Prognostic factors for chronic headache

A systematic review

OPEN

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ABSTRACT

Objective: To identify predictors of prognosis and trial outcomes in prospective studies of people with chronic headache.

Methods: This was a systematic review of published literature in peer-reviewed journals. We included (1) randomized controlled trials (RCTs) of interventions for chronic headache that reported subgroup analyses and (2) prospective cohort studies, published in English, since 1980. Participants included adults with chronic headache (including chronic headache, chronic migraine, and chronic tension-type headache with or without medication overuse headache). We searched key databases using free text and MeSH terms. Two reviewers independently extracted data and assessed the methodologic quality of studies and overall quality of evidence identified using appropriate published checklists.

Results: We identified 16,556 titles, removed 663 duplicates, and reviewed 199 articles, of which 27 were included in the review—17 prospective cohorts and 10 RCTs with subgroup analyses reported. There was moderate-quality evidence indicating that depression, anxiety, poor sleep and stress, medication overuse, and poor self-efficacy for managing headaches are potential prognostic factors for poor prognosis and unfavorable outcomes from preventive treatment in chronic headache. There was inconclusive evidence about treatment expectations, age, age at onset, body mass index, employment, and several headache features.

Conclusions: This review identified several potential predictors of poor prognosis and worse outcome postinterventions in people with chronic headache. The majority of these are modifiable. The findings also highlight the need for more longitudinal high-quality research of prognostic factors in chronic headache. *Neurology*® 2017;89:291–301

GLOSSARY

BMI = body mass index; **CDH** = chronic daily headache; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **HIT** = Headache Impact Test; **HMSE** = headache management self-efficacy; **RCT** = randomized controlled trial.

Chronic headache—headache occurring on 15 or more days per month for at least 3 months[1]—is a major cause of pain and disability. Chronic migraine affects around 1%–4% of the population[2,3] and chronic tension-type headache about 2.2%.[4] Approximately 25%–50% of those affected also have medication overuse headache, which has a population prevalence of 1%.[5] Chronic headache is a severely disabling long-term condition, with higher symptom frequency and severity than episodic headache.[6]

A wide range of demographic, clinical, psychological, and social factors may affect prognosis and treatment outcome for people with chronic headache.[7,8] Our aims were to identify factors that predict poor prognosis or are associated with differential treatment outcomes from

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Supplemental data at Neurology.org

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preventive treatment in patients with chronic headache. Factors can be differentiated between predictors of prognosis and moderators or mediators of treatment outcome.[9] Specifically; predictors are factors, measured at baseline, that affect outcome but do not interact with the intervention; moderators are factors, measured at baseline, that interact with the treatment to change outcome for a subgroup of participants; mediators are factors measured during or after treatment that influence outcomes, with or without interaction with the treatment.

Identifying those factors may improve the effectiveness and cost-effectiveness of future interventions for people living with chronic headache.[10]

METHODS This study was prospectively registered with the International Prospective Register of Systematic Reviews; PROSPERO 2015: CRD42015019848 (available at crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019848).

Identification of studies. We searched for English-language publications reporting randomized controlled trials (RCTs) or prospective cohort studies that reported on predictors, moderators, or mediators of outcome from peer-reviewed journals in Cochrane, MEDLINE/PubMed, Embase, PsychINFO, Web of Science, and ASSIA, supplemented by backward citation tracking, from January 1, 1980, to February 12, 2015. We updated the search on June 14, 2016 (appendix e-1 and table e-1 at Neurology.org).

We included RCTs with at least 20 patients per treatment arm at follow-up (in line with previous research[11]) that either (1) investigated moderators or mediators of outcome using a priori hypotheses or (2) analyzed subgroups post hoc; and prospective cohort studies that measured factors at baseline and used a timeline to outcomes at follow-up to explore the associations between factors. Study participants were adults (18 years and over) and had chronic headache as defined by the International Classification of Headache Disorders[1] with at least 15 headache days/month for at least 3 months. We included chronic headache, chronic migraine, and chronic tension-type headache, with or without medication overuse headache.

In RCTs that included episodic headache patients, at least 50% of the study population had to be chronic headache patients. In prospective cohort studies, prognostic factors had to be analyzed and reported separately for chronic headache. We excluded cross-sectional and prevalence studies, case-control studies, and studies that included any other chronic pain conditions. We used EPPI reviewer4 software to screen studies for inclusion/exclusion by title and abstract. Articles for possible inclusion were assessed in full. We extracted data from included studies on separate predeveloped forms for RCTs and prospective cohort studies separately, including the following items: author, year, title, headache type, number of participants, description of intervention and control groups (as applicable), factors assessed as potential predictors/moderators/mediators, outcomes, and results.

Quality assessment. RCTs were quality assessed with a set of questions adapted from the Cochrane Collaboration risk of bias tool[12] and we excluded any studies that yielded a high risk of bias score. We assessed sequence generation, allocation concealment, incomplete outcome data, and blinding of outcome assessment. Studies scoring 4–5 points were considered high quality, studies scoring 2–3 were considered medium quality, and studies that scored 0 or 1 were excluded. We assessed the level of evidence from subgroup analyses using the methodologic criteria for the assessment of moderators in systematic reviews of RCTs,[13] which score for a priori planned analysis, theory-driven selection of factors, measurement of moderators prior to randomization, quality of moderator measures, and explicit test of the interaction between moderator and treatment. Studies complying with all 5 criteria were considered as providing confirmatory evidence; those complying with criteria 3, 4, and 5 as providing exploratory evidence. All other studies were classified as providing insufficient evidence.

Methodologic quality coding of prospective cohort studies was carried out based on recommendations for evaluation of the quality of prognosis studies in systematic reviews.[14] We assessed if sampling frame and recruitment been described adequately, the frequency of loss to follow-up from sample, definition of outcomes of interest, if appropriate analyses were used, if statistical reporting was appropriate, if sample size was appropriate for statistical analysis, if measurement of all important confounders was adequately valid and reliable, and if most important baseline measures were included. We scored 1 point per item; studies scoring ≤5 points were considered low quality, studies scoring 6–9 points medium quality, and those scoring ≥10 out of 14 possible points were considered high quality.

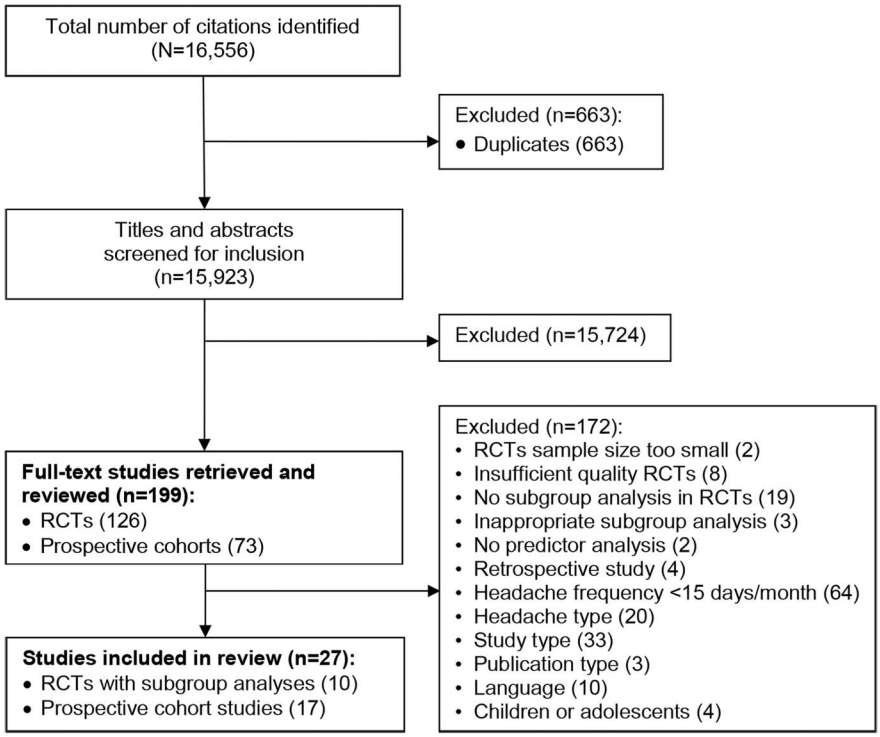
Finally, we assessed the overall quality of evidence for each potential factor with an adapted version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework,[15] considering phase of investigation, methodologic quality per studies, and potential inconsistency, indirectness, imprecision, publication bias, dose response effect, or potentially large effect sizes across all studies. We downgraded factors for inconsistency when estimates of the prognostic factor's association with outcomes varied in direction. We downgraded factors for indirectness when the included sample of most studies only represents a subset (i.e., chronic migraine only, or chronic tension-type headache only, or medication overuse headache only) of the whole population of interest (chronic headache). We downgraded quality for imprecision if the evidence was generated by few studies involving a small number of participants and most of the studies provided imprecise results or no relevant statistics or if evidence only was provided by single studies.

Data synthesis. Because of the high heterogeneity among studies regarding treatment and investigated prognostic factors, it was not possible to pool studies in a meta-analysis. We therefore present a narrative synthesis of the results, considering the overall quality of evidence as proposed by Huguet et al.[15]

RESULTS We identified 16,556 titles through database searches and removed 633 duplicates. A total of 15,923 studies were screened by title and abstracts and 15,724 records excluded. The remaining records were grouped into RCTs (126) and prospective cohort studies (73). After full text assessment, 27 studies were included (10 RCTs with subgroup analysis[16–25] and 17 prospective cohorts[5,26–41]) (figure).

Characteristics of included studies. Eight studies tested a general population of "chronic headache," 8 are specifically on "chronic migraine," 5 include participants with "chronic daily headache," 3 are

Figure Study flowchart



RCT = randomized controlled trial.

specifically on "chronic tension type headache," and 3 on "chronic headache forms with medication overuse." Outcomes assessed include headache-specific measures (headache frequency, intensity, and duration of headache attacks); measures of quality of life or headache-related disability; mood; coping and headache management self-efficacy (HMSE); days off work; persistence of chronic headache or reverting to episodic headache; relapse rates (from withdrawal therapy); or response to preventive treatment in responder analyses (table 1).

Randomized controlled trials. Six of the 10 included trials involved medication in at least one of their treatment arms.[16,20–25] Two studies examined subgroups in trials of psychological interventions,[17,20] with one study doing this alongside medication treatment.[20] One study assessed manual therapy,[18] while 3 studies looked at acupuncture.[19,22,23] Within the subgroup analyses in included RCTs, only 3 studies assessed potential moderators by providing an explicit interaction test with treatment.[19,20,23] All other RCTs provide, in the absence of an interaction test, findings about predictors of outcome only.

Prospective cohorts. The majority of the prospective cohort studies assessed potential predictors of response to treatment or withdrawal therapy outcome (n = 11), while 6 assessed predictors of prognosis, independent of treatment.

Methodologic quality. Of the 10 RCTs with subgroup analyses and of at least medium overall methodologic quality (table 2), only one study provided confirmatory evidence (based on methodologic assessment of subgroup analysis). Two studies provided exploratory evidence, and the remaining 7 provided insufficient evidence as they did not use an explicit interaction test, did not measure subgroup factor prior to randomization, or failed to measure subgroup factors by adequate (reliable and valid) measurements (table 3).

Of the 17 observational studies, 5 were of high methodologic quality, 10 were medium quality, and 2 were low quality (table 4).

Overall quality of evidence. The GRADE assessment resulted in an initial rating of the evidence for specific factors based on the phase of investigation of the studies. The majority of included studies consisted of phase 1, described as exploratory studies.[15] We did not rate any factors as overall high-quality evidence, as none of our factors had been investigated in a large number of cohort studies that were designed to confirm a hypothesized independent effect of the factor on the outcome (phase 2 study) or to test a conceptual model, which explains its underlying mechanisms (phase 3 study). We did not upgrade the quality of any factor for a dose response effect or a large effect size.

The initial rating per factor was further downgraded, as applicable, based on the methodologic

Table 1 Characteristics of included studies

Author and year	Country	Study sample size	Description of intervention (and control group) if applicable	Type of headache	Study type	Phase of investigation	Prognostic factor type	Methodologic quality
Boe 2007	Norway	102	Prednisolone or placebo	CH	RCT with subgroup analysis	1	Predictor of outcome	+
Boe 2009	Norway	80	Prednisolone or placebo	CDH (with MO)	RCT with subgroup analysis	1	Predictor of outcome	+
Bromberg 2012	USA	189	Web-based behavioral intervention vs waiting list	CM	RCT with subgroup analysis	1	Predictor of outcome	++
Castien 2011	Netherlands	82	Manual therapy or usual care	CTTH	RCT with subgroup analysis	1	Predictor of outcome	+
Ellis 2004	UK	401	Acupuncture or usual care	CH	RCT with subgroup analysis	1	Moderator	+
Holroyd 2009	USA	203	Placebo vs tricyclic antidepressant medication vs cognitive behavioral stress management therapy with placebo vs stress management therapy + antidepressant medication	CTTH	RCT with subgroup analysis	3	Moderator/ mediator	+++
Schulte-Mattler 2004	Germany	107	Botulinum toxin A vs placebo	CTTH	RCT with subgroup analysis	1	Predictor of outcome	+
Yang 2011	Taiwan	66	Acupuncture vs topiramate	CM	RCT with subgroup analysis	1	Predictor of outcome	+
Yang 2013	Taiwan	66	Acupuncture vs topiramate	CM	RCT with subgroup analysis	1	Moderator	++
Yurekeli 2008	Turkey	70	Sodium valproate vs placebo	CDH	RCT with subgroup analysis	1	Predictor of outcome	+
Bigal 2005	USA	176	Prophylactic medication	CM	Observational cohort (clinic-based)	2	Predictor of outcome	++
Buse 2011	USA	7,169	NA	CM	Observational cohort (population-based)	1	Predictor of prognosis	+++
Eross 2005	USA	61	Botulinum toxin A	CM	Open-label	1	Predictor of outcome	++
Fontanillas 2010	Spain	72	Prophylactic medication	CDH (with MO)	Long-term outcome study	1	Predictor of outcome	+
Gaul 2011	Germany	841	NA	CH	Long-term outcome study	1	Predictor of outcome	+++
Houle 2012	USA	55	NA	CH	Observational cohort	2	Predictor of prognosis	+++
Katsarava 2003	Germany	98	NA	CH	Long-term outcome study	1	Predictor of outcome	++
Katsarava 2004	Germany	96	NA	CH	Long-term outcome study	1	Predictors of outcome	++
Louter 2013	Netherlands	2,331	NA	CM	Observational cohort	1	Predictor of prognosis	++
Lu 2001	Taiwan	108	NA	CDH	Observational cohort	1	Predictor of prognosis	++
Luconi 2007	Italy	168	Prophylactic medication	CM	Observational cohort (clinic-based)	2	Predictor of outcome	++
Lundqvist 2011	Norway	195	NA	CH	Observational cohort	2	Predictor of prognosis	++
Matthew 2007	USA	82	Botulinum toxin A	CDH	Open-label	1	Predictor of outcome	+
Seok 2006	Korea	136	Prophylactic medication	CDH	Open-label	1	Predictor of outcome	++
Tribl 2001	Austria	55	NA	CDH	Long-term outcome study	1	Predictor of outcome	++

Continued

Table 1 Continued

Author and year	Country	Study sample size	Description of intervention (and control group) if applicable	Type of headache	Study type	Phase of investigation	Prognostic factor type	Methodologic quality
Zidverc-Trajkovic 2007	Serbia	240	Prophylactic medication	CH (with MO)	Open-label	1	Predictor of outcome	+++
Zwart 2003	Norway	32,067	NA	CH	Observational cohort	2	Predictor of prognosis	+++

Abbreviations: CDH = chronic daily headache; CH = chronic headache; CM = chronic migraine; CTTH = chronic tension-type headache; MO = medication overuse; NA = not applicable; RCT = randomized controlled trial.
Methodologic quality: for RCT subgroup analyses: + = insufficient evidence; ++ = exploratory evidence; +++ = confirmatory evidence; for observational studies: + = low quality; ++ = medium quality; +++ = high quality.

quality of the studies and potential inconsistency, indirectness, and imprecision of findings (table 5).

We present prognostic factors identified together regardless of the type of factor (predictor or moderator, mediator).

Potential prognostic factors with moderate-quality evidence. ***Depression and anxiety.*** Depression was consistently found to be a predictor of poor outcome. Depression predicted higher influence of headaches on normal daily life and ability to function (Headache Impact Test [HIT]–6 scores)[27] and having allodynia, more migraine days, a larger change in migraine days from baseline to follow-up and more medication days at follow-up,[34] lower response to prophylactic treatment,[35] lower response to prednisolone + withdrawal therapy,[25] and one study found that there was reduced response to placebo treatment when anxiety or mood diagnosis was present.[20] However, the same study also found that people with mood disorder benefit more from antidepressant therapy and behavioral therapy.

Medication overuse. Medication overuse was also consistently found to predict poor prognosis. Medication overuse predicted the presence of chronic headache at follow-up,[5,36,38,41] increase in headache days,[34] lower quality of life,[29] and unsuccessful detoxification.[29,40]

Headache management self-efficacy. Only one study[20] investigated a potential effect mediator within its analysis. The authors measured HMSE during the intervention (2 months postrandomization) and found it mediated the effects of antidepressant therapy and stress management therapy on headache-related disability and headache activity.

Sleep and stress. One study found that poor sleep and high stress predict headache severity in individuals with chronic headache. Conversely, high sleep and low stress showed a protective effect.[31]

Potential prognostic factors with low-quality evidence. ***Higher expectations.*** In both the acupuncture and topiramate groups in one study,[23] it was found that those with a higher general expectation of treatment showed a greater reduction in moderate or severe headache days compared to those with lower expectations.

Body mass index. A higher body mass index (BMI) did not predict more severe HIT-6 scores,[27] having allodynia, headache frequency, medication use,[34] or response to multidisciplinary treatment.[30] However,

Table 2 Risk of bias assessment in randomized controlled trials

Author and year	1. Did the study have an adequate randomization sequence?	2. Was allocation concealment carried out?	3. Were withdrawals and dropouts explained?	4. Was outcome assessment blinded?	5. Sufficient numbers (>20 in each arm)?	Score
Boe 2007	✓	✓	✓	✓	✓	5
Boe 2009	✓	✓	✓	✓	✓	5
Bromberg 2012	✓		✓		✓	3
Castien 2011		✓	✓	✓	✓	4
Ellis 2004	✓		✓		✓	3
Holroyd 2009			✓	✓	✓	3
Schulte-Mattler 2004	✓			✓	✓	3
Yang 2013	✓	✓		✓	✓	4
Yang 2011	✓	✓	✓	✓	✓	5
Yurekeli 2008				✓	✓	2

Studies scoring 4–5 points were considered higher quality (low risk of bias); studies scoring 2–3 were considered medium quality (moderate risk of bias).

Table 3 Quality assessment of randomized controlled trial subgroup analyses using methodologic criteria by Pincus et al.[13]

Author and year	Was subgroup specified a priori?	Was selection of subgroup factors theory/evidence driven?	Subgroup factors measured prior to randomization?	Were subgroup factors measured by reliable and valid measurements?	Was an explicit test of the interaction used?	Level of evidence
Boe 2007						Insufficient
Boe 2009			✓	✓		Insufficient
Bromberg 2012	✓		✓	✓	✓	Exploratory
Castien 2011	✓		✓			Insufficient
Ellis 2004					✓	Insufficient
Holroyd 2009	✓	✓	✓	✓	✓	Confirmatory
Schulte-Mattler 2004			✓			Insufficient
Yang 2011	✓		✓	✓		Insufficient
Yang 2013			✓	✓	✓	Exploratory
Yurekeli 2008	✓		✓	✓		Insufficient

Confirmatory evidence: Studies complying with all 5 criteria; exploratory evidence: studies complying with criteria 3, 4, and 5. All other studies were classified as providing insufficient evidence.

conversely, one study found that a higher BMI predicted a better response to preventive treatment and favorable HIT-6 scores postintervention.[25]

Age. Older age had no effect on the response to interventions, including prophylactic treatment,[25,35] web-based behavioral intervention,[17] and acupuncture.[23] Older age was also not associated with reverting from chronic to episodic migraine,[38] response to medication overuse,[29] having allodynia,[34] headache frequency or intensity,[39] or headache-related disability.[20]

In contrast, older age was found to predict worse HIT-6 scores,[27] later chronic daily headache (CDH),[5] lower response to botulinum toxin A treatment,[28] unsuccessful detoxification,[40] and more weekly analgesics used.[41] Conversely, one study found that older patients had better outcomes from multidisciplinary treatment.[30]

Age at onset. Older age at onset was a predictor for fewer migraine days, less use of medication at follow-up,[34] and better response to prophylactic medication,[40] but did not predict response to prophylactic treatment in another study.[35]

Baseline headache-related disability. Higher symptoms at baseline were found to predict higher rates of disability[27] and the transition to CDH.[5] In contrast, higher symptoms and disability at baseline were associated with successful detoxification,[40] and showed no significant association with response to treatment.[35]

Baseline headache frequency. The evidence from 7 studies was contradictory. Headache frequency did not differ between responders and nonresponders to prophylactic treatment,[35] and higher baseline frequency did not predict reverting to episodic migraine from chronic migraine after treatment.[38] It was not related to subsequent HIT-6 scores[26] in patients with chronic migraine. Conversely, higher headache frequency was related to later persistent chronic headache,[5] was found to increase the risk of having allodynia and more medication use days, but was also associated with a reduction in migraine days at follow-up.[34] Two studies found that higher frequency predicts favorable response to detoxification[40] and to multidisciplinary treatment.[30]

Baseline headache severity. One study[20] found that when looking at headache index as outcome, those with more severe headache had better treatment effects from stress management and antidepressant therapy than those with less severe headache. Another study[23] found that those with more than 20 moderate or severe headache days a month had a greater reduction in the mean number of moderate or severe headache days after acupuncture.

Employment. One study found that those who were employed had higher response rates to treatment compared to those on medical leave,[40] but 2 studies[25,38] found employment made no difference for persistence of CDH and number headache days at follow-up.

The evidence for all other factors was graded as very low quality (table 5).

DISCUSSION

Summary of results. In this review, we aimed to systematically identify predictors, moderators, and mediators of prognosis and outcomes in chronic headache from prospective studies, including prospective cohorts and trials of preventive interventions. Our findings suggest with moderate-quality evidence that depression/anxiety, medication overuse, poor sleep, high stress, and low HMSE are associated with worse outcomes. Lower-quality evidence suggests that higher expectations, age, age at onset, headache

Table 4 Methodologic quality of prospective cohort studies using methodologic criteria by Hayden et al.[14]

Author and year	Adequate description of sampling?	Attrition reported?	Outcome of interest reported?	Appropriate analyses?	Reporting of analyses appropriate?	Adequate sample size?	Valid measure of confounders?	No. of most important baseline measures reported as total? (total/7)	Total/ 14
Bigal 2005	P	N	Y	Y	N	Y	Y	4	8.5
Buse 2012	Y	N	Y	Y	Y	Y	Y	5	11
Eross 2005	Y	Y	Y	Y	Y	Y	N	3	9
Fontanillas 2010	N	Y	N	Y	N	Y	N	2	5
Gaul 2011	Y	N	Y	Y	Y	Y	Y	5	11
Houle 2012	Y	Y	Y	Y	Y	Y	Y	4	11
Katsarava 2003	N	Y	Y	Y	N	Y	N	3	7
Katsarava 2004	N	Y	Y	Y	N	Y	N	3	7
Louter 2013	Y	Y	Y	Y	Y	Y	Y	4	11
Lu 2001	Y	Y	Y	Y	Y	Y	Y	2	9
Luconi 2007	Y	Y	Y	Y	N	N	N	5	9
Lundqvist 2011	Y	Y	Y	Y	N	Y	Y	2	8
Matthew 2007	N	N	Y	Y	N	Y	N	2	5
Seok 2006	Y	Y	Y	Y	P	N	Y	3	8.5
Tribl 2001	Y	N	Y	Y	N	N	Y	5	9
Zidverc-Trajkovic 2007	Y	Y	N	Y	Y	Y	Y	7	13
Zwart 2003	Y	N	Y	Y	Y	Y	Y	4	10

≤5 Points = low quality; 6–9 points = medium quality; ≥10 points = high quality; N = no (0 points); P = partially (0.5 point); Y = yes (1 point).

frequency, intensity, BMI, disability scores, and employment are potential predictors. The highest-quality evidence we found suggests that psychosocial factors, anxiety and mood disorder, sleep and stress, and HMSE are potential prognostic factors. This is an important finding, as these factors are all potentially modifiable. Specifically, groups with low mood (anxiety and mood disorder) appear to respond better to antidepressants and stress management therapy. In the absence of anxiety and mood disorder, higher HMSE improves treatment outcomes. We also found some evidence that more positive expectations about treatment are associated with better outcomes. Our results also suggest that older patients and those with more severe headache might benefit from multidisciplinary treatment, which can address comorbidity and specifically tailor treatment to more complex needs. However, owing to the limited number of studies, it was not possible to identify prognostic factors from studies providing high-quality evidence. The number of studies identified matching our inclusion criteria for this review was low and overall quality of evidence was moderate, low, or very low, implying that confidence in the estimate is low.

Comparison with other studies and reviews. While most of the evidence on prognostic factors in the field focuses on studying the chronification process of headache or risk factors of developing chronic headache from episodic headache, we looked at patients with a diagnosis of chronic headache at baseline. Our findings indicate that there is potential for behavioral interventions targeting psychosocial prognostic factors in people living with chronic headache. Our results are in line with Smitherman et al.,[42] who suggest that depression, anxiety, and insomnia should be assessed in every treatment-seeking headache patient, particularly those with frequent attacks.[42] Our finding that self-efficacy can mediate treatment effects in chronic headache is in line with Peck and Smitherman,[43] who assessed HMSE as mediator for the relationship between headache severity and disability in a population of predominantly nonchronic headache sufferers. Self-efficacy has also been found to be associated with improvement of outcomes in other chronic pain conditions.[44–46]

Strengths and limitations of this review. The strength of this review is that we only included prospective longitudinal study types to ensure reliability and quality of results. These study designs are less prone to some types of bias and can most strongly suggest causation.[47] For the widest feasible scope and to identify all potential prognostic factors, we included RCTs with subgroup analyses, which are the ideal study

Table 5 Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile of overall quality

Potential prognostic factors	No. of studies	GRADE factors				No. of participants	Univariate or multivariate			Phase of investigation	Overall quality
		Study limitations	Inconsistency	Indirectness	Imprecision		+	0	–		
Psychosocial factors											
Depression and anxiety	5	✓	✓	X	✓	9,951			5	1 and 3	+++
Employment	3	X	✓	X	X	456	1	2		1	++
Higher expectations	1	X	✓	X	X	66	1			1	++
Headache management self-efficacy	1	✓	✓	X	X	203	1			3	+++
Sleep and stress	1	✓	✓	✓	X	80			1	2	+++
Headache features											
Allodynia	3	X	✓	X	X	2,479	1	1		1	+
Muscle tenderness	3	X	X	X	X	250	1	2		1	+
Throbbing	1	X	✓	X	X	66	1			1	+
Unilateral headache	2	X	X	X	X	148	1	1		1	+
Demographics											
Age at onset	3	✓	X	X	X	2,739	2	1		1	++
BMI	4	✓	X	X	✓	10,522		3	1	1 and 2	++
Age	15	✓	X	✓	✓	43,640	1	9	5	1, 2, and 3	++
Headache characteristics											
Migraine as subgroup	4	X	X	X	X	619	2	2		1	+
Headache severity	2	X	✓	X		269	2			1 and 3	++
Headache-related disability	4	✓	X	X	X	7,685		1	3	1 and 2	++
Headache frequency	7	✓	X	X	✓	4,000	2	3	2	1 and 2	++
Medication overuse	7	✓	✓	X	✓	36,215			7	1 and 2	+++
Drug type overused (ergots)	2	X	X	X	X	240	1		1	1	+
Drug type overused (analgesics)	3	X	X	X	X	266	1		1	1	+

Abbreviation: BMI = body mass index.
For univariate and multivariate analyses: + = number of significant effects with a positive value; 0 = number of nonsignificant effects; – = number of significant effects with a negative value. For GRADE factors: ✓ = no serious limitations; X = serious limitations or unclear (unable to rate based on available information). For overall quality: + = very low quality; ++ = low quality; +++ = moderate quality.

design to assess potential moderators and mediators of outcome, and prospective cohort studies (including observational cohort studies, long-term outcome studies, and open-label studies), which are the best study designs to assess predictors of prognosis independent of treatment. It would have been favorable to be able to analyze predictors, moderators, and mediators separately; however, the large heterogeneity between factors measured and scarcity of data did not allow us to do this and we presented factors measured by studies together regardless of the type of prognostic factors.

We adhered to our registered protocol, thus strengthening the credibility of the evidence synthesis. We assessed the methodology of included studies with the best available tools specific to the study designs of included primary studies and judged and reported the overall quality of the evidence based on the recommendations from the GRADE Working Group. The GRADE framework adapted to prognostic factor research is the best available tool for reporting the overall quality of the evidence of the potential prognostic factors since we could not carry out meta-analysis.

With regards to included participants, we rigorously only included studies on chronic headache types, with a chronic headache diagnosis as baseline, so the results are specific to this group of patients. Most of the research in the field reports on episodic headache, which has a much higher prevalence, but prognostic factors established in episodic headache are not necessarily transferable to chronic headache patients.

Limitations regarding the interpretation of the findings from this study should be taken into consideration. As we included more than one form of chronic headache, most of our findings are subject to some indirectness, as some findings came from studies specific for chronic tension-type headache, chronic migraine, or chronic medication overuse headache, and therefore we urge some caution with generalizability of findings for all forms of chronic headache. We could not present results for each of the included diagnostic groups separately because of a scarcity of data and some of the included primary studies including mixed groups and presenting overall results.

Publication bias is one of the most common biases in systematic reviews. As suggested by Huguet et al.,[15] we considered publication bias to exist across all factors as we did not have determinate factors investigated in large numbers of cohort studies purposefully designed to confirm hypothesized factors, and we therefore consequently downgraded the overall evidence.

Judging the overall quality of evidence per factor was difficult, as measurements used to assess the same factors were not necessarily related to the same outcomes. Furthermore, most study samples are small and factors were measured by single studies or a small amount of studies with comparatively small patient groups assessed. The included RCTs were underpowered for moderator analysis, which creates some imprecision of results, and relevant statistics were not consistently reported. Studies with otherwise good methodology were compromised by poor methodologic quality of their subgroup analysis. We specifically note the lack of RCTs that carried out prespecified subgroup analysis, which would provide higher-quality evidence, and the lack of theoretical framework of moderator and mediator analyses.[43,48] In this review, there was only one study that conducted prespecified subgroup analysis, and its reporting was difficult to interpret. The authors concluded that the moderator was significantly associated with treatment outcome before, during, and after treatment, but it was not clear if the significance was driven by the difference between placebo and the other 3 treatments across treatment time or the difference within treatment across treatment time. The mediator analysis reported in the same article adjusted for some covariates but there remains the potential for confounding of the mediator outcome association by other factors. Most of the included cohort studies did not specify the relationships they were testing a priori, and were therefore defined as phase I explanatory studies.

Implications for future research and clinical practice. Overall this review identified several potentially modifiable prognostic factors in chronic headache. However, the review findings also indicate that the evidence is scarce. No high-quality evidence was provided for any of the potential prognostic factors; therefore, no definite clinical conclusion can be drawn about factors predicting the prognosis of patients living with chronic headache or factors that influence or predict treatment response. The implication is that future research on prognostic factors in chronic headache should be ideally conducted as large, prospective, registered, and protocol-based studies with sufficient study populations and transparent reporting. Prespecified prediction analyses in large cohort studies are needed to confirm potential predictors. Further, a priori analysis plans for subgroups in RCTs are needed to assess moderators and mediators of treatment outcome.

AUTHOR CONTRIBUTIONS

Katrin Probyn: review concept and design, screening of studies, data extraction, quality assessment, interpretation of data, writeup. Hannah Bowers: data extraction, quality assessment, interpretation of data, writeup. Fiona Caldwell: review concept and design, screening of studies, data extraction. Dipesh Mistry: quality assessment, data extraction, interpretation of data. Martin Underwood: review concept and design, critical revision of manuscript. Manjit Matharu: review concept and design, critical

revision of manuscript. Tamar Pincus: project leader, review concept and design, study supervision, interpretation of data, critical revision of manuscript.

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DISCLOSURE

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