INPLASY

Genetically Validated Therapeutic Targets for Migraine and Cluster Headache: A Protocol for a Systematic Review of Mendelian Randomization Studies

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Giacon, M; Terrazzino, S.

Corresponding author:
Salvatore Terrazzino

salvatore.terrazzino@uniupo.it

Author Affiliation:
Department of Pharmaceutical Sciences, University of Piemonte Orientale.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 September 2025 and was last updated on 15 September 2025.

INTRODUCTION

Review question / Objective The main objective of this systematic review is to identify, critically appraise and summarize the causal evidence from all available Mendelian randomization (MR) studies on potential therapeutic targets for migraine and cluster headache.
In particular, our aim is to:
1. Evaluate the causal evidence for repurposing existing drug classes, such as statins and antihypertensives, for the prevention or treatment of migraine.
2. Identify and summarize the evidence for novel genetic and proteomic targets causally associated with the risk of migraine and its subtypes.
3. Identify and summarize the evidence for novel proteomic targets causally associated with the risk of cluster headache.
4. Evaluate the overall methodological quality and consistency of the current MR evidence base to inform the future direction of drug discovery in headache medicine.

Rationale Migraine and cluster headache are debilitating neurological disorders that place a significant burden on sufferers and healthcare systems worldwide. Despite advances in treatment, there remains a significant unmet clinical need as existing therapies are often insufficiently effective or have undesirable side effects. The traditional drug discovery process is hampered by a high failure rate, often due to a lack of robust target validation. Mendelian randomization (MR) has proven to be a powerful epidemiological method that strengthens causal inference in a way that traditional observational studies cannot.
The reason we focus exclusively on MR studies is because of their unique ability to strengthen causal inference. Mendelian randomization takes advantage of the natural, random selection of genetic variants at conception- a process equivalent to randomization in a clinical trial. In this framework, genetic variants that are robustly associated with a modifiable exposure (such as the expression of a drug target protein) are used as 'instrumental variables' or proxies for that

exposure. Because these genetic variants are randomly assigned at birth, they are generally not associated with the social, environmental, and behavioral confounders that can influence observational research. Furthermore, because an individual's genetic makeup is determined long before the onset of a disease, this method is not susceptible to reverse causality, in which the disease process itself could modify the exposure. By mimicking the design of a randomized controlled trial, MRI can therefore provide more reliable evidence of whether an association is likely to be causal, making it a powerful tool for validating or refuting potential therapeutic targets before they enter costly clinical trials.
Given the recent proliferation of high-quality MR studies in headache medicine, a systematic synthesis of these findings is both timely and necessary to consolidate results, assess their consistency, and highlight the most promising therapeutic candidates for future clinical and preclinical research.

Condition being studied Primary headache disorders, specifically migraine (including its subtypes, migraine with and without aura) and cluster headache.

METHODS

Search strategy A systematic literature search will be conducted to identify all relevant Mendelian randomization studies. The search strategy will combine keywords and Medical Subject Headings (MeSH) for two core concepts: the primary headache disorder (migraine, cluster headache) and the MR methodology. The search string will be adapted to the specific syntax and indexing terms of each database as required.
An example search string for PubMed will be:
("Migraine Disorders"[Mesh] OR migraine* OR "Cluster Headache"[Mesh] OR "cluster headache*") AND ("Mendelian Randomization Analysis"[Mesh] OR "Mendelian Randomization" OR "Mendelian Randomisation" OR "MR analysis" OR "genetic instrument*"[tiab] OR "instrumental variable*"[tiab] OR "genetically proxied"[tiab] OR "genetically predicted"[tiab]).
Additionally, the reference lists of included articles and relevant systematic reviews will be manually screened to identify any potentially eligible studies.

Participant or population The population of interest will consist of individuals with a primary headache disorder (migraine or cluster headache), with diagnoses based on large-scale Genome-Wide Association Study (GWAS) data.

Intervention The intervention/exposure will be any genetically proxied potential therapeutic target. Eligible exposures will include:
1. The expression level of a specific gene (proxied by eQTLs).
2. The circulating level of a specific protein (proxied by pQTLs).
3. The effect of a pharmacological drug class or target (proxied by genetic variants within or near the relevant gene(s), e.g., variants in HMGCR as a proxy for statin inhibition).

Comparator The comparison group is inherently defined within the MR design as individuals without the exposure-associated genetic variants.

Study designs to be included Only studies employing a Mendelian randomization (MR) design will be included.

Eligibility criteria Inclusion Criteria:
• Must be an original, peer-reviewed research article.
• Must employ a Mendelian randomization design.
• The primary outcome must be the risk or incidence of migraine or cluster headache.
• The exposure must be a genetically proxied therapeutic target (gene, protein, or drug effect).
Exclusion Criteria:
• Studies that do not use an MR design (e.g., traditional observational studies, randomized controlled trials, animal studies).
• Publications that are not original research (e.g., reviews, editorials, conference abstracts).
• Studies where the primary exposure is not a specific therapeutic target (e.g., studies focused on lifestyle or environmental traits, unless used in a formal mediation analysis of a primary target).

Information sources The search will be performed in four electronic databases: PubMed, Web of Science, Cochrane Library, and OpenGrey, from their inception without date restrictions.

Main outcome(s) The primary outcome for data extraction will be the main causal estimate for the association between a genetically proxied therapeutic target and the risk of migraine or cluster headache. For each key finding, we will extract the odds ratio (OR) and the corresponding 95% confidence interval (CI). Crucially, we will also document the specific Mendelian randomization method (e.g., inverse variance weighted [IVW], weighted median) that the original authors reported as the basis for their primary causal estimate, as this is essential for interpreting the result.

Additional outcome(s) Where available, data on specific headache subtypes (e.g., migraine with aura, migraine without aura) and results from validation, replication, and sensitivity analyses will be extracted to assess the robustness of the findings.

Data management Two reviewers (M.G. and S.T.) will independently screen titles and abstracts, followed by a full-text review of potentially eligible articles. These two reviewers will then independently extract data from the included studies using a standardized data extraction form. Any discrepancies will be resolved by discussion and consensus at each stage.

Quality assessment / Risk of bias analysis Two independent reviewers will formally assess the methodological quality of all included studies. Discrepancies will be resolved through discussion to reach a consensus. We will utilize a structured checklist based on the STROBE-MR statement, focusing on six critical domains for a valid Mendelian Randomization (MR) analysis.
a) Instrument Strength and Validity: We will verify that genetic instruments are strongly associated with the exposure, defined by an F-statistic > 10 to minimize weak instrument bias. This is a core assumption of MR.
b) Assessment of Horizontal Pleiotropy: We will check for formal testing of horizontal pleiotropy (i.e., that the genetic variant only affects the outcome via the exposure). This will be evaluated by reviewing the use of methods like the MR-Egger intercept test and the MR-PRESSO global test.
c) Use of Sensitivity Analyses: We will assess the robustness of findings by confirming that multiple sensitivity analyses with different underlying assumptions were performed. In addition to the primary inverse variance weighted (IVW) method, we will require at least two other methods, such as Weighted Median, Weighted Mode, or MR-Egger regression.
d) Independent Replication: We will assess if primary findings were validated in an independent cohort or through a meta-analysis of at least two non-overlapping datasets.
e) Assessment of Reverse Causality: We will verify whether the assumed causal direction from exposure to outcome was formally tested using methods like bidirectional MR or the Steiger filtering test.
f) Data Sources: We will confirm that studies used large-scale, publicly available GWAS summary statistics from reputable sources to ensure statistical power and minimize bias from sample overlap.
Based on this assessment, each study will be rated as "High," "Moderate," or "Low" quality.
High: The study meets nearly all criteria, including strong instruments, comprehensive pleiotropy tests, multiple sensitivity analyses, and either independent replication or a formal test for reverse causality.
Moderate: The study meets the core criteria (strong instruments, pleiotropy assessment, sensitivity analyses) but lacks independent replication or a formal test for reverse causality.
Low: The study fails to meet one or more core criteria (e.g., inadequate testing for pleiotropy, use of weak instruments).
No studies will be excluded based on quality alone; however, this assessment will inform the synthesis of results and the overall strength of evidence for each finding.

Strategy of data synthesis We will provide a narrative synthesis of the results from the included studies. Results will be grouped by disease (migraine or cluster headache) and then by therapeutic target (e.g., repurposed drugs, novel proteins). We will summarize the main causal estimates, p-values and the main results of the sensitivity and validation analyses.

Subgroup analysis We will systematically screen the included articles for subgroup analyses reported by the original authors. The results of these existing analyses will then be extracted and synthesized. In our synthesis, we will particularly focus on data that stratify outcomes by migraine subtype (i.e. migraine with aura versus migraine without aura), as this will allow us to assess the evidence for potential subtype-specific therapeutic targets based on the primary literature.

Sensitivity analysis The robustness of the evidence for each therapeutic target will be assessed by systematically summarizing the results of the sensitivity analyses reported in the included Mendelian randomization studies. In particular, we will extract data on the use and results of different sensitivity analysis methods (e.g. MR-Egger regression, weighted median, MR-PRESSO) where available. The consistency of causal estimates across these different analysis methods, as reported in the primary studies, will be a key factor in determining the overall confidence in each identified target. If a target shows consistent results across multiple sensitivity analyses, we will consider the evidence to be more robust. In contrast, if an objective shows significant variability in its causal estimate, depending on the sensitivity analysis method used,

the evidence will be interpreted with greater caution.

Language restriction No language restrictions will be applied during the literature search to ensure comprehensive coverage.

Country(ies) involved Italy.

Keywords Migraine; Cluster Headache; Mendelian Randomization; Therapeutic Targets; Drug Repurposing; Genetics; Systematic Review.

Dissemination plans The results of this systematic review will be disseminated through publication in a peer-reviewed scientific journal. The findings may also be presented at national and international conferences on headache medicine, neurology and human genetics.

Contributions of each author

Author 1 - Martina Giacon - Conceptualisation; Methodology; Data Collection; Writing – Original Draft.
Email: martina.giacon@uniupo.it
Author 2 - Salvatore Terrazzino - Conceptualisation; Methodology; Data Collection; Supervision; Writing – Review & Editing.
Email: salvatore.terrazzino@uniupo.it