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Anterior-superior hypothalamic volume in relation to vestibular symptom burden in migraine

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Abstract

Background. Vestibular symptoms are common in migraine, but it remains unclear whether hypothalamic structure varies with vestibular symptom burden beyond broad diagnostic grouping. We addressed this question in an exploratory MRI study centered on continuous vestibular symptom severity within a female-predominant migraine cohort.

Methods. The analytic sample comprised 41 patients with migraine and 23 healthy controls with usable 3D T1-weighted MRI. FreeSurfer 7.4.1 was used for hypothalamic subunit segmentation. Primary within-patient models regressed each of six hypothalamic outcomes on continuous Vertigo Symptom Scale (VSS) score, adjusting for age, sex, and estimated total intracranial volume, with Benjamini–Hochberg correction across the six-outcome VSS family. Questionnaire-based symptom scores were collected on the day of MRI acquisition.

Results. Within the migraine cohort, anterior-superior total volume showed a positive association with VSS (β = 0.136 per VSS point, 95% CI 0.038 to 0.233, P = 0.008; FDR = 0.046). Across the typical VSS range observed in the migraine cohort (interquartile range, 13 to 34 points; 21-point span), this coefficient corresponds to approximately 2.9 mm^3. Anterior-superior total volume was the only subregional outcome to survive FDR correction. Estimates were similar across robust standard-error, leave-one-out, and quadratic-age sensitivity analyses. Whole-hypothalamic associations were weaker and more model-dependent. Continuous DHI models converged on the same anatomical location but did not permit clear construct-level separation from VSS. Contextual migraine-versus-control comparisons showed no clear hypothalamic volumetric differences.

Conclusions. In this exploratory cross-sectional MRI study, anterior-superior hypothalamic volume was the only subregional measure showing a preliminary association with vestibular symptom burden. Findings arise from a female-predominant migraine sample and require external validation.

Background

Migraine is a complex brain disorder defined clinically by recurrent headache attacks and associated sensory or gastrointestinal symptoms. Many patients also report vestibular or audiovestibular complaints, including dizziness, motion sensitivity, or tinnitus [1–3]. Formal vestibular migraine criteria are deliberately stringent [2], yet real-world migraine cohorts often contain patients with meaningful vestibular symptom burden who do not fit neatly into a single diagnostic box. That gap supports treating vestibular symptom burden as a dimensional phenotype alongside categorical labels [4–5].

Recent neuroimaging work in vestibular migraine has pointed to distributed abnormalities across vestibular, salience, and pain-processing networks [6–7]. More broadly, migraine imaging has implicated the hypothalamus in homeostatic regulation, circadian timing, autonomic control, and attack-related brain dynamics [8–9]. Structural and microstructural hypothalamic abnormalities have also been reported in migraine cohorts and linked to clinically relevant attack features [10–12].

This made the hypothalamus a plausible structure through which vestibular symptom burden might be expressed. To index that burden, we prespecified the Vertigo Symptom Scale (VSS) as the primary symptom measure because it captures current vertigo and balance symptoms together with autonomic-anxiety accompaniments of dizziness [13]. By contrast, the Dizziness Handicap Inventory (DHI) emphasizes self-perceived disability [14] and was therefore treated as a supporting measure, not the primary exposure.

We therefore asked whether hypothalamic volume varied with vestibular symptom burden within migraine. No directional hypothesis was prespecified for subregional volume change. Because the dataset did not contain formal Bárány/ICHD-3 adjudication of vestibular migraine for all patients, the study was framed as a dimensional analysis of vestibular symptom burden and not as a formal vestibular-migraine case-definition study.

Methods

Study design and participants

This was a retrospective cross-sectional observational study based on a prospectively maintained clinical and imaging dataset collected at the Headache Clinic of the First Affiliated Hospital of Chongqing Medical University between December 2021 and June 2023. For the migraine arm, 1,190 headache-clinic patients were screened; 924 did not meet eligibility criteria and 199 declined participation. Sixty-seven provided written informed consent, and 63 underwent MRI; 4 consented participants did not present for MRI acquisition. Among the 63 scanned migraine participants, 3 were excluded because of incidental MRI abnormalities, 4 because they did not meet the source-cohort scan-state protocol, and 4 because of possible alternative vestibular or otologic disorders that could independently account for vestibular symptoms (for example benign paroxysmal positional vertigo, Ménière disease, persistent postural-perceptual dizziness, vestibular neuritis sequelae, or clinically significant ear disease). Of the remaining 52 migraine participants, 3 were excluded because baseline MMD could not be derived from the headache diary, 3 because of partial MRI data loss during transfer, and 5 because of MRI data quality issues, leaving 41 migraine participants for the present structural MRI analysis. Healthy controls were recruited separately and were not part of the headache-clinic screening cascade; 23 healthy controls with usable structural MRI were included in the present analyses.

The source cohort had been approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (approval No. CY2020-594), and all participants provided written informed consent at enrollment.The present secondary analysis was additionally approved by the same Ethics Committee (approval No.2026-0357-01). The report was prepared with reference to STROBE recommendations for observational studies and with attention to Sex and Gender Equity in Research (SAGER) guidance on sex reporting [15–16]. Because the analytic migraine cohort was overwhelmingly female (40/41), the findings are best read as applying to female-predominant migraine samples not as

evidence for sex-specific inference. Sex was therefore included as a biological covariate where possible, and a women-only sensitivity analysis was also performed.

Clinical variables

Questionnaire-based variables were collected on the day of MRI acquisition. They comprised demographic measures (age, sex, and BMI), vestibular measures (DHI and VSS total scores), headache impact measures (MIDAS and HIT-6), HADS total score, and disease duration. Baseline monthly migraine days (MMD) were diary-derived and not same-day state measures.

A binary vertigo-present variable was also available in the migraine cohort, but because it indexed symptom presence/absence rather than symptom burden, it was used only for sensitivity checks. The Vertigo Symptom Scale has no widely adopted clinical cut-off for this setting, so VSS tertiles were derived from the empirical 33rd and 67th percentiles within the migraine cohort for descriptive stratification and exploratory visualization only: low (0–16), middle (17–28), and high (29–82). These strata were not used for primary inference.

MRI acquisition and hypothalamic volumetry

MRI data were acquired on a Philips Ingenia DNA 3.0-T scanner equipped with a 32-channel head coil. Only the high-resolution 3D T1-weighted turbo spin-echo structural sequence was used in the present report. Key acquisition parameters were repetition time/echo time = 600/28 ms, excitation flip angle = 90°, field of view = 280 × 280 mm, matrix = 280 × 280, 327 reconstructed sections, nominal voxel size = 1.0 × 1.0 × 1.0 mm, and acquisition time approximately 6 min 5 s.

The source-cohort acquisition protocol scheduled MRI when no headache was present and required participants to avoid acute analgesics, sedative or hypnotic medication, caffeine-containing drinks, and alcohol for 24 h before scanning. Post-scan follow-up was used to identify scan-state protocol deviations requiring exclusion or repeat scanning where applicable. Structural image quality was reviewed immediately after acquisition, and scans not meeting quality requirements were excluded or repeated when feasible. Other MRI sequences were acquired in the broader imaging protocol but were not analyzed in the present study.

T1-weighted images were processed with FreeSurfer version 7.4.1 (https://surfer.nmr.mgh.harvard.edu). The automated pipeline included skull stripping, intensity normalization, Talairach registration, tissue segmentation, and hypothalamic subunit labeling using the FreeSurfer hypothalamic segmentation module described by Billot et al. [17]. Each hemisphere was partitioned into anterior-inferior, anterior-superior, tuberal-inferior, tuberal-superior, and posterior subunits, and bilateral totals together with whole hypothalamic left, right, and total volumes were extracted. Automated outputs were screened for gross processing failures or anatomically implausible labels before statistical analysis. Estimated total

intracranial volume (TIV) was extracted from the FreeSurfer output and included as a covariate to account for inter-individual differences in head size.

Statistical analysis

No a priori sample-size calculation was performed because this was an exploratory secondary analysis of a fixed dataset. Analyses were conducted in Python 3.11 using pandas, SciPy, and statsmodels. Complete-case data were used within each model, so sample sizes varied slightly across sensitivity analyses according to variable availability. Categorical variables were compared with Fisher's exact or chi-square tests as appropriate; continuous variables were compared with Welch t tests, Mann–Whitney U tests, one-way ANOVA, or Kruskal–Wallis tests according to distributional characteristics. No directional hypothesis was prespecified for subregional volumes. Continuous VSS was the sole primary exposure. The primary within-migraine models regressed each of six prespecified bilateral hypothalamic outcomes (five atlas-defined subregional totals plus whole hypothalamic total volume) on continuous VSS score, adjusting for age, sex, and TIV. Bilateral totals were prespecified to reduce multiplicity relative to side-specific modeling. Benjamini–Hochberg FDR correction was applied across this six-outcome VSS family. Parallel DHI models were treated as a separate supporting family and were FDR-corrected within that family instead of being pooled with the primary VSS tests. Interpretation centered on the anterior-superior subregion as the focal outcome, with whole hypothalamic total volume retained only as a global summary measure and the remaining subregions reported for context.

Sample-derived VSS tertiles were examined only as descriptive/exploratory strata. Exploratory tertile ANCOVA models used the same covariates as the primary models, but because subgroup sizes were small (n = 13–14) and tertile means appeared non-monotonic, these models were not treated as confirmatory evidence. To judge whether omnibus tertile effects were driven mainly by the middle tertile, we additionally examined adjusted low-versus-high contrasts for the primary outcomes.

Robustness checks for the focal anterior-superior association comprised HC3 robust standard errors, leave-one-out refitting, age² adjustment, and a women-only refit to verify that the result was not driven by the single male participant. Supporting analyses added BMI or HADS, ran parallel DHI models, and examined binary vertigo status or baseline headache-burden measures where appropriate. Nominal P values are reported for completeness and were interpreted only in supporting or secondary analyses when not FDR-adjusted.Results

Participant characteristics

The final analytic dataset included 64 participants (23 healthy controls and 41 patients with migraine). The migraine cohort was predominantly female (40/41), consistent with the epidemiology of migraine. Healthy controls were not administered VSS or DHI.

Table 1
Sample characteristics

Variable	HC (n = 23)	Migraine (n = 41)	P
Age, years	37.30 ± 8.69	38.83 ± 10.12	0.529
Female sex, n (%)	18 (78.3)	40 (97.6)	0.020
BMI, kg/m²	22.36 ± 1.53	21.58 ± 2.72	0.151
TIV, mm³	1220560 ± 193783	1158715 ± 170845	0.209
HADS total	8.0 (3.5–15.5)	17.0 (11.0–24.0)	0.002
DHI total	—	29.0 (10.0–46.0)	—
VSS total	—	22.0 (13.0–34.0)	—
Vertigo present, n (%)	—	18 (43.9)	—

Data are shown as mean ± SD, median (IQR), or n (%). HADS comparison used Mann–Whitney U; age, BMI, and TIV used Welch t tests; sex used Fisher's exact test. VSS, DHI, and binary vertigo status were not administered to healthy controls by design and were collected only in the migraine cohort.

Sample-derived VSS tertiles summarized the within-cohort symptom gradient

Migraine patients were stratified into sample-derived VSS tertiles to summarize the distribution behind the primary continuous analyses, not to define diagnostic groups or create a confirmatory contrast. VSS necessarily differed across strata by construction. DHI and HADS also varied across strata, whereas differences in other baseline headache measures were less consistent and are shown descriptively in Table 2.

Table 2
Migraine cohort characteristics by sample-derived VSS tertile (descriptive stratification)

Variable	Low (n = 14)	Middle (n = 13)	High (n = 14)	P
Age, years	40.79 ± 11.38	35.46 ± 10.15	40.00 ± 8.59	0.350
Female sex, n (%)	14 (100.0)	13 (100.0)	13 (92.9)	0.372
BMI, kg/m²	21.81 ± 3.19	20.85 ± 2.26	22.03 ± 2.67	0.503
Disease duration, years	17.5 (10.0–28.8)	20.0 (10.0–25.0)	16.0 (14.2–21.8)	0.975
Baseline MMD	18.5 (6.5–24.2)	9.0 (6.0–16.0)	12.5 (6.2–19.5)	0.366
MIDAS total score	12.0 (6.0–19.0)	19.0 (11.5–28.5)	28.5 (16.0–65.5)	0.060
HIT-6 score	59.71 ± 10.05	57.85 ± 12.86	66.43 ± 7.11	0.082
HADS total score	15.5 (8.0–20.8)	16.0 (8.0–22.0)	22.5 (17.0–28.8)	0.040
DHI total score	12.0 (4.0–24.2)	18.0 (12.0–56.0)	45.0 (30.0–70.0)	0.002
VSS total score	8.0 (5.0–12.8)	22.0 (19.0–25.0)	42.0 (34.8–53.0)	< 0.001

Age, BMI, and HIT-6 were compared using one-way ANOVA. Disease duration, baseline MMD, MIDAS, HADS, DHI, and VSS were compared using Kruskal–Wallis tests. Categorical variables used chi-square tests.

Primary continuous VSS models highlighted anterior-superior volume as the main subregional association

When VSS was modeled continuously in the primary within-patient analyses, anterior-superior total volume was positively associated with VSS (β = 0.136 per VSS point, 95% CI 0.038 to 0.233, P = 0.008; FDR = 0.046) and was the only subregional outcome to survive FDR correction(Fig. 1). Across the migraine-cohort VSS interquartile range shown in Table 1 (13 to 34 points), this coefficient corresponds to an adjusted anterior-superior volume difference of approximately 2.9 mm³ (95% CI 0.8 to 4.9 mm³); from the cohort median to the upper quartile (22 to 34 points), the corresponding difference is approximately 1.6 mm³. Whole hypothalamic total volume was not associated (β = 0.814, 95% CI -0.469 to 2.097, P = 0.206; FDR = 0.340) (Table 3). Descriptive side-specific anterior-superior models are provided in Supplementary Table S6; estimates were positive on both sides and somewhat stronger on the left.

Continuous DHI models pointed to the same anatomical location but did not allow clear construct-level separation from VSS. Across the same six primary outcomes, only anterior-superior total volume showed a nominal DHI association (β = 0.098, 95% CI 0.025 to 0.171, P = 0.010; FDR = 0.058), whereas the other DHI associations were clearly non-significant (Supplementary Table S4). Given the correlation between VSS and DHI, the two scales probably captured overlapping symptom content; this dataset cannot confidently separate burden from handicap at the individual scale.

Table 3
Primary continuous VSS models for hypothalamic volumes in the migraine cohort

Outcome	β per 1-point VSS	95% CI	P	FDR	Partial R^2
Anterior-superior (total)	0.136	0.038 to 0.233	0.008	0.046	0.182
Whole hypothalamus (total)	0.814	-0.469 to 2.097	0.206	0.340	0.044
Anterior-inferior (total)	0.088	-0.025 to 0.200	0.123	0.340	0.071
Posterior (total)	0.056	-0.300 to 0.413	0.750	0.750	0.003
Tuberal-inferior (total)	0.327	-0.255 to 0.909	0.262	0.340	0.035
Tuberal-superior (total)	0.223	-0.192 to 0.638	0.284	0.340	0.032

β coefficients represent the adjusted change in volume per 1-point increase in VSS. Models were adjusted for age, sex, and TIV. Partial R^2 values were derived from the model-specific t statistic for VSS and are provided as descriptive effect-size indices. Outcomes are ordered to highlight the focal anterior-superior subregional outcome, followed by the global whole-hypothalamus context measure and then the remaining subregions in ascending order of P values.

Exploratory VSS tertile contrasts were non-monotonic and are best interpreted cautiously

Exploratory ANCOVA across the sample-derived tertiles showed omnibus differences for several volumes, but the pattern was clearly non-monotonic, with the middle tertile often highest (Supplementary Table S5). Quadratic continuous VSS terms were not significant for either the anterior-superior or whole-total context models (Table S3), which does not support a confirmed nonlinear dose-response pattern in this sample. For whole hypothalamic total volume, the adjusted low-versus-high tertile contrast was clearly null (P = 0.519). For anterior-superior volume, the analogous contrast remained directionally positive and nominally significant (P = 0.011) but did not survive FDR across the six outcomes. Taken together, these findings suggest that anterior-superior was the only outcome to retain a signal across multiple codings, whereas the broader tertile omnibus results are more likely to reflect small-sample variability than confirmed non-monotonic biology. We therefore present the tertile analyses as descriptive context, not confirmatory evidence.

Sensitivity analyses contextualized the anterior-superior interpretation

VSS correlated with HADS total score (Spearman ρ = 0.40, P = 0.009) and more strongly with DHI (ρ = 0.63, P < 0.001), but multicollinearity was limited in the primary models (all VIFs < 2.8). Adding BMI or HADS did not attenuate the anterior-superior association; if anything, HADS adjustment modestly

increased the coefficient, which argues against simple anxiety-driven confounding, although the cross-sectional design does not support mediation inference.

Headache-burden variables were not significantly associated with either the focal anterior-superior outcome or whole-hypothalamic total volume (Table S2). HC3-robust and leave-one-out analyses yielded similar anterior-superior coefficients, and quadratic VSS terms were not significant for either anterior-superior or whole-total models (Table S3). The focal anterior-superior relationship is visualized in Fig. 2.

Broad case-control grouping did not show significant hypothalamic differences

In this modestly sized sample, contextual healthy-control versus migraine grouping showed no significant hypothalamic volumetric differences.

Overall recruitment, exclusion, and separate healthy-control enrollment are summarized in Fig. 3.

Discussion

We read this pattern as preliminary support for a symptom-dimensional account: within migraine, vestibular symptom burden aligned more clearly with anterior-superior hypothalamic volume than with broad migraine-control grouping. The focal association crossed the six-outcome FDR threshold in the primary sample and was stable across robust, leave-one-out, and age-adjusted checks. Whole-hypothalamic total volume showed weaker and more model-dependent estimates, and contextual migraine-versus-control comparisons showed no clear hypothalamic volumetric differences.

That case-control contrast should be read cautiously. In this modestly sized sample, broad migraine-versus-control grouping produced a context-setting null result not positive evidence against any migraine-related hypothalamic effect. Its value here is that it sharpened the within-patient question and reinforced the idea that symptom dimensions may be more informative than broad diagnostic grouping when the target structure is small and the clinical phenotype heterogeneous.

This phenotype-oriented framing is also the clinically appropriate one. The dataset did not include formal Bárány/ICHD-3 adjudication of vestibular migraine for all patients, and VSS is a symptom-burden scale, not a diagnostic instrument [2, 13, 18–19]. The study should therefore be read as an analysis of vestibular symptom burden within migraine, not as a case series of formally adjudicated vestibular migraine. That distinction matters because high VSS scores can arise across heterogeneous vestibular symptom profiles, whereas formal vestibular-migraine diagnosis requires additional temporal and phenomenological criteria not captured here [2, 18–19]. The source cohort did screen for and exclude alternative vestibular or otologic disorders considered sufficient to explain dizziness independently of migraine, although residual undetected non-migraine vestibular contributions cannot be excluded.

Recent anterior-hypothalamic findings in cluster headache and chronic migraine provide useful anatomical context, but they should not be treated as direct comparators. Using the same Billot segmentation framework, Ferraro et al. reported larger ipsilateral anterior-superior subunit volume in chronic cluster headache and an association with daily attack number [20]. Arkink et al. also reported anterior hypothalamic enlargement in cluster headache using region-of-interest VBM analyses [21]. In migraine, Chen et al. reported reduced whole and anterior hypothalamic volume in chronic migraine compared with controls [22], and other studies have described hypothalamic structural covariance or microstructural abnormalities [10–12]. The directions and metrics are not uniform, which argues against a simple interpretation in which larger volume directly indexes migraine burden. More conservatively, the present result fits a broader literature in which hypothalamic structural metrics vary with headache disorder, imaging method, and clinical dimension.

Within the Billot/FreeSurfer atlas, the anterior-superior subunit approximates preoptic and paraventricular territories [17], but an atlas-defined subunit does not support precise nuclei-level inference. The functional links discussed here therefore refer to the region in broad anatomical terms and cannot be assigned to a specific hypothalamic nucleus on the basis of this atlas. Even so, the location is anatomically plausible given homeostatic and autonomic functions implicated in migraine [8–9, 23–26]. Related vestibulo-autonomic work also supports considering this region in relation to sensory-state and body-state signaling [27–28], and broader literature links vestibular symptoms to anxiety-related balance processing and vestibular-metabolic interactions [29–30]. Our data, however, were purely structural; we did not measure autonomic physiology, endocrine state, or interoception directly. Although the anterior-superior association crossed the six-outcome FDR threshold in the primary sample, the study remains exploratory. These anatomical correspondences should therefore be treated as orienting context rather than mechanistic validation, and mechanistic interpretation should remain explicitly speculative.

Supporting analyses point in the same direction, but more tentatively. VSS correlated with HADS and DHI, yet VIFs were low and the anterior-superior association persisted after adding BMI or HADS. HADS adjustment slightly increased, not attenuated, the coefficient, which is not what one would expect from simple anxiety-driven confounding, although the cross-sectional design does not allow mediation inference. Both VSS and DHI pointed to the anterior-superior compartment as the only nominally associated outcome across the same six volumes. Given the correlation between the two scales, however, the dataset cannot confidently separate vestibular symptom burden from dizziness handicap. What it does suggest is that the anterior-superior signal aligns more closely with an active vestibular-symptom dimension than with simple symptom presence/absence or generic headache burden.

Tertile patterns still require caution. In 3 of the 6 primary outcomes—whole total, tuberal-inferior, and tuberal-superior—the middle tertile showed the highest mean volume, whereas quadratic continuous VSS terms were not significant. For whole hypothalamic total volume, the adjusted low-versus-high tertile contrast was clearly null (P = 0.519), indicating that the omnibus tertile signal at the whole-structure level was largely driven by the middle tertile and is most parsimoniously explained by sampling fluctuation in

a small subgroup. By contrast, both the middle and high tertiles exceeded the low tertile for anterior-superior volume, and the low-versus-high contrast remained directionally positive and nominally significant (P = 0.011), although it still failed FDR correction. This pattern is consistent with anterior-superior being the only outcome to retain a signal across multiple codings, while the broader tertile results are best treated as descriptive not evidence of confirmed non-monotonic biology.

Because only one migraine participant was male, the women-only refit was a limited influence check rather than a sex-effect analysis. Removing that participant left the anterior-superior estimate unchanged to the displayed precision. HC3-robust, leave-one-out, and age²-adjusted analyses likewise left the anterior-superior signal similar in direction and magnitude.

Several design features strengthen the analysis. All scans were acquired on the same scanner with the same T1 protocol and processed with the same FreeSurfer version. The analysis examined both whole-hypothalamic and bilateral subregional volumes, controlled multiplicity within prespecified primary outcome families, and kept the evidentiary distinction between continuous primary models and exploratory tertile analyses explicit.

Important limitations remain. The study was exploratory, single-cohort, and modest in size, especially for subgroup analyses. Healthy controls were recruited independently and should be viewed as a contextual reference rather than an epidemiologically matched comparison group. Because controls were not administered VSS or DHI, we could not test whether hypothalamic structure varies with vestibular symptom burden across the full sample. The migraine sample was overwhelmingly female, so the findings are best viewed as applying to female-predominant migraine samples and do not support sex-specific inference.

Several methodological and data limitations also affect interpretation. Segmentation-specific quality control was limited to screening for gross processing failures and anatomically implausible labels rather than formal inter-rater procedures, which matters when studying very small hypothalamic subunits. Alternative vestibular or otologic disorders were clinically screened for and excluded at source-cohort entry when judged sufficient to explain dizziness independently of migraine; residual undetected non-migraine vestibular contributions nevertheless remain possible. Preventive-treatment status at MRI, menstrual-cycle phase or other hormonal state [31–32], and longitudinal structural follow-up were not harmonized. The cross-sectional design also leaves directionality unresolved. Vestibular burden may relate to hypothalamic structure, pre-existing structural traits may predispose to higher vestibular burden, or both may reflect third variables. Independent validation in larger samples therefore remains essential.

Clinically, these results do not yet support a burden-based stratification strategy. The observed effect sizes were modest and are not suitable for individual-level classification or decision-making. Instead, the findings mainly justify prospective validation. Such studies should recruit larger female-predominant migraine cohorts, adjudicate formal vestibular migraine, and prespecify continuous symptom models. They should also track scan-state adherence and use longitudinal imaging to test whether anterior-

superior hypothalamic structure tracks vestibular symptom burden and whether that signal has prognostic or treatment relevance.

Conclusions

In this exploratory cross-sectional MRI study, anterior-superior hypothalamic volume emerged as the only candidate subregional correlate of vestibular symptom burden, whereas broader whole-structure and tertile patterns remained descriptive. Future work should first test this association in larger longitudinal and multi-cohort samples with prespecified continuous symptom models and formal vestibular-migraine adjudication. Biological or clinical interpretation should remain preliminary until those validations are available.

Abbreviations

ANCOVA
analysis of covariance
BMI
body mass index
DHI
Dizziness Handicap Inventory
FDR
false discovery rate
HADS
Hospital Anxiety and Depression Scale
HC
healthy control
HIT-6
6-item Headache Impact Test
MMD
monthly migraine days
TIV
total intracranial volume
VSS
Vertigo Symptom Scale.

Declarations

Ethics approval and consent to participate

The source cohort was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (approval No. CY2020-594), and all participants provided written informed consent.

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments. The present secondary analysis was additionally approved by the same Ethics Committee (approval No. 2026-0357-01)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

Liang Dong and Linyi Che contributed equally to this work. Liang Dong, Linyi Che, and Ge Tan conceived and designed the study. Liang Dong, Linyi Che, Wanqun Hu, Xiaoping Fan, Qinlian Huang, Ruonan Zhang, and Yuhui Xu were responsible for data collection and curation. Liang Dong and Linyi Che performed the statistical analyses and drafted the manuscript. Li Jiang, Ge Tan, and Jiying Zhou supervised the study and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

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Not applicable.

Availability of data and materials

The raw study dataset is not publicly available because it contains potentially identifiable clinical data. Qualified investigators may request access to de-identified analysis-ready data, the data dictionary, and statistical code from the corresponding author for methodologically sound proposals, subject to

institutional ethics approval, a data-use agreement, and approval by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

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Figures

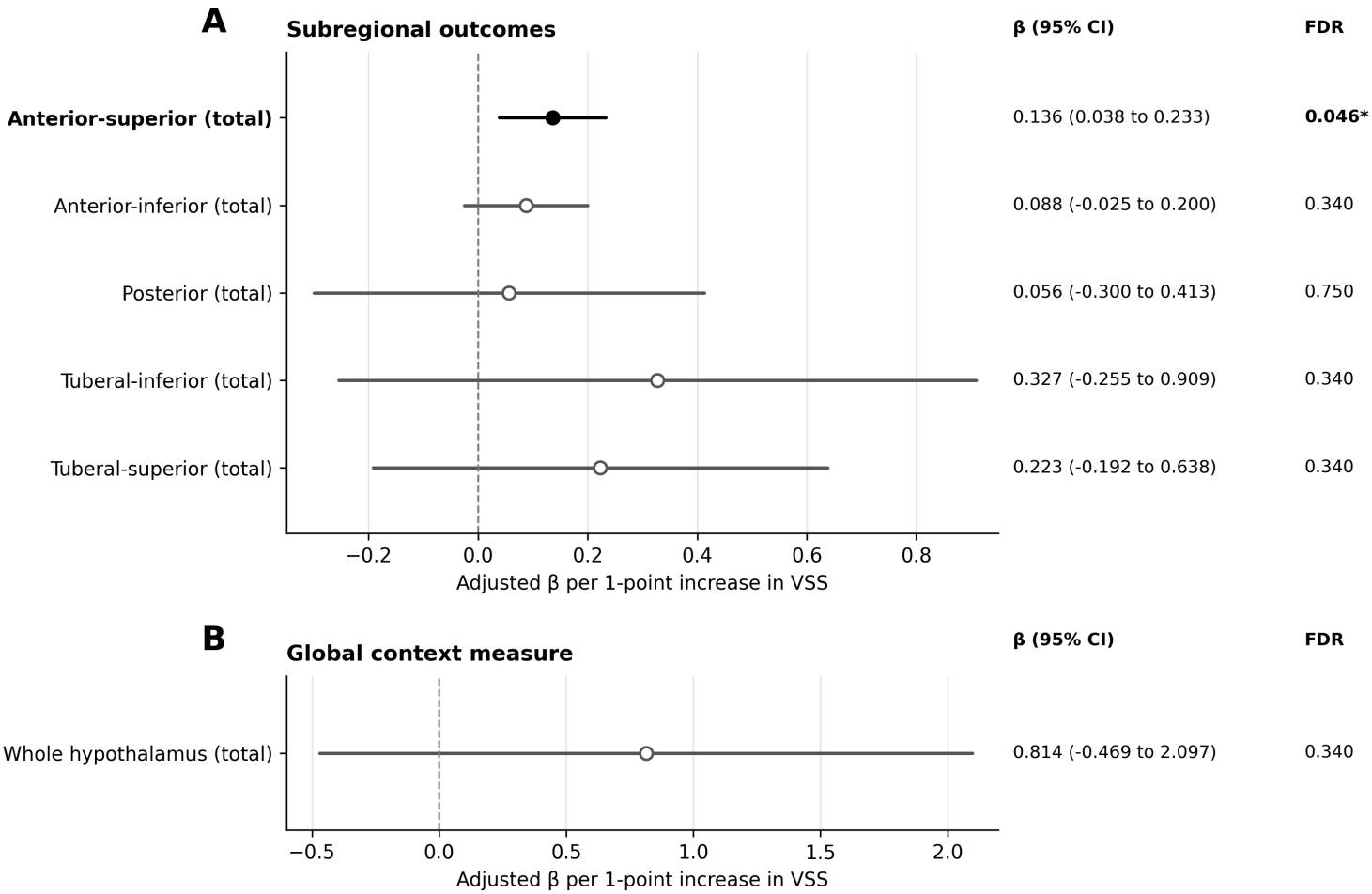


Figure 1

Forest plot of the six primary continuous VSS models in the migraine cohort. Panel A shows the five atlas-defined subregional outcomes and Panel B the whole hypothalamic total volume, displayed separately because the whole-hypothalamus summary outcome operates on a larger coefficient scale. Points represent adjusted β coefficients per 1-point increase in VSS; horizontal lines denote 95% confidence intervals. The dashed vertical line marks β = 0. The anterior-superior subregion was the only outcome whose 95% confidence interval excluded zero and which passed the prespecified FDR threshold. Raw coefficients and model details are reported in Table 3.

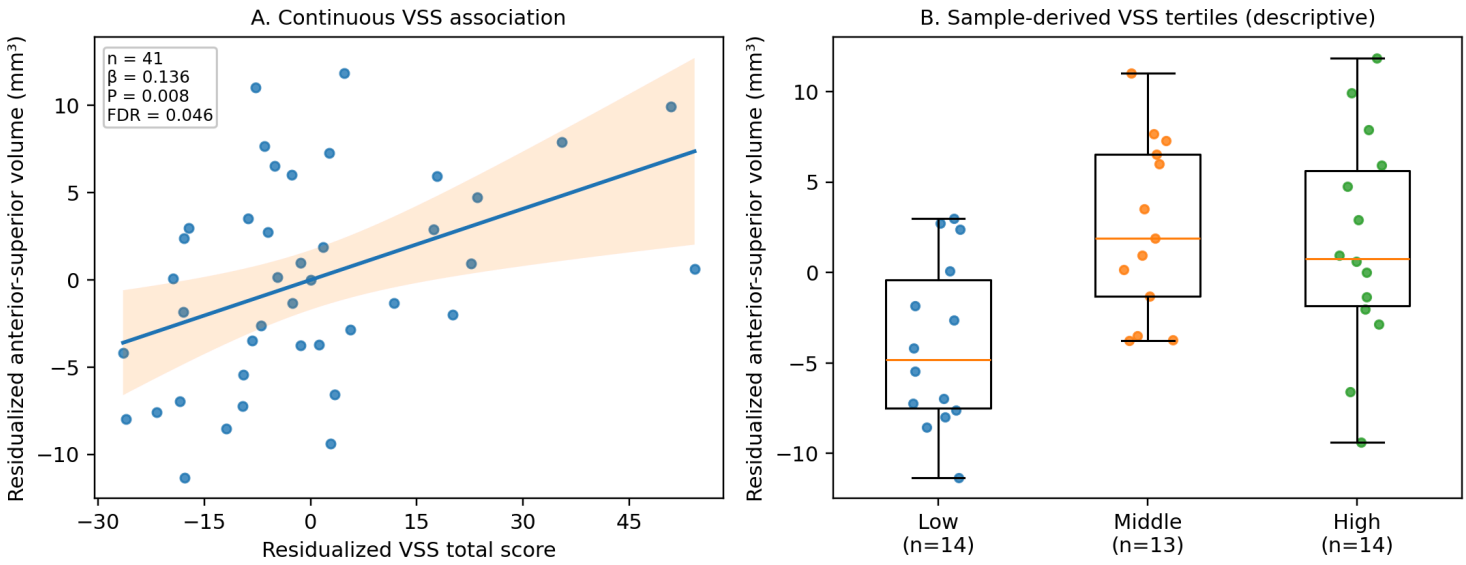


Figure 2

Focal anterior-superior associations with vestibular symptom burden in the migraine cohort. Panel A shows the partial association between VSS and anterior-superior total hypothalamic volume in the migraine cohort (n = 41) after residualizing both variables for age, sex, and TIV; the fitted line and shaded band represent the adjusted linear association and its 95% confidence interval. Panel B shows residualized anterior-superior total volume across the sample-derived low (n = 14), middle (n = 13), and high (n = 14) VSS tertiles as a descriptive, non-confirmatory stratification.

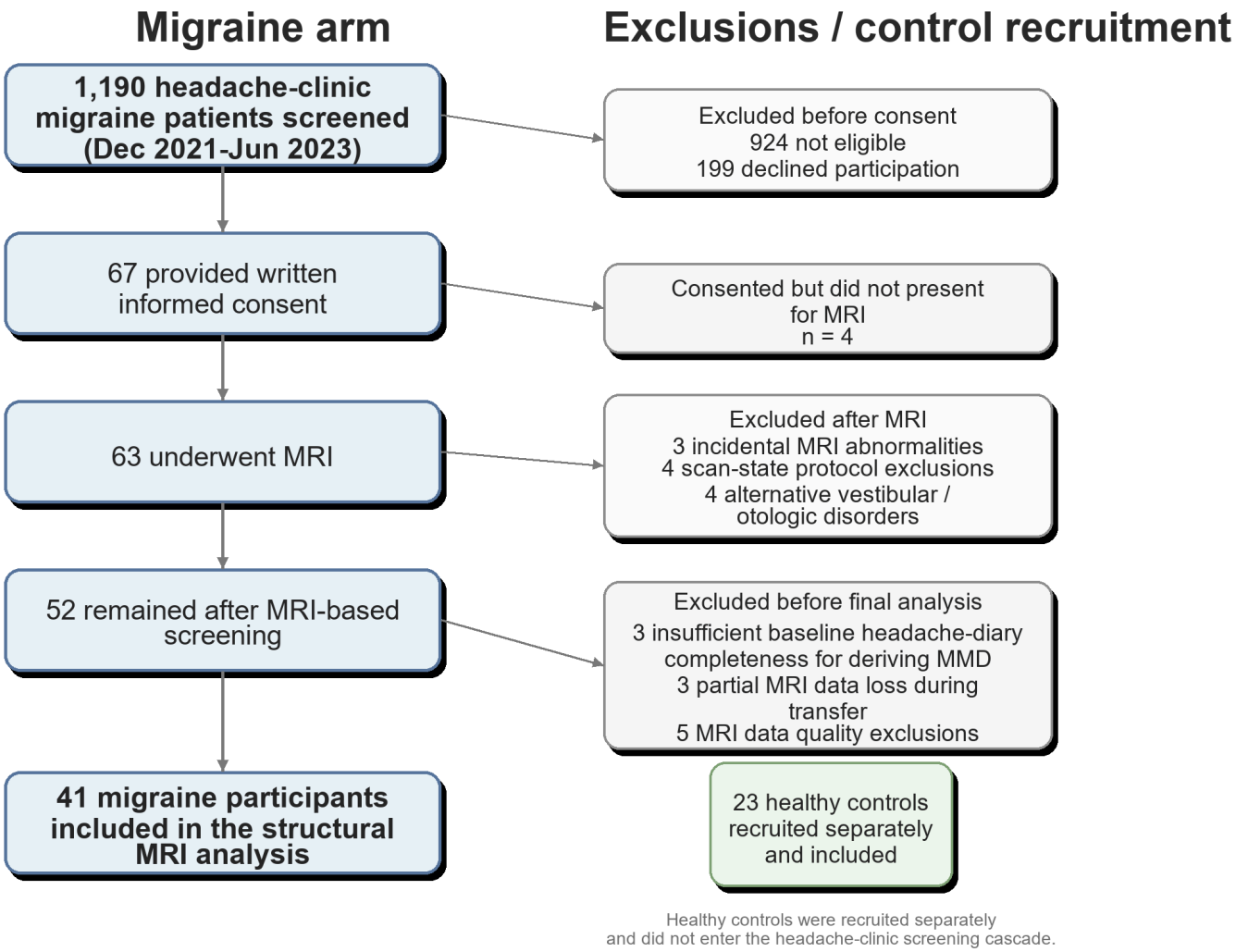


Figure 3

Participant flow for the migraine arm, with separately recruited healthy controls shown for context.

Supplementary Files

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- 03SupplementaryMaterialJHPv33.docx