**Prognostic factors for chronic headache – a systematic review**

**Authors**

Katrin Probyn MPH1, Hannah Bowers BsC1, Fiona Caldwell MsC1, Dipesh Mistry PhD2, Martin Underwood MD2, Manjit Matharu PhD3, Tamar Pincus PhD1 on behalf of the CHESS team

1. Department of Psychology, Royal Holloway, University of London, Egham Hill, Egham, Surrey. TW20 0EX.

2. Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry. CV4 7AL.

3. Headache Group, Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London. WC1N 3BG

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Figure: Flow chart

Appendix e 1, e - appendix: Search strategies (Embase and Medline)

Table e 1, e- appendix: assessed prognostic factors in all included studies

**Corresponding author**

Katrin Probyn, Royal Holloway University of London, Department of Psychology, Egham, Surrey, TW20 0EX, UK

Telephone: 07817566742

Email: [Katrin.probyn@rhul.ac.uk](mailto:Katrin.probyn@rhul.ac.uk)

Hannah Bowers: Hannah.Bowers.2010@live.rhul.ac.uk

Fiona Caldwell: Fiona.caldwell@rhul.ac.uk

Dipesh Mistry: D.Mistry@warwick.ac.uk

Martin Underwood: M.underwood@warwick.ac.uk

Manjit Matharu: M.matharu@uclmail.net

Tamar Pincus: T.pincus@rhul.ac.uk

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**Authors’ contributions**

Katrin Probyn: review concept and design, screening of studies, data extraction, quality assessment, interpretation of data, and write up.

Hannah Bowers: data extraction, quality assessment, interpretation of data and write up.

Fiona Caldwell: review concept and design, screening of studies, data extraction.

Dipesh Mistry: quality assessment, data extraction, and 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, and critical revision of manuscript.

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**Protocol and registration**

We prospectively registered this review with the International Prospective Register of Systematic Reviews; PROSPERO 2015:CRD42015019848. Available from <http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019848>

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**ABSTACT**

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

**Methods:** A systematic review of published literature in peer-reviewed journals**.** We included a) randomised controlled trials (RCTs) of interventions for chronic headache that reported subgroup analyses and b) prospective cohort studies, published in English, since 1980. Participants included adults with chronic headache (including; chronic headache, chronic migraine, chronic tension-type headache with or without medication overuse headache respectively).

We searched key databases using free text and MeSH terms. Two reviewers independently extracted data and assessed the methodological quality of studies and overall quality of evidence identified using appropriate published checklists.

**Results:** We identified 16556 titles, removed 663 duplicates, and reviewed 199 papers, 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 unfavourable outcomes from preventive treatment in chronic headache. There was inconclusive evidence about treatment expectations, age, age at onset, body mass index (BMI), employment and several headache features.

**Conclusions:** This reviews has identified several potential predictors of poor prognosis and worse outcome post interventions in people with chronic headache. The majority of these are modifiable. The findingsalsohighlight the need for more longitudinal high quality research of prognostic factors in chronic headache

**INTRODUCTION**

Chronic headache, that is headache occurring on 15 or more days per month for at least three months (1) is a major cause of pain and disability. Chronic migraine affects around 1% to 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 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**

**Identification of studies**

We searched for English-language publications reporting randomised controlled trials (RCTs) or prospective cohort studies that reported on predictors, moderators or mediators of outcome, from peer reviewed journals in *Cochrane, Medline/Pub Med, Embase, Psychinfo, Web of science, ASSIA* - supplemented by backward citation tracking, from 01/01/80 to 12/02/15. We updated the search on 14/06/2016.

We included RCTs, with at least 20 patients per treatment arm at follow up (in line with previous research(11)), that have either a) have investigated moderators or mediators of outcome using a-priori hypotheses or b) analysed sub-groups post-hoc; and prospective cohort studies, that measure factors at baseline and use 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 (ICHD) (1) with at least 15 headache days/months for at least 3 months. We included chronic headache, chronic migraine, chronic tension-type headache, with or without medication overuse headache respectively.

In RCTs that included also 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 analysed 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 pre developed 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/mediatos, 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 methodological criteria for the assessment of moderators in systematic reviews of randomised controlled trials (13) which score for a-priori planned analysis, theory-driven selection of factors, measurement of moderators prior to randomisation, quality of moderator measures, and explicit test of the interaction between moderator and treatment. Studies complying with all five criteria were considered as providing confirmatory evidence, those complying with criteria three, four and five as providing exploratory evidence. All other studies were classified as providing insufficient evidence.

Methodological 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 points 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 GRADE framework (15)considering phase of investigation, methodological 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 only) of the whole population of interest (chronic headache). We downgraded quality for imprecision if the evidence was generated by only few studies involving a small number of participants and most of the studies provide imprecise results or no relevant statistics or if evidence only provided by single studies (see table 5).

**Data synthesis**

Because of the high heterogeneity amongst studies regarding treatment and investigated prognostic factors it was not possible to pool studies in 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 16556 titles through database searches and removed 633 duplicates. 15923 studies were screened by title and abstracts and 15724 records excluded. The remaining records were grouped into RCTs (126) and prospective cohort studies (73). After full text assessment, twenty-seven studies were included (ten RCTs with subgroup analysis (16-25) and seventeen prospective cohorts (5, 26-41) (see figure 1).

**Characteristics of included studies**

Eight studies tested a general population of ‘chronic headache’, eight are specifically on ‘chronic migraine’, five include participants with ‘chronic daily headache’, three are specifically on ‘chronic tension type headache’; and three 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; days off work; persistence of chronic headache or reverting to episodic headache or assess relapse rates (from withdrawal therapy) or response to preventive treatment in responder analyses (see table 1).

Randomised Controlled Trials:

Six of the ten 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 three studies looked at acupuncture (19, 22, 23). Within the subgroup analyses in included RCTs only three 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 six assess predictors of prognosis, independent of treatment.

**Methodological quality**

Of the ten RCTs with subgroup analyses and of at least medium overall methodological quality (see table 2), only one study provided confirmatory evidence (based on methodological assessment of sub-group analysis). Two studies provided exploratory evidence, and the remaining seven provided insufficient evidence as they either did not use an explicit interaction test, did not measure subgroup factor prior to randomisation or failed to measure subgroup factors by adequate (reliable & valid) measurements (see table 3).

Of the seventeen observational studies, five were of high methodological quality; ten were medium quality and two 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 I’, 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 hypothesised independent effect of the factor on the outcome (phase II study) or to test a conceptual model, which explains its underlying mechanisms (phase III 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 methodological quality of the studies and potential inconsistency, indirectness, and imprecision of findings (see 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), having allodynia, more migraine days, a bigger 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 behavioural 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 their analysis. They measured headache management self-efficacy (HMSE) during the intervention (2 months post randomisation) 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 (BMI)

A higher BMI did not predict more severe HIT-6 scores (27), having allodynia, headache frequency, medication use (34), or response to multidisciplinary treatment (30). However conversely, one study found that a higher BMI predicted a better response to preventive treatment and favourable HIT-6 scores post intervention (25).

Age

Older age had no effect on the response to interventions, including prophylactic treatment (25, 35), web based behavioural 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 (BoNT 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 it 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 seven studies was contradictory. Headache frequency did not differ between responders and non-responders 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 predict favourable response to detoxification (40), and to multidisciplinary treatment (30).

Baseline headache severity

One study (20) found 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 two 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 (See 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 headache management self-efficacy are associated with worse outcomes. Lower quality evidence suggests higher expectations; age, age at onset, headache 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 headache management self-efficacy 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 headache management self-efficacy 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 focus 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 behavioural 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 assess headache management self-efficacy as mediator for the relationship between headache severity and disability in a population of predominantly non-chronic 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 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 favourable to be able to analyse 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. We believe that 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 generalisability 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 hypothesised 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 methodological quality of their subgroup analysis. We specifically note the lack of RCTs that carried out pre-specified sub-group 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 pre-specified 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 three treatments across treatment time or the difference within treatment across treatment time. The mediator analysis reported in the same paper 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.

**Conclusion and implications for future research and clinical practice**

Overall this review has 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. Pre specified prediction analysis in large cohort studies are needed to confirm potential predictors. Further, a-priori analysis plans for sub-groups in RCTs are needed to assess moderators and mediators of treatment outcome.

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Table 1 Characteristics of included studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author/Year** | **Country** | **Study Sample Size** | **Description of intervention (and control group) if applicable** | **Type of headache** | **Study type** | **Phase of investigation** | **Prognostic factor type** | **Methodological Quality** |
| Boe 2007 | Norway | 102 | Prednisolone or placebo | CH | RCT with subgroup analysis | 1 | Predictor of fo 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 behavioural intervention vs. waiting list | CM | RCT with subgroup analysis | 1 | Predictor or 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 (AM) vs. (cognitive behavioural) stress management therapy (SMT) with placebo vs. SMT+AM | 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 | 7169 | n/a | 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 | n/a | CH | Long term outcome study | 1 | Predictor of outcome | +++ |
| Houle 2012 | USA | 55 | n/a | CH | Observational cohort | 2 | Predictor of prognosis | +++ |
| Katsarava 2003 | Germany | 98 | n/a | CH | Long term outcome study | 1 | Predictor of outcome | ++ |
| Katsarava 2004 | Germany | 96 | n/a | CH | Long term outcome study | 1 | Predictors of outcome | ++ |
| Louter 2013 | Netherlands | 2331 | n/a | CM | Observational cohort | 1 | Predictor of prognosis | ++ |
| Lu 2001 | Taiwan | 108 | n/a | 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 | n/a | 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 | ++ |
| Tribl2001 | Austria | 55 | n/a | CDH | Long term outcome study | 1 | Predictor of outcome | ++ |
| Zidverc-Trajkovic 2007 | Serbia | 240 | Prophylactic medication | CH (with MO) | Open label | 1 | Predictor of outcome | +++ |
| Zwart 2003 | Norway | 32067 | n/a | CH | Observational cohort | 2 | Predictor of prognosis | +++ |

Legend: n/a= not applicable; CH= Chronic headache, CM=chronic migraine, CDH= chronic daily headache, CTTH= chronic tension type headache, MO= medication overuse

Methodological quality: for RCT subgroup analyses: + = insufficient evidence; ++ = exploratory evidence,; +++ = confirmatory evidence; For observational studies: + = low quality, ++ = medium quality, +++ = high quality

Table 2 Risk of Bias assessment in RCTs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author/Year** | **1) Did the study have an adequate randomisation sequence?** | **2) Was allocation concealment carried out?** | **3) Were withdrawals and dropouts explained?** | **4) Was outcome assessment blinded?** | **5) Sufficient N (>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 RCT subgroup analyses using methodological criteria by Pincus et al (13)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author/Year** | **Was subgroup specified a priori?** | **Was selection of subgroup factors theory/evidence driven?** | **Subgroup factors measured prior to randomisation?** | **Were subgroup factors measured by reliable & valid measurements?** | **Was an explicit test of the interaction used?** | **Level of evidence** |
| **Boe 2007** | **-** | **-** | **-** | **-** | **-** | **Insuff** |
| **Boe 2009** | **-** | **-** | **✓** | **✓** | **-** | **Insuff** |
| **Bromberg 2012** | **✓** | **-** | **✓** | **✓** | **✓** | **Expl** |
| **Castien 2011** | **✓** | **-** | **✓** | **-** | **-** | **Insuff** |
| **Ellis 2004** | **-** | **-** | **-** | **-** | **✓** | **Insuff** |
| **Holroyd 2009** | **✓** | **✓** | **✓** | **✓** | **✓** | **Confirm** |
| **Schulte-Mattler 2004** | **-** | **-** | **✓** | **-** | **-** | **Insuff** |
| **Yang 2011** | **✓** | **-** | **✓** | **✓** | **-** | **Insuff** |
| **Yang 2013** | **-** | **-** | **✓** | **✓** | **✓** | **Expl** |
| **Yurekeli 2008** | **✓** | **-** | **✓** | **✓** | **-** | **Insuff** |

*Conf indicates conﬁrmatory evidence: The study fulfilling all five criteria for moderator studies; Expl indicates exploratory evidence: The study meeting only three, four and five criteria for moderator studies; Insuff indicates insufﬁcient evidence: The study meeting criteria of explicit test of interaction between moderator and treatment and inadequate measurement of subgroup factors.*

Table 4 Methodological quality of prospective cohort studies using methodological criteria by Hayden et al (14)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year** | **Adequate description of sampling?** | **Attrition reported?** | **Outcome of interest reported?** | **Appropriate analyses?** | **Reporting of analyses appropriate?** | **Adequate sample size?** | **Valid measure of confounders?** | **Number 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-Trajkovic2007** | **Y** | **Y** | **N** | **Y** | **Y** | **Y** | **Y** | **7** | **13** |
| **Zwart 2003** | **Y** | **N** | **Y** | **Y** | **Y** | **Y** | **Y** | **4** | **10** |

***Y = Yes(1 point); P = Partially (0.5 point); N = No (0 points);***

*<=5 points: low quality, 6-9 points: med quality, >=10 points: high quality*

Table 5 GRADE evidence profile of overall quality

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **GRADE factors** | | | |  | **Univariate or Multivariate** | | |  |  |
| **Potential prognostic factors** | **Number of studies** | **Study limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Number of participants** | **+** | **0** | **-** | **Phase of investigation** | **Overall quality** |
| **Psychosocial factors** | | | | | | | | | | | |
| **Depression and anxiety** | 5 | ✓ | ✓ | X | ✓ | 9951 |  |  | 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 | 2479 | 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 | 2739 | 2 | 1 |  | 1 | **++** |
| **BMI** | 4 | ✓ | x | x | ✓ | 10522 |  | 3 | 1 | 1 and 2 | **++** |
| **Age** | 15 | ✓ | x | ✓ | ✓ | 43640 | 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 | 7685 |  | 1 | 3 | 1 and 2 | **++** |
| **Headache frequency** | 7 | ✓ | x | x | ✓ | 4000 | 2 | 3 | 2 | 1 and 2 | **++** |
| **Medication overuse** | 7 | ✓ | ✓ | x | ✓ | 36215 |  |  | 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 | **+** |

***For uni- and multivariate analyses: + = number of significant effects with a positive value; 0 = number of non-significant effects; - = number of significant effects with a negative value. For GRADE factors: ✓ = no serious limitations; x = serious; unclear, unable to rate item based on available information.***

***For overall quality: + = very low quality, ++ = low quality, +++ = moderate quality***