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Title: Sex differences in experimental pain among healthy children: A systematic review and meta-analysis

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Corresponding Author: Ms. Katelynn Elizabeth Boerner, BSc. (Hons)

Corresponding Author's Institution: Dalhousie University

First Author: Katelynn Elizabeth Boerner, BSc. (Hons)

Order of Authors: Katelynn Elizabeth Boerner, BSc. (Hons); Kathryn A Birnie, B.A. (Hons); Line Caes, Ph.D.; Meghan G Schinkel, BSc. (Hons); Christine T Chambers, Ph.D.

Abstract: Sex differences in response to experimental pain are commonly reported in systematic reviews in the adult literature. The objective of the present research was to conduct a systematic review and meta-analysis of sex differences in healthy children's responses to experimental pain (e.g., cold pressor, heat pain, pressure pain) and, where possible, to conduct analyses separately for children and adolescents. A search was conducted of electronic databases for published papers in English of empirical research using experimental pain tasks to examine pain-related outcomes in healthy boys and girls between 0 and 18 years of age. Eighty articles were eligible for inclusion and were coded to extract information relevant to sex differences. The systematic review indicated that, across different experimental pain tasks, the majority of studies reported no significant differences between boys and girls on pain-related outcomes. However, the meta-analysis of available combined data found that girls reported significantly higher pain intensity compared to boys in studies where the mean age of participants was greater than 12 years. Additionally, a meta-analysis of heat pain found that boys had significantly higher tolerance than girls overall, and boys had significantly higher heat pain threshold than girls in studies where the mean age of participants was 12 years or younger. These findings suggest that developmental stage may be relevant for understanding sex differences in pain.

SEX DIFFERENCES IN EXPERIMENTAL PAIN IN CHILDREN

Abstract

Sex differences in response to experimental pain are commonly reported in systematic reviews in the adult literature. The objective of the present research was to conduct a systematic review and meta-analysis of sex differences in healthy children’s responses to experimental pain (e.g., cold pressor, heat pain, pressure pain) and, where possible, to conduct analyses separately for children and adolescents. A search was conducted of electronic databases for published papers in English of empirical research using experimental pain tasks to examine pain-related outcomes in healthy boys and girls between 0 and 18 years of age. Eighty articles were eligible for inclusion and were coded to extract information relevant to sex differences. The systematic review indicated that, across different experimental pain tasks, the majority of studies reported no significant differences between boys and girls on pain-related outcomes. However, the meta-analysis of available combined data found that girls reported significantly higher pain intensity compared to boys in studies where the mean age of participants was greater than 12 years. Additionally, a meta-analysis of heat pain found that boys had significantly higher tolerance than girls overall, and boys had significantly higher heat pain threshold than girls in studies where the mean age of participants was 12 years or younger. These findings suggest that developmental stage may be relevant for understanding sex differences in pain.

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Sex differences in experimental pain among healthy children: A systematic review and meta-analysis

Katelynn E. Boerner^{1,3}

Kathryn A. Birnie^{1,3}

Line Caes³

Meghan Schinkel^{1,3}

Christine T. Chambers^{1,2,3}

¹Psychology and Neuroscience and ²Pediatrics, Dalhousie University

³Centre for Pediatric Pain Research, IWK Health Centre

Correspondence should be addressed to:

Katelynn E. Boerner

Centre for Pediatric Pain Research

K8536 (8th floor, Children’s site)

IWK Health Centre

5850/5980 University Avenue

Halifax, Nova Scotia, Canada, B3K 6R8

Telephone: 1-902-470-6769

Facsimile: 1-902-470-7118

E-mail: katelynn.boerner@dal.ca

Sex differences in experimental pain among healthy children:

A systematic review and meta-analysis

Sex differences represent a rapidly growing body of literature in the areas of biology, medicine, and neuroscience, as researchers attempt to illuminate the mechanisms that underlie differences between men and women [14]. According to the World Health Organization, sex refers to the biological and physiological distinctions between women and men. This can be contrasted with gender, which is defined as a psychosocial construct that embodies the attributes, behaviours, and roles that a given society considers to be acceptable for men and women [116].

Sex differences are commonly reported in adult pain, with numerous reviews providing evidence of greater prevalence rates of acute and chronic pain among women, with women also demonstrating greater sensitivity to experimental pain tasks, though the strength of this effect differs between pain modalities, outcome measures, and time points, and is considered to be a controversial phenomena [37,73,87]. The abundance of literature on adult sex differences in pain has allowed researchers to explore mechanisms through which pain differs in men and women, including both biological and psychosocial mechanisms [27,37,56,86]. Such research has important implications with regards to the assessment and treatment of pain in adults, such as recent advances in theories of “personalized pain management” through research on the differential analgesic responding of men and women [80]. Due to developmental factors it is inappropriate to generalize adult findings to pediatric populations, and the literature on sex differences in children’s pain is comparatively sparse.

Epidemiological studies of chronic pain in childhood suggest that prevalence of chronic pain is greatest among adolescent girls, with the emergence of sex differences in chronic pain conditions seen around the time of pubertal development [58]. These findings are concordant

with speculation from the adult literature that sex hormones are one of the mechanisms through which sex differences in pain perception and responding are explained [4,43]. Given the complexity of the numerous factors implicated in the development of chronic pain, a systematic review of research on sex differences in healthy children's pain is needed to fully understand and explore potential mechanisms. Experimental pain provides a starting point for such examinations, controlling for many of the confounding factors that complicate interpretations of results in studies of clinical pain. Prior reviews have only provided narrative descriptions of select studies of sex differences in experimental pain among children and adolescents [55,77]. The primary objectives of the present study were to: (1) systematically review the existing literature on sex differences in responses to experimental pain in healthy children, and (2) meta-analyze data from published studies on experimental pain in boys and girls to provide a further investigation of sex differences beyond those statistics reported in published articles. Additionally, where possible, meta-analyses were to be conducted separately for children (participant mean age less than 12 years) and adolescents (participant mean age of 12 years or older). Finally, an additional objective was to examine the reporting practices of sex and gender in the studies included in the review.

Methods

Search method

A search was conducted of key electronic databases (PsycINFO, EMBASE, CINAHL, PubMed) from the inception of databases through November 2012. The basic structure of the search strategy was as follows: [((pediatric) OR child) OR adolescent] AND [pain] AND [(((((((experimental pain) OR cold pressor) OR quantitative sensory test) OR water load) OR heat pain) OR thermal pain) OR pressure pain) OR exercise task], searching primarily titles and

abstracts of these key databases, using truncations as appropriate for the database (e.g., child*, adolescen*, quantitative sensory test*). Keywords were chosen to capture the population age range of interest, studies that included pain as an outcome, and to focus the search specifically on studies including an experimental pain task.

Eligibility criteria

Eligibility criteria required that included articles be: (1) An empirical investigation using an experimental pain task to examine pain-related outcomes (pain intensity, pain tolerance, pain threshold, pain affect, facial activity in response to pain, or physiological responses to pain); (2) Published in manuscript form in English; (3) Studies using community/healthy samples of children between 0 and 18 years of age only (or a healthy control group included in studies of clinical populations); (4) Studies that included both boys and girls. Experimental pain tasks were defined as any task that was intended to induce pain for which a pain-related outcome was measured.

Screening for eligibility, coding, and requests for missing data

The initial search revealed 519 unique abstracts, once duplicates were removed. Each abstract was reviewed by two co-authors (K.E.B. and K.A.B.) to determine eligibility. If eligibility could not be determined from the abstract, the full article was examined. A total of 440 abstracts were excluded for the following primary reasons: participants did not complete an experimental pain task ($n=33$, 7.5%), the study did not measure any pain-related outcomes ($n=8$, 1.8%), the abstract was not published in manuscript form (e.g., dissertations, book chapters, conference abstracts, $n=46$, 10.5%), the article was not published in English ($n=8$, 1.8%), the study was conducted with a clinical sample and did not include a healthy control group ($n=69$, 15.7%), the study included individuals outside of the 0-18 years of age range ($n=254$, 57.7%),

the study sample was composed of only boys or only girls ($n=8$, 1.8%), the study was conducted with animals ($n=14$, 3.2%).

Therefore, from the initial search, 79 articles were identified as being eligible. Each of the 79 articles were read and data was extracted by a study author (K.E.B., K.A.B., L.C., or M.S.) using an author-created coding form that documented sample characteristics, details of the experimental pain tasks performed, and details related to any pain-related outcomes measured (including mean and standard deviation of the pain outcome for both boys and girls, as well as the results of any statistical tests conducted to examine sex differences). During coding, three additional articles were identified as being eligible for inclusion, as they were referenced in the paper as reporting on additional results from the same study sample [82,102,108]. These three articles were also coded and included in the study, resulting in a total of 82 articles coded for inclusion. See Figure 1 for a study flowchart employing the PRISMA model[74].

Coding sheets were examined to identify missing data. Authors were contacted and asked to supply data for any article that did not include the following: age range of participants, mean age of participants, mean and standard deviation for boys and girls separately for any pain outcome. When applicable, data was requested for baseline/control experimental pain tasks (i.e., tasks that did not involve an intervention or experimental manipulation) and for healthy/community samples only. Two attempts were made to contact the corresponding author of each paper where data was missing. Based on author responses, two articles that had originally been included in the review [11,103] were excluded, as it was revealed that the sample fell outside of the 0-18 year old age range. This resulted in a final total of 80 articles included, reporting on 81 separate studies, as one article reported on two studies with separate samples [109].

Overlapping samples

Every attempt was made to avoid the inclusion of overlapping samples in the review, as this would involve an over-representation of a subset of children. If it was unclear whether samples were overlapping, authors were emailed to confirm this information. Where it was known that samples were overlapping (i.e., >1 study included in the review that reported on the same sample of children), the authors of the present review went back to the first published study from that sample and worked forward chronologically through multiple publications reporting on the same sample of children, making note of outcomes the first time that full data was reported (e.g., means and standard deviations of pain outcome for boys and girls separately, and statistics regarding sex differences). If full data was not available from any of the studies involved in the overlapping sample, the authors were contacted and asked to provide data about the first chronological incidence of reporting. Where it was unclear whether samples were overlapping, the authors were contacted and asked to indicate whether multiple publications reported on the same sample of children. If authors did not respond, the studies were assumed to represent different samples of children and were treated as such in the review.

Data Analytic Approach

Information from data extraction coding sheets were entered into SPSS 20, and information from the systematic review was summarized using descriptive statistics. Due to the low number of studies included in the systematic review, results were combined across different experimental pain tasks. Sufficient data was available to conduct meta-analyses separately for cold pressor pain, heat pain, and pressure pain. Data needed to be available from at least two studies to conduct a meta-analysis for a particular pain outcome. All data suitable for pooling was analyzed with RevMan 5.2 software using a fixed-effects analysis (unless otherwise

indicated), as heterogeneity across studies was not observed or was low for each outcome [95]. Heterogeneity was calculated using the I^2 statistic, with 0-40% interpreted as heterogeneity that might not be important, 30-60% taken as moderate heterogeneity, and 75-100% representing considerable heterogeneity [48]. For each study, the standardized mean difference and a 95% confidence interval was calculated. In studies where the same pain task was administered more than one time and the results of each trial were reported separately (or when the same pain outcome was measured more than one time within a pain task and data was reported for each time point), only data from the first trial/measurement was included. Note that when the same pain task was administered under different conditions but the order was counterbalanced across participants [76], a pooled mean was taken of pain outcomes across both conditions, as it could not be determined which pain task was administered first for each participant. The following formulas were used to pool means and SDs: pooled mean = $[(\text{mean1} \times N1) + (\text{mean2} \times N2) / (N1 + N2)]$ and pooled SD = square root of $[(SD1^2)(N1-1) + (SD2^2)(N2-1)] / N1 + N2 - 2$. A pooled mean was also calculated for studies that reported results of the same pain task performed at multiple body locations (e.g., pressure pain measured at the neck and shoulder).

Given that many studies of sex differences in adult pain have speculated about the role of sex hormones in the development of sex differences in pain, the meta-analysis was also conducted separately for studies in which the mean age of participants was greater than or equal to 12 years of age, and those studies in which the mean age of participants was less than 12 years of age. This age was chosen as the cut-off as it represents the age at which many girls and boys have entered puberty, and as such (in the absence of measures of pubertal status) provides a proxy for the emergence of sex hormones[83]. Note that this approach was only taken for cases in which data was available for at least two studies in each age group. If the mean age of

participants was not available because it was not reported or because the data suitable for pooling was from a subset of participants rather than the entire sample, categorization was determined by the age range of participants or the mean age of participants in the entire sample.

Results

Published accounts of sex differences in pain outcomes

Results of the systematic review are presented for each pain outcome measure summarized across experimental pain tasks. Note that several studies ($n=25$, 30.9%) had children complete more than one different type of experimental pain task, and results from statistical tests of sex differences were included for each unique pain task, even if it was performed on the same sample of children. Tables 1 through 4 provide the results of the systematic review separately by experimental pain induction method. Note that the following studies eligible for inclusion in the systematic review conducted **additional** experimental pain tasks (e.g., fabric prickliness test, ischemic pain, brush allodynia, manual palpation, dynamic mechanical allodynia, tactile pain sensitivity) but did not conduct statistical tests examining sex differences in healthy children and therefore are not included in Tables 1-4: [6,18,49,89,111,115].

Pain intensity. Of the pain tasks **where it was reported that statistical tests of sex differences in pain intensity were conducted** ($n=21$ pain tasks from 18 unique studies), 90.5% reported no sex differences, and 9.5% indicated girls reported significantly higher levels of pain intensity than boys.

Pain threshold. Of the pain tasks **where it was reported that statistical tests of sex differences in pain threshold were conducted** ($n=16$ pain tasks from 9 unique studies), 68.8%

reported no sex differences, and 31.2% indicated that boys had a significantly higher pain threshold than girls.

Pain tolerance. Of the pain tasks where it was reported that statistical tests of sex differences in pain tolerance were conducted ($n=16$ pain tasks from 16 unique studies), 75% reported no sex differences, 12.5% indicated that girls had a higher pain tolerance than boys, and 12.5% indicated that boys had a higher pain tolerance than girls.

Pain affect. Of the pain tasks where it was reported that statistical tests of sex differences in pain affect were conducted ($n=7$ pain tasks from 5 unique studies), 85.7% reported no sex differences, and 14.3% indicated that girls reported greater pain affect than boys in response to an experimental pain task.

Facial activity in response to pain. Of the pain tasks where it was reported that statistical tests of sex differences in facial activity in response to pain were conducted ($n=8$ pain tasks from 8 unique studies), 75% reported no sex differences, and 25% indicated that boys displayed greater facial activity in response to pain than girls.

Physiological responses to pain. Of the pain tasks where it was reported that statistical tests of sex differences in physiological responses to pain were conducted ($n=6$ pain tasks reporting on 9 measures of physiological responses from 4 unique studies¹), 88.8% reported no sex differences, and 11.1% indicated that boys had a greater physiological response (blood pressure) to pain than girls.

Meta-analysis of sex differences in cold pressor pain

¹Note that one of the studies required children to participate in >1 experimental pain task ([78]: CPT, heat pain, pressure pain) and measured two physiological responses (salivary and blood cortisol) after the completion of all three tasks. Additionally, another included study measured physiological responses to cold pressor pain with multiple modalities ([38]: physiological responses measured using heart rate, skin conductance, respiratory rate, EMG, blood pressure, and skin temperature). Results from statistical tests of sex differences were included for each unique pain task and physiological response measure, even if it was performed on the same sample of children.

When full data was not available in the published manuscript, authors were contacted and requested to provide data for the meta-analytic portion of this research. Of the 49 requests for data sent, 9 responses (18.4%) were received indicating that the data was not available, and 27 responses (55.1%) provided additional data. When this was combined with the data available from published manuscripts, data for meta-analysis was available from 33 separate samples, with a combined total of 2109 unique participants (1069 girls and 1040 boys).

Pain intensity. Data from 19 studies (published in 18 separate articles) were entered into the meta-analysis, which compared self-reported pain intensity during the cold pressor task in a total of 628 girls and 633 boys [16,26,39,40,54,75,76,78,82,84,85,93,94,96,99,105,106,109]. Pain intensity was measured using a variety of self-report tools, including the Faces Pain Scale (original [7] and revised [47] versions), numerical rating scales, visual analogue scales, and the Coloured Analogue Scale [66]. This analysis revealed a standardized mean difference (SMD) of 0.10 [-0.01, 0.21] and an I^2 of 0%, indicating no observed heterogeneity. While the mean self-reported pain intensity of girls was greater than boys, this effect was not significant ($Z = 1.76, p = .08$).

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from 12 studies were entered into the meta-analysis, with a total of 302 girls and 303 boys [16,26,39,54,75,76,82,84,85,93,96,99]. This analysis revealed a SMD of 0.01 [-0.15, 0.17], an I^2 of 0%, and no significant differences between boys and girls on self-reported pain intensity ($Z = 0.08, p = .93$).

However, a significant effect was present in the studies with a mean age of equal to or greater than 12 years, in which seven studies (from six published articles) were entered into the

meta-analysis, with a total of 321 girls and 330 boys [40,78,94,105,106,109]. This analysis revealed a SMD of 0.19 [0.03, 0.34], an I^2 of 33%, and a significant difference in which girls reported significantly greater pain intensity in response to the cold pressor task than boys ($Z = 2.35, p = .02$).

Pain threshold. Data from six studies were entered into the meta-analysis, which compared pain threshold in a total of 154 girls and 149 boys [23-25,93,94,96]. This analysis revealed a SMD of 0.12 [-0.11, 0.35] and an I^2 of 15%, indicating low heterogeneity. This effect was not significant ($Z = 1.02, p = .31$), indicating no significant differences in pain threshold during the cold pressor task between boys and girls. As all but one study had a mean age less than 12 years old, the meta-analysis was not conducted separately for different age groups.

Pain tolerance. Data from 18 studies (published in 17 separate articles) were entered into the meta-analysis, which compared pain tolerance in a total of 628 girls and 600 boys [16,23-26,54,60,76,78,84,85,93,94,96,99,109,113]. This analysis revealed a SMD of 0.04 [-0.07, 0.16] and an I^2 of 0%, indicating no observed heterogeneity. This effect was not significant ($Z = 0.72, p = .47$), indicating no difference between boys and girls on pain tolerance during the cold pressor task.

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from 14 studies were entered into the meta-analysis, with a total of 366 girls and 342 boys [16,23-26,54,60,76,84,85,93,96,99,113]. This analysis revealed a SMD of 0.07 [-0.08, 0.22], an I^2 of 0%, and no significant differences between boys and girls on pain tolerance during the cold pressor task ($Z = 0.93, p = .35$).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which four studies (from three published articles) were included, with a total of 262 girls and 258 boys [78,94,109]. This analysis revealed a SMD of 0.00 [-0.17, 0.18], an I^2 of 0%, and no significant differences between boys and girls on pain tolerance during the cold pressor task ($Z = 0.03, p = .98$).

Pain affect. Data from nine studies were entered into the meta-analysis, which compared self-reported pain affect in a total of 308 girls and 327 boys [16,61,76,78,82,93,94,96,104]. Pain affect was measured using several self-report tools, including the Facial Affective Scale [65], the Children's Fear Scale [67], and numerical rating scales and visual analogue scales for "pain discomfort" or "pain unpleasantness." This analysis revealed a SMD of 0.02 [-0.13, 0.18] and an I^2 of 0%, indicating no observed heterogeneity. This effect was not significant ($Z = 0.29, p = .77$), indicating no difference between boys and girls on self-reported pain affect during the cold pressor task.

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from six studies were entered into the meta-analysis, with a total of 183 girls and 207 boys [16,61,76,82,93,96]. This analysis revealed a SMD of 0.02 [-0.13, 0.18], an I^2 of 0%, and no significant differences between boys and girls on pain affect during the cold pressor task ($Z = 0.29, p = .77$).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which three studies were included, with a total of 125 girls and 120 boys [78,94,104]. This analysis revealed a SMD of 0.08 [-0.17, 0.33], an I^2 of 0%, and no

significant differences between boys and girls on pain affect during the cold pressor task ($Z = 0.65, p = .52$).

Facial expression of pain. Data from six studies were entered into the meta-analysis, which compared facial expressions of pain in a total of 118 girls and 127 boys [16,40,59,75,105,106]. Scores for facial expression in response to pain were coded in each study using the Child Facial Coding System [15] or the Facial Action Coding System [28] (note that how facial expression scores were calculated differed across studies in that some studies reported a score based on all facial action units, while others calculated a score based on only those facial action units that have been identified as corresponding to expressions of pain). This analysis revealed a SMD of 0.00 [-0.26, 0.25] and an I^2 of 0%, indicating no observed heterogeneity. This effect was not significant ($Z = 0.03, p = .98$), indicating no difference between boys and girls on facial expressions in response to the cold pressor task.

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from three studies were entered into the meta-analysis, with a total of 81 girls and 82 boys [16,59,75]. This analysis revealed a SMD of 0.08 [-0.22, 0.39], an I^2 of 0%, and no significant differences between boys and girls in facial expressions in response to the cold pressor task ($Z = 0.53, p = .60$).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which three studies were included, with a total of 62 girls and 70 boys [40,105,106]. This analysis revealed a SMD of 0.02 [-0.33, 0.36], an I^2 of 40%, and no significant differences between boys and girls on facial expression in response to the cold pressor task ($Z = 0.09, p = .93$).

Physiological reaction. Data from four studies were entered into the meta-analysis, which compared physiological reactions to the cold pressor task in a total of 154 girls and 149 boys [16,26,39,75]. In each of the included studies, physiological reactions were measured using participant heart rate. This analysis revealed a SMD of 0.09 [-0.24, 0.41] and an I^2 of 0%, indicating no observed heterogeneity. This effect was not significant ($Z = 0.52, p = .60$), indicating no significant differences in heart rate in response to the cold pressor task between boys and girls. As all included studies had a mean age less than 12 years old, the meta-analysis was not conducted separately for different age groups.

Meta-analysis of sex differences in experimental heat pain

Meta-analyses were conducted for pain intensity, tolerance, and threshold for experimental heat pain. There was insufficient data available to conduct analyses for pain affect, facial expression, or physiological responses.

Pain intensity. Data from three studies were entered into the meta-analysis, which compared self-reported pain intensity in a total of 154 girls and 155 boys during experimental heat pain [13,39,78]. Pain intensity was measured using numerical rating scales and visual analogue scales. This analysis revealed a SMD of 0.07 [-0.15, 0.30] and an I^2 of 0%, indicating no observed heterogeneity. No significant differences between boys and girls on self-reported pain intensity during heat pain were observed ($Z = 0.63, p = .53$). As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Pain threshold. Data from three studies were entered into the meta-analysis, which compared pain threshold in a total of 179 girls and 183 boys [8,9,39]. This analysis revealed a SMD of -0.31 [-0.52,-0.11] and an I^2 of 0%, indicating no observed heterogeneity. This effect

was significant ($Z = 2.96$, $p = .003$), indicating that boys had a significantly higher heat pain threshold than girls.

As two of the included studies reported means and standard deviations separately by age group, it was possible to conduct a meta-analysis to separately examine study samples for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from three studies were entered into the meta-analysis, with a total of 104 girls and 107 boys [8,9,39]. This analysis revealed a SMD of -0.34 [$-0.61, -0.07$], an I^2 of 0%, and a significant difference in which boys had significantly higher heat pain threshold than girls ($Z = 2.46$, $p = .01$).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which data from two studies were included, with a total of 75 girls and 76 boys [8,9]. This analysis revealed a SMD of -0.27 [$-0.60, 0.05$], and an I^2 of 0%. While the mean pain threshold of boys was greater than the mean pain threshold of girls, this effect was not significant ($Z = 1.68$, $p = .09$).

Pain tolerance. Data from two studies were entered into the meta-analysis, which compared pain tolerance in a total of 152 girls and 148 boys [13,64]. Note that as heterogeneity was high in this comparison ($I^2=91\%$) a random effects model was used. This analysis revealed a SMD of -1.26 [$-2.29, -0.23$] with a significant effect ($Z = 2.40$, $p = .02$), indicating that boys had significantly higher tolerance of heat pain than girls. As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Meta-analysis of sex differences in experimental pressure pain

Meta-analyses were conducted for pain intensity and threshold for experimental heat pain. There was insufficient data available to conduct analyses for pain tolerance, pain affect, facial expression, or physiological responses.

Pain intensity. Data from two studies were entered into the meta-analysis, which compared self-reported pain intensity in a total of 164 girls and 160 boys undergoing experimental pressure pain [78,107]. Pain intensity was measured using numerical rating scales and visual analogue scales. This analysis revealed a standardized mean difference (SMD) of 0.17 [-0.5, 0.39] and an I^2 of 0%, indicating no observed heterogeneity. No significant differences between boys and girls on self-reported pain intensity during pressure pain were observed ($Z = 1.51, p = .13$). As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Pain threshold. Data from two studies were entered into the meta-analysis, which compared pain threshold in a total of 81 girls and 62 boys [71,107]. Note that as heterogeneity was high in this comparison ($I^2=78\%$) a random effects model was used. This analysis revealed a SMD of -0.35 [-1.08,0.39] and this effect was not significant ($Z = 0.93, p = .35$), indicating no significant differences in pain threshold during experimental pressure pain between boys and girls. As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Reporting practices of sex and gender variables

Of the 81 included studies, 41 studies (50.6%) had reported results of statistical tests examining sex differences for at least one pain-related outcome (note that this included studies that merely reported that sex differences were or were not present, even if the authors did not include numerical values of the statistical test conducted or the mean values of the different

groups). Nine studies (11.1%) reported entering sex as a covariate in their analyses. Two studies (2.5%) reported using a validated measure of child gender (e.g., the *Children's Sex Role Inventory* [10]) to examine the relationship between child gender and pain outcomes [78,109].

With regards to terminology use, 36 studies (44.4%) used the appropriate terminology when referring to “sex” or “gender”, according to the definitions of sex and gender set out by the World Health Organization [116]. Of the remaining studies, 29 studies (35.8%) used the term “gender” when grouping participants based on sex, 7 studies (8.6%) used the terms “sex” and “gender” interchangeably throughout the article, and 9 studies (11.1%) did not use either term at all.

Discussion

Systematic review and meta-analysis of sex differences

The results of this systematic review indicate that the majority of studies on children's responses to experimental pain report no significant sex differences on pain-related outcomes.

However, the meta-analysis of cold pressor pain intensity revealed that girls reported significantly higher pain intensity than boys when pooling data from studies that had a mean age >12 years, an age typically associated with onset of pubertal development in both boys and girls [83]. While such an approach to examining age is crude, a more detailed analyses by age and/or pubertal status was not feasible with the information available. Nonetheless, this analysis offers preliminary support for the hypothesis that sex differences in experimental cold pressor pain, similar to chronic pain, emerge in adolescence and could possibly be related to the emergence of sex hormones [58]. This is in line with findings in other areas of research, in which the emergence of sex differences of other disorders and conditions (e.g., anxiety, depression) are seen at puberty [21,22,57]. A more explicit examination of the role of sex hormones and pubertal

stages in the development of sex differences is needed to control for other factors that could be contributing to sex differences in adolescents (e.g., different methodologies used in research groups that study children vs. adolescents).

A meta-analysis of sex differences in response to experimental heat pain revealed that boys had significantly higher pain threshold and pain tolerance than girls, with no significant differences in pain intensity. Unlike cold pressor pain, the sex difference in heat pain threshold was still significant in studies where children had a mean age of 12 years or lower. These results should be interpreted with caution, as heat pain is not often used among children, and as such, the meta-analysis may have not been adequately powered to accurately represent the strength of sex difference effects in heat pain in children, particularly when split by age group.

In adults, pressure pain produces the largest sex differences of all experimental pain tasks [88]. In the present meta-analysis, no sex differences were observed in experimental pressure pain. The small number of studies using heat and pressure pain limits the ability to draw conclusions regarding effects of different experimental pain tasks. Inspection of available results from the systematic review does not appear to support task-specific sex effects, though more research in this area is certainly needed. In particular, examination of possible sex differences in pain emerging at different developmental stages for different types of pain tasks are currently lacking in children [37,87].

Reporting practices of sex and gender

In recent years, organizations such as the International Association for the Study of Pain have increasingly encouraged researchers to consider sex and gender in their research and to use appropriate terminology [42]. Despite the majority of studies having a representative sample of both boys and girls, less than half of included studies reported tests of sex differences in pain-

related outcomes. Only two of the 81 studies included in this review reported on measures of child gender and its relationship to pain outcomes. Additionally, despite increasing awareness of the distinction between sex and gender, use of terminology in reviewed articles was often inappropriate, with the most common issue being use of the term “gender” when referring to the categorical distinction between boys and girls. Appropriate reporting is critical for advancing our understanding of the role of these variables in pain.

Strengths, Limitations, & Future Directions

A strength of the present research was the use of a meta-analytic approach, which allowed for pooling of data to examine sex effects and including data from studies that otherwise were not powered to look at sex differences. Additionally, the excellent response rate of authors providing data allowed for a quantitative synthesis of a large number of studies beyond what is available in the published literature. With regards to limitations, any systematic review or meta-analysis is subject to methodological variability across studies. For example, measurement of pain outcomes occurred at different times (e.g., several studies examined pain intensity at the beginning of the pain task, while others examined worst pain upon task completion). Rules were implemented regarding data extraction to control this variability (e.g., only the first measure of pain intensity taken was used), however some methodological variability remained unavoidable (e.g., the first measure of pain intensity may have occurred at different times across studies) and may have impacted the findings [73]. While physiological measures of pain have been commonly reported in adult reviews of sex differences in experimental pain, these measures are often not specific to pain and should be interpreted with caution [37]. Finally, while the majority of meta-analyses conducted had low or no observed heterogeneity, observed heterogeneity was high for a few select analyses undertaken (heat pain tolerance and pressure pain threshold).

The division of the meta-analysis by mean age of participants has several limitations. While the mean age indicated whether the majority of children were under/over the age of 12 years, many of the studies would have included children and adolescents at various stages of pubertal development in both groups. As such, the presence of potential sex differences in those children who had undergone puberty may have been washed out because they were being considered along with pre-pubertal children. Previous research has had conflicting conclusions whether pubertal status or age is more important for understanding the development of sex differences in children's pain [62,90]. As pubertal status was only measured in two studies in the present review [3,64], age was used as a proxy, however, this was not ideal and future research is need to replicate our age-related findings.

The heterogeneity of methods in the included studies, as well as the wide age ranges precludes conclusive statements regarding the effects of sex on healthy children's pain experience. Future research will require studies explicitly designed to examine sex differences in various age groups across pubertal development (which may include measurement of pubertal stage and/or presence of sex hormones in addition to age). Such studies may require large samples to be able to detect the small sex difference effects presented in this review, which are similar to the small-medium effect sizes seen in adult reviews [37]. Overall, for the cold pressor task, all standardized mean difference scores were less than 0.2 (range: 0.0-0.19), indicating very small effect sizes[19]. Heat pain tasks showed more variability in effect sizes, from small for pain intensity and threshold ($SMD = 0.07$ and -0.31 , respectively), to quite large for pain tolerance ($SMD = -1.26$). Pressure pain tasks demonstrated small effect sizes for pain intensity and threshold ($SMD = 0.17$ and $-.035$, respectively). Researchers may consider using the effect sizes from the present study in calculating sample sizes, should they wish to examine sex

differences in their own research. While many of the studies included in the present review did not report significant sex differences, this may have been due to insufficient power to detect such effects. For example, a t-test comparing boys and girls with a significance level of .05 and power of 0.8 would require close to 400 participants in each group to detect a small effect size, which is much larger than the standard sample size for experimental pain studies. Schmitz and colleagues [90] recently demonstrated important future directions for the field through the inclusion of large sample sizes and methodology designed explicitly to examine sex differences across pubertal development. Researchers should consider conducting similar studies looking at additional pain outcomes (e.g., pain intensity) and using different experimental pain paradigms.

With regards to future research directions, it will also be important for investigators to continue examining the impact of gender on pain responses in childhood and adolescence. A recent meta-analysis of the impact of gender roles on experimental pain responses in adults supports the role of gender schema theory in influencing differential pain responding in men and women [1]. As gender schemas are known to be incorporated and understood by children at a young age, it will be important to examine the developmental trajectory of gender influences [79]. Sex differences in other psychosocial variables also deserve further investigation, such as children's pain coping styles and parental behaviour in response to pain. Finally, a similar systematic meta-analytic approach should be applied to clinical pain in children.

In summary, the majority of published accounts of sex differences in pain outcomes in healthy children reported no significant differences between boys and girls on any pain outcomes. However, the meta-analysis of available combined data found that girls reported significantly higher increased pain intensity compared to boys in studies where the mean participant age was greater than 12 years. Additionally, a meta-analysis of heat pain found that boys had significantly

higher tolerance than girls, and boys had significantly higher heat pain threshold than girls in studies where the mean participant age was 12 years or younger. Researchers should continue to include analyses of both sex and gender, as well as developmental factors such as puberty, to better understand how the sex differences observed in adult pain develop from childhood.

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SEX DIFFERENCES IN EXPERIMENTAL PAIN IN CHILDREN

Boerner et al. 25 word summary for ‘Sex differences in experimental pain among healthy children: A systematic review and meta-analysis

Meta-analysis found that girls had increased pain intensity on the cold pressor task, and lower pain tolerance and threshold in response to heat pain.

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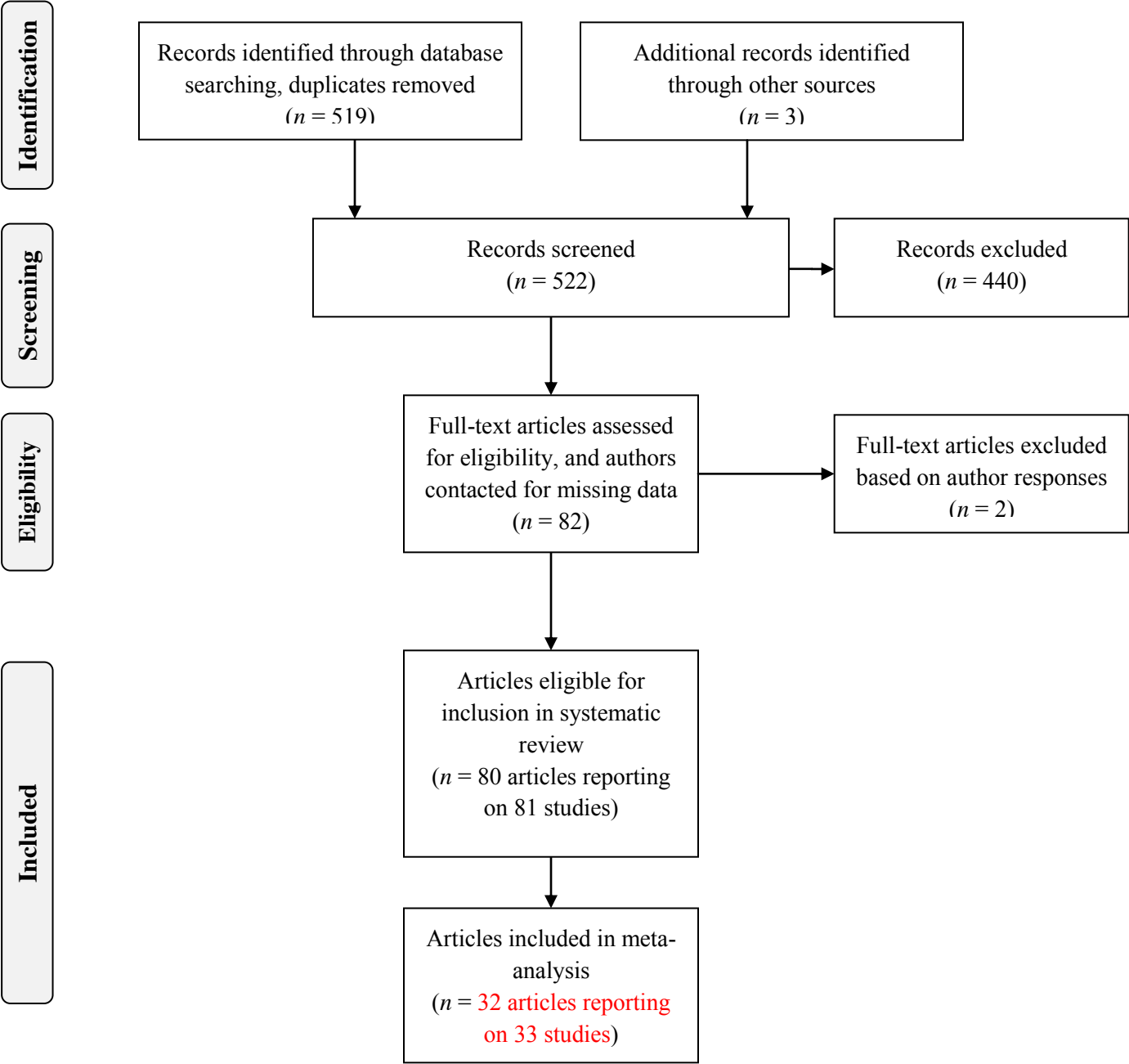


Figure 1. PRISMA flow diagram of the process of identification and screening of articles for inclusion in the systematic review and meta-analysis.

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Table 1. Studies examining sex differences in experimental cold pain.

Authors	Sample Size		Mean age (range)	Method (location)	Pain outcomes					
	Boys	Girls			Intensity	Threshold	Tolerance	Affect	Facial activity	Physiological responses
Allen et al. 2009 ^a [3]	119	116	12.7 (8-18)	CPT (dominant hand)						G=B
Blankenburg et al. 2010 [8]	88	88	NR (6-16)	QST cold pain threshold (face, hand, foot)		G<B				
Blankenburg et al. 2011 ^b [9]	88	85	NR (7-14)	QST cold pain threshold (hands)		G=B				
Chambers et al. 2002[16]	60	60	9.74 (8-12)	CPT (left hand)	G=B		G=B	G=B	G<B	G=B
Coldwell et al. 2002[20]	38	37	9.7 (8-11)	CPT (right forearm)	G=B					
Foster et al. 2003[38]	53	47	12.43 (8-17)	CPT (left hand)						G=B and G<B ^c
Goodman et	48	48	12.6	CPT	G=B	G=B	G=B		G=B	

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al. 2003[40]			(10-14)	(non-dominant hand)					
Jaaniste et al. 2007[54]	38	41	9.16 (7-12)	CPT (non-dominant arm)	G=B	G=B			
Larochette et al. 2006[59]	25	25	9.74 (8-12)	CPT (arms)			G=B		
LeBaron et al. 1989 ^d [61]	19	18	NR (6-12)	CPT (arms)		G=B	G>B		
Miller et al. 1994[72]	23	21	NR (8-11)	CPT (non-dominant forearm)		G>B			
Moon et al. 2008[75]	37	36	8.04 (4-12)	CPT (hand)	G=B			G=B	G=B
Myers et al. 2006 ^a [78]	120	120	12.7 (8-18)	CPT (non-dominant hand)	G=B	G=B	G=B		
Piira et al. 2002[85]	22	31	9.08 (7-14)	CPT (dominant arm)		G=B			
Piira et al.	55	65	10.16	CPT	G=B	G=B			

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2006[84]			(7-14)	(non-dominant arm)				
Trapanotto et al. 2009 [96]	78	63	10.1 (8-12)	CPT (non-dominant arm)	G=B	G=B	G=B	G=B
Tsao et al. 2002 ^d [99]	19	32	NR (8-10)	CPT (arms)	G=B		G=B	
Verhoeven et al. 2012 ^e [104]	39	42	13.6 (9-18)	CPT (left hand)				G=B
Vervoort et al. 2009 ^f [106]	32	30	12.46 (9-15)	CPT (left hand)				G=B
Vervoort et al. 2011 ^e [105]	22	16	14.5 (10-18)	CPT (hands)	G=B			G<B
Vierhaus et al. 2011[109] (Study #1)	53	65	12.74 (10-17)	CPT (non-dominant forearm)	G>B		G=B	
Vierhaus et al. 2011[109] (Study #2)	81	67	12.8 (10-17)	CPT (non-dominant forearm)	G>B		G=B	

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Weiss et al. 2011[113]	31	30	4.21 (3-5)	CPT (non- dominant hand)	G=B	
Zeltzer et al. 1989 ^g [117]	NR	NR	NR (6-12)	CPT (arms)	G>B	G>B

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold and tolerance indicate greater pain sensitivity. NR = not reported.

The following studies using experimental cold pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript: [6,23-26,36,39,60,68-70,76,81,82,91-94]

^a Evans et al. 2008 [29], Evans et al. 2008 [31], Evans et al. 2009 [30], Haas et al. 2011 [44], Lu et al. 2007 [63], Tsao et al. 2004 [102], Tsao et al. 2006 [100], Tsao et al. 2006 [101], and Tsao et al. 2012 [97] reported on results of the cold pressor task with the same sample of children.

^b Hirschfeld et al. 2012 [49] reported on results of a cold pain threshold test re-testing the same sample of children.

^c No sex differences were found on the majority of physiological outcomes in response to pain (heart rate, skin conductance, respiratory rate, EMG, or skin temperature), but boys had significantly higher blood pressure than girls.

^d Fanurik et al. 1993 [32] and Tsao et al. 2003 [98] reported on results of the cold pressor task with the same sample of children.

^e Studies reported on results from the same sample of children.

^f Caes et al. 2011 [12] reported on results of the cold pressor task with the same sample of children.

^g LeBaron et al. 1989 [61] reported on results of the cold pressor task with the same sample of children.

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Table 2. Studies examining sex differences in experimental heat pain.

Authors	Sample Size		Mean age (range)	Location	Pain outcomes					
	Boys	Girls			Intensity	Threshold	Tolerance	Affect	Facial activity	Physiological responses
Allen et al. 2009 ^a [3]	119	116	12.7 (8-18)	Forearms						G=B
Blankenburg et al. 2010 [8]	88	88	NR (6-16)	Face, hand, foot		G<B				
Blankenburg et al. 2011 ^b [9]	88	85	NR (7-14)	Hands		G<B				
Lu et al. 2005 ^a [64]	120	124	12.73 (8-18)	Forearms			G=B			
Myers et al. 2006 ^a [78]	120	120	12.7 (8-18)	Forearms	G=B			G=B		
Vervoort et al. 2012 [108]	32	30	13.08 (11-15)	Right wrist	G=B		G<B		G=B	

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold and tolerance indicate greater pain sensitivity. NR = not reported.

The following studies using experimental heat pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript:[6,13,39,46,52,53,68,69,114,115]

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^a Evans et al. 2008 [29], Evans et al. 2008 [31], Evans et al. 2009 [30], Haas et al. 2011 [44], Lu et al. 2007 [63], Tsao et al. 2004 [102], Tsao et al. 2006 [100], Tsao et al. 2006 [101], and Tsao et al. 2012 [97] reported on results of the cold pressor task with the same sample of children.

^b Hirschfeld et al. 2012 [49] reported on results of a heat pain threshold test re-testing the same sample of children.

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Table 3. Studies examining sex differences in experimental pressure pain.

Authors	Sample Size		Mean age (range)	Location	Pain outcomes					
	Boys	Girls			Intensity	Threshold	Tolerance	Affect	Facial activity	Physiological responses
Allen et al. 2009 ^a [3]	119	116	12.7 (8-18)	Fingers						G=B
Blankenburg et al. 2010[8]	88	88	NR (6-16)	Face, hand, foot			G<B			
Blankenburg et al. 201 ^b [9]	88	85	NR (7-14)	Hands			G=B			
Chaves et al. 2007 ^c [17]	9	7	8.33 boys and 8.71 girls (7-12)	Face, hand			G=B			
Han et al. 2012[45]	258	247	7.9 (4-11)	Forearm			G=B			
Hogeweg et al. 1995[50]	33	36	11.5 boys and 11.5 girls (6-17)	Joints of the elbow, wrist, knee, and ankle, and paraspinally			G=B			
Hogeweg et al.	33	36	11.4	Joints of the			G=B ^d			

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1996[51]			(6-17)	elbow, wrist, knee, and ankle, and paraspinally		
Metsahonkala et al. 2006[71]	22	37	NR (13)	Five cranial and neck- shoulder points and three extracephalic points	G<B	
Myers et al. 2006 ^a [78]	120	120	12.7 (8-18)	Fingers	G=B	G=B
Tsao et al. 2004 ^a [102]	60	58	12.6 (8-18)	Fingers		G<B
Vervoort et al. 2008 ^c [107]	40	44	11.82 (9-15)	Neck, shoulder	G=B and G>B ^f	G=B

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold and tolerance indicate greater pain sensitivity. NR = not reported.

The following studies using experimental pressure pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript:[2,5,18,33-35,112,115]

^a Evans et al. 2008 [29], Evans et al. 2009 [30], Evans et al. 2008 [31], Haas et al. 2011 [44], Lu et al. 2007 [63], Lu et al. 2005[64], Tsao et al. 2012 [97], Tsao et al. 2006 [100], and Tsao et al. 2006 [101] reported on results of the cold pressor task with the same sample of children.

^b Hirschfeld et al. 2012 [49] reported on results of the pressure pain threshold test re-testing the same sample of children.

^c Note that this sample conducted sex difference statistics combining both the healthy control group and the clinical sample (mean age is presented for healthy sample only).

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^d This study reported that there were no significant sex differences except for at the knee in ages 12-17 years, where G<B.

^e Goubert et al. 2009 [41] reported on results of the pressure pain threshold test with the same sample of children.

^f Note that while no sex differences were present during the pressure pain threshold test phase (which was the result included in the systematic review, as it was the first trial of the pressure pain task), in the experimental phase girls reported a significantly higher pain intensity than boys.

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Table 4. Studies examining sex differences in other experimental pain tasks.

Pain task	Authors	Sample Size		Mean age (range)	Location	Pain outcomes	
		Boys	Girls			Intensity	Threshold
Mechanical pain	Bar-Shalita et al. 2009[6]	18	16	7.75 (NR)	Forearm	G=B ^a	
	Blankenburg et al. 2010[8]	88	88	NR (6-16)	Face, hand, foot	G=B	G=B
	Blankenburg et al. 2011 ^b [9]	88	85	NR (7-14)	Hands	G=B	G=B
Wind-up ratio	Blankenburg et al. 2010[8]	88	88	NR (6-16)	Face, hand, foot	G=B	
	Blankenburg et al. 2011 ^b [9]	88	85	NR (7-14)	Hands		G=B
Water load task	Walker et al. 2006[110]	60	60	11.46 (8-15)	Abdomen	G=B ^c	

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold indicate greater pain sensitivity. Note that columns for pain tolerance, pain affect, facial activity in response to pain, and physiological responses to pain are not included in the present table, as none of these outcomes were measured for the listed pain tasks. NR = not reported.

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The following studies using experimental mechanical pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript:[46,114,118]

^a Note that this sample conducted sex difference statistics combining both the healthy control group and the clinical sample (mean age is presented for healthy sample only).

^b Hirschfeld et al. 2012 [49] reported on results of a mechanical pain threshold test and wind-up ratio re-testing the same sample of children.

^c Combined abdominal pain/discomfort score.