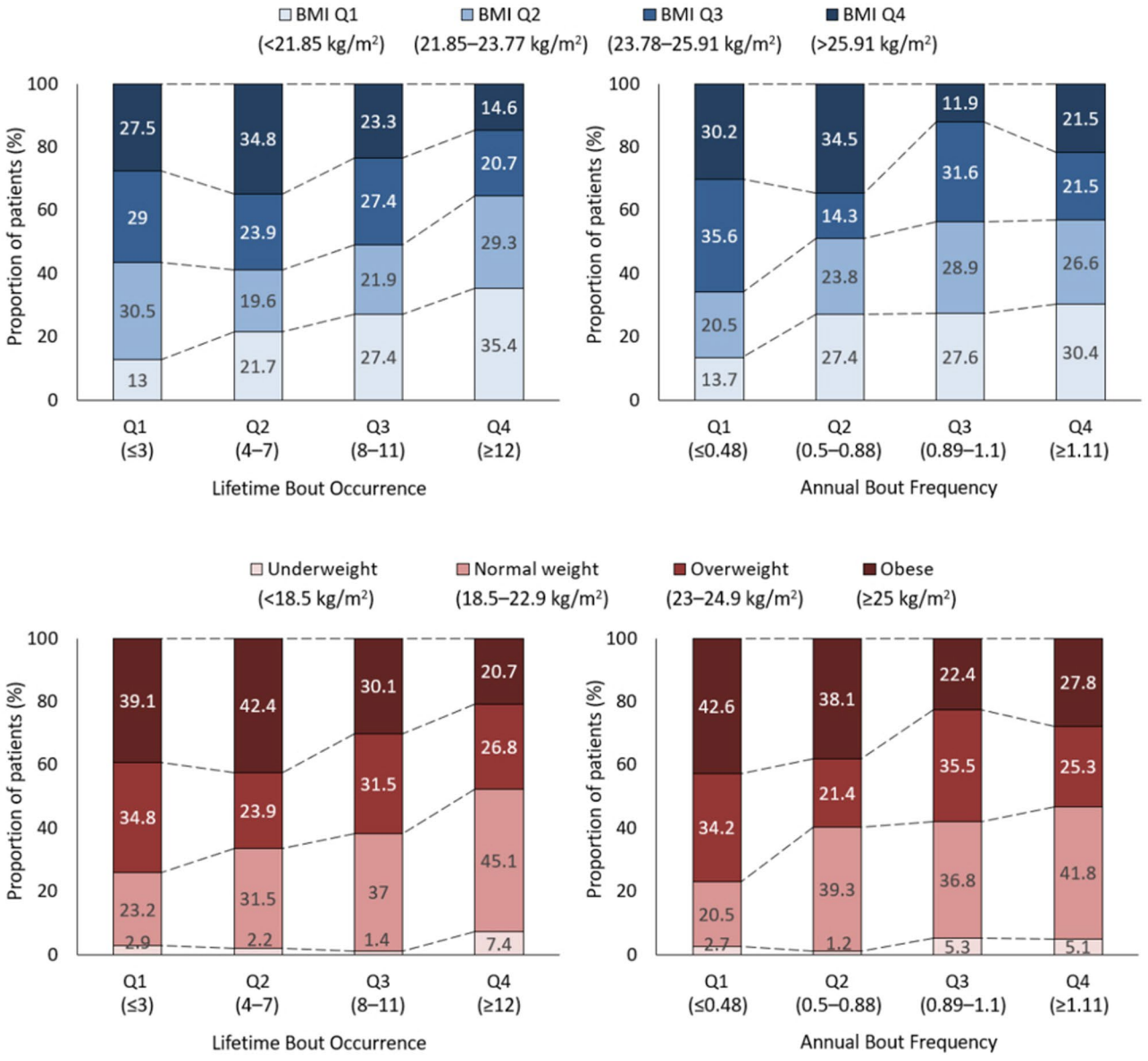


Fig. 1 Proportion of patients in BMI quartiles and obesity category stratified by lifetime bout occurrence and annual bout frequency
Abbreviations: BMI, body mass index; Q, quartile

frequency quartiles (aOR: 0.53; 95% CI: 0.3–0.95) in a dose-dependent manner ($P = 0.016$ and $P = 0.014$).

Association of obesity with lifetime bout occurrence and annual bout frequency

Compared to the normal-weight group, the obese group was inversely associated with lifetime bout occurrence ≥ 10 (OR: 0.32; 95% CI: 0.18–0.57) and with lifetime bout occurrence quartiles (OR: 0.44; 95% CI: 0.27–0.71) (Table 3). After adjusting for potential covariates, these associations remained significant, with an aOR of 0.25 (95% CI: 0.12–0.5) and an OR of 0.4 (95% CI: 0.23–0.68).

For bout frequency, the obese group was inversely associated with bout frequency ≥ 1 (OR: 0.49; 95% CI: 0.28–0.85) and with bout frequency quartiles (OR: 0.49; 95% CI: 0.3–0.8) (Table 3). In multivariable-adjusted models, these inverse associations remained significant with an aOR of 0.51 (95% CI: 0.29–0.91) and an OR of 0.52 (95% CI: 0.32–0.86).

Subgroup analysis was conducted to determine whether the associations of obesity with lifetime bout occurrence and bout frequency were consistent across prespecified subgroups (Fig. 2). In all subgroups, the obese group was inversely associated with lifetime bout occurrence ≥ 10 and bout frequency ≥ 1 compared to the normal weight group.

Table 2 Binary and ordinal logistic regression analysis: multivariable-adjusted odds ratios of body mass index for lifetime bout occurrence and annual bout frequency

	Per 1 kg/m^2 increase in BMI (*N* = 316)	Quartiles of BMI (kg/m^2)				*P for trend*
		1st quartile ≤ 21.83 (*N* = 78)	2nd quartile 21.85–23.77 (*N* = 79)	3rd quartile 23.78–25.91 (*N* = 79)	4th quartile > 25.91 (*N* = 80)	
Overall bout occurrence						
Binary (≥ 10 vs. ≤9)						
Unadjusted OR	0.86 (0.80–0.93)	reference	0.64 (0.34–1.21)	0.40 (0.21–0.76)	0.25 (0.13–0.50)	< 0.001
P	< 0.001		0.175	0.006	< 0.001	
Multivariable-adjusted OR*	0.83 (0.76–0.91)	reference	0.63 (0.30–1.35)	0.38 (0.17–0.81)	0.19 (0.08–0.43)	< 0.001
P	< 0.001		0.243	0.012	< 0.001	
Quartiles (≤ 3, 4–7, 8–11, and ≥ 12)						
Unadjusted OR	0.90 (0.85–0.96)	reference	0.57 (0.32–1.00)	0.47 (0.26–0.83)	0.37 (0.21–0.66)	0.001
P	0.002		0.052	0.01	0.001	
Multivariable-adjusted OR†	0.89 (0.84–0.95)	reference	0.73 (0.39–1.37)	0.52 (0.28–0.97)	0.39 (0.21–0.72)	0.002
P	0.002		0.339	0.042	0.003	
Bout frequency (number of bouts per year)						
Binary (≥ 1 vs. <1)						
Unadjusted OR	0.89 (0.82–0.96)	reference	0.68 (0.36–1.27)	0.75 (0.40–1.41)	0.34 (0.18–0.67)	0.004
P	0.002		0.232	0.379	0.002	
Multivariable-adjusted OR‡	0.90 (0.83–0.97)	reference	0.80 (0.41–1.54)	0.88 (0.45–1.69)	0.40 (0.20–0.78)	0.016
P	0.006		0.516	0.71	0.008	
Quartiles (≤ 0.48, 0.5–0.88, 0.89–1.1, and ≥ 1.11)						
Unadjusted OR	0.90 (0.85–0.96)	reference	0.82 (0.46–1.44)	0.56 (0.32–1.00)	0.45 (0.25–0.80)	0.003
P	0.003		0.496	0.05	0.007	
Multivariable-adjusted OR‡	0.92 (0.86–0.98)	reference	0.91 (0.51–1.62)	0.59 (0.33–1.05)	0.53 (0.30–0.95)	0.014
P	0.013		0.769	0.076	0.035	

Potential variables with $P < 0.05$ in univariable analysis were entered in multivariable-adjusted models

Abbreviations: BMI, body mass index; OR, odds ratio; CH, cluster headache; ASC, the Allodynia Symptom Checklist

*Adjusted for current smoking, age of CH onset, duration of CH disease, attack severity, seasonal propensity, and ASC-12 score

†Adjusted for age of CH onset, duration of CH disease, attack severity, seasonal propensity, and ASC-12 score

‡Adjusted for age and seasonal propensity

Discussion

In this study, higher BMI and obesity were inversely associated with lifetime bout occurrence and annual bout frequency in patients with ECH. These results suggest that obese patients with ECH may experience fewer lifetime bout and infrequent annual bout occurrences than those with normal weight or lower BMI. The association remained consistent across various clinical subgroups. These findings indicate that obesity may play a novel role in influencing bout periodicity in ECH.

The well-established negative impact of obesity on migraine makes these findings noteworthy, as they contradict general expectations of obesity's role [9]. To our knowledge, this study is the first to suggest a possible paradoxical role of obesity on the disease course and activity of ECH. Along with obesity, age and seasonal propensity were also significant factors for annual bout frequency (Additional Table 5 and Additional Fig. 2). For lifetime bout occurrence, age was not an independent predictor. In contrast, onset age and disease duration were significant associated factors, suggesting that patients with earlier onset age and longer disease duration have a higher possibility of experiencing frequent cluster bouts. Interestingly, age emerged as an independently associated factor for annual bout frequency. The inverse association between age and annual bout frequency correlates with a conventional idea that the occurrence of cluster bouts can gradually diminish with age as bouts become infrequent, whereas remission periods get longer [1, 6]. Next, despite the possible impact of smoking on ECH [19], the association between smoking and lifetime bout occurrence did not reach statistical significance (Additional Table 3). In terms of annual bout frequency, smoking was not an associated factor (Additional Table 5). Notably, seasonal propensity was also a consistent predictor for both lifetime bout occurrence and annual bout frequency. Given that seasonal propensity is considered a clinical hallmark of circadian features of CH, these results suggest that the hypothalamus and suprachiasmatic nucleus (SCN), a center of the biological clock, could play a crucial role in determining occurrence and frequency of cluster bouts [1–3, 20–22]. As with seasonal

Table 3 Binary and ordinal logistic regression analysis: multivariable-adjusted odds ratios of obesity by the body mass index criteria for lifetime bout occurrence and annual bout frequency

	Obesity criteria by BMI (kg/m^2) category			
	Underweight BMI, < 18.5 (*N* = 11)	**Normal weight BMI, 18.5–22.9 (*N* = 109)**	**Overweight BMI, 23.0–24.9 (*N* = 91)**	**Obese BMI ≥ 25.0 (*N* = 105)**
Lifetime bout occurrence				
Binary (≥ 10 vs. ≤9)				
Unadjusted OR	1.01 (0.29–3.53)	reference	0.48 (0.27–0.85)	0.32 (0.18–0.57)
P	0.979		0.012	< 0.001
Multivariable-adjusted OR*	0.79 (0.18–3.41)	reference	0.43 (0.22–0.85)	0.25 (0.12–0.50)
P	0.759		0.015	< 0.001
Quartiles (≤ 3, 4–7, 8–11, and ≥ 12)				
Unadjusted OR	1.69 (0.53–5.32)	reference	0.60 (0.36–0.99)	0.44 (0.27–0.71)
P	0.366		0.046	0.001
Multivariable-adjusted OR†	1.33 (0.39–4.49)	reference	0.59 (0.34–1.02)	0.40 (0.23–0.68)
P	0.644		0.063	0.001
Bout frequency (number of bouts per year)				
Binary (≥ 1 vs. <1)				
Unadjusted OR	1.71 (0.47–6.20)	reference	0.91 (0.52–1.60)	0.49 (0.28–0.85)
P	0.409		0.767	0.012
Multivariable-adjusted OR‡	1.56 (0.41–5.86)	reference	0.97 (0.54–1.74)	0.51 (0.29–0.91)
P	0.409		0.93	0.025
Quartiles (≤ 0.48, 0.5–0.88, 0.89–1.1, and ≥ 1.11)				
Unadjusted OR	1.39 (0.45–4.28)	reference	0.66 (0.40–1.09)	0.49 (0.30–0.80)
P	0.565		0.112	0.005
Multivariable-adjusted OR‡	1.21 (0.39–3.77)	reference	0.62 (0.37–1.04)	0.52 (0.32–0.86)
P	0.736		0.074	0.011

Potential variables with $P < 0.05$ in univariable analysis were entered in multivariable-adjusted models

Abbreviations: BMI, body mass index; OR, odds ratio; CH, cluster headache; ASC, the Allodynia Symptom Checklist

*Adjusted for current smoking, age of CH onset, duration of CH disease, attack severity, seasonal propensity, and ASC-12 score

†Adjusted for age of CH onset, duration of CH disease, attack severity, seasonal propensity, and ASC-12 score

‡Adjusted for age and seasonal propensity

propensity, the impact of obesity on bout periodicity in CH may be first linked to its effect on the hypothalamus. A current understanding of the pathophysiological model of CH attributes bout occurrence of CH to an inherited misalignment between primary circadian pacemaker SCN and extra-SCN clocks [1–3, 20, 21]. This internal circadian disruption may be worsened by neurohumoral and behavioral factors, lowering the threshold for bout recurrence [20]. In this sense, we postulate that obesity may raise this threshold by weakening disruptions in circadian regulation.

Over the past two decades, the connection between obesity and the hypothalamus has gained special attention, positioning obesity as a metabolic inflammatory disease. In this context, obesity-associated inflammatory processes in the hypothalamus refer to hypothalamic inflammation [23]. This condition is known for deregulating energy homeostasis in the hypothalamus, resulting in insulin resistance, glucose intolerance, and obesity. The exact impact of hypothalamic inflammation on the circadian biology of CH remains unexplored [21, 23]. However, an assumption for our findings is that hypothalamic inflammation might directly alter the circadian biology of CH, leading to a regulation in the occurrence and frequency of cluster bouts. The possible biological link between obesity and the hypothalamus is supported by recent neuroimaging studies: a large-scale study of 1,351 young adults reported a positive association between hypothalamic volume and BMI [24], and a resting-state functional magnetic resonance imaging study revealed that BMI affects the hypothalamic microstructure and connectivity to the limbic region [25]. Since accumulating neuroimaging studies have consistently indicated that the hypothalamus could play a role in CH genesis [26], obesity-associated alterations in hypothalamic structure and functional connectivity may be a possible elucidation for regulating the influence of obesity on cluster bout periodicity.

Next, the association between obesity and bout periodicity can be accounted for by biomarkers. Obesity is a chronic low-grade inflammatory state, and previous studies have explored the link between migraine and obesity

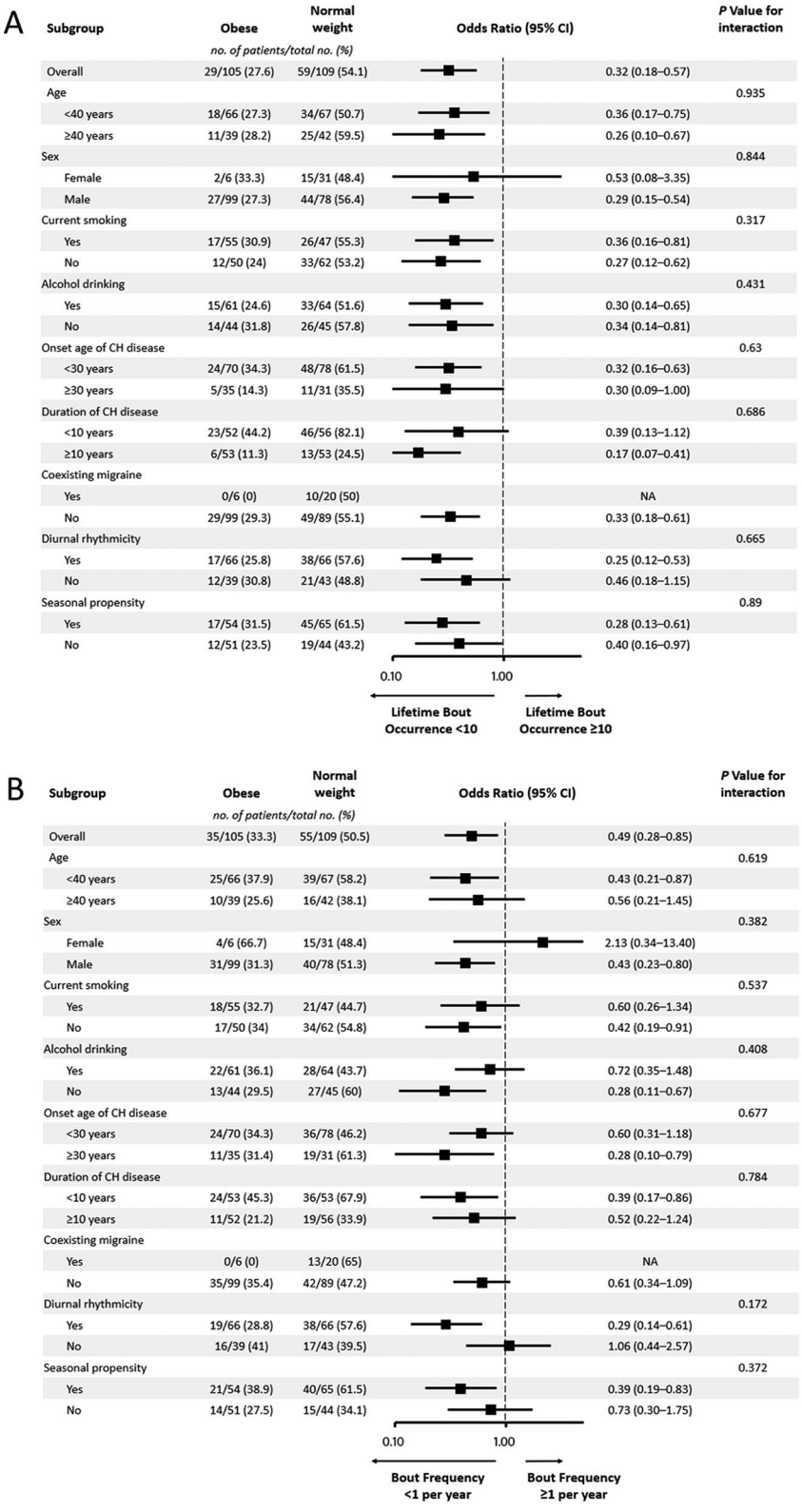


Fig. 2 Odds ratio of obesity for lifetime bout occurrence and annual bout frequency according to prespecified subgroups
Abbreviations: CI, confidence interval; CH, cluster headache; NA, not applicable

through proinflammatory biomarkers [27]. Similarly, various potential biomarkers for CH have been studied during the last decade; however, the results have been inconsistent and mostly non-specific [28]. Among adipokines, obesity was typically associated with low adiponectin levels, whereas several studies have shown increased adiponectin in patients with migraine, conflicting the obesity-migraine association [27, 29, 30]. This suggests that the paradoxical effect of obesity on the bout periodicity of CH in this study might be due to low levels of adiponectin in obesity. However, unlike migraine, adiponectin's role has remained largely unexamined in CH and warrants further studies. Lastly, obesity and associated lifestyle factors were linked to increased daily cortisol production and an enhanced cortisol response to stress [31, 32]. Given the strong and rapid preventive effect of corticosteroids in CH [33, 34], increased cortisol levels and associated responsiveness in obese patients may support the regulation of obesity on CH bout periodicity.

This study has certain limitations. First, due to its cross-sectional design, our findings lack a causal relationship and should be interpreted cautiously. Second, some key variables (lifetime bout occurrence, onset of CH, and total disease duration) were based on patient recall at recruitment. This increased the risk of recall bias, lowering the internal validity. Third, since all patients in this study were Korean, our results may not directly apply to populations of other ethnicities or cultures. Fourth, the prevalence of obesity in our study was somewhat lower at 33.2% compared to the 38.4% reported in a recent nationwide population-based survey in Korea [35]. This discrepancy may align with the protective influence of obesity on ECH and should be validated in future population-based studies. Fifth, in our previous study, the BMIs between CCH and ECH were not significantly different [36]. Since our study data only includes Korean patients, the proportion of CCH was only 3.5%, which is considerably low compared to Western patients. In this context, the impact of obesity on CCH should be further investigated in studies that analyze datasets with a sufficient number of patients diagnosed with CCH.

Conclusions

In the present study, higher BMI and obesity were inversely associated with lifetime bout occurrence and annual bout frequency in ECH. These results suggest that neurobiological aspects of obesity may suppress cluster bout periodicity. However, the exact mechanisms to justify our findings largely remains unclear. Further preclinical and clinical studies are needed to confirm our findings.

Abbreviations

aOR	Multivariable-adjusted odds ratio
BMI	Body mass index
CCH	Chronic cluster headache
CH	Cluster headache
CI	Confidence interval
ECH	Episodic cluster headache
IQR	Interquartile range
GAD-7	The Generalized Anxiety Disorder 7-item scale
HIT-6	The 6-item Headache Impact Test
ICHD	The International Classification of Headache Disorders
ICHD-3	The third edition of the International Classification of Headache Disorders
IRB	Institutional review board
KCHR	Korean cluster headache registry
OR	Odds ratio
PHQ-9	The Patient Health Questionnaire 9-item scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-02061-9.

Supplementary Material 1

Acknowledgements

None.

Author contributions

All authors have made substantial contributions to this research. B.S. Kim and S.J. Cho conceptualized and designed the study. All authors collected the data. B.S. Kim and S.J. Cho performed the statistical analysis and drafted the manuscript. All authors contributed to interpretation of the data and revised the manuscript. All authors read and approved the final version of the manuscript. Drs B.S. Kim and S.J. Cho had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

This research was supported by the Korean Headache Society.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee in each participating hospital and complied with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients fully understood the study aims and gave informed written consent before their participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea
[2]Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
[3]Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Republic of Korea
[4]Department of Neurology, Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea
[5]Department of Neurology, Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea
[6]Department of Neurology, Severance hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

[7]Department of Neurology, Institute of Health Science, Gyeongsang National University College of Medicine, Gyeonsang National University Hospital, Jinju, Republic of Korea
[8]Department of Neurology, College of Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea
[9]Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[10]Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Keun Jae Bong-gil 7, Hwaseong, Gyeonggi-do 18450, Republic of Korea

Received: 9 February 2025 / Accepted: 2 May 2025
Published online: 20 June 2025

References

1. Wei DY, Yuan Ong JJ, Goadsby PJ (2018) Cluster headache: epidemiology, pathophysiology, clinical features, and diagnosis. Ann Indian Acad Neurol 21(Suppl 1):S3–s8
2. Petersen AS, Lund N, Goadsby PJ, Belin AC, Wang SJ, Fronczek R et al (2024) Recent advances in diagnosing, managing, and Understanding the pathophysiology of cluster headache. Lancet Neurol 23(7):712–724
3. Kim M, Yu JK, Kim YH (2024) Update on cluster headaches: from genetic to novel therapeutic approaches. Headache Pain Res 25(1):42–53
4. Schor LI, Pearson SM, Shapiro RE, Zhang W, Miao H, Burish MJ (2021) Cluster headache epidemiology including pediatric onset, sex, and ICHD criteria: results from the international cluster headache questionnaire. Headache 61(10):1511–1520
5. Nesbitt AD, Goadsby PJ (2012) Cluster headache. BMJ 344:e2407
6. Bahra A, May A, Goadsby PJ (2002) Cluster headache: a prospective clinical study with diagnostic implications. Neurology 58(3):354–361
7. Worldwide trends in underweight and obesity (2024) From 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet 403(10431):1027–1050
8. Flegal KM, Kit BK, Orpana H, Graubard BI (2013) Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 309(1):71–82
9. Westgate CSJ, Israelsen IME, Jensen RH, Eftekhari S (2021) Understanding the link between obesity and headache- with focus on migraine and idiopathic intracranial hypertension. J Headache Pain 22(1):123
10. Bigal ME, Liberman JN, Lipton RB (2006) Obesity and migraine: a population study. Neurology 66(4):545–550
11. Burish MJ, Pearson SM, Shapiro RE, Zhang W, Schor LI (2021) Cluster headache is one of the most intensely painful human conditions: results from the international cluster headache questionnaire. Headache 61(1):117–124
12. Choi YJ, Kim BK, Chung PW, Lee MJ, Park JW, Chu MK et al (2018) Impact of cluster headache on employment status and job burden: a prospective cross-sectional multicenter study. J Headache Pain 19(1):78
13. Kim BS, Chung PW, Kim BK, Lee MJ, Chu MK, Ahn JY et al (2022) Diagnostic delay and its predictors in cluster headache. Front Neurol 13:827734
14. Kim SK, Chu MK, Kim BK, Chung PW, Moon HS, Lee MJ et al (2024) An analysis of the determinants of the Health-Related quality of life in Asian patients with cluster headaches during cluster periods using the time Trade-Off method. J Clin Neurol 20(1):86–93
15. Haam JH, Kim BT, Kim EM, Kwon H, Kang JH, Park JH et al (2023) Diagnosis of obesity: 2022 update of clinical practice guidelines for obesity by the Korean society for the study of obesity. J Obes Metab Syndr 32(2):121–129
16. Kim BS, Park JW, Sohn JH, Lee MJ, Kim BK, Chu MK et al (2019) Associated factors and clinical implication of cutaneous allodynia in patients with cluster headache: A prospective multicentre study. Sci Rep 9(1):6548
17. Kim BS, Chung PW, Kim BK, Lee MJ, Park JW, Chu MK et al (2020) The impact of remission and coexisting migraine on anxiety and depression in cluster headache. J Headache Pain 21(1):58
18. Haywood KL, Mars TS, Potter R, Patel S, Matharu M, Underwood M (2018) Assessing the impact of headaches and the outcomes of treatment: A systematic review of patient-reported outcome measures (PROMs). Cephalalgia 38(7):1374–1386
19. Ferrari A, Zappaterra M, Righi F, Ciccarese M, Tiraferri I, Pini LA et al (2013) Impact of continuing or quitting smoking on episodic cluster headache: a pilot survey. J Headache Pain 14(1):48
20. Coppola G, Abagnale C, Sebastianelli G, Goadsby PJ (2024) Pathophysiology of cluster headache: from the trigeminovascular system to the cerebral networks. Cephalalgia 44(2):3331024231209317
21. Naber WC, Fronczek R, Haan J, Doesborg P, Colwell CS, Ferrari MD et al (2019) The biological clock in cluster headache: A review and hypothesis. Cephalalgia 39(14):1855–1866
22. Hong Y, Kang MK, Chu MK, Cho SJ, Im HJ (2024) Cluster headache characteristics and the severity of obstructive sleep apnea: insights from polysomnography analysis. Headache Pain Res 25(1):63–71
23. Sonnefeld L, Rohmann N, Geisler C, Laudes M (2023) Is human obesity an inflammatory disease of the hypothalamus? Eur J Endocrinol 188(3):R37–r45
24. Brown SSG, Westwater ML, Seidlitz J, Ziauddeen H, Fletcher PC (2023) Hypothalamic volume is associated with body mass index. Neuroimage Clin 39:103478
25. Spindler M, Thiel CM (2023) Hypothalamic microstructure and function are related to body mass, but not mental or cognitive abilities across the adult lifespan. Geroscience 45(1):277–291
26. Silvestro M, Tessitore A, Orologio I, Battista G, Siciliano M, Tedeschi G et al (2022) Cluster headache pathophysiology: what we have learned from advanced neuroimaging. Headache 62(4):436–452
27. Rivera-Mancilla E, Al-Hassany L, Villalón CM, MaassenVanDenBrink A (2021) Metabolic aspects of migraine: association with obesity and diabetes mellitus. Front Neurol 12:686398
28. Søborg MK, Jensen RH, Barloese M, Petersen AS (2024) Biomarkers in cluster headache: A systematic review. Headache 64(1):98–116
29. Peterlin BL, Sacco S, Bernecker C, Scher AI (2016) Adipokines and migraine: A systematic review. Headache 56(4):622–644
30. Abbasi M, Noori-Zadeh A, Seidkhani-Nahal A, Kaffashian M, Bakhtiyari S, Panahi S (2019) Leptin, adiponectin, and resistin blood adipokine levels in migraineurs: systematic reviews and meta-analyses. Cephalalgia 39(8):1010–1021
31. van Rossum EF (2017) Obesity and cortisol: new perspectives on an old theme. Obes (Silver Spring) 25(3):500–501
32. Hewagalamulage SD, Lee TK, Clarke IJ, Henry BA (2016) Stress, cortisol, and obesity: a role for cortisol responsiveness in identifying individuals prone to obesity. Domest Anim Endocrinol 56(Suppl):S112–S120
33. Obermann M, Nägel S, Ose C, Sonuc N, Scherag A, Storch P et al (2021) Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial. Lancet Neurol 20(1):29–37
34. Sohn JH, Lee MJ, Cho SJ (2021) Update on treatment of cluster headache. J Korean Neurol Assoc 39(3):113–120
35. Jeong SM, Jung JH, Yang YS, Kim W, Cho IY, Lee YB et al (2024) 2023 obesity fact sheet: prevalence of obesity and abdominal obesity in adults, adolescents, and children in Korea from 2012 to 2021. J Obes Metab Syndr 33(1):27–35
36. Cho SJ, Lee MJ, Kim BK, Moon HS, Chung PW, Sohn JH et al (2019) Clinical features of chronic cluster headache based on the third edition of the international classification of headache disorders: A prospective multicentre study. PLoS ONE 14(8):e0221155

Publisher's note