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Migraine-Related Disability According to Headache Frequency Subclassifications: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Salvia Bioelectronics BV.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - MSM is chair of the medical advisory board of the CSF Leak Association; has served on advisory boards for AbbVie, Eli Lilly, Lundbeck, Pfizer, Salvia, and TEVA; has received payment for educational presentations from AbbVie, Eli Lilly, Lundbeck, Organon, Pfizer, and TEVA; has received grants from Abbott, Medtronic, and Ehlers Danlos Society; and has a patent on system and method for diagnosing and treating headaches (WO2018051103A1, issued). Within the past 24 months, HY has received funding from AHS Early-Stage Investigator Research Award; institutional support for serving as an investigator from Teva, Abbvie, Ipsen, Pfizer, Parema; consultant/ad-board fees from Salvia, Abbvie, Pfizer, Cerenovus; and royalties from Cambridge University Press and MedLink. DE received consulting fees from Salvia BioElectronics BV in her capacity as an independent medical writer. RC received consulting fees from Salvia BioElectronics BV in her capacity as an independent biostatistician. TS, within the prior 24 months, has received consulting fees from AbbVie, Amgen, Eli Lilly, Linpharma, Lundbeck, Salvia BioElectronics, Scilex, Theranica, and royalties from UpToDate. He holds/held stock options in Allevalux, Aural Analytics, and Nocira. He has received research funding from the American Heart Association, Flinn Foundation, Henry Jackson Foundation, National Headache Foundation, National Institutes of Health, Patient-Centered Outcomes Research Institute, Pfizer, Spark Neuro, and United States Department of Defense. MLM reports personal fees for advisory boards, speaker panels, or investigation studies from Allergan, Amgen, Astellas, ATI, BMS, Boehringer, Boston Scientific, CoLucid, Convergence, Eli Lilly, GlaxoSmithKline, Grunenthal, Eli Lilly, IPSEN Lundbeck, Medtronic, MSD, Novartis, Perfood, Pfizer, Reckitt Benckiser, Saint-Jude, Salvia BioElectronics, Sanofi-Aventis, Teva, UCB, UPSA, and Zambon. MO received scientific support, travel support, and/or consulting fees from Biogen Idec, Novartis, Sanofi/Genzyme, Pfizer, Teva, Ely Lilly, Noema Pharma, and Salvia BioElectronics. He received research grants from Allergan, Electrocore, Heel, and the German Ministry for Education and Research (BMBF).

INPLASY registration number: INPLASY2024120039

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 December 2024 and was last updated on 21 July 2025.

INTRODUCTION

Review question / Objective To systematically review and synthesize the burden of headache-related disability in migraine according to headache frequency subclassifications, including low-frequency episodic migraine (LFEM), high-frequency episodic migraine (HFEM), and chronic migraine (CM).

Rationale Although several studies have recently published data on migraine-related disability in

episodic migraine subclassifications, to the best of our knowledge, a comprehensive review synthesizing these findings is lacking. To address this evidence gap, we conducted a systematic review and meta-analysis of disability outcomes in headache frequency subclassifications of migraine, with a focus on characterizing disability in the subset of migraineurs with HFEM.

Condition being studied We are studying migraine, a complex neurological disorder characterized by recurrent, disabling headache attacks, associated with a combination of nausea, vomiting, photophobia, and phonophobia]. Individuals may also experience cognitive impairment, dizziness, and fatigue, among other symptoms.

METHODS

Search strategy PubMed search strategy:
#1. "low frequency" OR "high frequency" OR LFEM OR HFEM
#2. "8-14" OR "9-14" OR "10-14"
#3. #1 OR #2
#4. disab* OR burden OR resourc* OR work OR econom*
#5. migraine[MeSH Terms] OR migrain*
#6. #4 AND #5
#7. #3 AND #6
#8. subgroup* OR subdivid* OR divid* OR stratif*
#9. frequency OR "headache days" OR "migraine days"
#10. #8 AND #9
#11. #10 AND #6
#12. #7 OR #11

Cochrane Library search strategy:
#1. low frequency OR “high frequency” OR LFEM OR HFEM
#2. 8-14 OR “9-14” OR “10-14”
#3. #1 OR #2
#4. disab* OR burden OR resourc* OR work OR econom*
#5. MeSH descriptor: [Migraine Disorders] this term only
#6. migrain*
#7. #5 OR #6
#8. #4 AND #7
#9. #3 AND #8
#10.† (“low frequency” OR “high frequency” OR LFEM OR HFEM OR “8-14” OR “9-14” OR “10-14”) AND (disab* OR burden OR resourc* OR work OR econom*) AND migrain*
#11. subgroup* OR subdivid* OR divid* OR stratif*
#12. frequency OR “headache days” OR “migraine days”
#13. #11 AND #12
#14. #13 AND #8
#15.† (subgroup* OR subdivid* OR divid* OR stratif*) AND (frequency OR “headache days” OR “migraine days”) AND (disab* OR burden OR resourc* OR work OR econom*) AND migrain*
#16. #9 OR #15
#17.† ((“low frequency” OR “high frequency” OR LFEM OR HFEM OR “8-14” OR “9-14” OR “10-14”) AND (disab* OR burden OR resourc* OR work OR econom*) AND migrain*) OR ((subgroup* OR subdivid* OR divid* OR stratif*) AND (frequency OR “headache days” OR “migraine days”) AND (disab* OR burden OR resourc* OR work OR econom*) AND migrain*)
†Included as checksums only, not required.

Participant or population Patients with migraine.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included Noninterventional.

Eligibility criteria Eligible studies reported migraine-related disability outcomes from a noninterventional study that included adults with CM and subclassifications of EM (eg, LFEM and HFEM). ICHD criteria were not required. Disability outcomes were migraine-specific, validated for use in migraine populations, or reflected migraine impact or impairment.
Exclusions: Publications that were not peer-reviewed, had no full-text manuscript available, presented no original data, or relevant data could not be extracted for the population(s) of interest.

Information sources We searched the PubMed and CENTRAL electronic databases. Other sources included Google Scholar and reference lists of retrieved publications.

Main outcome(s) The following data were extracted from eligible publications: study design and setting variables, sample size variables, MHD or monthly migraine days (MMD) subgroup definitions, and headache-related disability data.

Quality assessment / Risk of bias analysis The risk of bias was assessed for each included study using the Joanna Briggs Institute (JBI) critical appraisal tools, considering the following items:
1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?

4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?
Bias was rated according to the number of "yes" answers: high risk (≤4), moderate risk (5-6), or low risk (7-8).

Strategy of data synthesis Headache frequency thresholds for LFEM, HFEM, and CM, along with disability parameters, were determined post hoc based on the available studies after grouping according to headache frequency measure, HFEM subgroup, disability parameter, and study setting. meta-analysis was conducted on disability parameter groups containing at least 3 studies to ensure the validity of the analysis in the presence of heterogeneity. For continuous disability variables, we conducted a random-effects meta-analysis of single means to calculate the overall mean. For categorical disability variables, we conducted a random effects meta-analysis for single proportions. All data pooling was performed using inverse variance weighting. We used the I-squared test (I^2) to assess heterogeneity between studies. Comparisons of mean values and proportions between (i) study settings (population-based and clinic-based) and (ii) headache frequency subgroups (LFEM, HFEM, and CM) were conducted using linear and logistic mixed models, with the study setting or frequency subgroup as a categorical predictor and publication as a random effect to account for between-study heterogeneity. P-values were corrected for multiple testing (n = 3) using Bonferroni correction.

Subgroup analysis Not applicable.

Sensitivity analysis A sensitivity analysis was performed by evaluating and comparing the pooled estimates from a fixed-effect and random effects meta-analysis. An additional sensitivity analysis was performed that examined the effect of removing studies at high risk of bias (if applicable).

Country(ies) involved UK, USA, Belgium, France, Germany.

Keywords Migraine, high-frequency episodic migraine, chronic migraine, disability, diagnostic criteria, headache, classification.

Contributions of each author

Author 1 - Manjit Matharu - Author 1 contributed to study conceptualization, methodology, review, and editing. The author approved the final manuscript.
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Author 8 - Mark Obermann - Author 8 - contributed to review and editing. The author approved the final manuscript.