**Systematic review of childhood and adolescent risk and prognostic factors for recurrent headaches**

**Short Running Title: Childhood risk and prognostic factors for headaches**

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**Disclosures:**

This research is funded by the Canadian Institutes of Health Research (grant #226950). PJM’s research is supported by a Canada Research Chair. JAH holds a Professorship in Epidemiology supported by Dalhousie University and the Canadian Chiropractic Research Foundation.The authors have no conflicts of interest to declare.

# Abstract

# Little is known about childhood and adolescent risk and prognostic factors for recurrent headaches. This systematic review: (1) Examined longitudinal evidence about factors associated with onset and course of recurrent headaches in childhood or adolescence, using meta-analysis where possible; and (2) Evaluated the quality of this evidence using a modified GRADE framework. Through searching electronic databases, reference lists of included studies, and an electronic mail list we identified and included 23 articles reporting 19 cohorts. From the included studies we explored 27 risk factors for recurrent headaches, 27 prognostic factors for persistence of recurrent headaches, and 6 prognostic factors for presence of headache-related disability. The quality of evidence for most associations is low or very low. There is moderate quality evidence that females are at risk of developing recurrent headaches and of headaches persisting. There is high quality evidence suggesting that children with negative emotional states manifested through anxiety, depression or mental distress are not at risk of developing headache, but moderate quality evidence suggests that the presence of comorbid negative emotional states in children with headaches is associated with increased risk of headache persistence. Due to the small number of studies, further investigation is needed to increase confidence in existing evidence and to explore new risk and prognostic factors.

**Perspective:** This is a review of the evidence about childhood and adolescent risk and prognostic factors for the onset of recurrent headaches and their course. Understanding these factors can help identify childrens’ risk and may suggest ways to reduce this risk.

**Keywords:** headache, child, adolescent, risk factors, prognostic factors **1. Introduction**

Headache disorders are ranked in the top three most common diseases in the world, with world-wide prevalence of tension-type headache (21%) and migraine (15%) ranking second and third on the list, respectively.55 In adults, the life-time prevalence of tension-type and migraine headache, according to the International Classification of Headache Disorders, is reported to be 46% and 14%, respectively.51 Regardless of headache diagnosis, it has been reported that up to 90% of children and adolescents will have at least one headache over the course of a 1 year period, with 26-32% of Canadian adolescents aged 12-19 years reporting at least weekly headaches.19, 30, 49 Headaches, particularly migraines, can have significant impact on daily functioning, quality of life, work or school productivity, and social interaction,10, 48 and are often associated with comorbid conditions.6 Migraine is ranked as the eighth leading cause of world-wide disability.55 Long-term prognosis of headaches is often poor (e.g.,4, 5, 15); for example Brattberg10 found that 24% of children with headaches reported experiencing pain 13 years later as young adults. The high prevalence and the level of associated disability and poor prognosis makes recurrent headaches costly at both individual and societal levels. The yearly direct medical cost of migraine per adults was estimated to be $2,571 USD,23 and in eight European countries the direct and indirect costs of migraine per adult was estimated to be €1,222.34 In children and adolescents with headaches, the estimated cost over a 6-month period has been €692, with greater expenses for children and adolescents with migraine.37

Over the last decade, emerging risk and prognostic research has attempted to answer questions such as: ‘What children are more likely to develop headaches?’ (e.g.,9, 17) or, ‘What is the most likely course of headaches in a particular child?’(e.g.,49, 52). Research attempting to answer these questions is an important step towards early prevention. Quality evidence about early life risk and prognostic factors can be useful to inform health care professionals about what contributes to the development, persistence and aggravation of headaches over time.1, 41, 45 Health care professionals can then make early health care decisions with the goal of informing strategies aimed to reduce risk of onset and worsening of headaches, ultimately reducing associated individual and societal costs.

It is currently difficult to predict or prevent children’s future development and course of headaches. The development or prognosis of chronic or recurrent pain, including headaches, is not yet well understood, as this type of research is in its early stages.27 Moreover, the interpretation of findings derived from initial primary risk and prognostic studies is often hampered by study heterogeneity in population, risk/prognostic factors and outcomes, assessment measures, analyses, and inconsistent results.28 There is emerging research investigating the influence of factors that place children at risk of developing headaches, as well as of factors that affect the prognosis of children with headaches;17, 33, 36, 52, 59 no synthesis of these empirical findings into a coherent body of knowledge has been conducted.

For these reasons our review focused on recurrent headaches and assessed available longitudinal evidence about the following research questions: What risk factors in childhood and adolescence have been investigated and found to be associated with the onset of recurrent headaches, and what childhood and adolescent prognostic factors have been investigated and found to be associated with persistence of recurrent headaches and presence of headache-related disability? What is the direction and strength of the relationship between these investigated risk or prognostic factors and the outcomes? What is the quality of evidence of these relationships?

# 2. Methods

A systematic review protocol was developed to guide the review process (available on request) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)39 reporting guidelines. This systematic review is part of a larger comprehensive project aimed to identify childhood risk and prognostic factors for chronic pain. Results will be published separately for the main pain conditions identified, to maintain sufficient detail about each of the pain conditions. This paper therefore focuses on the results of childhood risk and prognostic factors for recurrent headaches.

*2.1 Search Strategy*

As this systematic review is part of a larger comprehensive project aimed to identify risk and prognostic factors for any type of chronic pain condition, our search strategy was built to identify longitudinal risk and prognostic studies. We utilized methodology filters validated for detecting risk and prognostic studies,26, 60, 61 and chronic pain terms (e.g., headache, headache disorders, migraine, cephalalgia) defined through consensus by a group of pediatric pain experts, and population terms (e.g., children, adolescents, teen, youth, young) to limit the search to studies exploring children and adolescents. We searched electronic databases (PubMed, EMBASE, PsycINFO, CINAHL, and Web of Science) from date of database inception until July 2015. We hand-searched the reference listsof included studies and also consulted with the Pediatric Pain mail list for additional relevant studies. Search strategies for each database were built and run by an experienced reference librarian (see search strategies for each database in Supplementary File 1).

*2.2 Eligibility criteria*

Studies were initially screened for inclusion if they (1) were a full-text published prospective or retrospective longitudinal cohort study with at least three months of follow-upand(2)aimed to quantitatively investigate factors at ages 5-18 that could be associated with risk of onset of recurrent headaches, or associated with the prognosis of recurrent headaches defined in terms of persistence of recurrent headaches or presence of headache-related disability. Recurrent headaches were operationally defined as headaches occurring at least once per month. Although we recognize that this cut-off point was set arbitrarily, it was set for the purpose of encompassing only those studies that have investigated frequent and regular headache subtypes, which are the ones that normally impact individual’s life. This definition has been used in several studies exploring childhood headache (e.g.,17, 18, 54, 56). Headache-related disability was defined as restriction in the ability to function within the environment as result of recurrent headaches. An arbitrary follow-up period of three-months was selected to ensure a duration of time large enough to determine whether the onset or persistence of recurrent headaches occurring at least once per month was present. Studies exploring risk of recurrent headaches onset were defined as those that examined risk factors at baseline in participants without existing headache, and measured the association between those risk factors and the subsequent onset of recurrent headaches at follow up, in comparison to participants who remained headache-free over time. Studies exploring prognosis of recurrent headache persistence were defined as those that examined prognostic factors at baseline in participants with existing recurrent headaches, and measured the association between those prognostic factors and the subsequent persistence of recurrent headaches at follow-up, in comparison to participants who no longer had headaches, or were in remission. We excluded (1) studies that were not published in English, (2) studies with a cross-sectional design, or (3) studies with populations that had cognitive impairments or life-threatening illnesses, since these subgroups may be more at risk of worse health outcomes.53

*2.3 Study Selection*

Two reviewers (MT, CS) screened titles and abstracts retrieved from the search strategy for two preliminary options: ‘exclude’ or ‘potentially eligible’. Inter-rater reliability was consistently monitored at this stage by having the two reviewers rate ten randomly selected sets of 150 abstracts throughout the screening process. Inter-rater reliability was assessed using Cohen’s Kappa.13, 31 Discrepancies between the two reviewers were resolved through discussion and mediated by a third person (AH) if necessary.

Using the eligibility criteria, the same two reviewers independently assessed 150 full-text articles randomly selected of all those identified as ‘potentially eligible’ during the title and abstract screening. Inter-rater reliability from the 150 full-text articles was assessed using Cohen’s Kappa.13, 31 Reviewers were not blinded to authors’ names, institutions, or journal title. After the 150 full-text screening, the remaining full-text articles were screened by one of the reviewers (MT or CS). Any study that did not clearly meet exclusion criteria were discussed and mediated by a third reviewer (AH) if needed. During screening of the full-text articles, the articles specifically addressing risk or prognostic factors for recurrent headaches, the focus of the review reported here, were noted and used to summarize the findings.

*2.4 Data Extraction*

Two reviewers (MT, CS) independently extracted data for a subset of 16 studies randomly selected of those identified for inclusion for our comprehensive project. Data for the remaining studies was extracted by one reviewer (MT or AH) and then checked by a second reviewer (CS, MT or AH).

The following data were extracted: (1) study characteristics (i.e., study design, sample size, response and attrition rate, recruitment setting, study criteria, length of follow-up); (2) patient characteristics (i.e., age, type of headache, duration of headaches); (3) outcome variable measured; (4) risk/prognostic factors (i.e., definition, self or proxy report, assessment measure); (5) data analysis (i.e., type of analysis, confounding adjustment, confounders), and (6) measures of association between the risk/prognostic factor and the outcome including univariate and multivariate effect sizes with their 95% of confidence intervals. When effect size and confidence intervals were not provided, they were calculated based on the raw data if reported. Consequently when effect sizes were not provided, for cases with dichotomous outcomes, we planned to calculate odds ratio and the 95% confidence interval of odds ratio. In cases with continuous outcomes, we planned to calculate standardized mean differences and the 95% confidence intervals for the standard mean differences. Study authors were contacted when any data for extraction were not clearly reported and/or missing.

*2.5 Mapping prognostic factors, risk factors and outcomes to the ICF-CY*

The WHO ICF-CY (World Health Organization’s International Classification of Functioning, Disability and Health for Children and Youth classification system63) was used as a conceptual framework for mapping the risk, prognostic factors, and outcomes measured in the included studies onto pre-existing categories. The ICF-CY provides a hierarchical classification system for categorizing functioning and disability, specifically for: (1) body functions, (2) body structures, (3) activities and participation, (4) environmental factors, and (5) personal factors. The linking of ICF-CY categories to each risk, prognostic, and outcome variable was established consensually by two reviewers (AH, MT) with disagreements resolved through consultation with all co-authors. Additional categories were developed as needed to allow more specific mapping of identified risk/prognostic factors. These were not defined a priori, instead, they were defined after extracting all data from the included studies when knowing what factors and outcomes had been investigated. Throughout this article, the ICF-CY categories to which the prognostic, risk, and outcome variables were mapped onto, will be referred to as “factors”.

*2.6 Data analysis*

To evaluate the direction and strength of the relationship between the investigated risk or prognostic factors and the outcome, we performed meta-analyses using a random-effects model whenever data for the same factor were available from at least four studies, combining separately adjusted and unadjusted results. Comprehensive Meta-analysis software was used to perform these analyses. We did not encounter any association exploring a continuous outcome variable, therefore, all of the meta-analyses were converted to odds ratio to yield a common measure of effect. The studies with time-to-event data were excluded for the meta-analysis. Potential influences on the effect size were investigated using exploratory subgroup analyses. The potential moderating factors explored were: (1) type of headache (tension-type headache *vs.* migraine); (2) duration of follow-up (short follow-up: 5 years or less *vs.* long follow-up: more than 5 years); (3) risk of methodological bias (low *vs.* high risk of bias); (4) setting (clinical setting *vs.* non-clinical setting). Subgroup analyses by type of headache and risk of methodological bias were determined a priori, the rest of the subgroup analyses were identified a posteriori. Subgroup analyses were only performed when there were at least two studies in at least one of the subgroups.

Meta-analyses were rarely possible due to the low number of available studies exploring the same factors. When meta-analyses were possible, they only took into account the evidence derived from those primary studies with sufficient data to be entered into the analysis. For this reason, we also qualitatively summarized the research findings derived from all included primary studies. When summarizing findings from a qualitative perspective, we used forest plots to visually present unpooled effects from each individual primary study and visually explored differences and similarities. Taking into account that all the selected studies used dichotomous outcome variables, we qualitatively considered that results were ‘consistent’ across studies when all studies using the same form of analysis (i.e., univariate vs multivariate analysis) reported the same direction of a relationship, either a significant positive relationship, a significant negative relationship or no significant relationship between the factor and the outcome. We considered that there was a ‘trend’ in the results, when the effect size for all studies were on the same side of the line of no effect and the majority, but not all, of the two-sided 95% confidence limits around the effect size were on the same side of the line of no effect when comparing limits between studies. Finally, we considered results across studies as ‘inconsistent’, when one study or more, did not report the same finding as the others reporting the explored association. In these instances either the effect sizes were on opposite sides of the line of no effect and the two-sided confidence limits did not always fall on the same side of the line of not effect, or the effect sizes for all the studies were on the same side of the line of no effect and the two-sided confidence limits did not commonly fall on the same side of the line of no effect.

When comparing findings from multiple publications reporting on the same cohort (e.g.,57-59) with differences in sample (e.g., migraine *vs.* chronic daily headache) or follow-up durations (e.g., 2 *vs.* 8 years), we included data from the manuscript with 1) evidence from the largest sample size, 2) from the sample with migraine headache (when applicable), and 3) evidence with the longest follow-up.

*2.7 Applying the GRADE framework for assessing quality of evidence*

We used a modification of the GRADE framework to assess the overall quality of evidence of risk/prognostic factors and their association with outcomes of interest. GRADE was developed originally to help assess the quality of evidence as part of systematic reviews for treatment interventions.22 GRADE was then adapted and used as a framework to rate the overall quality of evidence for prognostic studies.28 We used this framework to judge the overall quality of evidence for each risk/prognostic factor associated with each of the outcomes of interest across studies. Evidence was rated as high, moderate, low and very low quality (see Supplementary File 2 for a definition of the quality levels). We followed the approach of Huguet et al28 and downgraded the quality of evidence according to: phase of investigation, study limitations, inconsistency, indirectness, imprecision, and publication bias, each of which are briefly described here. The quality of evidence of a determinate association was downgraded for phase of investigation if evidence came from studies which were elaborated in the earlier phase of investigation to generate hypothesis. Study limitations downgraded the quality of evidence when results were mainly from studies with high or moderate risk of bias. Inconsistency was identified when variability in the results across studies was present without plausible explanation that was not clinically meaningful, or if evidence came from a single study. The quality of evidence of a determinate association was downgraded if the prognostic factor, outcome, or study sample did not reflect the research question. Imprecision was determined if the evidence came from studies with insufficient sample sizes, there was no precision in the estimation of the effect size within each study, and there were few studies with small numbers of participants across studies. Publication bias was always considered to be present and negatively influencing the quality of evidence, unless the factor predicting outcome was repetitively investigated by phase 2 or 3 studies and no effects were reported in those studies. We upgraded the quality of evidence based on: large effect sizes and exposure-response gradients. At least moderate effects sizes had to be reported by most of the studies, and elevated levels of the risk/prognostic factor had to lead to larger effect sizes over lower levels of the factor, respectively, to upgrade the quality of evidence. We judged the quality of evidence both when meta-analyses were possible and when results from individual studies were summarized qualitatively.

Assessment of all of the GRADE factors was pilot tested with two reviewers (AH, MT) for four studies included in this review. Consequently, with the exception of ‘study limitations’, the GRADE-based evaluations were assessed by one reviewer (MT) and discussed with another reviewer (AH) when there was any uncertainty. The ‘study limitations’ factor was assessed independently by two reviewers (MT, CS, or AH) for all studies using the Quality In Prognosis Studies (QUIPS) methodological checklist tool as recommended by Hayden et al.24, 25 Inter-rater reliability of the QUIPS ‘study limitations’ rating was assessed using Cohen’s Kappa.13, 31

**3. Results**

*3.1 Results of search*

The comprehensive project search yielded 85,714 articles once duplicates were removed, 44 additional articles were identified through scanning references of included articles, and nine were identified through consultation with the electronic Pediatric Pain mail list. A flow chart outlining the selection process is presented in Figure 1. Inter-rater reliability for all of the titles and abstracts retrieved for the comprehensive project was substantial (kappa = 0.77). Inter-rater reliability for screening the 150 randomly-selected full-text articles was appropriate (kappa = 0.73). A total of 23 reports related to risk or prognostic factors for headaches were identified and selected for inclusion in this review. When extracting information from included studies, 16 authors from 19 articles were contacted through email when extracting data for clarification and/or additional information. Ten of the authors responded about twelve articles, but six actually provided information that was needed from seven articles, the remaining authors did not provide the information requested most often due to unavailability of the data. For the GRADE-based evaluations pilot tested with two reviewers for four studies, a substantial level of agreement was met (kappa = 0.734). Study limitations assessed by two independent reviewers had acceptable interrater reliability for all studies (kappa = 0.76).

*3.2 Included Study Characteristics*

Twenty-three manuscripts reporting 19 prospective cohorts published from 1993-2015 met our study criteria and were included in this review. Eleven manuscripts explored factors potentially associated with headache onset, 15 explored associations with persistence of recurrent headache, and one explored prognostic factors associated with presence of headache-related disability in individuals that reported to be experiencing recurrent headaches at baseline. See Table 1 for characteristics of the studies included in this review, Appendix 1 for the study limitations assessed using the QUIPS methodological checklist tool,24, 25 and Appendices 2-4 for information about how each outcome, prognostic and risk factor was operationally defined.

*3.3 Risk factors for onset of recurrent headaches*

Twenty-seven factors were explored as potential risk factors for onset of recurrent headaches in 10 non-clinical cohorts in the included studies (5 community-based and 5 school-based cohorts). Follow-up duration in the studies ranged from 1-9 years (mean 3.1 years) and sample sizes at follow-up from 262 to 3,151 (mean 1,297), Table 1. According to our modified GRADE-based assessment, the overall quality of evidence for the qualitative summary of results was rated as high for two associations, moderate for one*;* low for two; and very low for 22. The GRADE-based assessment for the evidence derived from the two meta-analyses that summarized the evidence for two of the factors was rated as high and very low, Table 2. The evidence for these factors primarily comes from exploratory analysis conducted in early, hypothesis-generating stages of investigation.

*3.3.1 Potential risk factors most commonly explored for recurrent headaches*

Of the 27 factors that were explored as potential risk factors for recurrent headaches, 23 (85%) were explored in only one or two cohorts. The three factors explored most often included emotional functions expressed through the manifestation of negative emotional states (explored in six cohorts), female sex (explored in five cohorts), and stressful life events (explored in three cohorts).

*3.3.1.1 Emotional functions*. Six studies reporting results from six different cohorts (9,584 subjects) investigated whether emotional functions expressed through the manifestation of negative emotional states (i.e., anxiety, depression and mental distress) could act as a potential risk factor for onset of recurrent headaches.7, 18, 33, 35, 43, 54 Four of these studies, which involved 3,968 subjects, had sufficient data available from multivariate analyses for conducting a meta-analysis.7, 18, 43, 54 Negative emotional functions were not found to be significantly associated with the development of recurrent headaches (OR=1.06; 95% CI = 0.93-1.20), Figure 2. There was no evidence of heterogeneity between studies (Q-value(3)=3.42, p=0.47). When qualitatively summarizing the unpooled univariate data from independent studies, a trend across studies was observed. This trend suggests that an increasing presence of negative emotions may be associated with an increased chance of developing recurrent headaches (Figure 3a). However, consistent with the meta-analysis, this relationship consistently disappears across studies when the influence of confounding variables including gender, age, and socioeconomic level are accounted for7, 18, 35, 43, 54 (see Figure 3b). For both the qualitative and quantitative findings, the explored association between a range of negative emotions and onset of recurrent headaches is supported by high quality of evidence according to the GRADE-based assessment.

*3.3.1.2 Female sex*. Five out of six studies providing unadjusted data (n=9,162)8, 17, 32, 35, 42 were included in the meta-analysis to investigate female as a risk factor for recurrent headaches. Females were found to be more likely than males to develop recurrent headaches (OR=1.64; 95% CI= 1.09-2.47), Figure 4. Although there was evidence of significant heterogeneity (Q-value(4)=21.13, p=0.0002), we were unable to explore whether some of the effect size dispersion could be explained by potential moderators, due to an insufficient number of available studies. We could only tentatively explore differences in effects for the subgroup of studies that used a short follow-up period. The meta-analysis revealed that females are not more likely to develop recurrent headaches in the short-term than males (k=4, n=8,529, OR=1.51; 95% CI=0.93-2.44). From a qualitative perspective, when considering results derived from univariate analysis, although most of studies concluded that female sex in children and adolescents was a significant risk factor for recurrent headaches, this finding was inconsistent across all studies, Figure 3c.8, 17, 32, 35, 42 One study35 used multivariate analyses to explore whether female sex was associated with onset of recurrent headaches. This study, including a cohort of Taiwanese adolescents aged 13-14 which followed annually for two years, reported a statistically significant association between female sex and the onset of recurrent headaches. The overall quality of evidence derived from the quantitative analysis was very low but the overall quality of evidence qualitatively summarizing the findings supporting female as a risk factor is moderate, meaning that it is likely that there is an association between female and onset of headache, but we should have low confidence in the pooled estimate of effect. We downgraded the quality of evidence derived from the quantitative analysis since the majority of studies were exploratory with serious risk of methodological bias (including lack of conceptual framework to guide analyses, selective reporting of their results, and failure to account for potential confounding variables), and there was unexplained heterogeneity in results across studies. We downgraded the quality of evidence derived from the summary of qualitative findings due to the study limitations but also upgraded due to moderate size of effect estimates in the majority of studies.

*3.3.1.3 Stressful life events*. Three cohort studies involving 6,284 subjects investigated whether childhood stressful life events could increase risk of recurrent headaches.18, 35, 42 There were not enough data available to pool and conduct a meta-analysis. Univariate results reported in these three cohorts consistently revealed an association between onset of recurrent headaches and the presence of past or current stressful life events, such as divorce of parents, working mother, abuse, school problems (see Figure 3d). Findings around the role of stressful life events were, however, inconsistent in the multivariate analyses when potential confounders were controlled for. When Gabmann et al18 controlled for the influence of age, hyperactivity, anxiety/depression in males and females separately, the association between life events and onset of recurrent headaches disappeared. Lu et al35, however, did find that the presence of life events in adolescents was a risk factor for recurrent headache, after controlling for sex, socioeconomic status, family environment, headache characteristics, and other health conditions (see Figure 3e). Unlike the other studies exploring the association between stressful life events and onset of recurrent headaches, Lu et al35 investigated the onset of chronic daily headaches instead of any form of recurrent headaches. These findings may imply that stressful life events are not independently associated with the onset of recurrent headaches in general; rather, recurrent headaches in general are likely associated with other factors (e.g., emotional functioning, stress, age, sex). The quality of evidence for this association was downgraded to low due to the early phase of investigation, imprecision of the results and poor methodological quality of the primary studies due poor risk factor and outcome measurement and due to the majority of studies reporting inadequate follow-up response rates (>20% drop out rates).

*3.3.2 Potential risk factors associated with the highest quality of evidence*

When explored qualitatively, high quality evidence was available for emotional functions expressed through the manifestation of negative emotional states and for sustaining attention as potential risk factors for recurrent headaches. One factor, female sex, was associated with moderate quality of evidence when it was summarized qualitatively. Two factors, stressful life events and agreeableness, were scored as low quality of evidence. All other factors were rated with very low overall quality of evidence.

*3.3.2.1 Sustaining attention*. Three studies7, 18, 54 consistently reported univariate and multivariate evidence that symptoms of difficulty sustaining attention (e.g., unable to sit still, restless or hyperactive, unable to concentrate or pay attention) were not associated with an increased risk of developing headaches at follow-up (see Figure 3f). For example, Virtanen et al54 followed a Finland birth cohort of 3,513 children aged between 10.8 and 12.3 years old at baseline for three years; they found no relationship between difficulty in sustaining attention and headache onset when controlling for sex and behavioral problems.

*3.4 Prognostic factors for persistence of recurrent headaches*

A total of 27 potential prognostic factors were investigated for their relationship to persistence of recurrent headaches, from 12 cohort studies, including clinical (n=6), school (n=5), and community-based (n=1), cohorts, and reported in 15 manuscripts (see Table 3). Follow-up durations in the included studies ranged from 1-21 years (mean 8.6), with sample sizes of 27-1,415 (mean 254), Table 3. Of these factors, 18 have been investigated in two or more cohort studies. According to our modified GRADE-based assessment, the overall quality of evidence for the qualitative summary of results was rated as moderate for two associations, low for two associations, and very low for 23 associations. The overall quality of evidence associated with these factors was mainly downgraded because most were derived from exploratory studies designed to generate hypothesis as well as due to methodological limitations and publication bias. The overall quality of evidence for the only association that we were able to summarize from quantitative perspective was low.

*3.4.1 Potential prognostic factors most commonly explored for the persistence of recurrent headaches*

Female sex was the most common prognostic factor investigated in included cohorts (n=10), followed by duration of pain episodes (n=4) and age of pain onset (n=4).

*3.4.1.1 Female sex*. Six studies providing unadjusted data (n=1,104)8, 20, 32, 40, 42, 48 were included in the meta-analysis to investigate whether female sex was a risk factor for persistence of headaches. Females were more likely than males to report persistent headaches over time (OR=2.67; 95% CI=2.28-3.14), Figure 5. There was no evidence of heterogeneity between the studies (Q-value(5)=4.37, p=0.50). Subgroup analyses confirmed that there were not differences in the effect sizes between studies that explored short-term effects (k=2, n=400, OR=2.31; 95% CI=1.38-3.85) and long-term effects (k=4, n=704, OR=2.63; 95% CI=1.70-4.06) (total between Q-value(1)=0.14; p=0.71); or between studies that explored the effect in a clinical setting (k=2, n=127, OR=3.82, 95% CI=-1.76-8.30) and a non-clinical setting (k=4, n=977, OR=2.51; 95% CI=2.00-3.15) (total between Q-value(1)=0.10; p=0.31). We were not able to compare the potential effect of type of headache or the methodological quality since there was not data.. However, a subgroup analysis including only the two studies that investigated migraineurs40, 48 showed that females who have migraine are not more likely to report persistence of migraine over time than males (n=82, OR=2.40; 95% CI=0.95-6.03). When summarizing from a qualitative perspective, results from univariate analyses were inconsistent across studies, but type of headache could explain, in part, some of these inconsistencies as described above, where the studies following a cohort of migraineurs consistently showed that females were not at a higher risk (see Figure 6a). Similar findings were reported in results derived from multivariate models, which we could only explore from a qualitative perspective since there were not enough studies to run a meta-analysis. Stanford et al49, studying a Canadian cohort of young individuals with recurrent headaches in general (without specification of the headache diagnosis), found female sex to be a statistically significant prognostic factor for persistence of recurrent headaches when controlling for self-esteem and anxiety or depression over a period of eight years. However, Wang et al57, Termine et al52, and Monastero et al40 all consistently reported, when studying cohorts of young migraineurs, female sex not to be a prognostic factor for persistence of migraine, Figure 6b. We judged quality of evidence for the qualitative summary of findings to be moderate, with evidence for the meta-analysis downgraded to low due to studies being in the early phase of investigation and possible study limitations.

*3.4.1.2 Duration of pain episodes*.When explored in both univariate and multivariate analyses for four cohorts, increasing duration of headache episodes was consistently not found to be a prognostic factor of headache persistence, Figure 6c.29, 48, 52, 57 However, the quality of evidence was low. There were no differences in findings when exploring from a qualitative perspective the subgroup of results from the three studies exploring persistence of migraine.48, 52, 57

*3.4.1.3 Age of pain onset*. The univariate and multivariate results from four studies20, 40, 52, 58 consistently reported that younger age of headache onset was not associated with persistence of recurrent headaches at follow-up, Figure 6d. This finding is based on low quality of evidence.

*3.4.2 Potential prognostic factors with the highest associated quality of evidence*

None of the investigated potential prognostic factors were associated with high level of evidence in their relationship to persistent headache. The only factors assessed as to have moderate quality of evidence were female sex and emotional functions expressed through the manifestation of negative emotions when evidence was summarized from a qualitative perspective*.* All other factors were rated with low or very low overall quality of evidence.

*3.4.2.1 Emotional functions*. Three prospective studies explored whether emotional functions expressed through the manifestation of negative emotions could be a prognostic factor for persistence of recurrent headaches.21, 49, 58 Individual prognostic factors from the studies belonging to the emotional functions category encompassed negative emotions, including anxiety and/or depression. The results from both univariate and multivariate results consistently reported that the presence of anxiety and/or depression symptoms at baseline was associated with the persistence of recurrent headaches at follow-up. Guidetti et al21 examined a clinical sample of 100 migraine and tension-type headache sufferers between the ages of 14-18 over a period of eight years. Of those remaining in the study at follow-up (n=77), those with anxiety disorders at baseline (including separation anxiety, overanxious disorder, and social phobia) were found to be significantly more likely to still report recurrent headaches at follow-up. Similar findings for major depression associated with persistence of recurrent headaches over a period of two years were reported in a cohort of adolescents with chronic daily headache aged 12-1458, and over an eight-year period in a population-based study of youth with recurrent headaches in general aged 10-1150 (see Figure 6e). The quality of evidence was judged to be moderate; it was downgraded for poor methodological quality of primary studies and potential publication bias, and upgraded for large reported effects.

*3.5 Prognostic factors for presence of headache-related disability*

We identified one study, a school-based cohort of 103 adolescents aged between 12 and 14 years with chronic daily headache that were followed over a period of 8 years.61 The study investigated six potential prognostic factors associated with presence of headache-related disability: lifetime duration of pain, type of chronic daily headache, medication overuse, sex, age, and previous injury (See Supplementary File 3 for information about how each prognostic factor was operationally defined). Headache-related disability was assessed using the Migraine Disability Assessment (MIDAS) questionnaire. This was a phase 1 study designed to generate hypotheses.59 The quality of evidence for all six associations was very low, lowered mainly due to having only one study available to provide evidence for the relationship explored (Supplementary File 4).

**4. Discussion**

The first aim of this review was to identify the potential risk and prognostic factors for recurrent headaches using the ICF-CY classification scheme as a framework. The overall number of studies included in our review was small, particularly for research related to headache-related disability, while evidence for protective factors for recurrent headaches have not yet been studied. This indicates that the investigation of contributors to headaches and their course is still at an early phase in existing literature. Regardless of the limited research, factors related to ICF-CY components “body functions” and “personal factors” were studied far more frequently than “activity and participation” or “environmental” factors. This finding signifies that recurrent headaches, especially during childhood and adolescence, is considered more at the individual structure-level rather than from a broader contextual perspective, which may limit our understanding of modifiable risk factors and prognostic factors. Knowledge about modifiable factors at both individual and contextual levels can have direct clinical implications for initiating targeted prevention and intervention initiatives. However, precisely as a result of the evidence for contributors being very limited, there are no studies yet that have explored how potential risk and prognostic factors may be effectively modified and whether this actually improves health outcomes in the long term.1 Our review highlights the need to conduct more etiological and prognostic studies of headaches. It also particularly highlights the need to emphasize research on exploring which factors are associated with greater headache-related disability, taking into account that migraine, a common type of headache, is one of most disabling global health problems.55 Also, more research exploring modifiable risk and prognostic factors within the lives of children and adolescents is necessary, to inform the delivery of more effective preventive interventions.

The second aim of this review was to summarize the quality of risk and prognostic evidence according to the GRADE framework.28 The overall quality of most of the investigated risk and prognostic factors is low or very low, which means that our confidence in the majority of the prognostic, risk factors which have been investigated so far is very limited. The quality of evidence was affected mainly by limitations associated with: (1) the evidence coming generally from explanatory studies conducted in an early, hypothesis-generating phase of investigation; (2) publication bias as a result of only a very small number of published studies exploring each association; and (3) many associations are explored in only one study, which makes evaluating inconsistency in results across studies impossible. This small number of studies negatively impacts the overall quality of evidence, because it is an indicator that the evidence is not well established. Further primary research of longitudinal studies exploring factors associated with both the onset and persistence of recurrent headaches is needed not only to identify what predicts onset and course of headaches over time but also to increase the overall quality of the existing evidence. Research in this field should expand beyond exploratory research designs to include hypothesis-testing studies. The majority of the studies in this review were exploratory in design, conducting analyses that were not guided by hypotheses, yet explored multiple variables. The quality of evidence of primary studies would significantly improve if studies used a confirmatory research methodology that built upon hypotheses, derived from theoretical frameworks or preliminary findings derived from these existing studies presented in this review. This future research should replicate and validate risk and prognostic factors that have been mentioned in this review and have a very low or low quality of body of evidence associated and explore whether the risk and prognostic factors such as female sex or stressful life events may differ according to type of recurrent headaches as some preliminary evidence seems to indicate. We also encourage future research using similar sets of outcome variables and assessment tools for measurement of prognostic and risk factors and outcomes.

The ICF-CY is a comprehensive classification system encompassing all child and youth health and health-related domains which facilitates the communication between various health care professionals and researchers accessing the framework. However, this comprehensiveness can make the applicability of ICF-CY for clinicians and researchers a challenge. In our review, we reviewed more than 1,400 categories to link each of the investigated factors and outcomes with existing ICF-CY categories. At the same time, this comprehensiveness makes it difficult to go into detail. We found that existing ICF-CY categories did not always allow us to go the level of specificity that we wanted. For example, the variables ‘headache intensity’ or ‘headache duration’, although very often investigated, are not explicitly named in their corresponding ICF-CY category “pain in the head and neck”). For this review, therefore, we developed sub-categories to correspond to existing broad ICF-CY categories. Precisely, to facilitate the application of ICF-CY, health condition-specific ICF-CY Core Sets have been developed and provided to researchers and health care professionals (e.g., cerebral palsy).47 Similar efforts have facilitated the application of ICF Core Sets for common health-related conditions in adults (e.g., depression, diabetes, musculoskeletal conditions).12, 46, 50 Our review in conjunction with other studies in the area (e.g., PedIMMPACT 38, reviews of pediatric pain measures, e.g.,14, controlled trials), could provide preparatory research to develop an ICF-CY Core set for pediatric chronic pain conditions that captures the typical spectrum of limitations in functioning and disability that children and adolescents with chronic pain. This core set could guide the development and testing of models illustrating the relationship between ICF-CY dimensions as they relate to onset and course of headaches and ultimately provide clearer direction for the development, testing and reporting of clinical interventions.

The clinical implications of this review are limited by the overall quality of available evidence. However, the risk and prognostic factors with higher quality of evidence might serve clinicians to prompt areas of exploration for prevention of new or continued headaches when working with children and adolescents. There is moderate quality evidence that suggests that being female is associated with higher risk of developing recurrent headaches and experiencing persistence of recurrent headaches over time. There is also moderate quality evidence that suggests children and adolescents with recurrent headaches and comorbid anxiety or depression are at risk of continuing to report recurrent headaches over time. Therefore, we recommend clinicians to consider that these factors may partially contribute to the continuation of headaches when patients present with acute and chronic headaches. It is equally important to consider that there is high quality evidence that negative emotions manifested through symptoms of anxiety, depression or mental distress are notlikely independent risk factors for onset of recurrent headaches. However, it is important for clinicians to attend these mental health issues when they are present as they contribute to other health and mental health outcomes.16, 62 However, all of these recommendations need further investigation since we do not currently know whether actions addressing these suggestions would prevent headaches and/or reduce likelihood of continued headache and headache-related disability.

The strength of this review lies in the fact that this is the first comprehensive and rigorous review that provides a state-of-art summary of the factors in childhood and adolescence associated with increased (or decreased) risk of developing headache, continuation of recurrent headaches, and presence of headache-related disability over time. However, this systematic review is not exempt of limitations. First, due to the small number of studies included we were only able to combine the results of studies from a quantitative perspective when summarizing findings reported in studies that investigated the role of female sex in the development and persistence of recurrent headaches and the role of emotional functions in the persistence of recurrent headaches. As a result, we are not able to judge at this stage the relative importance of the different risk and prognostic factors identified in this review. Second, we were not always able to take into account all of the existing evidence, since 30 % of the studies did not fully report their findings. This may have introduced bias. Third, we must be careful when interpreting the results derived from subgroup analyses, since they were performed on a small numbers of studies which limit the power of analysis. These results should be used for generating hypotheses.44 Fourth, we have synthesized the evidence on causal associations between one single potential risk or prognostic factor and an outcome variable explored in primary studies using either univariate analyses or, in the best scenario, multivariate analyses controlling for different counfounding effects. However, even in these best scenarios, the varaiables controlled for within each analysis may differ, and we cannnot guarantee that any of the single identified associations would remain in new multivariate models since there are multiple contributing factors to the onset and persistence of recurrent headaches that may have not yet been taken into account. Finally, we did not include descriptive cohort studies, which could have also provided additional evidence regarding both risk and prognostic factors.

In conclusion, a relatively small number of studies have investigated a wide range of potential childhood and adolescence risk factors and prognostic factors for recurrent headaches. This is a research area at a very early stage of understanding. We are confident in saying that female sex is a likely risk and prognostic factor for onset and persistence of recurrent headaches. Manifesting negative emotions through anxiety and depression is not a risk factor for onset of recurrent headaches but is likely a prognostic factor for persistence of recurrent headaches. We do not have enough confidence to conclude about what happens with the remaining factors that have been investigated in this area. Primary research is recommended on contextual risk and prognostic factors of headaches, headache diagnosis subtypes. It is important to confirm and validate single potential risk and prognostic factors that have already started to be investigated but still are associated with a low or very low quality of evidence. When doing this all studies should control for confounding variables important to the outcome of interest (e.g., age, sex, socioeconomic status). This would allow increase the validity in synthesizing the available findings. It is also necessary to start to validate multivariable causal and prognostic models.

**Acknowledgements:**

We want to thank Dr. Susan Tupper (Community Health and Epidemiology, University of Saskatchewan, Canada) and Dr. Katherine Harman (School of Physiotherapy, Dalhousie University, Canada) for their advice on using the WHO ICF-CY. We also want to acknowledge Charlene Soobiah (CS) for her assistance during screening and data extraction. **References**

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**Figure Legends**

*Figure 1.* Study selection flowchart

*Figure 2.* Forest plot of meta-analysis for negative emotional functions as a risk factor for onset of recurrent headaches

*Figure 3.* Forest plots of selected risk factors for onset of recurrent headaches

*Figure 4.* Forest plot of meta-analysis for female sex as a risk factor for onset of recurrent headaches

*Figure 5.* Forest plot of meta-analysis for female sex as a prognostic factor for persistence of recurrent headache

*Figure 6.* Forest plots of selected prognostic factors for persistence of recurrent headaches

Appendix 1. Methodological quality of included primary studies, organized by cohort

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study Participation:**  The study sample adequately represents the population of interest | **Study Attrition:**  The study data from participants not lost to follow-up accurately represent the sample | **Prognostic/risk factor measurement:**  The prognostic/risk factor is valid and measured in a similar way for all participants | **Outcome measurement:**  The outcome is valid and measured in a similar way for all participants | **Confounding measurement:**  Important potential confounding factors are appropriately accounted | **Analysis:**  The statistical analysis is appropriate, and all primary outcomes are reported | **Risk of bias assessment** |
| Barke et al2 | High | High | Low | Low | Low | Low | **Moderate** |
| Battistella et al3 | Low | High | Moderate | Low | High | High | **High** |
| Blaauw et al7 | Low | Low | Low/Moderate | Low | Low | Low | **Low** |
| Brattberg8 | Moderate | Low | Low | Low | High | Moderate | **Moderate** |
| Brna et al11 | Unclear | Low | Low | Low | High | High | **Moderate** |
| GaBmann et al18 | Low | Unclear | Low | Moderate | Low | Moderate | **Low** |
| GaBmann et al17 | Low | Unclear | Low | Moderate | Low | Moderate | **Low** |
| Guidetti & Galli20 | Low | High | Low | Low | High | Moderate | **Moderate** |
| Guidetti et al21 | Low | Low | Low | Low | High | Moderate | **Moderate** |
| Kienbacher et al29 | Moderate | Low | Moderate | Low | Unclear | Moderate | **Moderate** |
| Larsson & Sund32 | Low | Low | Low | Low | High | High | **Moderate** |
| Lien et al33 | Low | Moderate | Low | Low | Low | Low | **Low** |
| Lu et al35 | Low | Moderate | Low | Low | Low | Moderate | **Low** |
| Monastero et al40 | Low | Low | Low | Low | Low | Moderate | **Low** |
| Ozge et al42 | Low | Moderate | Low | Low | High | High | **Moderate** |
| Pine et al43 | Low | Low | Low | Low | Low | Low | **Low** |
| Siniatchkin et al48 | Unclear | Low | Low | Low | High | High | **Moderate** |
| Stanford et al49 | Low | High | Moderate | Moderate | Moderate | Moderate | **Moderate** |
| Termine et al52 | Low | Low | Low | Low | Low | Moderate | **Low** |
| Virtanen et al54 | Low | Low | Low | Low | Low | Moderate | **Low** |
| Wang et al57 | Unclear | Low | Low | Low | Moderate | Moderate | **Moderate** |
| Wang et al58 | Unclear | Low | Low | Low | Unclear | High | **Moderate** |
| Wang et al59 | Unclear | Low | Low | Low | Unclear | High | **Moderate** |

Appendix 2. Operationalization of risk factors assessed for onset of headache

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ICF-CY | ICF-CY Sub category | Risk factor | Measurement | Scale | Study |
| Body Functions | Emotional functions | Self-report of anxiety or depression symptoms | Score on the Symptom Check List -5 | Continuous | Blaauw et al7 |
| Parent report of anxiousness/ depressiveness | Frequency of feeling unhappy, sad or depressed, fearful or anxious, bad dreams, worrying | Ordinal | GaBmann et al18 |
| Self-report of mental distress | Average score of 1.85 or greater on Hopkins Symptoms Checklist | Dichotomous | Lien et al33 |
| Self-report of depression symptoms | Score of 19 or greater on the Adolescent Depression Inventory | Dichotomous | Lu et al35 |
| Interviewer-assessed major depressive disorder diagnosis | Diagnosis based on the DSM-III or DSM-III-R | Dichotomous | Pine et al43 |
| Parent report of depression and anxiety symptoms | Score on the Internalizing Behaviours Scale from the Multidimensional Inventory of Children’s Social Behaviour | Continuous | Virtanen et al54 |
| Agreeableness | Self-report of quarrelling with teachers, fighting in school | Score on School Adjustment of an ad hoc questionnaire | Continuous | Blaauw et al7 |
| Parent report of aggressive behaviour | Frequency of child’s aggressive behavior in last 3 months | Ordinal | GaBmann et al18 |
| Parent report of compliance | Score on the Adaptive Behaviours Scale from the Multidimensional Inventory of Children’s Social Behaviour | Continuous | Virtanen et al54 |
| Psychic stability | Parent report of external anger expression | Score on the State-Trait Anger Expression Inventory-2 for items of child’s reaction when angry or annoyed | Ordinal | GaBmann et al18 |
| Extraversion | Parent report of social activity engagement | Score on the Adaptive Behaviours Scale from the Multidimensional Inventory of Children’s Social Behaviour | Continuous | Virtanen et al54 |
| Sustaining attention | Self-report of problems concentrating in class | Score on School Adjustment of an ad hoc questionnaire | Continuous | Blaauw et al7 |
| Parent report of difficulty sustaining attention | Frequency of the child’s behaviors for: not being able to sit still, being restless or hyperactive, not being able to concentrate or pay attention for long | Ordinal | GaBmann et al18 |
| Parent report of inattention | Score on the Externalizing Behaviours Scale from the Multidimensional Inventory of Children’s Social behaviour | Continuous | Virtanen et al54 |
| Impulse control | Parent report of impulsivity | Score on the Externalizing Behaviours Scale from the Multidimensional Inventory of Children’s Social Behaviour | Continuous | Virtanen et al54 |
| Content of thought | Pain catastrophizing | Score on Pain Catastrophizing Scale for Children (PCS-C) | Continuous | Barke et al2 |
| Control of thought | Somatosensory amplification | Score on Pain Catastrophizing Scale for Children (PCS-C) | Continuous | Barke et al2 |
| Pain in head and neck | Self-report of any migraine vs. other/none | Presence of migraine or probable migraine vs. other headache or none | Dichotomous | Lu et al35 |
| Self-report of headache frequency | Headache greater than 7 days per month | Dichotomous | Lu et al35 |
| Activity Participation | Carrying out daily routine | Self-report of any headache- related disability | 4 point scale: No disability to Severe disability | Ordinal | Lu et al35 |
| Handling stress | Stress coping | Score on the German Coping Questionnaire for Children and Adolescents (SVF-KJ) | Continuous | Barke et al |
| Informal relationships with friends | Self-report of number of good friends | One good friend or less vs. more than one good friend | Dichotomous | GaBmann et al17 |
| Family relationships | Parent report of satisfaction with family, parent/child relations | Frequency of satisfaction with family relationships | Ordinal | GaBmann et al17 |
| Self-report of parent-child relations | Presence of or parent-child relationship measured by conflict, cohesion, amount of parenting time vs. no report of poor relationship | Dichotomous | Lu et al35 |
| Maintaining health | Self-report of physical activity | Score on the Self-Administered Physical Activity Checklist | Ordinal | GaBmann et al17 |
| Managing medications | Self-report of use of pain killers | Acute headache medication usage > 1 day per month | Dichotomous | Lu et al35 |
| Maintaining educational program | Parent report of time spent on homework | Spending much time vs. spending little time on homework | Dichotomous | GaBmann et al18 |
| School education | Parent report of danger in repeating grade | Parent perception of whether child is in danger in repeating a grade | Dichotomous | GaBmann et al18 |
| Recreation and leisure | Parent-report of available leisure time | Available time child has per day to play or have time to themselves | Ordinal | GaBmann et al17 |
| Environment | Immediate family | Self-report of having siblings | No siblings vs. having siblings | Dichotomous | Ozge et al42 |
| Self-report of having siblings with HA | Having sibling with headache vs. no sibling with headache | Dichotomous | Ozge et al42 |
| Attitudes of immediate family members | Parent report of parental management of child headache | Score on the Illness Behaviour Encouragement Scale | Ordinal | GaBmann et al17 |
| Personal factors | Female sex | Female sex | Female vs. male sex | Dichotomous | Brattberg8, GaBmann et al17, Larsson & Sund32, Lu et al35, Ozge et al42 |
| Age | Parent report of age | Age, in years | Continuous | GaBmann et al17 |
| Self-report of working mother | Having mother who works outside of the home vs. mother at home | Dichotomous | Ozge et al42 |
| Parent report of child’s school stress | How often child is bullied or afraid of school | Ordinal | GaBmann et al18 |
| Self-report of acute family distress | Presence of acute family distress in past year (tight household budget, parental unemployment, divorce/separation, health issues of the participants or family members) | Dichotomous | Lu et al35 |
| Obesity | Self-report of obesity measurement | Obese BMI according to age and gender specific criteria of Taiwan Department of Health | Dichotomous | Lu et al35 |
| SES | Self-report of low parental socioeconomic status | Below average or poor economic status vs. middle class or wealthy | Dichotomous | Lu et al35 |

Appendix 3. Operationalization of risk factors assessed for persistence of headache

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ICF-CY | ICF-CY Sub category | Definition | Measurement | Scale | Study |
| Body functions | Emotional functions | Psychologist-assessed anxiety | Anxiety disorder diagnosis (including separation anxiety, overanxious disorder, social phobia) diagnosed using the DSM-III-R | Dichotomous | Guidetti et al 21 |
| Self-report of anxiety or depression symptoms | Score on the Emotional Disorder Scale from the Feelings and Behaviour Questionnaire | Ordinal | Stanford et al49 |
| Psychologist-assessed major depression | Major depression assessed by the Mini-international Neuropsychiatric Interview | Dichotomous | Wang et al 58 |
| Experience of self | Self-report of low self-esteem | Score on the General Self Scale of the Self Description Questionnaire | Ordinal | Stanford et al49 |
| Pain in head and neck | Self-report of lifetime duration of pain | Time from onset of headache, in months | Continuous | Kienbacher et al29 |
| Headache of 2 years or longer in duration vs. less than 2 years | Dichotomous | Wang et al 59 |
| Self-report of age of headache onset | Pre-pubertal vs. post-pubertal age of first attending headache clinic | Dichotomous | Guidetti & Galli20 |
| Headache onset younger than 11 years vs. older than 11 years | Dichotomous | Monastero et al40 |
| Case records of age of headache onset | Headache onset younger than 12 years vs. older than 12 years | Dichotomous | Termine et al52 |
| Self-report of age of headache onset | Headache onset younger than 13 years vs. older than 13 years | Dichotomous | Wang et al 58 |
| Physician-assessed diagnosis | Migraine vs. tension-type headache diagnosis based on the International Headache Society Criteria (1988) | Dichotomous | Battistella et al3 |
| Migraine vs. tension-type headache diagnosis based on the International Headache Society Criteria (1988) | Dichotomous | Brna et al11 |
| Migraine vs. tension-type headache diagnosis based on the International Headache Society Criteria (1988) | Dichotomous | Guidetti & Galli20 |
| Physician-assessed headache intensity | Mild severity vs. moderate/severe | Dichotomous | Brna et al11 |
| Self-report of headache severity | Severity assessed from 1-5 | Continuous | Siniatchkin et al48 |
| Mild severity vs. moderate/severe | Dichotomous | Wang et al 57 |
| Self-report of headache frequency | More than 5 headache days per month vs. less than 5 days | Dichotomous | Wang et al 57 |
| Number of days with migraine per month | Continuous | Siniatchkin et al48 |
| Frequency of headache days | Continuous | Kienbacher et al29 |
| Self-report of duration of headache episodes | Duration of headache episodes | Continuous | Kienbacher et al29 |
| Headaches lasting 2 hours or greater vs. less than 2 hours | Dichotomous | Wang et al 57 |
| Duration of migraine attacks, in hours | Continuous | Siniatchkin et al48 |
| Case records of duration of headache episodes | Headaches lasting 12 hours or more vs. less than 12 hours | Dichotomous | Termine et al52 |
| Self-report of headaches aggravated by physical activity | Headaches that are aggravated by physical activity vs. no aggravation | Dichotomous | Kienbacher et al29 |
| Headache aggravated by physical activity vs. no aggravation | Dichotomous | Wang et al 57 |
| Self-report of unilateral pain | Unilateral, bilateral, or changing headaches | Ordinal | Kienbacher et al29 |
| Unilateral vs. bilateral headaches | Dichotomous | Wang et al 57 |
| Self-report of pulsating pain | Pulsating pain vs. no pulsating | Dichotomous | Kienbacher et al29 |
| Pulsating pain vs. no pulsating | Dichotomous | Wang et al 57 |
| Case records of type of aura | Visual aura vs. visual-sensory-aphasic aura | Dichotomous | Termine et al52 |
| Case records of headache triggers | Any known headache triggers vs. none | Dichotomous | Termine et al52 |
| Self-report of migraine w/ aura | Chronic daily headache with aura vs. no aura | Dichotomous | Wang et al 59 |
| Sensation of pain | Physician-assessed headache associated vomiting | Migraine with vomiting vs. migraine without vomiting | Dichotomous | Battistella et al3 |
| Self-report of vomiting associated with headache | Migraine with vomiting vs. migraine without vomiting | Dichotomous | Kienbacher et al29 |
| Vomiting accompanying headache vs. no vomiting | Dichotomous | Wang et al 57 |
| Self-report of headache associated with photo/phonophobia | Headache with photophobia vs. headache without photophobia | Dichotomous | Kienbacher et al29 |
| Photophobia or phonophobia accompanying headache vs. none | Dichotomous | Wang et al 57 |
| Self-report of headache associated with aura | Headache with aura vs. headache without aura | Dichotomous | Kienbacher et al29 |
| Case records of headache associated with aura | Headache with aura vs. headache without aura | Dichotomous | Termine et al52 |
| Menstruation functions | Self-report of menstruation | Menstruation onset vs. no menstruation | Dichotomous | Stanford et al49 |
| Pubertal functions | Self-report of puberty onset | 4-point Likert scale ranging from ‘has not started’ to ‘seems completed’ | Ordinal | Stanford et al49 |
| Activity Participate | Managing medications | Case records of use of headache medication | Symptomatic medication intake for headache vs. no medication intake | Dichotomous | Termine et al52 |
|  | Self-report of use of headache medication | Use of pain killer medication vs. no use | Dichotomous | Wang et al 57 |
| Seeking assistance | Parental report of hospitalization | Child stayed overnight in hospital in past year vs. no overnight stay | Dichotomous | Stanford et al49 |
| Environ. | Immediate family | Self-report of family history of pain | Having mother with headache vs. mother without headache | Dichotomous | Ozge et al42 |
|  | Self-report of family history of migraine | Any first degree relatives with migraine at baseline vs. no relatives with migraine | Dichotomous | Monastero et al40 |
|  | Case records of family history of headache | Family history of headache vs. no family history | Dichotomous | Termine et al52 |
| Personal factors |  | Female sex | Female vs. male sex | Dichotomous | Brattberg8, Guidetti & Galli20, Kienbacher et al29, Larsson & Sund32, Monastero et al40, Ozge et al42, Siniatchkin et al48, Stanford et al49, Termine et al52, Wang et al 57 |
|  | Older age | Age, in years | Continuous | Kienbacher et al29, Larsson & Sund32, Wang et al 57 |
|  | Parent report of stressful life events | Number of events causing child great amount of worry or unhappiness | Continuous | Stanford et al49 |
|  | Parent report of previous injury | Number of injuries requiring medical attention | Continuous | Stanford et al49 |
|  | Psychologist-assessed comorbid disorders | Multiple diagnoses vs. one or none, including anxiety, sleep, adjustment, elimination, eating, mood, and school disorders according to the DSM-III-R | Dichotomous | Guidetti et al 21 |
|  |  | Psychiatric comorbid disorders | Any diagnosis including schizophrenia, anxiety, depression vs. none | Dichotomous | Wang et al 59 |

Appendix 4. Operationalization of outcome variables

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Outcome | Definition | Measurement |
| Barke et al2 | Onset | Self-report of onset of headache | Ad-hoc questionnaire asking about presence of headache once or more per month in the last six months |
| Battistella et al3 | Persistence | Self-report of persistence of headache, including migraine, tension-type, idiopathic stabbing and unclassified headache | Ad-hoc questionnaire based on the International Headache Society guidelines |
| Blaauw et al7 | Onset | Self-report of onset of headache, migraine, or non-classifiable headache | Ad-hoc questionnaire asking about presence of recurring headache for the past 12 months |
| Brattberg8 | Onset | Self-report of onset of headache | Ad-hoc question asking about presence of headache once per week or more for at least half a year |
| Persistence | Self-report of persistence of headache |
| Brna et al11 | Persistence | Self-report of persistence of headache, including migraine and tension-type, | Standardized questionnaire based on the International Headache Society guidelines |
| GaBmann et al18 | Onset | Parent report of onset of headache | Ad-hoc question asking about presence of headache at least once per month for more than six months |
| GaBmann et al17 |
| Guidetti & Galli20 | Persistence | Self-report of persistence of headache, including migraine and tension-type | Interview with physician based on the International Headache Society guidelines |
| Guidetti et al21 | Persistence |
| Kienbacher et al29 | Persistence | Self-report of persistence of headache, including migraine and tension-type | Semi-structured questionnaire based on the International Headache Society guidelines |
| Larsson & Sund32 | Onset | Self-report of onset of headache | Ad-hoc questionnaire |
| Persistence | Self-report of persistence of headache |
| Lien et al33 | Onset | Self-report of onset of headache | Ad-hoc question asking about being troubled by pain in the head in the last twelve months |
| Lu et al35 | Onset | Self-report onset of Chronic Daily Headache | Validated headache questionnaire for adolescents based on the International Classification of Headache Disorders-2 |
| Monastero et al40 | Persistence | Self-report of persistence of migraine | Semi-structured telephone questionnaire and diagnostic interview based on the International Headache Society guidelines |
| Ozge et al42 | Onset | Self-report of onset of headache | Questionnaire asking about headache frequency at least once per month, diagnosis based on the International Classification of Headache Disorders-2 |
| Persistence | Self-report persistence of headache |
| Pine et al43 | Onset | Self-report of onset of headache, including migraine or tension-type | Ad-hoc questionnaire about presence of headache interfering with daily activities |
| Siniatchkin et al48 | Persistence | Self-report of persistence of migraine without aura | Structured interviews with diagnoses based on the International Headache Society guidelines |
| Stanford et al49 | Onset | Self-report of onset of headache | Ad-hoc questionnaire about feeling headache once per month or more over the previous six months |
| Persistence | Self-report of persistence of headache |
| Termine et al52 | Persistence | Self-report of persistence of migraine | Interview with neurologist with diagnosis based on the International Classification of Headache Disorders-2 |
| Virtanen et al54 | Onset | Self-report of onset of headache | Ad-hoc question about headache once per month or more over the previous few months |
| Wang et al57 | Persistence | Self-report of persistence of chronic daily headache | Interview with neurologist with diagnosis based on the International Classification of Headache Disorders-2 |
| Wang et al58 | Persistence |
| Wang et al59 | Persistence |
| HA-disability | Self-report of headache-related disability | Interview with neurologist using the Migraine Disability Assessment Scale |