Sex differences in the efficacy of psychological therapies for the management of chronic and recurrent pain in children and adolescents: A systematic review and meta-analysis

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Abstract

Sex differences in chronic pain are reported to emerge during adolescence, although it is unclear if this includes responses to treatment. We conducted a meta-analysis to examine whether sex differences were present on outcome variables at pre-treatment, and whether the efficacy of psychological therapies for pediatric chronic pain differs between boys and girls at post-treatment and follow-up time points. Searches were conducted, extending two existing Cochrane reviews of randomized-controlled trials examining the efficacy of psychological therapies for chronic and recurrent pain in children and adolescents. Forty-six articles were eligible for inclusion, and data were extracted regarding pain, disability, anxiety, and depression in boys and girls at pre-treatment, post-treatment, and follow-up time points. No published study reported outcome data separately by sex, so authors of all studies were contacted and 17 studies provided data. Twice as many girls ($n = 1760$) were enrolled into clinical trials of psychological therapies for pediatric chronic pain than boys ($n = 828$). Girls reported higher depression and anxiety at pre-treatment than boys. Girls with headache also reported significantly greater pre-treatment pain severity. Treatment gains were consistent across the sexes. One exception was for post-treatment disability in children with non-headache pain conditions; girls exhibited a significant effect of treatment relative to control condition (SMD= -0.50[-0.80,-0.20], $p < .01$), but no such effect was observed for boys (SMD= -0.08[-0.44,0.28], $p = .66$). Future research should examine whether mechanisms of treatment efficacy differ between boys and girls, and consider the impact of pre-treatment sex differences on response to treatment.

Keywords: sex differences; psychological therapy; chronic pain; children; adolescents; systematic review; meta-analysis

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1. Introduction

Evidence for psychological therapy for chronic pain is characterized by heterogeneity of sample, treatment content, and effect [61]. The next generation of therapies will need to be sensitive to individual differences and tailor treatment for specific effects [9]. Accounting for sex (male/female) and gender (characteristics, attributes, behaviours that society/culture considers masculine or feminine) can help contextualise pain behaviour [88]. We know sex matters for pharmacological treatments; it influences treatment-seeking behaviours, responses to analgesics, and even provider's responses to individuals with pain [36,40,56,63]. But we do not know if, or how, sex affects psychological interventions for pain [20].

Epidemiologically, sex differences in chronic pain prevalence appear in adolescence [18,21,45], reflecting theories that sex hormones emerging during puberty explain the differential experience of pain in males and females [4,29,79]. However, alongside these biological explanations, male-female differences have their origins in early social-developmental periods in which children learn to express and behave in a gender-specific way when in pain. Girls are thought to be socialized to express feelings and seek support whereas boys are expected to be stoic [73,81]. In chronic pain, girls report using more social support seeking, while boys use more distraction to cope with pain [43,55]. Girls in chronic pain and community samples appear to engage in more catastrophizing, particularly rumination [13,43], and girls with chronic pain report fewer positive pain-related self-statements [32]. Given these coping differences, it is reasonable to hypothesize that the few observations we have of differential treatment efficacy by patient sex [30,65] may actually reflect a general, if unexamined, pattern.

Although it is important to consider male-female variation in treatment responses, the majority of clinical trials for psychological therapies in children and adolescents are not directly designed to study this possibility. Samples sizes are often too small to reliably detect such effects, making it difficult to determine whether sex impacts the efficacy of psychological therapies for chronic pain in children and adolescents. The number of clinical trials in children has grown over the past few years [17,22], and it is timely to consider pooling the data across these studies to explore whether sex differences are present in the efficacy of psychological therapies for pediatric chronic

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pain. While this has been suggested for reviews of treatments for chronic pain, a recent study suggested that only 8% of reviews examine intervention sex effects [15].

We present a systematic review and meta-analyses to examine the influence of patient sex on the efficacy of psychological therapies for chronic and recurrent pain in children and adolescents. The primary aim was to explore sex differences in pain, disability, anxiety, and depression at pre-treatment, post-treatment, and follow-up time points. As gender is rarely measured in this literature, no explicit investigation of the impact of gender in psychological therapies for pediatric chronic pain was conducted. However, a secondary aim was to measure sex *and* gender reporting practices within trials, and findings interpreted considering the potential contributions of sex *and* gender.

2. Methods

This review was registered on the Prospero register of systematic reviews (registration number: CRD42015017848). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was used to guide reporting. Figure 1 provides the PRISMA flow diagram [60] for the current study.

Figure 1 here

2.1 Search strategy

Searches were based on the strategies from two existing Cochrane reviews of psychological therapies for chronic pain in children and adolescents: 1) '*Psychological therapies for the management of chronic and recurrent pain in children and adolescents*' [17] and 2) '*Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents*' [22]. These existing reviews were chosen as a starting point because of the rigorous nature of such reviews, which are the standard for evaluating and synthesizing the results from clinical trials. All articles included in the original reviews were considered for possible inclusion in the present review. Additionally, the searches from the original reviews were updated since the time of the last search, and new articles were screened for eligibility.

2.2 Eligibility criteria and screening

Eligibility criteria for the present analyses required that included articles be: (1) a randomized-controlled trial (RCT) published in English in a peer-reviewed journal; (2) at least one arm of the included trial must be a credible, primarily psychological intervention with the aim of changing thoughts, behaviours, and/or mood of the individual to assist with coping with chronic pain; (3) have at least 10 participants in each treatment arm at each extracted time point; (4) include participants (defined as children and adolescents where the majority of the sample was age 18 years or younger) with chronic, non-cancer pain.

Forty-four articles were identified from the original Cochrane reviews. Additional articles were identified by updating searches from the Cochrane reviews since last publication. The updated search was run on March 24, 2015 for all articles added to the databases since the time of the last search (464 before duplicates removed from the update of the review by Eccleston and colleagues [17] on in-person psychological therapies, and 229 before duplicates removed from the update of the review by Fisher and colleagues [22] of remotely-delivered interventions). Once duplicates were removed, 523 titles remained and were screened for eligibility by two co-authors (K.E.B. and E.K.), disagreements were resolved through discussion. After title screening, 39 full-text articles were screened by two co-authors (K.E.B. and E.K.) to determine eligibility for inclusion. Of these, two were eligible for inclusion [5,33]. Thirty-seven articles were excluded for the following reasons: 5 were not an RCT, 1 described a study protocol, 1 did not include a sample of only chronic pain patients, 1 study focused on adherence rather than treatment of chronic/recurrent pain patients, 8 had adult samples, 2 had insufficient psychotherapeutic content, 12 were conference abstracts, 3 did not have the full-text available in English, and 1 was a dissertation. Additionally, three articles were deemed eligible [38,54,78], but reported secondary/additional analyses of trials that had already been included in the Cochrane reviews, so were not included [42,53]. In total, 46 articles were identified as being eligible for data extraction.

Each of the eligible articles were read and data were extracted by a study author (K.E.B.) using an author-created data extraction form that documented sample characteristics, treatment characteristics, reporting practices for sex and gender variables,

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and measures of pain, disability, anxiety, and depression at pre-treatment, post-treatment, and follow-up. Data extraction was checked by a second study author (E.K.). Consistent with the previous Cochrane reviews [17,22], post-treatment was defined as the first assessment point after treatment had been completed. Follow-up was defined as the assessment point between 3 and 12 months following the end of treatment; if more than one follow-up assessment was available, the latter time-point was extracted¹. For studies in which a wait-list control design was employed, data were not extracted for any follow-up time-points in which the control group had received treatment. When both parent-report and child-self-report were available for outcomes, child self-report was extracted.

Consistent with the previous Cochrane reviews [17,22], outcomes were analysed separately for headache and non-headache pain conditions, in attempt to minimize heterogeneity within the groups with regards to pain characteristics and measurement of outcomes. For headache pain outcomes, pre-treatment outcomes were extracted as continuous data, and post-treatment and follow-up outcomes were extracted as continuous data as well as dichotomous clinical reduction in headache severity (i.e., how many participants did/did not experience at least a 50% improvement from pre- to post-treatment). In accordance with the recommendations of the International Headache Society and the American Headache Society, headache frequency was considered the primary outcome of interest and was prioritized during data extraction [68]. If headache frequency was not available, headache pain intensity or duration was extracted. Consistent with previous reviews [22], headache pain outcomes are referred to as 'headache severity'. For all other outcomes, the most appropriate measure was used, as per the previously published Cochrane reviews [17,22]. Readers are referred to the previously published Cochrane reviews for a complete list of which measures were extracted for each outcome, noting that in some cases a proxy measure for the exact outcome was used (e.g., using a scale of stress or catastrophizing as a measure of anxiety), and occasionally the measure used was not described in the original RCT, but was mentioned in subsequent publications from the same dataset (for the sake of

¹ Note that for Levy et al. 2010 [53] data from the 6-month time point (the latest follow-up point reported in the original manuscript) were used in the present meta-analysis.

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consistency, we always refer to only the original publication of the RCT in the present manuscript).

For studies that included mixed groups of both headache and non-headache, authors were asked to provide data for each group separately [31], however, if this was not possible data were included in both analyses as appropriate [34,66]. If any of the outcome measures at any time-point were not available separately for each sex, authors were contacted and asked to supply the missing data. For each case of missing data, authors were contacted no more than twice. Of the 44 requests for data made, 17 responses (38.6%) provided the requested data [1,3,5,7,11,27,28,31,34,42,53,66,69,70,80,83,84]. Thirteen responses (29.5%) indicated that the data was no longer available [10,12,37,46,49,51,57,58,64,67,71,75,76], the authors of 14 studies could not be contacted or did not reply to the request for data [6,16,19,26,47,48,50,52,72,77,82,85,86], and authors of two eligible studies were not contacted, as they did not measure any of the extracted outcomes [24] or the sample included only girls and could not be included in the meta-analysis of sex differences [41]. Table 1 summarizes the characteristics of the studies that were and were not included in the meta-analysis.

Table 1 here

2.3 Data analytic approach

A minimum of two studies per comparison group was required to conduct meta-analysis for a particular outcome. Studies needed to include both boys and girls to be included in the meta-analysis. Additionally, a minimum of two participants per group was required to include the study in a meta-analysis for a particular outcome (i.e., data needed to be available from at least two girls in the treatment group, two girls in the control group, two boys in the treatment group, and two boys in the control group). All data suitable for inclusion in the meta-analysis were analysed using RevMan 5.3 software, employing a random-effects model. For dichotomous outcomes (i.e., clinically significant reduction in headache severity), Mantel-Haenszel methods were used for analysis and the risk ratio (RR) was reported calculated using 95% confidence intervals (CI). To aid with

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interpretation of the results, the number needed to treat to benefit (NNTB) was calculated. For continuous outcomes, standardised mean differences (SMD) were calculated, also reporting 95% CI. Heterogeneity, presented as the I^2 statistic, was interpreted as per the guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* [35], with 0-40% heterogeneity considered to be likely not important, 30-60% and 50-90% representing moderate and substantial levels of heterogeneity respectively, and 75% or greater representing considerable heterogeneity.

For the pre-treatment baseline time point, analyses were conducted to compare the differences on each outcome between boys and girls. For the post-treatment and follow-up time points, the treatment condition was compared to the control condition separately for boys and girls, and subgroup analyses were conducted using a chi-square test to examine the differences between samples of boys and girls (i.e., whether the variability in effects between the subgroups of boys and girls was due to true sex differences and not due to chance). Subgroup analyses is an acceptable methods of examining sex effects in reviews [15]. Studies were analysed all together, and then separately for headache and non-headache pain conditions. Forest plots for each of the analyses are available as Supplementary Material.

Data examining the reporting practices of sex- and gender-related variables and analyses were summarized using descriptive statistics.

3. Results

The following results present meta-analyses with data from the seventeen studies [1,3,5,7,11,27,28,31,34,42,53,66,69,70,80,83,84] from which data split by sex was made available by study authors. Data were available from a grand total of 1164 participants (316 boys and 848 girls)². The specific studies included and the respective sample sizes are provided for each individual analysis presented below.

² Sample sizes was calculated based on the sample sizes provided by authors at the pre-treatment time point (if sample sizes differed between outcomes, the largest sample size was included here).

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3.1 Sex differences at pre-treatment baseline

The statistics for the following meta-analyses examining overall differences between boys and girls at pre-treatment are provided in Table 2.

Table 2 here

3.1.1 Pain

All Chronic Pain Conditions. Data from fifteen studies [3,5,7,11,28,31,34,42,53,66,69,70,80,83,84] were entered into the meta-analysis, which revealed no differences in pain between girls and boys at the pre-treatment time point.

Headache. Data from eight studies [5,7,11,31,34,66,69,70] were entered into the meta-analysis, which revealed that girls reported significantly greater headache severity than boys at pre-treatment.

Non-Headache. Data from ten studies [3,28,31,34,42,53,66,80,83,84] were entered into the meta-analysis, which revealed no differences in pain between girls and boys at the pre-treatment time point.

3.1.2 Disability

All Chronic Pain Conditions. Data from thirteen studies [1,7,11,28,31,42,53,66,69,70,80,83,84] were entered into the meta-analysis, which revealed no differences in disability between girls and boys at the pre-treatment time point³.

Headache. Data from seven studies [1,7,11,31,66,69,70] were entered into the meta-analysis, which revealed that there were no significant differences in disability between girls and boys at the pre-treatment time point.

Non-Headache. Data from eight studies [28,31,42,53,66,80,83,84] were entered into the meta-analysis, which revealed no differences in disability between girls and boys at the pre-treatment time point.

³ Note that for the study by Barry and von Baeyer [7], the mean and standard deviation of one of the groups (control group boys, $n=6$) was zero. As the RevMan software will not permit an entry with a standard deviation of zero, a value of 10^{-11} was entered as the standard deviation to perform the calculation. Removing this study from the analysis did not change the overall significance of the results.

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3.1.3. Anxiety

All Chronic Pain Conditions. Data from five studies [31,42,53,80,83] were entered into the meta-analysis, which revealed that girls reported significantly higher anxiety than boys at pre-treatment.

Headache. As only one study of headache [31] included a measure of anxiety appropriate for the present analysis, no analyses could be conducted regarding sex differences in pre-treatment anxiety.

Non-Headache. Data from five studies [31,42,53,80,83] were entered into the meta-analysis, which indicated that prior to entering treatment, girls with chronic non-headache pain reported significantly greater anxiety than boys.

3.1.4 Depression

All Chronic Pain Conditions. Data from five studies [31,42,53,66,83] were entered into the meta-analysis, which revealed that girls reported significantly greater symptoms of depression than boys at pre-treatment.

Headache. Data from two studies [31,66] were entered into the meta-analysis, which revealed that girls reported significantly higher depression than boys at pre-treatment.

Non-Headache. Data from five studies [31,42,53,66,83] were entered into the meta-analysis, which indicated that prior to entering treatment, girls with chronic non-headache pain reported significantly greater symptoms of depression than boys.

3.2 Outcomes at the post-treatment time point

The meta-analysis statistics of treatment effect for boys and girls at the post-treatment time point, and subgroup analyses examining sex differences, are provided in Table 3.

Table 3 here

3.2.1 Pain

All Chronic Pain Conditions. Data from fourteen studies [5,7,11,28,31,34,42,53,66,69,70,80,83,84] were entered into the meta-analysis, which compared pain between treatment and control groups at the post-treatment time point.

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The analysis found that pain was significantly lower in the groups that received the psychological therapies compared to the control groups at post-treatment in both girls and boys⁴. The test of sex subgroup differences was not significant.

Headache. Data from eight studies [5,7,11,31,34,66,69,70] were entered into the meta-analysis which compared headache severity at the post-treatment time point between treatment and control groups. The analysis of treatment compared to control groups found that pain was significantly lower in the groups that received the psychological therapies compared to the control groups at post-treatment for both girls and boys⁵. The test of sex subgroup differences was not significant.

Data from eight studies [5,7,11,31,34,66,69,70] were entered into the meta-analysis which compared the number of children in the treatment and control groups who had a clinically significant (50% or greater) reduction in headache severity at the post-treatment time point. The analysis of treatment compared to control groups found that the number of patients who experienced a clinically significant reduction in headache severity at post-treatment was significantly greater in the psychological therapy treatment groups compared to the control group for girls (NNTB = 4.98), and boys (NNTB = 3.34)⁶. The test of sex subgroup differences was not significant.

Non-Headache. Data from nine studies [27,28,31,34,42,53,66,80,83,84] were entered into the meta-analysis, which compared pain between treatment and control groups at the post-treatment time point. This effect of treatment was significant for both girls and boys. The test of sex subgroup differences was not significant.

⁴ All trials, with the exception of one, examined cognitive-behavioural or behavioural therapies. If the only trial evaluating psychodynamic psychotherapy is removed [5], the effect becomes $p = .05$ for boys, stays significant for girls ($p < .01$), and there are still no significant subgroup differences ($p = .79$).

⁵ All trials, with the exception of one, examined cognitive-behavioural or behavioural therapies. If the only trial evaluating psychodynamic psychotherapy is removed [5], the effect of treatment is no longer significant ($p = .08$) for boys, but remains significant ($p = .02$) for girls, and there are no significant subgroup differences ($p = .67$).

⁶ If the only trial evaluating psychodynamic psychotherapy is removed [5], the effect of treatment remains significant for both girls ($p = .04$; NNTB = 5.05) and boys ($p = .04$; NNTB = 3.91), and there are no significant subgroup differences ($p = .93$).

3.2.2 Disability

All Chronic Pain Conditions. Data from thirteen studies [1,7,11,28,31,42,53,66,69,70,80,83,84] were entered into the meta-analysis, which compared disability between treatment and control groups at the post-treatment time point. The analysis revealed that for girls disability was significantly lower at post-treatment in the groups that received the psychological therapies than the control groups, but that this treatment effect was not observed in boys (i.e., there was no difference between treatment and control conditions at the post-treatment time point for boys). However, the test of sex subgroup differences was not significant.

Headache. Data from seven studies [1,7,11,31,66,69,70] were entered into the meta-analysis, which compared disability between treatment and control groups at the post-treatment time point for children with headache. The analysis of treatment compared to control groups revealed that disability was significantly lower at post-treatment in the groups that received the psychological therapies than the control groups for both girls and boys. The test of sex subgroup differences was not significant.

Non-Headache. Data from eight studies [28,31,42,53,66,80,83,84] were entered into the meta-analysis, which compared disability between treatment and control groups at the post-treatment time point. The analysis of treatment compared to control group for girls indicated that disability was significantly lower at post-treatment in the groups of girls that received the psychological therapies than the control groups. However, when the analysis was repeated with only the boys who participated in the included trials, there was no significant difference between the treatment and control groups. The test of sex subgroup differences indicated there was *not* a significant difference between boys and girls; though 67.8% of the variability in effect estimates between boys and girls at the post-treatment time point was due to genuine differences between the sex subgroups, rather than chance.

3.2.3. Anxiety

All Chronic Pain Conditions. Data from five studies [31,42,53,80,83] were entered into the meta-analysis, which compared anxiety between treatment and control groups at the post-treatment time point. The analysis indicated that there was no

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significant difference between treatment and control conditions on post-treatment anxiety for girls or boys. The test of sex subgroup differences was not significant.

Headache. As only one study of headache [31] included a measure of anxiety appropriate for the present analysis, no analyses could be conducted examining anxiety at the post-treatment time point in children with headache.

Non-Headache. Data from five studies [31,42,53,80,83] were entered into the meta-analysis, which compared anxiety at the post-treatment time point between treatment and control groups. The analysis of treatment compared to control groups indicated that anxiety did not differ significantly in the groups that received the psychological therapies than the control groups at post-treatment for both girls and boys. The test of sex subgroup differences was not significant.

3.2.4 Depression

All Chronic Pain Conditions. Data from four studies [31,53,66,83] were entered into the meta-analysis, which compared depression between treatment and control groups at the post-treatment time point. The analysis indicated that there was no significant difference between treatment and control conditions on post-treatment depression for girls or boys. The test of sex subgroup differences was also not significant.

Headache. Data from two studies [31,66] were entered into the meta-analysis, which compared depression between treatment and control groups at the post-treatment time point for children with headache. The analysis indicated that there was no significant difference between treatment and control conditions on post-treatment depression for girls or boys. The test of sex subgroup differences was not significant.

Non-Headache. Data from four studies [31,53,66,83] were entered into the meta-analysis, which compared depression between treatment and control groups at the post-treatment time point. The analyses indicated that depression did not differ significantly in the groups that received the psychological therapies than the control groups at post-treatment for girls or boys. The test of sex subgroup differences was not significant.

3.3 Outcomes at the follow-up time point

The meta-analysis statistics of treatment effect for boys and girls at the follow-up time point, and subgroup analyses examining sex differences, are provided in Table 4.

 Table 4 here

3.3.1 Pain

All Chronic Pain Conditions. Data from six studies [3,34,42,53,69,83] were entered into the meta-analysis, which compared pain at the follow-up time point between treatment and control groups. The analysis indicated that pain did not differ between the groups that received psychological therapies compared to the control groups at follow-up, both for girls and boys. The test of sex subgroup differences was not significant.

Headache. Data from two studies [34,69] were entered into the meta-analysis, which compared headache severity at the follow-up time point between treatment and control groups. The analysis indicated that for both girls and boys, pain did not differ between the groups that received psychological therapies compared to the control groups at the follow-up time point. The test of sex subgroup differences was not significant.

Data from two studies [34,69] were entered into the meta-analysis, which compared headache severity at the follow-up time point between treatment and control groups. The analyses indicated that there were no more children who had experienced a clinically significant reduction in headache severity at follow-up in the psychological therapy group compared to the control group in girls (NNTB = 4.68) or boys (NNTB = 3.29). The test of sex subgroup differences was not significant.

Non-Headache. Data from five studies were entered into the meta-analysis [3,34,42,53,83], which compared pain between treatment and control groups. The analyses indicated that pain was not significantly different at follow-up between the groups that received the psychological therapies and the control groups for girls and boys. The test of sex subgroup differences was not significant.

3.3.2 Disability

All Chronic Pain Conditions. Data from five studies [1,42,53,69,83] were entered into the meta-analysis, which compared disability at the follow-up time point between treatment and control groups. The analysis indicated that there was no

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significant difference between treatment and control conditions for girls or boys. The test of sex subgroup differences was not significant.

Headache. Data from two studies [1,69] were entered into the meta-analysis, which compared disability in children with headache at the follow-up time point between treatment and control groups. The analysis of treatment compared to control groups, indicating that at the follow-up time point children who received psychological therapies reported significantly lower disability compared to children in the control group, for both girls and boys. The test of sex subgroup differences was not significant.

Non-Headache. Data from three studies were entered into the meta-analysis [42,53,83] which compared disability between treatment and control groups at the follow-up time point. The analyses indicated that disability at follow-up did not differ significantly in the groups that received the psychological therapies than the control groups for girls or boys. The test of sex subgroup differences was not significant.

3.3.3. Anxiety

All Chronic Pain Conditions. Data from three studies [42,53,83] were entered into the meta-analysis, which compared anxiety between treatment and control groups at the follow-up time point. The analysis indicated that there was no significant difference between treatment and control conditions for girls or boys. The test of sex subgroup differences was not significant.

Headache. As none of the included studies reported a measure of anxiety at the follow-up time point that was appropriate for the present analysis, no analyses could be conducted for this outcome.

Non-Headache. The analyses for non-headache chronic pain included the same three studies [42,53,83] from the analysis described above examining anxiety at follow-up for all chronic pain conditions. Please refer to the above analysis.

3.3.4 Depression

All Chronic Pain Conditions. Data from three studies [42,53,83] were entered into the meta-analysis, which compared depression between treatment and control groups at the follow-up time point. The analysis indicated that there was no significant difference between treatment and control conditions for girls or boys. The test of sex subgroup differences was not significant.

Headache. As none of the included studies reported a measure of depression at the follow-up time point that was appropriate for the present analysis, no analyses could be conducted for this outcome.

Non-Headache. The analyses for non-headache chronic pain included the same three studies [42,53,83] from the analysis described above examining depression at follow-up for all chronic pain conditions. Please refer to the above analysis.

3.4 Reporting practices for sex- and gender-related variables

Terminology. Similar to what has been observed in experimental research on pediatric pain [8], a variety of terminology was used to describe the distinction between boys and girls in the 46 included studies. “Sex” was used in 37% (n=17) of included RCTs, “gender” in 35% (n=16), and the remaining articles either used the two terms interchangeably (7%, n=3) or not at all (22%, n=10). All studies reported the number of boys and girls in the entire study sample, or this information could be inferred from the data provided, and the majority of studies also provided the number of each sex within each treatment arm (85%, n=39). One study did not include any male participants, though this was due to not having been successful in recruiting boys, rather than an intentional omission [41].

Sex distribution at enrolment and drop-outs. More than twice as many girls (n=1760) entered clinical trials as boys (n=828)⁷. Only 13% (n=6) of studies that included both boys and girls specified the sex of all participants that dropped out of the trial after randomization. Three additional studies did not indicate the sex of participants who dropped out of the trial, but conducted statistical tests to examine differences in

⁷ Total number enrolled includes all participants who entered into the trial and were randomized to a treatment condition, including participants who eventually dropped out of the trial or were lost to follow-up, wherever this information was available. Of note, approximately a quarter of studies provided only the sample size split by sex for participants who completed the trial, therefore the available information was used in calculating these totals. One study [80] reported different numbers of girls and boys in the table of demographic variables (15 boys, 31 girls) and the text (14 boys, 32 girls); the data from the table were extracted for the present tally. Additionally, one study [51] described enrolling 44 girls, but that one withdrew during the baseline phase (presumably prior to randomization), and therefore only the 43 girls who were randomized were included in the present tally.

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dropout sex (two studies reported no differences, one found boys to be more likely to drop out than girls), and three studies reported the sex of some but not all of the participants who dropped out, or sex could be inferred for some participants because of pronouns used in their description or the reason they dropped out of the trial (e.g., pregnancy).

Clinician sex. A minority (24%, $n=9$) of studies where the therapy was conducted in-person (i.e., not including studies where therapist contact was primarily by email, phone, etc.) reported the sex of the therapist or clinician providing the intervention in the arm that was specified as the psychological treatment condition (or provided the name/identity of the clinician from which sex could be inferred), with female clinicians being more common in studies that did report this information (18 female clinicians; 3 male clinicians)⁸.

Consideration of sex in randomization, statistical analyses, and discussion. Of the 45 studies that included both boys and girls in their samples, many studies described attempts to evenly distribute participants across treatment groups based on sex and/or described statistical tests conducted to ensure a relatively equal distribution of boys and girls (76%, $n=34$). Three studies (7%) included sex as a covariate or corrected for sex in their statistical analyses. The majority of studies that had both girls and boys in their sample did not report conducting statistical tests to examine sex differences either pre- or post-treatment (82%, $n=37$). None of the studies that examined sex differences in treatment effects or pain outcomes found a significant difference between boys and girls. Two studies did report significant sex differences in headache (e.g., at pre-treatment), but not in relation to treatment outcomes [7,19]. None of the included studies examined the relationship between child sex and treatment outcomes as mediated or moderated by another variable, nor did they examine the relationship between another variable on treatment outcomes as mediated or moderated by child sex. Additionally, no studies employed a validated measure of child gender to examine the impact of the child's endorsement of typically masculine or feminine behaviours on treatment outcomes. The majority of the 46 studies included (83%, $n=38$) did not discuss male-female differences

⁸ One study [7] did not list the sex of *all* therapists involved, but did describe that each session was co-led by one male and one female member of the team of therapists.

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in the Discussion section of the paper. Those that did mention sex or gender differences in the Discussion primarily did so to indicate that a lack of examination of sex differences as a limitation of their study, or highlighted this issue as a direction for future research.

4. Discussion

We explored whether there were differences in boys and girls entered into published clinical trials of psychological treatments for chronic pain. Girls were more anxious and depressed than boys, and for headache trials, girls reported more pain at pre-treatment. No sex differences were found for disability. In terms of treatment, effects reported in previous Cochrane reviews [17,22] were intact for boys and girls post-treatment, with one exception: the previously reported positive effect of treatment on disability was only found for girls.

These results suggest that treatment of psychological distress is important in girls presenting for treatment for chronic pain. Anxiety is related to poorer outcomes in cognitive-behavioural treatment of pediatric chronic pain [14], and earlier intervention may be required for girls to prevent development of significant distress. Since this and the original Cochrane reviews [17,22] found no differences in anxiety and depression between treatment and control groups, there is a need to recognize distress in the treatment of chronic pain, particularly for girls. Additionally, amongst children with headache, girls reported significantly greater pain severity at pre-treatment than boys. Such pre-treatment differences are important to acknowledge, as the severity of initial symptom presentations may impact how an individual engages with treatment.

The primary focus was to determine whether response to psychological treatment was consistent between boys and girls, both immediately post-treatment and at follow-up. Findings were similar to those reported in the original reviews that did not split by sex [17,22]. However, when we considered children with non-headache pain, psychological therapies were effective at reducing disability at post-treatment for girls but there was no significant difference in disability ratings amongst boys assigned to the treatment compared to controls. Given that boys and girls did not differ in pre-treatment disability, the findings cannot simply be explained by a ceiling effect with girls having more gains to be made than boys. It is possible that the disability measures did not tap into domains

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that are relevant to boys. It is also possible that the treatment gains for disability in girls was related to their increased pre-treatment psychological distress (i.e., while treatment did not significantly impact anxiety or depression, addressing psychological functioning may have increased engagement in previously avoided activities, thus improving disability). There may be factors related to sex and gender (e.g., expectations around masculine responses to pain, such as stoicism and reluctance to share the emotional aspects of the experience) that account for a lack of response to psychological therapy. The subgroup analysis of sex differences was not significant ($p = .08$), and replication with larger samples are needed to determine whether this finding represents a true, although weak, sex difference. More than twice as many girls entered clinical trials than boys, which is counter to the general trend of underrepresentation of females that hinders gender-based investigations [23,25,39]. Whilst this may reflect the higher prevalence of chronic pain in adolescent girls compared to boys [45], a large proportion of the patients enrolled were of pre-pubescent age (where sex differences in chronic pain is not as frequently observed), therefore this is not a complete explanation. The disproportionate representation of girls could reflect other sex-related factors, such as differences in healthcare referral practice, patient and/or parent willingness to engage in health care services, clinical trials, or psychological therapies for pain [2,44]. Overall, few treatment gains were reported for either boys or girls on the majority of outcomes, particularly at the follow-up. Although consistent with previous research [17,22], the current findings illustrate the need for larger samples to enable consideration of sex differences in the long-term efficacy of psychological therapies for pediatric chronic pain.

Similar to the general literature on clinical trials [23,74], reporting practices around sex and gender were poor. No study reported outcomes separately for boys and girls, and so authors were contacted, and few reported on the sex of the therapist or clinician providing treatment. Previous research on therapeutic alliance and treatment completion in psychotherapy has shown that outcomes may be influenced by the sex-match between adolescent patients and their therapist [87]. There is a need to examine whether aspects of treatment content are more beneficial for boys compared to girls, whether treatment delivery (e.g., male vs. female clinician, distance vs. in-person, individual vs. group) differs in efficacy and preferences for boys and girls, and whether

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there are developmental or psychological (e.g., anxiety) considerations that interact with sex. Since few trials reported the sex of treatment dropouts, it is difficult to know whether this was proportionately equal between boys and girls. Such knowledge would help clinicians identify any systematic bias in dropout rates based on sex, and determine whether sex-specific treatment approaches may improve retention.

This review is subject to limitations typical of meta-analyses, including variability between treatment studies (e.g., differences in measures, lengths and format of treatment, treatment delivery etc.). As no data were suitable for extraction from the original published studies, analyses were subject to data made available from authors. Data were not available from many of the older studies (see Table 1), which tended to report on samples of adolescents. Much of the data included in the meta-analysis comprised primarily of children from the pre-pubescent age range, which may have introduced potential bias and contributed to the general lack of sex differences observed in treatment effects. Additionally, some study data were based on participants who completed the trial (i.e., excluded participants that were lost to follow-up or discontinued treatment even if they completed pre-treatment measures), while others provided all data available at each time-point regardless of dropouts. Samples were predominantly female, and may have meant analyses including girls were more likely to detect effects due to sample size. Heterogeneity tended to be larger for the analyses conducted with girls than those with boys, which again may have been due to the discrepancies in sample size. Interpretation of the present results should take into account these limitations, as well as the inherent variability introduced by combining different types of pain conditions into the same analyses. While Table 1 demonstrates the non-headache studies included in meta-analysis comprised primarily of patients with abdominal pain, the inclusion of other pain conditions may have an impact on the treatment response and potentially sex differences [45]. Similarly, the differences in type (e.g., migraine vs. tension-type) and frequency (e.g., episodic vs. chronic) of headache conditions may also have introduced heterogeneity that masks potential differences.

Given the variability between the samples of boys and girls at pre-treatment, this raises questions around how best to consider pre-treatment sex differences. We encourage authors to consider the potential impact of sex in clinical trials, to incorporate sex into

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their analyses where appropriate, and to consider pre-treatment sex differences. Findings related to sex differences may differ based on whether authors choose to report participant outcomes in relation to their own baseline (e.g., a 50% reduction in headache severity), as opposed to applying a standardized cut-off of treatment “success” to all participants (e.g., number of patients who reported headache pain less than a 3/10 on a numerical rating scale), which may inflate the appearance of treatment success among boys who had lower pain ratings at baseline. Increased reporting of sex- and gender-related variables of the sample and therapist, and treatment dropouts would add to our understanding of the impact of sex and gender on treatment outcomes. Due to the potential for small effect sizes, sex difference research would generally benefit from recommendations to increase sample sizes in clinical trials, as well as including sex-based analyses in meta-analyses of results [74]. Further research is required to determine whether observed differences between boys and girls are attributable to true differences in the experience of pain and related symptoms, versus sex differences in measurement and reporting.

Though not possible here, future research would benefit from examining children and adolescents separately. Sex differences in chronic pain prevalence and some pain responses have been reported to emerge around the time of puberty, and therefore sex-specific effects of psychological therapies may be stronger in adolescents than children [8,45]. Similar research should also be conducted in adult samples, and examining treatment outcomes beyond the core domains examined in the present review (e.g., sleep, treatment compliance and satisfaction, associated physical symptoms, health service utilization).

Finally, while the biological effects of sex likely have an influence on the response of individuals to psychological therapies for pain management, socially-imposed gender roles and expectations can impact treatment efficacy and pain outcomes [2,59,62]. Future research would benefit from including measures of masculinity and femininity, taking a dimensional approach to the problem in question beyond the binary distinction of sex.

As chronic pain treatments advance towards providing personalized options, sex offers a dimension on which differences appear in general presentation prior to

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commencing treatment and in the efficacy of the treatment. Such information may help to provide informed care decisions, and should encourage researchers to consider incorporating sex and other individual difference variables into the design and analyses of clinical trials.

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6. Conflict of interest statement

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Figure 1. PRISMA study flow diagram

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Table 1. Summary of characteristics of studies that were and were not included in meta-analysis.

Primary author	Year	Pain condition categorization	Participant mean age (range)	Number of girls	Number of boys
<i>Studies included in meta-analysis</i>					
Abram	2007	Headache	12.7 (10-18)	45	36
Alfven	2007	Non-headache (<i>abdominal pain</i>)	9.9 (6-18)	36	12
Balottin	2014	Headache	9.67 (6-18)	20	13
Barry	1997	Headache	9.4 (7-12)	19	10
Connelly	2006	Headache	10 (7-12)	18	19
Groß	2013	Non-headache (<i>abdominal pain</i>)	9.6 (7-12)	25	4
Gulewitsch	2013	Non-headache (<i>abdominal pain or irritable bowel syndrome</i>)	9.4 (6-12)	24	14
Hechler	2014	Headache & Non-headache (<i>abdominal pain, musculoskeletal pain, other</i>)	14 (9-17)	87	27
Hicks	2006	Headache & Non-headache (<i>abdominal pain</i>)	11.7 (9-16)	30	17
Kashikar-Zuck	2012	Non-headache (<i>fibromyalgia</i>)	15 (11-18)	105	9
Levy	2010	Non-headache (<i>abdominal pain</i>)	11.21 (7-17)	145	55
Palermo	2009	Headache & Non-headache (<i>abdominal or musculoskeletal pain</i>)	14.8 (11-17)	35	13
Powers	2013	Headache (<i>migraine</i>)	14.4 (10-17)	107	28

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Rapoff	2014	Headache	10.2 (7-12)	25	10
Stinson	2010	Non-headache (<i>juvenile idiopathic arthritis</i>)	14.6 (12-18)	31	15
van der Veek	2013	Non-headache (<i>abdominal pain</i>)	11.9 (7-18)	75	29
van Tilburg	2009	Non-headache (<i>abdominal pain</i>)	10.25 (6-15)	23	9
<i>Studies not included in meta-analysis</i>					
Barakat	2010	Non-headache (<i>sickle cell disease</i>)	14.17 (12-18)	22	15
Bussone	1998	Headache	11.4 (11-15)	17	18
Cottrell	2007	Headache	14.1 (12-17)	15	15
Duarte	2006	Non-headache (<i>abdominal pain</i>)	9.1 (5-13)	22	10
Fitchel	2001	Headache	15.4 (13-18)	25	11
Gil	1997	Non-headache (<i>sickle cell disease</i>)	11.9 (N/A)	23	26
Griffiths	1996	Headache (<i>migraine</i>)	11.3 (10-12)	21	21
Hickman	2015	Headache	(13-17)	23	9
Humphreys	2000	Non-headache (<i>abdominal pain</i>)	9.8 (4-18)	38	26
Kashikar-Zuck	2005	Non-headache (<i>fibromyalgia</i>)	15.8 (13-17)	30	0
Kroener-Herwig	2002	Headache (<i>migraine, tension-type headache, combined</i>)	12.1 (10-14)	34	41
Labbe	1984	Headache (<i>migraine</i>)	10.8 (7-16)	14	14
Labbe	1995	Headache (<i>vascular or migraine</i>)	12 (8-18)	13	17
Larsson	1987a	Headache (<i>migraine, tension-type headache, or both</i>)	N/A (16-18)	40	6
Larsson	1987b	Headache	17 (16-18)	34	2

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Larsson	1990	Headache	17 (16-18)	43	5
Larsson	1996	Headache	N/A (10-15)	25	1
McGrath	1988	Headache	13.1 (11-18)	69	30
McGrath	1992	Headache (<i>migraine</i>)	N/A (11-18)	63	24
Osterhaus	1997	Headache (<i>migraine, tension-type headache, mixed</i>)	15.2 (12-22)	29	10
Passchier	1990	Headache	13.7 (N/A)	65	54
Richter	1986	Headache (<i>migraine</i>)	12.9 (9-18)	34	17
Robins	2005	Non-headache (<i>abdominal pain</i>)	11.4 (6-16)	39	30
Sanders	1994	Non-headache (<i>abdominal pain</i>)	9.2 (7-14)	28	16
Sartory	1998	Headache (<i>migraine</i>)	11.3 (8-16)	17	26
Scharff	2002	Headache (<i>migraine or tension-type headache</i>)	12.8 (7-17)	24	12
Trautmann	2010	Headache (<i>migraine, tension-type headache, combined</i>)	12.7 (10-18)	39	32
Vlieger	2007	Non-headache (<i>abdominal pain or irritable bowel syndrome</i>)	13.3 (8-18)	39	13
Wicksell	2009	Headache & Non-headache (<i>mixed</i>)	14.8 (10-18)	25	7

Note. N/A = not available. Number of girls and boys is reported at enrolment, including those that may have later dropped out of treatment (if available).

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Table 2. Meta-analysis statistics for sex differences at the pre-treatment time point.

	Sample size girls	Sample size boys	SMD[CI]	Heterogeneity	Effect
Pain					
All chronic pain conditions	775	276	0.09 [-0.05,0.23]	$I^2 = 0\%$	$Z = 1.24, p = .21$
Headache	310	126	0.26 [0.03,0.50]	$I^2 = 9\%$	$Z = 2.24, p = .03^b$
Non-Headache	530	180	0.02 [-0.17,0.20]	$I^2 = 5\%$	$Z = 0.16, p = .87$
Disability					
All chronic pain conditions	726	264	0.07 [-0.07,0.22]	$I^2 = 2\%$	$Z = 0.98, p = .33$
Headache	300	130	0.08 [-0.14,0.29]	$I^2 = 0\%$	$Z = 0.73, p = .47$
Non-Headache	461	147	0.18 [-0.06,0.41]	$I^2 = 23\%$	$Z = 1.48, p = .14$
Anxiety					
All chronic pain conditions	435	129	0.38 [0.17,0.60]	$I^2 = 6\%$	$Z = 3.56, p < .01^b$
Headache ^a	-	-	-	-	-
Non-Headache	379	112	0.42 [0.11,0.73]	$I^2 = 40\%$	$Z = 2.66, p < .01^b$
Depression					
All chronic pain conditions	444	130	0.47 [0.24,0.70]	$I^2 = 19\%$	$Z = 3.96, p < .01^b$
Headache	91	30	0.87 [0.44,1.30]	$I^2 = 0\%$	$Z = 3.95, p < .01^b$
Non-Headache	388	113	0.35 [0.13,0.56]	$I^2 = 0\%$	$Z = 3.15, p < .01^b$

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Note. ^a Insufficient data for meta-analysis; ^b Girls > Boys; SMD = standardized mean difference; CI = confidence interval

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Table 3. Meta-analysis statistics of treatment effect for the post-treatment time point for boys and girls separately, and subgroup analyses examining sex differences.

	Sample size	SMD[CI]	Heterogeneity	Effect	Subgroup analyses for sex differences
Pain					
All chronic pain conditions					
	Girls <i>n</i> = 672	-0.27 [-0.47,-0.08]	I ² = 29%	<i>Z</i> = 2.74, <i>p</i> < .01 ^a	
	Boys <i>n</i> = 239	-0.37 [-0.69,-0.05]	I ² = 23%	<i>Z</i> = 2.26, <i>p</i> = .02 ^a	
					$\chi^2 = 0.25, p = .61, I^2 = 0\%$
Headache					
Severity	Girls <i>n</i> = 295	-0.31 [-0.54,-0.08]	I ² = 0%	<i>Z</i> = 2.60, <i>p</i> < .01 ^a	
	Boys <i>n</i> = 121	-0.48 [-0.94,-0.03]	I ² = 24%	<i>Z</i> = 2.10, <i>p</i> = .04 ^a	
					$\chi^2 = 0.45, p = .50, I^2 = 0\%$
Reduction of ≥50% in headache severity					

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Girls $n = 295$	1.81 ^b [1.19,2.75]	$I^2 = 13\%$	$Z = 2.77, p < .01^a$
Boys $n = 121$	1.74 ^b [1.09,2.77]	$I^2 = 0\%$	$Z = 2.34, p = .02^a$

$$\chi^2 = 0.01, p = .90, I^2 = 0\%$$

Non-Headache

Girls $n = 435$	-0.31 [-0.59,-0.03]	$I^2 = 44\%$	$Z = 2.19, p = .03^a$
Boys $n = 145$	-0.49 [-0.98,-0.00]	$I^2 = 39\%$	$Z = 1.96, p = .05^a$

$$\chi^2 = 0.39, p = .53, I^2 = 0\%$$

Disability

All chronic pain conditions

Girls $n = 656$	-0.40 [-0.62,-0.18]	$I^2 = 41\%$	$Z = 3.58, p < .01^a$
Boys $n = 223$	-0.22 [-0.49,0.05]	$I^2 = 0\%$	$Z = 1.57, p = .12$

$$\chi^2 = 1.05, p = .31, I^2 = 4.5\%$$

Headache

Girls $n = 276$	-0.40 [-0.70,-0.09]	$I^2 = 31\%$	$Z = 2.51, p = .01^a$
Boys $n = 109$	-0.39 [-0.78,0.00]	$I^2 = 0\%$	$Z = 1.94, p = .05^a$

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

$$\chi^2 = 0.00, p = .98, I^2 = 0\%$$

Non-Headache

Girls $n = 415$	-0.50 [-0.80,-0.20]	$I^2 = 49\%$	$Z = 3.26, p < .01^a$
Boys $n = 127$	-0.08 [-0.44,0.28]	$I^2 = 0\%$	$Z = 0.44, p = .66$

$$\chi^2 = 3.11, p = .08, I^2 = 67.8\%$$

Anxiety^c

All chronic pain conditions

Girls $n = 393$	-0.21[-0.53,0.10]	$I^2 = 57\%$	$Z = 1.31, p = .19$
Boys $n = 117$	-0.21 [-0.59,0.16]	$I^2 = 0\%$	$Z = 1.13, p = .26$

$$\chi^2 = 0.00, p = .99, I^2 = 0\%$$

Non-Headache

Girls $n = 339$	-0.06 [-0.28,0.16]	$I^2 = 3\%$	$Z = 0.57, p = .57$
Boys $n = 103$	-0.35 [-0.75,0.05]	$I^2 = 0\%$	$Z = 1.70, p = .09$

$$\chi^2 = 1.49, p = .22, I^2 = 32.7\%$$

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Depression

All chronic pain conditions

Girls $n = 297$	0.07 [-0.16,0.29]	$I^2 = 0\%$	$Z = 0.56, p = .57$
Boys $n = 104$	-0.15 [-0.67,0.37]	$I^2 = 39\%$	$Z = 0.57, p = .57$

$$\chi^2 = 0.55, p = .46, I^2 = 0\%$$

Headache

Girls $n = 89$	-0.00 [-0.43,0.42]	$I^2 = 0\%$	$Z = 0.02, p = .98$
Boys $n = 25$	-0.23 [-1.02,0.57]	$I^2 = 0\%$	$Z = 0.56, p = .58$

$$\chi^2 = 0.23, p = .63, I^2 = 0\%$$

Non-Headache

Girls $n = 243$	0.06 [-0.19,0.32]	$I^2 = 0\%$	$Z = 0.49, p = .63$
Boys $n = 92$	-0.11 [-0.67,0.44]	$I^2 = 34\%$	$Z = 0.40, p = .69$

$$\chi^2 = 0.32, p = .57, I^2 = 0\%$$

Note. SMD = standardized mean difference; CI = confidence interval

^a Treatment > Control

^b Value presented is the risk ratio, rather than standardised mean difference, as the outcome is dichotomous

^c Insufficient data to conduct headache-only analyses

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Table 4. Meta-analysis statistics of treatment effect for the follow-up time point for boys and girls separately, and subgroup analyses examining sex differences.

	Sample size	SMD[CI]	Heterogeneity	Effect	Subgroup analyses for sex differences
Pain					
All chronic pain conditions					
	Girls $n = 404$	-0.21 [-0.51,0.09]	$I^2 = 51\%$	$Z = 1.37, p = .17$	
	Boys $n = 119$	-0.06 [-0.42,0.31]	$I^2 = 0\%$	$Z = 0.30, p = .77$	
					$\chi^2 = 0.40, p = .53, I^2 = 0\%$
Headache					
Severity					
	Girls $n = 119$	-0.69 [-1.62,0.25]	$I^2 = 68\%$	$Z = 1.44, p = .15$	
	Boys $n = 37$	-0.45 [-1.12,0.22]	$I^2 = 0\%$	$Z = 1.33, p = .18$	
					$\chi^2 = 0.16, p = .69, I^2 = 0\%$

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Reduction of
 $\geq 50\%$ in headache
 severity

Girls $n = 119$	1.97 ^b [0.48,8.04]	$I^2 = 62\%$	$Z = 0.94, p = .34$
Boys $n = 37$	2.01 ^b [0.36,11.13]	$I^2 = 71\%$	$Z = 0.80, p = .42$

$$\chi^2 = 0.00, p = 0.99, I^2 = 0\%$$

Non-Headache

Girls $n = 306$	-0.20 [-0.57,0.17]	$I^2 = 58\%$	$Z = 1.06, p = .29$
Boys $n = 93$	0.02 [-0.40,0.44]	$I^2 = 0\%$	$Z = 0.09, p = .92$

$$\chi^2 = 0.60, p = .44, I^2 = 0\%$$

Disability

All chronic pain
 conditions

Girls $n = 398$	0.18 [-0.41,0.04]	$I^2 = 20\%$	$Z = 1.61, p = .11$
Boys $n = 123$	-0.27 [-0.75,0.21]	$I^2 = 37\%$	$Z = 1.11, p = .27$

$$\chi^2 = 0.11, p = .75, I^2 = 0\%$$

SEX DIFFERENCES IN THERAPY FOR PEDIATRIC PAIN

Headache

Girls $n = 138$	-0.40 [-0.74,-0.06]	$I^2 = 0\%$	$Z = 2.31, p = .02^a$
Boys $n = 54$	-0.71 [-1.27,-0.16]	$I^2 = 0\%$	$Z = 2.52, p = .01^a$

$$\chi^2 = 0.89, p = .35, I^2 = 0\%$$

Non-Headache

Girls $n = 260$	-0.07 [-0.33,0.18]	$I^2 = 7\%$	$Z = 0.57, p = .57$
Boys $n = 69$	0.07 [-0.41,0.55]	$I^2 = 0\%$	$Z = 0.28, p = .78$

$$\chi^2 = 0.26, p = .61, I^2 = 0\%$$

Anxiety^c

All chronic pain conditions

Girls $n = 261$	-0.09[-0.48,0.30]	$I^2 = 60\%$	$Z = 0.44, p = .66$
Boys $n = 70$	-0.06 [-0.69,0.56]	$I^2 = 30\%$	$Z = 0.20, p = .84$

$$\chi^2 = 0.00, p = .95, I^2 = 0\%$$

Depression^c

All chronic pain conditions

Girls $n = 261$	-0.07[-0.31,0.17]	$I^2 = 0\%$	$Z = 0.55, p = .58$
Boys $n = 70$	0.21 [-0.27,0.69]	$I^2 = 0\%$	$Z = 0.86, p = .39$

$$\chi^2 = 1.03, p = .31, I^2 = 3.2\%$$

Note. SMD = standardized mean difference; CI = confidence interval

^a Treatment > Control

^b Value presented is the risk ratio, rather than standardised mean difference, as the outcome is dichotomous

^c Insufficient data to conduct analyses for headache and non-headache separately