PAIN® 153 (2012) 602–618

PAIN®

www.elsevier.com/locate/pain

A systematic literature review of 10 years of research on sex/gender and experimental pain perception – Part 1: Are there really differences between women and men?

Mélanie Racine [a,b], Yannick Tousignant-Laflamme [c], Lorie A. Kloda [d], Dominique Dion [e], Gilles Dupuis [a,f], Manon Choinière [b,g,*]

[a] Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada
[b] Centre de recherche, Centre hospitalier de l'Université de Montréal (CRCHUM), Montreal, Quebec, Canada
[c] École de réadaptation, Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Quebec, Canada
[d] Life Sciences Library, McGill University, Montreal, Quebec, Canada
[e] Department of Family Medicine and Emergency, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada
[f] Research Centre, Montreal Heart Institute, Montreal, Quebec, Canada
[g] Department of Anaesthesiology, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 15 February 2011
Received in revised form 15 November 2011
Accepted 22 November 2011

Keywords:
Sex
Gender
Pain sensitivity
Experimental studies
Healthy subjects
Systematic review

ABSTRACT

The purpose of this systematic review was to summarize and critically appraise the results of 10 years of human laboratory research on pain and sex/gender. An electronic search strategy was designed by a medical librarian and conducted in multiple databases. A total of 172 articles published between 1998 and 2008 were retrieved, analyzed, and synthesized. The first set of results (122 articles), which is presented in this paper, examined sex difference in the perception of laboratory-induced thermal, pressure, ischemic, muscle, electrical, chemical, and visceral pain in healthy subjects. This review suggests that females (F) and males (M) have comparable thresholds for cold and ischemic pain, while pressure pain thresholds are lower in F than M. There is strong evidence that F tolerate less thermal (heat, cold) and pressure pain than M but it is not the case for tolerance to ischemic pain, which is comparable in both sexes. The majority of the studies that measured pain intensity and unpleasantness showed no sex difference in many pain modalities. In summary, 10 years of laboratory research have not been successful in producing a clear and consistent pattern of sex differences in human pain sensitivity, even with the use of deep, tonic, long-lasting stimuli, which are known to better mimic clinical pain. Whether laboratory studies in healthy subjects are the best paradigm to investigate sex differences in pain perception is open to question and should be discussed with a view to enhancing the clinical relevance of these experiments and developing new research avenues.

1. Introduction

Various population-based studies suggest that women are more likely to experience a variety of chronic pain syndromes and tend to report more severe pain, at a higher frequency, and in a greater number of body regions, than men [8,16–18,20,48,63,74,124,127,140,167,184]. Nevertheless, women were commonly excluded from preclinical and clinical studies because of their greater biological complexity (ie, reproductive cycle). In 1990, the National Institutes of Health introduced a policy requiring that women be commonly part of medical and behavioural research. This resulted in growing interest from the scientific community and governmental organizations for more comprehensive research to explore sex differences and led to greater funding in the field.

Three important review papers [13,58,185] paved the way for an entire series of studies on sex/gender variations in experimental and clinical pain perception. These authors concluded that women have significantly greater pain sensitivity than men, but they also acknowledged that the observed differences are not always consistent, are relatively minor, and are affected by numerous confounding variables. Using the data reported by Fillingim and Maixner [58], Riley et al. [156] conducted a meta-analysis and concluded

* Corresponding author at: Centre de recherche, Centre hospitalier de l'Université de Montréal (CRCHUM) – Hôtel-Dieu, Masson Pavilion, 3850 St. Urbain Street, Room 8-211, Montreal, Quebec, Canada H2W 1T7. Tel.: +1 514 890 8000x14082; fax: +1 514 412 7027.
E-mail address: manon.choiniere@umontreal.ca (M. Choinière).

0304-3959/$36.00
doi:10.1016/j.pain.2011.11.025

that the lack of sex differences observed in many studies could be attributed to insufficient statistical power. They recommended that 41 subjects per group were necessary to provide adequate power to measure sex differences in heat, pressure, ischemic, and electrical pain threshold and tolerance, assuming a large to moderate effect size.

A tremendous number of laboratory studies on sex differences in human pain perception were published between 1998 and 2008. What have we learned in these 10 years of research? Are there really differences between females (F) and males (M) in experimental pain responsiveness? Do biopsychosocial factors alter pain sensitivity differently in F and M healthy subjects? In the last 15 years, 28 review papers have investigated this issue [4,5,11,13–15,19,35–37,41,51,52,56,58,60,85,93,121,129,136,147,156,157,159,170,186,188]. The selection criteria of the studies included in the above review papers are often not mentioned. Study weaknesses (eg, lack of statistical power) are not always discussed. In other cases, most of the emphasis is put on a single measure of a given outcome that is statistically significant while all the others are not. All these factors may contribute to bias the conclusions of some of these review papers. Finally, very few of them adopted a systematic approach to review the literature [31,46], and they all focused on a single aspect of pain-related sex differences [147,156,157].

The objectives of the present systematic review were 2-fold: (1) to summarize and critically appraise the results of 10 years of research on sex/gender differences in response to experimentally induced pain in healthy humans, employing high-quality methodology; and (2) to synthesize the literature on the role of various biopsychosocial factors that may contribute to sex/gender differences in pain sensitivity. The results of this review are reported in 2 consecutive papers. The present paper (Part 1) is aimed a priori at testing the hypothesis that healthy F have greater pain sensitivity than M. The companion article (Part 2) provides the results of a review on factors that may influence sex-related pain perception.

2. Methods

2.1. Overview of the research systematic review design (Part 1 and Part 2)

This systematic review was conducted according to guidelines from the Centre for Reviews and Dissemination [25] and the PRISMA Statement [29]. A computer-based strategy was designed and conducted with the assistance of an expert medical librarian (L.K.) to retrieve studies published from 1998 to 2008. Databases from across several disciplines were searched to cover the interdisciplinary nature of the topic, including those in biology, medicine, mental health, and nursing. The following databases were searched: MEDLINE, EMBASE, CINAHL, BIOSIS, and PsycINFO. Articles were retrieved with search terms combining sex/gender differences and experimental pain (see sample search strategy in Appendix A). The results were limited to English language and human adults. Searches were conducted separately in each database, and the records exported to citation software, after which duplicates were removed. Additional references were retrieved by snowball searching (scanning the reference lists of all relevant publications). To ensure comprehensive retrieval [101], citation searches were conducted in important earlier review papers on the topic of sex/gender and pain (eg, Fillingim et al. [56]) and in 3 complementary databases using ISI Thomson's Web of Science, Elsevier's Scopus, and Google Scholar. Beginning with the review papers, these databases identify subsequent publications that cite these in their reference lists. Citation searches enable locating potentially relevant studies that may not have been retrieved by traditional subject searching.

All articles that examined sex differences in experimental pain perception in healthy subjects were retrieved even if this was not the primary focus of the study, as long as the words sex, gender, women, men, females, and males were mentioned in the publication title, abstract, or subject headings. Electronic database searches yielded 2510 records. An additional 195 studies were identified through supplemental strategies. After identifying and removing duplicate records, 2218 unique records remained. They were screened by one of the reviewers (M.R.) to remove those that were irrelevant and retrieved incorrectly. At this stage, 239 potential studies remained for eligibility determination and inclusion. Three reviewers (M.R., M.C., Y.T-L.) independently assessed these articles for potential inclusion and excluded 67 of them, leaving a total of 172 articles. Exclusion criteria were the following:

- Studies that focused only on paediatric or elderly populations,
- Studies on nonhealthy subjects, such as patients with chronic pain, unless information was available for a control group of healthy participants,
- Studies on trials of drugs (eg, morphine) or substances (eg, nicotine, caffeine) with the exception of studies investigating the effects of gonadal hormones on pain perception (see companion article published in the next issue of Pain®),
- Studies where subjects were not actively submitted to an experimental pain task (eg, video),
- Review papers, letters to the editor, commentaries, and abstracts, along with nonresearch publications such as editorials and books.

Fig. 1 provides details of the study retrieval, screening, and eligibility process.

2.2. Part 1 of the systematic review: selection and evaluation of included studies

To make the present review as clear and parsimonious as possible and to protect us against type I over type II errors, additional selection criteria were employed and the following methodology was adopted to report the results:

- Nonpharmacological studies that concerned induction or manipulation strategies (eg, relaxation vs stress conditions) before inducing experimental pain were excluded unless data were available from a control group of healthy subjects.
- Studies that examined the role of biopsychosocial variables in sex/gender-related differences in pain responses were included in the present paper if there was no significant interaction effect between the variable under study (eg, anxiety) and sex/gender.
- When more than one instrument was deployed to assess pain intensity or unpleasantness, priority was given in the following order to the visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale (VRS) [91], and McGill Pain Questionnaire (MPQ) [122,123], and only these results were reported.
- When more than one measure of pain intensity or unpleasantness was adopted and inconsistent results were obtained, priority was given in the following order to the mean/total, area under the curve, and peak/maximum, and only these results were reported.
- Whenever multiple body sites were tested or when varying experimental conditions (eg, different temperatures, dosages, or exercise conditions) were employed in a given study for a particular outcome measure (eg, pain threshold), the results were reported accordingly in Tables identified with the letter "a" but were summarized in Tables identified with the letter "b" using an approach where the sex difference had to be present in more than 50% of the observations/conditions to be

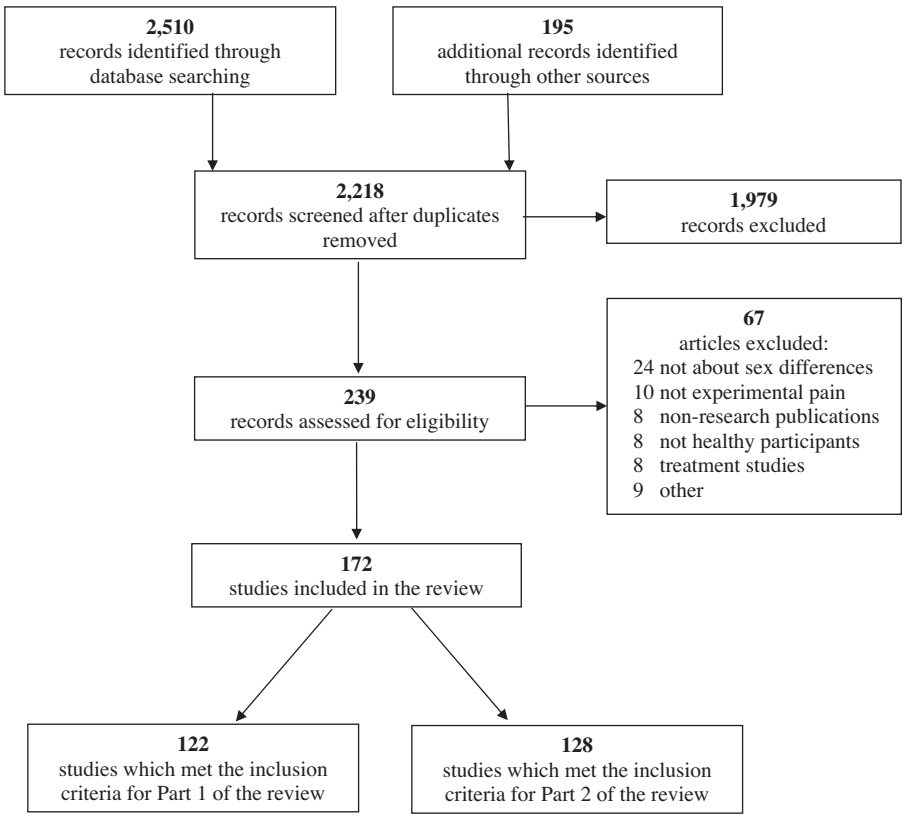

Fig. 1. Flow diagram of the study selection and eligibility process.

reported as such. For example, if the test stimulus in a given pain modality was applied to 3 different body sites to examine sex differences in pain threshold, the difference had to be significant in at least 2 of the 3 sites to be reported in Tables "b" under the modality "pain threshold."

A total of 122 of the 172 articles met the above inclusion criteria, were analyzed, and were summarized. We did not use a meta-analytic methodology for various reasons. First, we felt that a systematic review approach was more appropriate given (1) the nature of the primary objective of our work – that is, to systematically assemble, critically appraise, and synthesize all relevant studies [34], and (2) the broad scope of the topic we wished to cover (multiple pain modalities and various outcome measures). Other reasons we were not able to perform a meta-analysis were related to: (1) the significant heterogeneity of the study methods (eg, different types of stimulus within a given pain modality, sites of application, intensity, duration, etc.), and (2) the lack of sufficient or adequate information to enable calculation of effect sizes (eg, SDs) and other measures required in a meta-analytic methodology, thereby reducing considerably the number of articles otherwise included in the review. Finally, a meta-analysis should ideally start with an unbiased systematic review, as pointed out by Manchikanti et al. [118]. However, the task associated with the systematic review of more than 120 articles divided by pain modalities and outcome measures and the use of techniques to assess heterogeneity and incorporate it into a weighting scheme is of such a magnitude that the addition of multiple meta-analyses on subgroups of studies was not feasible. As a result, the present review, although systematic and comprehensive, remains a narrative one with all the limitations it encompasses, including the absence of exact information about the potential influence of methodological variability on the detection of presence/absence of sex differences.

3. Results

Sex differences in experimental pain perception have been assessed with various types of stimuli that induced cold pain (CP), heat pain (HP), pressure pain (PP), ischemic pain (IP), muscle pain (MP), chemical pain (ChP), electrical pain (EP), and visceral pain (VP). Outcome measures (dependent variables) included pain threshold (PTh), pain tolerance (PTol), pain intensity (PInt), and pain unpleasantness (PUnp). PTh refers to the least experience of pain that can be identified by a subject, while PTol is defined as the highest level of pain that a subject is ready to tolerate [89]. PInt and/or PUnp are assessed with valid and reliable instruments, such as a VAS, NRS, VRS [91,149], and/or MPQ [122,123].

3.1. Cold pain (CP)

A total of 32 studies that examined sex-related differences in CP perception were retrieved. The majority of them used the cold-pressor task, in which the subject was asked to immerse in cold water a part of his/her body (eg, arm) for a period varying generally from 1 minute up to maximum PTol. As shown in Tables 1a and 1b, no clear pattern of sex differences emerged across the various outcome measures except for PTol, where 80% of the studies found that F tolerated significantly less pain than M. The results also showed that there was no difference in PTh between F and M, as reported in 77% of the experiments. A relatively good number of studies also failed to find a significant sex difference in PInt (60%) and PUnp (62%) ratings. The same pattern of results was observed for stimulation of longer duration (5 minutes or more). Harju [75] obtained results in an unexpected direction for PTh and PTol, but it is important to point out that her sample size was very small (8 F and 8 M per site tested). Furthermore, her results reached statistical significance for only one of the tested sites.

Table 1a
Human studies on sex differences in the perception of experimentally induced cold pain.

Author	Year	Sample size			Site	Type of stimulus and duration	PTh	PTol	PInt	PUnp
		Tot	F	M						
Liou et al. [112]	1999	100	50	50	Hand Foot	CT (parameters not mentioned)	F = M (2/2 sites)	–	F = M (2/2 sites)	–
Hentschel [81]	1999	40	24	16	Both hands together	CPT 2 °C Up to 360 s	–	F < M	–	–
Hellström & Lindberg [78]	2000	41	22	19	Hand	CPT 4 °C Up to 420 s	F = M	F < M	F > M	–
Nayak et al. [132]	2000	226	113	113	Hand	CPT 0–2 °C Up to 360 s	–	F < M	F = M	–
Sullivan et al. [177]	2000	80	42	38	Arm	CPT 2–4 °C 60 s	–	–	F > M	–
Zeichner et al. [190]	2000	42	24	18	Foot	CPT 0–4 °C 120 s	–	–	F = M	–
Helfer & McCubbin [77]	2001	55	29	26	Hand	CPT 4 °C Up to 120 s	–	–	F = M	–
Myers et al. [130]	2001	104	50	54	Hand	CPT 1–3 °C Up to 300 s	F < M	F < M	–	–
Raak & Wahren [153]	2001	37	20	17	Hand	CT Down to 5 °C	F = M	–	–	–
al'Absi et al. [3]	2002	65	34	31	Hand	CPT 0–4 °C 90 s	–	–	F > M	–
Harju [75]	2002	48	24	24	Thenar muscle Upper arm Knee Foot	CT 33 °C to 10 °C	F > M for thenar muscle F = M (3/3 sites)	–	F < M for upper arm F = M for knee F > M for foot	–
Manning & Fillingim [119]	2002	24	12	12	Upper forearm	CPT 1 °C Up to PTol	F < M	F < M	–	–
Sanford et al. [163]	2002	144	78	66	Hand	CPT 0–2 °C Up to PTol	–	F < M	F = M	–
al'Absi & Peterson [2]	2003	76	38	38	Hand	CPT 0–4 °C 90 s	–	–	F > M	F = M
Robinson et al. [158]	2003	40	~20	~20	Hand	CPT 2 °C Up to PTol	F = M	F < M	F = M	–
Sarlani et al. [164]	2003	40	20	20	R-L hands	CPT 30 °C, 25 °C, 20 °C, 15 °C, 10 °C Up to 90 s	–	F < M (2/2 sites)	F > M (2/2 sites)	F > M (2/2 sites)
Zimmer et al. [191]	2003	76	37	39	R-L forearms	CPT 5 °C Up to PTol	–	F = M[a] (2/2 sites)	F = M (2/2 sites)	F = M (2/2 sites)

(*continued on next page*)

Table 1a (*continued*)

Author	Year	Sample size			Site	Type of stimulus and duration	PTh	PTol	PInt	PUnp
		Tot	F	M						
Dixon et al. [44]	2004	203	112	91	Both arms together	CPT 0–2 °C Up to 300 s	–	F < M	F > M	F > M
Edwards et al. [45]	2004	57	31	26	Hand	CPT 5 °C Up to 240 s	F < M	F < M	–	–
Essick et al. [49]	2004	34	17	17	8 positionally matched sites on the right and left sides of the face	CT 32 °C to 0 °C Up to PTh	F = M (8/8 sites)	–	–	–
Kim et al. [99]	2004	617	369	248	Hand	CPT 2–4 °C Up to 180 s	–	F < M	F > M	–
Kim et al. [100]	2004	500	306	194	Hand	CPT 2–4 °C Up to 180 s	–	F < M	F > M	–
Jones et al. [94]	2004	80	40	40	Hand	CPT 1 °C Up to 240 s	F = M	F = M	F = M	F = M
Logan & Gedney [113]	2004	100	48	52	Forehead	Ice pack 1 °C 120 s	–	–	F = M	–
Mitchell et al. [125]	2004	26	14	12	Hand	CPT 1 °C, 3 °C, 5 °C, 7 °C Up to 300 s	–	F < M	F = M	F = M
Thorn et al. [180]	2004	219	129	90	Forearm	CPT 0–2 °C Up to 300 s	–	F < M	F > M	F > M
Garofalo et al. [66]	2006	66	44	22	Hand	CPT 1– 4 °C Up to PTol	–	F = M	F = M	–
Keogh et al. [98]	2007	50	27	23	Forearm	CPT 1 °C Up to 120 s	F = M	F < M	F = M	–
Stening et al. [174]	2007	26	16	10	Hand	CPT 1–2 °C Up to 300 s	–	F = M	F = M	F = M
Defrin et al. [42]	2008	25	15	10	Forearm	CT 32 °C up to PTh	F = M	–	–	–
Hirsh et al. [82]	2008	100	66	34	Hand	CPT 1.5 °C–2.5 °C Up to 180 s	F = M	F < M	F = M	–
Tousignant-Laflamme et al. [182]	2008	83	41	42	Arm	CPT 7 °C, 10 °C, 12 °C 120 s	–	–	F > M	–

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; Tot, total; F, female; M, male; CT, contact thermode; CPT, cold-pressor task; L, left; R, right.

[a] The multivariate effect of sex on the pain variables was not statistically significant.

Table 1b
Summary of the results of 32 studies on cold pain.

	Outcomes			
	PTh [a]	PTol	PInt	PUnp
Number of experiments that measured the outcome	13	20	25	8
Expected direction of sex differences	F < M	F < M	F > M	F > M
Proportion of experiments that found sex differences in the expected direction	23%	80%	40%	38%

PTh, pain threshold; PTol, pain tolerance; Pint, pain intensity; PUnp, pain unpleasantness; F, female; M, male.
[a] It should be noted that Harju [75] reported sex differences in the opposite direction for PTh (F > M) at the thenar muscle and PInt (F < M) at the upper arm.

Only 2 studies included a 3-week [113] or a 9-month [66] follow-up measure, and neither of them reported a change over time in the pain responses of F and M.

3.2. Heat pain (HP)

Thirty-four studies that investigated HP to compare pain sensitivity in F and M were reviewed. The vast majority of them used a contact thermode, while others employed a heat lamp, CO_2 laser, or hot water bath (immersion of the upper limb in hot water). As depicted in Tables 2a and 2b, results regarding PTh and PInt did not show a consistently distinctive pattern. Nearly half of the studies revealed that F had significantly higher values than M, while the other half did not observe any difference. Only 5 studies measured PUnp, and 60% of them found that M and F had similar ratings. Interestingly, as with CP, around 80% of HP studies disclosed that F exhibited significantly lower PTol than M. The pattern of results appears to be similar regardless of the duration of noxious stimulation. If we exclude studies that were underpowered according to the criterion of Riley et al. [156], the conclusions regarding PTh and PTol remain the same for this pain modality. As with CP, Garofalo et al. [66] did not find any change in HP responses over time in F and M in their 3-week follow-up session.

3.3. Pressure pain (PP)

A total of 33 studies involving 36 experiments on PP were retrieved from the literature search. Of these, 31 experiments used a pressure algometer, while the other 5 employed Semmes-Weinstein filaments. Testing was carried out on specific tender and non-tender points located at multiple body sites. It is important to mention that the primary purpose of several studies reported in Table 3a was to measure mechanisms, such as descending nociceptive inhibitory control (see companion article), or they were primarily aimed at measuring ChP sensitivity. In these cases, only baseline PP measures are reported. The results in Tables 3a and 3b demonstrate that in a great majority of studies, F reported lower PTol (86%) compared to their M counterparts, but no sex difference emerged in terms of PInt ratings (83%). Only 41% of the studies found a significant sex difference in PTh, but if we consider only the studies (5/34) that had sufficient statistical power ($n \geqslant 41$/group) [156], all of them found that F exhibited lower PTh than M, irrespective of the body sites tested. These data are consistent with those of Chesterton et al. [28], who used a different mode of PP stimulation (14 measures over a period of 60 minutes). Their results also showed that F had significantly lower PTh than M, and there was no interaction between sexes and time. In another study, Hastie et al. [76] conducted a cluster analysis of pain sensitivity in 188 healthy participants who submitted to a series of pain tasks, including PP. Their results revealed 4 distinct clusters, one of which was associated with PP insensitivity. The percentage of F (19%) was significantly lower in this cluster compared to M (81%). It is noteworthy that 4 out of 5 studies that deployed Semmes-Weinstein filaments (as opposed to pressure algometer) failed to discern a significant sex difference in any of the outcome measures. Komiyama and De Laat [104] were the only ones who found that F had lower PTh than M. These authors also reported that F rated their PInt as significantly less severe than M. Finally, only 1 study [104] examined PP sensitivity changes over time. The PTh or PInt results obtained in the 3-week sessions revealed no significant interaction between sexes and time.

3.4. Ischemic pain (IP)

Tables 4a and 4b present the results from 6 studies that induced IP with a tourniquet procedure. All studies that measured PTh, PTol, and PUnp ratings showed comparable results in F and M, while only 1 of 4 studies (25%) reported that F had higher PInt ratings than M. According to Riley et al. [156], most of these studies were sufficiently powered to find significant sex differences on PTh and PTol. Taken together, the data do not support the hypothesis that F had greater sensitivity to IP than M. They are also consistent with the results of cluster analysis conducted by Hastie et al. [76], where there was no significant difference in the percentage of F and M in the IP cluster.

3.5. Muscle pain (MP)

MP was induced experimentally by various types of procedures. Eleven of the 25 retrieved studies used muscle exercise, 6 injected glutamate and 8 hypertonic saline. It should be mentioned that several MP studies also assessed the PP modality in their experimental procedure, but these results are not discussed here (see companion article). As reported in Tables 5a and 5b, only one study measured PTh [33] or PTol [146], and neither of them found a significant difference between sexes. A similar pattern emerged in the 3 studies that assessed PUnp. The PInt results for exercise-induced MP revealed that 7 out of 11 studies (64%) failed to detect a difference between F and M, while 2 observed that F reported greater PInt, and 2 others obtained results in the opposite direction. Dannecker et al. [40] measured residual MP 48 hours later after the exercise session and found lower PInt ratings in F compared to M, while no sex differences were observed for PTh. In a more recent study, Dannecker et al. [39,40] did not replicate their findings regarding PInt whenever the F were evaluated at 24, 48, or 72 hours. The same was true for their PUnp. Karibe et al. [96] used a tooth-clenching exercise to induce MP, and their results showed that the initial PInt sex difference (F > M) did not persist at 1, 6, and 24 hours post-chewing. For glutamate-induced MP, half of the studies (3/6) reported that F had higher PInt than M, while the other half did not. The results regarding MP induced by hypertonic saline injection are more consistent, with 88% of the studies observing no sex-related differences in PInt responses. In summary, no distinctive pattern between F and M emerged on any outcome measures in MP studies.

3.6. Electrical pain (EP)

Tables 6a and 6b display the results of 10 studies that assessed sex differences in EP sensitivity in various body parts after

Table 2a
Human studies on sex differences in the perception of experimentally induced heat pain.

Author	Year	Sample size			Site	Type of stimulus and duration	PTh	PTol	PInt	PUnp
		Tot	F	M						
Fillingim et al. [59]	1998	49	27	22	Volar forearm R-L masseter muscles	CT 38 °C to 50 °C Up to PTol	F < M[a] (1/3 sites)	F < M (3/3 sites)	–	–
Paulson et al. [141]	1998	20	10	10	Volar forearm	CT 50 °C 60 s	–	–	F > M	–
Fillingim et al. [54]	1999	209	117	92	Volar forearm	CT 32 °C to 52 °C Up to PTol	F < M	F < M	–	–
Fillingim et al. [57]	1999	37	19	18	Volar forearm	CT 32 °C to 50 °C Up to PTol	F < M	–	–	–
Liou et al. [112]	1999	100	50	50	Hand Foot	CT 30 °C to 51 °C 1 °C/s	F = M (2/2 sites)	–	F = M (2/2 sites)	–
Sheffield et al. [169]	2000	51	25	26	Volar forearm	CT 45 °C to 49 °C 5 s	–	–	F = M	F = M
Lautenbacher et al. [111]	2001	40	20	20	R-L forearm – proximal part R-L forearm – distal part	CT (parameters not mentioned)	F = M (4/4 sites)	–	–	–
Raak & Wahren [153]	2001	47	25	22	Hand	CT Up to 48 °C	F < M	–	–	–
Rhudy & Meagher [155]	2001	40	20	20	Index finger	Radiant light 8 s	F = M	–	–	–
Derbyshire et al. [43]	2002	21	10	11	Hand	50-W CO_2 laser 90 s	F = M	–	–	–
Harju [75]	2002	48	24	24	Thenar muscle Upper arm Knee Foot	CT 3 °C to 50 °C Up to PTol	F < M[a] (1/4 sites)	F = M (4/4 sites)	F = M[b] (3/3 sites)	–
Lugo et al. [114]	2002	351	228	123	R-L hands	Hot water immersion 48 °C ± 0.5 °C 15 s	–	–	F > M (2/2 sites)	–
Pickering et al. [144]	2002	42	21	21	Thenar hand	CT 37 °C to 52 °C Up to PTol	F < M	F = M	–	–
Wise et al. [189]	2002	148	87	61	Volar forearm	CT 33 °C to 51 °C Up to PTol	F < M	F < M	F = M	F > M
Jones et al. [95]	2003	144	75	69	Forearm – distal part	CT 30 °C to 52 °C	F = M	F < M	F = M	–
Sarlani et al. [164]	2003	40	20	20	R-L hands	Hot water immersion 37 °C, 41 °C, 44 °C, 47 °C 90 s	–	F < M (2/2 sites)	F > M (2/2 sites)	F > M (2/2 sites)
Chung et al. [30]	2004	100	50	50	Not mentioned	CT 36 °C to 49 °C Duration N/A	–	–	F > M	–
Edwards et al. [45]	2004	198	115	83	Volar forearm	CT 32 °C to 52 °C Up to PTol	F < M		F > M	–
Kim et al. [100]	2004	500	306	194	Volar forearm	CT 35 °C, 43° to 49 °C 1 °C/5 s	–	–	F > M	–
Kim et al. [99]	2004	617	369	248	Volar forearm	CT 35 °C,43° to 49 °C 1 °C/5 s	–	–	F > M	–
Essick et al. [49]	2004	34	17	17	8 positionally matched sites on the R-L sides of the face	CT 32 °C to 50 °C Up to PTh	F = M (8/8 sites)	–	–	–
Fillingim & Edwards [53]	2005	110	56	54	Volar forearm	CT 32 °C to 52 °C Up to PTol	F < M	F < M	–	–
Fillingim et al. [55]	2005	167	96	71	Volar forearm	CT 32 °C to 52 °C Up to PTol	F < M	F < M	–	–

Table 2a (*continued*)

Author	Year	Sample size			Site	Type of stimulus and duration	PTh	PTol	PInt	PUnp
		Tot	F	M						
Tousignant-Laflamme et al. [183]	2005	39	20	19	Hand	Hot water immersion 47 °C 160 s	–	–	F = M	F = M
Jensen & Petersen [92]	2006	85	41	44	Volar forearm	CT 32 °C to 52 °C Up to PTh	F = M	–	–	–
					Upper arm	CT 45 °C 60 s	–	–	F = M	–
Kunz et al. [109]	2006	40	20	20	R-L thigh	CT 1 °C above PTh 600 s	F = M (2/2 sites)	–	F = M (2/2 sites)	–
Moulton et al. [128]	2006	28	17	11	Foot	CT 45 °C to 50 °C 16 s	F = M	–	–	–
Chao et al. [26]	2007	70	37	33	Forearm Lateral malleolus	CT 35 °C to 51 °C Terminated after 16 evoked potentials recorded	–	–	F > M (2/2 sites)	–
Quiton & Greenspan [151]	2007	62	30	32	Lower leg	CT 37 °C to 50.5 °C 15 s	F < M (2/2 T°)	–	–	–
Defrin et al. [42]	2008	25	15	10	Forearm	CT 32 °C up to PTh 2 °C/30 s	F < M	–	–	–
Lautenbacher et al. [110]	2008	40	20	20	Hand	Hot water immersion 46 °C 360 s	–	–	F > M	–
Nishino et al. [137]	2008	60	30	30	Volar forearm	CT 40 °C up to PTh 0.25 °C/s	F = M	–	–	–
Quiton & Greenspan [152]	2008	64	32	32	Lower leg	CT 37 °C to 50.5 °C 15 s	F < M (2/2 T°)	–	–	F = M
Tousignant-Laflamme et al. [182]	2008	83	41	42	Volar forearm	CT 32 °C up to PTh 120 s	F = M	–	–	–

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; Tot, total; F, females; M, males; CT, contact thermode; R, right; L, left; N/A, not available.

[a] This result is not included in Table 2b given that the difference was not present in more than 50% of the sites or experimental conditions.

[b] PInt was not measured at the thenar muscle site.

Table 2b
Summary of the results of 34 studies on heat pain.

	Outcomes			
	PTh	PTol	PInt	PUnp
Number of experiments that measured the outcome	24 (9)[a]	9 (5)	17	5
Expected direction of sex differences	F < M	F < M	F > M	F > M
Proportion of experiments that found sex differences in the expected direction	46% (56%)	78% (100%)	53%	40%

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; F, females; M, males.

[a] The number and % of studies with sufficient statistical power to detect sex differences on heat PTh and PTol ($n \geqslant 41$ subjects per group) based on Riley et al.'s [156] meta-analysis appear in parenthesis.

electrical stimulation. Of the 8 studies that measured electrical PTh, half of them observed a significant difference between F and M, while the other half did not. However, it should be noted that none of the studies that failed to find a significant difference had a sufficient number of participants to meet the statistically powered criterion of Riley et al. [156]. The same is true for the 2 studies that examined PTol (F = M). PInt ratings of EP were assessed in 5 studies. Although 2 of them showed that F reported significantly more intense pain in comparison to M, the others did not. Four studies used EP stimulation to elicit the nociceptive flexion reflex (NFR or RIII reflex) in F and M [1,61,131,168]. The NFR is triggered by electrocutaneous stimulation of the sural nerve, giving rise to a withdrawal response from the biceps femoris muscle. The level of stimulation required to elicit the NFR is a measure of spinal nociceptive sensitivity and is viewed as an objective index of PTh in humans [172]. Two of these 4 studies [61,131] discerned that F required significantly lower intensities of electrical stimulation than M to elicit the NFR. al'Absi et al. [1] used the MPQ to measure NFR PInt and found significantly higher ratings in F compared to M subjects. Mylius et al. [131] obtained results in the opposite direction: F reported significantly lower VAS ratings of PInt and PUnp. However, these sex differences disappeared when the PTh values of NFR were controlled statistically. One study [142] used EP to elicit the nociceptive-specific blink reflex (NBR), which is a

Table 3a
Human studies on sex differences in the perception of experimentally induced pressure pain.

Author	Year	Sample size			Site	Type of stimulus and duration	PTh	PTol	PInt
		Tot	F	M					
Isselee et al. [90]	1998	21	9	12	R-L temporalis muscles R-L masseter muscles R-L thumbs	PA	F = M (6/6 sites)	–	–
Koltyn [102]	1999	29	14	15	Forefinger	PA	F < M	–	–
Fredriksson et al. [62]	2000	24	12	12	TMJ Masseter muscle Temporalis muscle Mental protuberance First metacarpal bone Frontal bone	Electronic PA	F < M[a] (2/6 sites)	–	–
Sterling et al. [175]	2000	95	50	45	Median nerve Ulnar nerve Radial nerve	Electronic PA	F < M (3/3 sites)	–	–
Koltyn et al. [103]	2001	31	16	15	Forefinger before maximal isometric exercise Forefinger before submaximal isometric exercise	PA	F < M (2/2 conditions)	–	F = M (2/2 conditions)
Bek et al. [12]	2002	40	20	20	3rd finger Deltoid muscle Thenar muscle Quadriceps muscle	PA	F < M[a] (1/4 sites)	F < M (4/4 sites)	–
Manning & Fillingim [119]	2002	24	12	12	Biceps Pectoralis Rear deltoid Quadriceps	PA	F < M (3/4 sites)	–	–
Pickering et al. [144]	2002	42	21	21	2nd to 5th fingers	Electronic PA	F = M	F < M	–
Sarlani & Greenspan [166]	2002	20	10	10	2nd to 4th fingers	Electronic PA	F = M	–	–
Chesterton et al. [28]	2003	240	120	120	1st dorsal inter-osseous muscle	PA	F < M	–	–
Dannecker et al. [40]	2003	67	35	32	Biceps brachii	PA	F = M	–	–
Nordahl & Kopp [138]	2003	31	21	10	Glabella (forehead) TMJ lateral TMJ posterior	Electronic PA	F < M[a] (1/3 sites)	–	–
Svensson et al. [178]	2003	35	17	18	R-L masseter muscles	PA	F = M (2/2 sites)	–	–
Ge et al. [69]	2004	21	10	11	R-L masseter muscles Posterolateral neck muscles	PA	F < M[a] (1/4 sites)	–	–
Maquet et al. [120]	2004	100	50	50	18 tender points proposed for the diagnosis of FM	PA	F < M (18/18 sites)	F = M (2/2 sites)	F = M (2/2 sites)
Goddard et al. [72]	2004	18	10	8	R-L masseter muscles	PA	–	–	F = M (2/2 sites)
Sarlani et al. [165]	2004	50	25	25	2nd to 4th fingers	Electronic PA	F = M	–	–
Fillingim et al. [55]	2005	167	96	71	Trapezius muscle Masseter muscle Ulna	PA	F < M (3/3 sites)	–	–
Komiyama & De Laat [104]	2005	32	16	16	R-L cheek skin R-L maxilla gingiva Tongue tip Thenar skin	Semmes-Weinstein filaments	F < M[a] (3/6 sites)	–	F < M[a] (3/6 sites)
					R-L masseter muscles Thenar muscle	PA	F < M(3/3 sites)	F < M (3/3 sites)	F = M (3/3 sites)
Ge et al. [70]	2005	28	14	14	R-L trapezius muscles Posterolateral neck muscles	PA	F = M (4/4 sites)	–	–
Nie et al. [133]	2005	24	12	12	Tibialis anterior Tibia periosteum Web of the hand	Electronic PA	F = M (3/3 sites)	–	F = M (3/3 sites)
Nie et al. [135]	2005	24	12	12	11 muscle sites in the neck and shoulder	PA	F = M (11/11 sites)	–	–

Pud et al. [150]	2005	40	17	23	R-L hands	Semmes-Weinstein filaments	–	–	F = M (2/2 sites)
Ge et al. [71]	2006	30	15	15	R-L trapezius muscles Posterolateral neck muscles	PA	F < M (2/4 sites)	–	–
Soetanto et al. [173]	2006	178	89	89	Index finger	Electronic PA	F < M	F < M	F > M
Ayesh et al. [10]	2007	43	19	24	Skin above TMJ R-L TMJs	Semmes-Weinstein filaments	F = M(11/11 sites)	–	–
					Skin above TMJ TMJ	PA	F = M (2/2 sites)	F < M (2/2 sites)	–
Garcia et al. [65]	2007	30	18	12	Mean of 18 tender points proposed for the diagnosis of FM	PA	F < M[a] (1/2 means of the sites)	–	–
					Mean of 6 control points located in hypothenar eminence, tibia and ulna			–	–
Komiyama et al. [106]	2007	44	22	22	Cheek skin Maxillary gingiva Tongue tip Thenar skin	Semmes-Weinstein filaments	F < M(3/4 sites)	–	F < M(3/4 sites)
					Masseter muscles Thenar muscle	PA	F < M(2/2 sites)	F < M(2/2 sites)	F < M[a] (1/2 sites)
Arendt-Nielsen et al. [9]	2008	20	10	10	5 test sites around both knee joints	PA	F < M (10/10 sites)	–	–
Hoeger Bement et al. [84]	2008				Index finger	PA	F < M[a] (1/3 sessions)	–	F > M (3/3 sessions)
Session 1		33	16	17					
Session 2		27	14	13					
Session 3		22	11	11					
Komiyama et al. [105]	2008	36	18	18	R-L anterior maxilla gingivae R-L posterior maxilla gingivae Tongue tip	Semmes-Weinstein filaments	F = M (5/5 sites)	–	F = M (5/5 sites)
Lautenbacher et al. [110]	2008	40	20	20	Ring finger Middle finger Index finger	Electronic PA	F < M (3/3 sites)	–	–
Rosen et al. [162]	2008	30	15	15	Finger Masseter muscle	PA	F = M	–	–

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; Tot, total, F, females; M, males; R, right; L, left; PA, pressure algometer; TMJ, temporomandibular joint; FM, fibromyalgia.
Note: Pain unpleasantness (PUnp) was not measured in any of the studies.

[a] This result is not included in Table 3b, given that the difference was not present in more than 50% of the tested sites or experimental conditions.

Table 3b
Summary of the results of 33 studies on pressure pain.

	Outcomes		
	PTh	PTol	PInt[a]
Number of experiments that measured the outcome	34 (5)[b]	7 (2)	12
Expected direction of sex differences	F < M	F < M	F > M
Proportion of experiments that found sex differences in the expected direction	41% (100%)	86% (50%)	17%

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; F, females; M, males.
[a] It should be noted that Komiyama et al. [106] reported results in the opposite direction for PInt (ie, F < M for 3/4 sites in their experiment with Semmes-Weinstein filaments, and F < M for 1/2 sites for PA).
[b] The number and % of studies with sufficient statistical power to detect sex differences on pressure PTh and PTol (n ⩾ 41 subjects per group) based on Riley et al.'s [156] meta-analysis appear in parentheses.

Table 4a
Human studies on sex differences in the perception of experimentally induced ischemic pain.

Author	Year	Sample size			Site	Type of stimulus and duration	PTh	PTol	PInt	PUnp
		Tot	F	M						
Pinerua-Shuhaibar et al. [145]	1999	32	15	17	Arm	Arm cuff	F = M	F = M	F = M	F = M
Rollnik et al. [160]	2001	80	40	40	Arm	Arm cuff	–	–	F = M	–
Campbell et al. [23]	2004	135	59	76	Arm	Arm cuff	–	–	F > M	F = M
Edwards et al. [45]	2004	198	115	83	Arm	SETT	F = M	F = M	–	–
Fillingim & Edwards [53]	2005	110	56	54	Arm	SETT	F = M	F = M	F = M	F = M
Fillingim et al. [55]	2005	167	96	71	Arm	SETT	F = M	F = M	–	–

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; Tot, total; F, females; M, males; SETT, submaximal effort tourniquet test.

Table 4b
Summary of the results of 6 studies on ischemic pain.

	Outcomes			
	PTh	PTol	PInt	PUnp
Number of experiments which measured the outcome	4 (3)[a]	4 (3)	4	3
Expected direction of sex differences	F < M	F < M	F > M	F > M
Proportion of experiments which found sex differences in the expected direction	0% (0%)	0% (0%)	25%	0%

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; F, females; M, males.
[a] The number and % of studies with sufficient statistical power to detect sex differences on ischemic PTh and PTol (n ⩾ 41 subjects per group) based on Riley et al.'s [156] meta-analysis appear in parentheses.

trigeminofacial brainstem reflex that is triggered by electrical stimulation of the supraorbital nerve. It is a noninvasive and reliable electrophysiological technique to measure the nociceptive transmission state of the trigeminal system in humans [47,97,161]. The authors found that F needed significantly lower electrical stimulation than M to trigger the NBR, but they did not differ in terms of perceived PInt. In summary, the present set of studies does not provide sufficient evidence to conclude that F have greater sensitivity to EP than M. No clear pattern of sex differences emerged with either the NFR or the NBR.

3.7. Chemical pain (ChP)

Topical application or intradermal injection of capsaicin is a well-known human model of ChP. Capsaicin, the main active ingredient of chili pepper, is a chemical irritant that activates the transient receptor potential ion channel vanilloid type 1 and thereby induces pain by stimulating unmyelinated polymodal C-fibre afferents [24,171]. We retrieved a total of 3 studies that used capsaicin to induce ChP. Frot et al. [64] reported that F (n = 10) rated their pain as more intense and unpleasant than M (n = 10) after topical application of this product, but these differences disappeared after removal of the cream. Jensen and Petersen [92] used a heat/capsaicin sensitization model and observed comparable PInt ratings in both sexes (F = 44, M = 41). Gazerani et al. [67] failed to replicate their own findings in 2 experiments (F = 14, M = 14) they conducted with the same intradermal dose of capsaicin: the first experiment revealed a significant sex difference, while the second did not. Lundström et al. [116] used an olfactometer to administer painful chemical intranasal trigeminal stimuli in healthy human subjects and examined sex-related hemispheric differences in event-related potentials (see companion article). When the subjects were asked to rate the intensity of their pain, no significant differences emerged between F (n = 16) and M (n = 12). In summary, there is no clear evidence to support the view that F experience more intense experimental ChP than M.

3.8. Visceral pain (VP)

The clinical literature suggests that a higher proportion of F than M develop chronic VP disorders [86,179]. The reasons for this F predominance are not well understood. However, there is evidence supporting F and M differences in some basic gastrointestinal functions [88]. Only 2 studies [83,143] met the eligibility criteria for inclusion in the present review. Several studies measured visceral or rectal distension, but their stimuli were not described as painful (only unpleasant), so they are not reviewed here. Hobson et al. [83] conducted an investigation into cortical activation after painful oesophagus electrical stimulation on 8 F and 8 M subjects (see also companion article) and did not find a sex difference in terms of PTh or PInt. Pedersen et al. [143] experimentally induced PP, CP, and HP in the lower part of the oesophagus. Their results showed that F (n = 11) and M (n = 11) had similar thermal PTh and PInt ratings. This was also true for pressure PInt.

Table 5a
Human studies on sex differences in the perception of experimentally induced muscle pain.

Author	Year	Sample size			Site	Type of stimulus and duration	PTh	PTol	PInt	PUnp
		Tot	F	M						
Exercise-induced pain										
Cook et al. [33]	1998	52	26	26	Leg	Cycle ergometer-maximal exercise test	F = M	–	F < M	–
Plesh et al. [146]	1998	14	7	7	Jaw	Chewing exercises – MVBF	–	F = M	F = M	–
Poudevigne et al. [148]	2002	42	21	21	Biceps	Eccentric elbow flexor exercise – 3 MVC conditions	–	–	F = M (3/3 conditions)	–
Karibe et al. [96]	2003	36	19	17	Masticatory muscles	Chewing exercises for 6 min	–	–	F > M (after 5 min)	–
Dannecker et al. [40]	2003	67	35	32	Biceps	Eccentric elbow flexor exercise		–	F < M	–
Dannecker et al. [38]	2005	95	47	48	Biceps	Eccentric elbow flexor exercise MVC	–	–	F = M	F = M
Nie et al. [135]	2005	24	12	12	Neck and shoulder muscles	Eccentric shoulder muscle exercise MVC	–	–	F = M	–
Torisu et al. [181]	2006	23	11	12	Jaw	Tooth-clenching exercise-MVBF	–	–	F = M	–
Nie et al. [134]	2007	24	12	12	Shoulder	Eccentric shoulder muscle exercise MVC		–	F = M	–
Dannecker et al. [39] Study 2	2008	55	32	23	Biceps	Eccentric elbow flexor exercise MVC	–	–	F = M	F = M
Hoeger Bement et al. [84] Experiment 2	2008	27	14	13	Biceps	Eccentric elbow flexor exercise – 3 MVC conditions	–	–	F > M (3/3 conditions)	–
Glutamate-induced pain										
Cairns et al. [21]	2001	18	10	8	Masseter muscle	0.2 mL: 0.1 mol/L 0.5 mol/L, 1.0 mol/L	–	–	F > M (3/3 doses)	–
Svensson et al. [178]	2003	35	17	18	Masseter muscle	0.2 mL: 1.0 mol/L	–	–	F > M	–
Cairns et al. [22]	2003	24	13	11	Masseter muscle	0.2 mL: 1.0 mol/L	–	–	F = M	–
Ge et al. [70]	2005	28	14	14	Trapezius muscle	0.4 mL: 2.0 mol/L	–	–	F = M	–
Gazerani et al. [68]	2006	30	15	15	Forehead	0.1 mL: 0.001 mol/L, 0.01 mol/L, 0.1 mol/L	–	–	F > M (3/3 doses)	–
Torisu et al. [181]	2006	23	11	12	Masseter muscle	0.2 mL: 1.0 mol/L	–	–	F = M	–
Hypertonic saline-induced pain										
Stohler et al. [176]	2001	21	9	12	Masseter muscle	Infusion of 5.0% solution up to pain	–	–	F = M	–
Ge et al. [69]	2004	21	11	10	Trapezius muscles	0.5 mL of 5.8%	–	–	F = M	–
Ge et al. [70]	2005	19	9	10	Trapezius muscles	0.5 mL of 5.8%	–	–	F = M	–
van Selms et al. [187]	2005	28	13	15	Masseter muscle	0.1 mL of 6.0%	–	–	F = M	–
Ge et al. [71]	2006	30	15	15	Trapezius muscles	0.5 mL of 5.8%			F = M	F = M
Falla et al. [50]	2008	18	9	9	Trapezius muscle	0.4 mL of 5.8%	–	–	F > M	–
Henderson et al. [79]	2008	22	11	11	Leg	0.5 mL, 0.2 mL of 5.0%	–	–	F = M (2/2 doses)	–
Henriksen et al. [80]	2008	20	10	10	Vastus medialis muscle	1 mL of 5.8%	–	–	F = M	–

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; Tot, total; F, females; M, males; MVBF, maximum voluntary bite force; MVC, maximum voluntary contraction.

Table 5b
Summary of the results of 25 studies on muscle pain.

	Outcomes			
	PTh	PTol	PInt[a]	PUnp
Number of experiments that measured the outcome	1	1	25	3
Expected direction of sex differences	F < M	F < M	F > M	F > M
Proportion of experiments that found sex differences in the expected direction	0%	0%	24%	0%

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; F, females; M, males.
[a] It should be noted that Dannecker et al. [40] and Cook et al. [33] reported results in the opposite direction for PInt (F < M).

4. Discussion

To our knowledge, the present paper is the first to provide a review of the experimental pain literature on sex differences in the perception of various kinds of noxious stimulation in healthy humans, using a systematic and thorough methodology to identify relevant studies and critically examine their results. This review revealed that 10 years of laboratory research have not been successful in producing a clear and consistent pattern of sex differences in human pain sensitivity, even with the use of deep, tonic, long-lasting stimuli that are known to better mimic clinical pain [154,170]. The retrieved studies suggest that F and M have comparable detection threshold for CP and IP, while PP thresholds are lower in F than M. There is strong scientific evidence that F tolerate less pressure and thermal pain (cold and heat) than their M counterparts, but it is not the case for tolerance to IP, which is comparable in both sexes. The majority of the studies that measured PInt and PUnp show no sex differences in many pain modalities. The presence/absence of sex differences in response to experimental pain seems to vary as a function of the pain modalities being tested and the outcome measures being examined, which argues against the concept of greater generalized pain sensitivity in F subjects in a laboratory setting [73,76].

Our observations seem to contradict the main conclusions of previous review papers that women have greater pain responsiveness than men for most pain modalities in the laboratory setting [56,58,126]. One reason that could explain this discrepancy might be the conservative criteria we employed to select studies and

Table 6a
Human studies on sex differences in the perception of experimentally induced electrical pain.

Author	Year	Sample size			Site	PTh	PTol	PInt	PUnp
		Tot	F	M					
Electrical pain stimulation									
Alon et al. [6]	1999	20	11	9	Gastrocnemius muscle	F = M	F = M	–	–
Chapman et al. [27]	1999	20	9	11	Fingertip	–	F = M	F = M	–
Alstergren & Forstrom [7]	2003	40	29	11	Between thumb and index finger	F = M	–	–	–
Komiyama et al. [107]	2005	24	12	12	Skin above mental nerve	F < M	–	F > M	–
Lund et al. [115]	2005	58	29	29	Between thumb and index	F < M	–	–	–
Komiyama et al. [108]	2006	24	12	12	Skin above foramen	F < M	–	F > M	–
Ayesh et al. [10]	2007	43	19	24	Skin above TMJ into TMJ	F = M (2/2 sites)	–	F = M	–
Ogura et al. [139]	2007	129	59	70	Mucosa near nasopalatine nerve Mucosa near greater palatine nerve	F < M (2/2 sites)	–	–	–
Rosen et al. [162]	2008	30	15	15	Maxillary incisor Fingertip	F < M[a] (1/2 sites)	–	–	–
Maffiuletti et al. [117]	2008	40	20	20	Motor threshold of quadriceps femoris muscle Supramotor threshold of quadriceps muscle	–	–	F > M[a] (1/2 tests)	–
Nociceptive flexion reflex									
France & Suchowiecki [61]	1999	83	44	39	Sural nerve	F < M	–	–	–
Serrao et al. [168]	2004	36	20	16	Sural nerve	F = M	–	–	–
al'Absi et al. [1]	2005	137	59	78	Sural nerve	F = M	–	F > M	–
Mylius et al. [131]	2005	40	20	20	Sural nerve	F < M	–	F < M	F < M
Nociceptive specific blink reflex									
Peddireddy [142]	2005	30	15	15	Supraorbital nerve	F < M	–	F = M	–

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; Tot, total; F, females; M, males; TMJ, temporomandibular joint.
[a] This result is not included in Table 6b, given that the difference was not present in more than 50% of the tested sites or experimental conditions.

Table 6b
Summary of the results of 15 studies on electrical pain.

	Outcomes			
	PTh	PTol	PInt[a]	PUnp[a]
Number of experiments that measured the outcome	13[b]	2	8	1
Expected direction of sex differences	F < M	F < M	F > M	F > M
Proportion of experiments that found sex differences in the expected direction	53%	0%	38%	0%

PTh, pain threshold; PTol, pain tolerance; PInt, pain intensity; PUnp, pain unpleasantness; F, females; M, males.
[a] It should be noted that Mylius et al. [131] reported sex differences in the opposite direction for PInt and PUnp (F < M).
[b] Riley et al. [156] did not calculate effect sizes for neurophysiological studies involving nociceptive flexion reflex or nociceptive specific blink reflex. Of the 10 studies that used electrical pain stimulation, only one had sufficient statistical power ($n \geqslant 41$ subjects per group) based on Riley et al.'s [156] meta-analysis, and this study revealed a sex difference on this measure.

analyse their findings while taking their number and weaknesses (eg, statistical power) into account when the results are reported and discussed. Another reason for our divergent conclusions is that we tried to avoid emphasizing a single measure of a given outcome that was statistically significant while all others were not – to reduce bias in the conclusions [32].

In their meta-analysis, Riley et al. [156] argued that the lack of sex differences in laboratory pain responses could be attributed to insufficient statistical power in the majority of studies. Our results regarding PTh and PTol for PP, IP, and EP are consistent with those reported by Riley et al. [156], while our conclusions on HP remain the same, even if we exclude underpowered studies. Additional meta-analyses are needed to estimate the required sample size for other pain modalities.

Like any other review articles, this one has its limitations. A first one is that potentially relevant articles could have been excluded if they reported on sex differences in pain perception but did not include the terms "pain," "sex," "gender," "males," "men," "females," and "women" in their publication title, abstract, or subject headings. However, the present systematic review included more studies than any previously published papers, even if it used explicit criteria for study inclusion and exclusion, often missed from several past narrative reviews. As a result, the present paper provides a comparatively more comprehensive review of the literature, thereby adding a useful informative resource in this field of research. It is noteworthy that our literature search was limited to the English language, leading to a possible bias against publications in other languages, and thereby restraining the generalizability of conclusions to different cultural groups. To try to minimize this effect, we accessed the EMBASE database, which indexes English language publications from Europe and Asia. It is our belief that incorporating EMBASE in our systematic search retrieved numerous studies never before included in reviews of the literature on sex differences in pain, and this should be viewed as a strength.

4.1. Recommendations and directions for future research

Despite the limitations of the present systematic literature review, our results have several important implications. These are summarized in the following recommendations and suggestions for future research in the field.

4.1.1. Laboratory studies on sex-related differences in pain sensitivity should be performed on healthy volunteers of various ages and particularly on participants with painful pathologies

It is well known that the vast majority of laboratory studies in the field are conducted with convenience samples of healthy university students of young age who are far from being representative of the general population. Nevertheless, the most recent studies continue to use this type of sample, and one can wonder why healthy subjects of different age groups, who will also differ

on various sociodemographic variables, are not often included. Understanding sex differences across the lifespan is certainly a relevant and interesting research avenue. Moreover, as stated in the most recent critical review by Fillingim et al. [56], laboratory research regarding sex and pain has had limited clinical impact. Future experimental studies should aim at enhancing clinical relevance and perhaps focus more on populations that suffer from different types of chronic pain, instead of healthy subjects, since it is well known that women are at greater risk of chronic pain. Conducting laboratory investigations in this population could not only help in guiding clinicians for tailoring pain interventions according to sex, but they could also provide a better understanding of the factors/mechanisms that contribute differences in the way women and men experience pain. However, research in this field poses several ethical and methodological challenges. For example, many patients with chronic pain use more than one type of analgesic medication, and it is often ethically difficult, if not impossible, to impose a wash-out period prior to study entry. Wide variations in the origin and duration of the pain, its impact on various aspects of daily living (eg, work, psychological well-being), hormonal status, and presence/absence of comorbidities are only some of the few factors that must be considered in the selection criteria for such types of studies, which often require very large sample sizes along with sophisticated statistical analyses to account for sample heterogeneity.

4.1.2. Primary and secondary outcomes should be defined beforehand

It is not rare to see researchers in this field use multiple pain modalities (CP, HP, IP, PP) with numerous outcomes (PTh, PTol, PInt, and PUnp), which are themselves assessed in different body sites with various tools (VAS, NRS, MPQ) and analyzed with different statistics (eg, PInt mean, total, area under the curve, peak/maximum). We should avoid describing F and M as being different in terms of their pain responsiveness if only 1 or 2 of these measures reach the level of statistical significance. We need to be more cautious with study designs, particularly regarding the choice of the primary and secondary outcomes.

4.1.3. Sample size should be estimated as a function of the primary outcome and an effect size of clinical significance

In their meta-analysis, Riley et al. [156] estimated that 41 subjects per group are necessary to provide adequate power (0.70) to test for sex differences in PTh and/or PTol when using HP, PP, IP, and/or EP modalities (many statisticians could argue that a power value of 0.70 is much too low, and rather recommend a value of at least 0.80 [87]). We retrieved 63 laboratory studies between 1998 and 2008 that had such an experimental design. Only 22% of them met the required sample size. Considering the large inter-individual variability in experimental pain responses [52], sample size must be rigorously calculated by taking into account the primary outcome and expected effect size, which should, of course, be of clinical significance [87]. Accordingly, authors should always report power estimates and the effect size of the main outcome measures.

4.1.4. Standardized and more uniform testing procedures need to be adopted

It is often difficult to draw clear conclusions from a set of studies because of the large heterogeneity in the methods used to assess a given pain modality (eg, different types of stimulus within a given pain modality, sites of application, intensity, duration, etc.). Considering that methodological variability may potentially influence findings about sex differences in pain perception, all efforts should be made to standardize and uniform the testing procedures across research laboratories.

4.2. Conclusion

A plethora of laboratory studies on healthy women and men were conducted between 1998 and 2008 to assess sex-related differences in pain perception, but no consistent conclusion could be drawn. At present, could we state that this field of research is somewhat stagnant? It seems that we are beyond describing and exploring sex differences in pain sensitivity and are late in elucidating the mechanisms that explain these differences in clinical pain states. It is legitimate to question ourselves about the relevance of pursuing this type of studies. Are there other avenues to explore? How can we refine our experimental models to ensure a greater likelihood of translating the findings to the clinic? To optimize the approach and gathering useful information, would it be more relevant to pursue laboratory investigations of sex differences in participants with painful pathologies? Innovative experimental protocols with healthy subjects could still be relevant, but need to take into account the above recommendations with regard to methodological issues. In summary, whether laboratory studies in healthy subjects are the best paradigm to investigate sex differences in pain perception is open to question and should be discussed with a view to enhancing the clinical relevance of these experiments and developing new research avenues.

Conflict of interest statement

The authors report no conflicts of interest.

Acknowledgements

Mélanie Racine was a Canadian Institutes of Health Research (CIHR) Strategic Training Fellow in Pain: Molecules to Community (PM2C). This work was supported by grants from the Foundation of the Montreal Heart Institute and the Foundation of the CRCHUM to Dr. Manon Choinière. The authors thank Miss Maryse Ménard for her help in the preparation of this manuscript and to Mrs. Suzanne Boderleau for having put together the table and prepared the list of references. Thanks are also due to Mr. Ovid M. Da Silva for manuscript review and editing.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2011.11.025.

References

[1] al'Absi M, France CR, Ring C, France J, Harju A, McIntyre D, Wittmers LE. Nociception and baroreceptor stimulation in hypertension-prone men and women. Psychophysiology 2005;42:83–91.
[2] al'Absi M, Petersen KL. Blood pressure but not cortisol mediates stress effects on subsequent pain perception in healthy men and women. Pain 2003;106:285–95.
[3] al'Absi M, Petersen KL, Wittmers LE. Adrenocortical and hemodynamic predictors of pain perception in men and women. Pain 2002;96:197–204.
[4] Aloisi AM. Gonadal hormones and sex differences in pain reactivity. Clin J Pain 2003;19:168–74.
[5] Aloisi AM, Bonifazi M. Sex hormones, central nervous system and pain. Horm Behav 2006;50:1–7.
[6] Alon G, Kantor G, Smith GV. Peripheral nerve excitation and plantar flexion force elicited by electrical stimulation in males and females [including commentary by Snyder-Mackler L with author response]. J Orthop Sports Phys Ther 1999;29:208–17.
[7] Alstergren P, Forstrom J. Acute oral pain intensity and pain threshold assessed by intensity matching to pain induced by electrical stimuli. J Orofac Pain 2003;17:151–9.
[8] Andersson HI, Ejlertsson G, Leden I, Rosenberg C. Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. Clin J Pain 1993;9:174–82.

[9] Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. Pain 2008;140:465–71.
[10] Ayesh EE, Jensen TS, Svensson P. Somatosensory function following painful repetitive electrical stimulation of the human temporomandibular joint and skin. Exp Brain Res 2007;179:415–25.
[11] Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med 2001;16:266–75.
[12] Bek N, Uygur F, Bayar B, Armutlu K. Analysis of age and gender related differences in pressure pain threshold and pressure pain tolerance levels. Pain Clin 2002;14:309–14.
[13] Berkley KJ. Sex differences in pain. Behav Brain Sci 1997;20:371–80.
[14] Berkley KJ, Zalcman SS, Simon VR. Sex and gender differences in pain and inflammation: a rapidly maturing field. Am J Physiol Regul Integr Comp Physiol 2006;291:R241–4.
[15] Bernardes SF, Keogh E, Lima ML. Bridging the gap between pain and gender research: a selective literature review. Eur J Pain 2008;12:427–40.
[16] Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. Pain 2001;89:127–34.
[17] Blyth FM, March LM, Cousins MJ. Chronic pain-related disability and use of analgesia and health services in a Sydney community. Med J Aust 2003;179:84–7.
[18] Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287–333.
[19] Bruehl S, McCubbin JA, Harden RN. Theoretical review: altered pain regulatory systems in chronic pain. Neurosci Biobehav Rev 1999;23: 877–90.
[20] Buskila D, Abramov G, Biton A, Neumann L. The prevalence of pain complaints in a general population in Israel and its implications for utilization of health services. J Rheumatol 2000;27:1521–5.
[21] Cairns BE, Hu JW, Arendt-Nielsen L, Sessle BJ, Svensson P. Sex-related differences in human pain and rat afferent discharge evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2001;86:782–91.
[22] Cairns BE, Wang K, Hu JW, Sessle BJ, Arendt-Nielsen L, Svensson P. The effect of glutamate-evoked masseter muscle pain on the human jaw-stretch reflex differs in men and women. J Orofac Pain 2003;17:317–25.
[23] Campbell TS, Hughes JW, Girdler SS, Maixner W, Sherwood A. Relationship of ethnicity, gender, and ambulatory blood pressure to pain sensitivity: effects of individualized pain rating scales. J Pain 2004;5:183–91.
[24] Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;389:816–24.
[25] Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in healthcare. York, UK: University of York; 2009.
[26] Chao CC, Hsieh ST, Chiu MJ, Tseng MT, Chang YC. Effects of aging on contact heat-evoked potentials: the physiological assessment of thermal perception. Muscle Nerve 2007;36:30–8.
[27] Chapman CR, Oka S, Bradshaw DH, Jacobson RC, Donaldson GW. Phasic pupil dilation response to noxious stimulation in normal volunteers: relationship to brain evoked potentials and pain report. Psychophysiology 1999;36:44–52.
[28] Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101:259–66.
[29] Chou R, Norris S, Carson S, Chan BKS. Drug class review on drugs for neuropathic pain. Portland, OR: Oregon Health & Science University; 2009.
[30] Chung JWY, Wong TKS, Clark CWC. Gender differences in pain responses to calibrated noxious heat stimuli: a sensory decision theory analysis. Pain Clin 2004;16:131–7.
[31] Clarke M. The QUORUM statement. Lancet 2000;355:756–7.
[32] Cochrane Bias Methods Group. Types of Bias. Available from: <http://www.ohri.ca/bmg/types_bias.html> [accessed 04.11.2009].
[33] Cook DB, O'Connor PJ, Oliver SE, Lee Y. Sex differences in naturally occurring leg muscle pain and exertion during maximal cycle ergometry. Int J Neurosci 1998;95:183–202.
[34] Cook DJ, Sackett DL, Spitzer WO. Methodologic guidelines for systematic reviews of randomized control trials in health care from the Potsdam Consultation on Meta-Analysis. J Clin Epidemiol 1995;48:167–71.
[35] Craft RM. Sex differences in drug- and non-drug-induced analgesia. Life Sci 2003;72:2675–88.
[36] Craft RM. Modulation of pain by estrogens. Pain 2007;132:S3–S12.
[37] Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. Eur J Pain 2004;8:397–411.
[38] Dannecker EA, Hausenblas HA, Kaminski TW, Robinson ME. Sex differences in delayed onset muscle pain. Clin J Pain 2005;21:120–6.
[39] Dannecker EA, Knoll V, Robinson ME. Sex differences in muscle pain: self-care behaviors and effects on daily activities. J Pain 2008;9:200–9.
[40] Dannecker EA, Koltyn KF, Riley III JL, Robinson ME. Sex differences in delayed onset muscle soreness. J Sports Med Phys Fitness 2003;43:78–84.
[41] Dao TT, LeResche L. Gender differences in pain. J Orofac Pain 2000;14: 169–84.
[42] Defrin R, Benstein-Sheraizin A, Bezalel A, Mantzur O, Arendt-Nielsen L. The spatial characteristics of the painful thermal grill illusion. Pain 2008;138: 577–86.
[43] Derbyshire SW, Nichols TE, Firestone L, Townsend DW, Jones AK. Gender differences in patterns of cerebral activation during equal experience of painful laser stimulation. J Pain 2002;3:401–11.
[44] Dixon KE, Thorn BE, Ward LC. An evaluation of sex differences in psychological and physiological responses to experimentally-induced pain: a path analytic description. Pain 2004;112:188–96.
[45] Edwards RR, Haythornthwaite JA, Sullivan MJ, Fillingim RB. Catastrophizing as a mediator of sex differences in pain: differential effects for daily pain versus laboratory-induced pain. Pain 2004;111:335–41.
[46] Egger M, Davey Smith DG, Altman DG. Systematic reviews in health care: meta analysis in context. London: BMJ Books; 2001.
[47] Ellrich J. Trigeminal nociceptive reflexes. Mov Disord 2002;17:S41–4.
[48] Eriksen J, Jensen MK, Sjogren P, Ekholm O, Rasmussen NK. Epidemiology of chronic non-malignant pain in Denmark. Pain 2003;106:221–8.
[49] Essick G, Guest S, Martinez E, Chen C, McGlone F. Site-dependent and subject-related variations in perioral thermal sensitivity. Somatosens Mot Res 2004;21:159–75.
[50] Falla D, Arendt-Nielsen L, Farina D. Gender-specific adaptations of upper trapezius muscle activity to acute nociceptive stimulation. Pain 2008;138:217–25.
[51] Fillingim RB. Sex, gender, and pain: women and men really are different. Curr Rev Pain 2000;4:24–30.
[52] Fillingim RB. Individual differences in pain responses. Curr Rheumatol Rep 2005;7:342–7.
[53] Fillingim RB, Edwards RR. Is self-reported childhood abuse history associated with pain perception among healthy young women and men? Clin J Pain 2005;21:387–97.
[54] Fillingim RB, Edwards RR, Powell T. The relationship of sex and clinical pain to experimental pain responses. Pain 1999;83:419–25.
[55] Fillingim RB, Kaplan L, Staud R, Ness TJ, Glover TL, Campbell CM, Mogil JS, Wallace MR. The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. J Pain 2005;6:159–67.
[56] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley III JL. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10:447–85.
[57] Fillingim RB, Maddux V, Shackelford JA. Sex differences in heat pain thresholds as a function of assessment method and rate of rise. Somatosens Mot Res 1999;16:57–62.
[58] Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. Pain Forum 1995;4:209–21.
[59] Fillingim RB, Maixner W, Kincaid S, Silva S. Sex differences in temporal summation but not sensory-discriminative processing of thermal pain. Pain 1998;75:121–7.
[60] Fillingim RB, Ness TJ. Sex-related hormonal influences on pain and analgesic responses. Neurosci Biobehav Rev 2000;24:485–501.
[61] France CR, Suchowiecki S. A comparison of diffuse noxious inhibitory controls in men and women. Pain 1999;81:77–84.
[62] Fredriksson L, Alstergren P, Kopp S. Absolute and relative facial pressure-pain thresholds in healthy individuals. J Orofac Pain 2000;14:98–104.
[63] Fricker J. Pain in Europe. Cambridge, UK: Mundipharma International Ltd.; 2003. p. 1–23. Available from: <www.painineurope.com> [accessed 01.04.2009].
[64] Frot M, Feine JS, Bushnell MC. Sex differences in pain perception and anxiety. A psychophysical study with topical capsaicin. Pain 2004;108:230–6.
[65] Garcia E, Godoy-Izquierdo D, Godoy JF, Perez M, Lopez-Chicheri I. Gender differences in pressure pain threshold in a repeated measures assessment. Psychol Health Med 2007;12:567–79.
[66] Garofalo JP, Lawler C, Robinson R, Morgan M, Kenworthy-Heinige T. The role of mood states underlying sex differences in the perception and tolerance of pain. Pain Pract 2006;6:186–96.
[67] Gazerani P, Andersen OK, Arendt-Nielsen L. Site-specific, dose-dependent, and sex-related responses to the experimental pain model induced by intradermal injection of capsaicin to the foreheads and forearms of healthy humans. J Orofac Pain 2007;21:289–302.
[68] Gazerani P, Wang K, Cairns BE, Svensson P, Arendt-Nielsen L. Effects of subcutaneous administration of glutamate on pain, sensitization and vasomotor responses in healthy men and women. Pain 2006;124:338–48.
[69] Ge HY, Madeleine P, Arendt-Nielsen L. Sex differences in temporal characteristics of descending inhibitory control: an evaluation using repeated bilateral experimental induction of muscle pain. Pain 2004;110:72–8.
[70] Ge HY, Madeleine P, Arendt-Nielsen L. Gender differences in pain modulation evoked by repeated injections of glutamate into the human trapezius muscle. Pain 2005;113:134–40.
[71] Ge HY, Madeleine P, Cairns BE, Arendt-Nielsen L. Hypoalgesia in the referred pain areas after bilateral injections of hypertonic saline into the trapezius muscles of men and women: a potential experimental model of gender-specific differences. Clin J Pain 2006;22:37–44.
[72] Goddard G, Karibe H, McNeill C. Reproducibility of visual analog scale (VAS) pain scores to mechanical pressure. Cranio 2004;22:250–6.
[73] Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, Gold MS, Holdcroft A, Lautenbacher S, Mayer EA, Mogil JS, Murphy AZ, Traub RJ. Studying sex and gender differences in pain and analgesia: a consensus report. Pain 2007;132:S26–45.
[74] Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. JAMA 1998;280:147–51.
[75] Harju EL. Cold and warmth perception mapped for age, gender, and body area. Somatosens Mot Res 2002;19:61–75.

[76] Hastie BA, Riley III JL, Robinson ME, Glover T, Campbell CM, Staud R, Fillingim RB. Cluster analysis of multiple experimental pain modalities. Pain 2005;116:227–37.
[77] Helfer SG, McCubbin JA. Does gender affect the relation between blood pressure and pain sensitivity? Int J Behav Med 2001;8:220–9.
[78] Hellström B, Lundberg U. Pain perception to the cold presser test during the menstrual cycle in relation to estrogen levels and a comparison with men. Integr Physiol Behav Sci 2000;35:132–41.
[79] Henderson LA, Gandevia SC, Macefield VG. Gender differences in brain activity evoked by muscle and cutaneous pain: a retrospective study of single-trial fMRI data. Neuroimage 2008;39:1867–76.
[80] Henriksen M, Christensen R, Alkjaer T, Lund H, Simonsen EB, Bliddal H. Influence of pain and gender on impact loading during walking: a randomised trial. Clin Biomech 2008;23:221–30.
[81] Hentschel U. Emotional stability and facial activity as predictors for pain tolerance. Percept Motor Skills 1999;89:783–90.
[82] Hirsh AT, George SZ, Bialosky JE, Robinson ME. Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. J Pain 2008;9:806–12.
[83] Hobson AR, Furlong PL, Worthen SF, Hillebrand A, Barnes GR, Singh KD, Aziz Q. Real-time imaging of human cortical activity evoked by painful esophageal stimulation. Gastroenterology 2005;128:610–9.
[84] Hoeger Bement MK, Dicapo J, Rasiarmos R, Hunter SK. Dose response of isometric contractions on pain perception in healthy adults. Med Sci Sports Exerc 2008;40:1880–9.
[85] Holdcroft A. Integrating the dimensions of sex and gender into basic life sciences research: methodologic and ethical issues. Gend Med 2007;4:S64–74.
[86] Holdcroft A, Berkley KJ. Sex and gender differences in pain and its relief. In: McMahon SB, Koltzenburg M, editors. Wall and Melzack's textbook of pain. London, UK: Elsevier Churchill Livingstone; 2006. p. 1181–97.
[87] Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research. Philadelphia: Lippincott Williams & Wilkins; 2007.
[88] Hutson WR, Roehrkasse RL, Wald A. Influence of gender and menopause on gastric emptying and motility. Gastroenterology 1989;96:11–7.
[89] International Association for the Study of Pain. IASP pain terminology. Available from: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Defi...isplay.cfm&ContentID=1728 2010 [accessed 15.09.2010].
[90] Isselee H, De Laat A, Bogaerts K, Lysens R. Short-term reproducibility of pressure pain thresholds in masticatory muscles measured with a new algometer. J Orofac Pain 1998;12:203–9.
[91] Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk CL, Melack R, editors. Handbook of pain assessment. New York: The Guilford Press; 2001. p. 15–34.
[92] Jensen MT, Petersen KL. Gender differences in pain and secondary hyperalgesia after heat/capsaicin sensitization in healthy volunteers. J Pain 2006;7:211–7.
[93] Jones A, Zachariae R. Gender, anxiety, and experimental pain sensitivity: an overview. J Am Med Womens Assoc 2002;57:91–4.
[94] Jones A, Zachariae R. Investigation of the interactive effects of gender and psychological factors on pain response. Br J Health Psychol 2004;9:405–18.
[95] Jones A, Zachariae R, Arendt-Nielsen L. Dispositional anxiety and the experience of pain: gender-specific effects. Eur J Pain 2003;7:387–95.
[96] Karibe H, Goddard G, Gear RW. Sex differences in masticatory muscle pain after chewing. J Dent Res 2003;82:112–6.
[97] Katsarava Z, Ellrich J, Diener HC, Kaube H. Optimized stimulation and recording parameters of human 'nociception specific' blink reflex recordings. Clin Neurophysiol 2002;113:1932–6.
[98] Keogh E, Mounce C, Brosnan M. Can a sexually dimorphic index of prenatal hormonal exposure be used to examine cold pressor pain perception in men and women? Eur J Pain 2007;11:231–6.
[99] Kim H, Neubert JK, Rowan JS, Brahim JS, Iadarola MJ, Dionne RA. Comparison of experimental and acute clinical pain responses in humans as pain phenotypes. J Pain 2004;5:377–84.
[100] Kim H, Neubert JK, San Miguel A, Xu K, Krishnaraju RK, Iadarola MJ, Goldman D, Dionne RA. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain 2004;109:488–96.
[101] Kloda LA. Use Google Scholar, Scopus and Web of Science for comprehensive citation tracking. Evid Based Libr Inf Pract 2007;2:87–90.
[102] Koltyn KF, Focht BC, Ancker JM, Pasley J. Experimentally induced pain perception in men and women in the morning and evening. Int J Neurosci 1999;98:1–11.
[103] Koltyn KF, Trine MR, Stegner AJ, Tobar DA. Effect of isometric exercise on pain perception and blood pressure in men and women. Med Sci Sports Exerc 2001;33:282–90.
[104] Komiyama O, De Laat A. Tactile and pain thresholds in the intra- and extra-oral regions of symptom-free subjects. Pain 2005;115:308–15.
[105] Komiyama O, Gracely RH, Kawara M, Laat AD. Intraoral measurement of tactile and filament-prick pain threshold using shortened Semmes-Weinstein monofilaments. Clin J Pain 2008;24:16–21.
[106] Komiyama O, Kawara M, De Laat A. Ethnic differences regarding tactile and pain thresholds in the trigeminal region. J Pain 2007;8:363–9.
[107] Komiyama O, Wang K, Svensson P, Arendt-Nielsen L, De Laat A. Gender difference in masseteric exteroceptive suppression period and pain perception. Clin Neurophysiol 2005;116:2599–605.
[108] Komiyama O, Wang K, Svensson P, Arendt-Nielsen L, De Laat A. Reproducibility of the masseteric exteroceptive suppression period using stimulus-response curves. J Oral Rehabil 2006;33:741–8.
[109] Kunz M, Gruber A, Lautenbacher S. Sex differences in facial encoding of pain. J Pain 2006;7:915–28.
[110] Lautenbacher S, Kunz M, Burkhardt S. The effects of DNIC-type inhibition on temporal summation compared to single pulse processing: does sex matter? Pain 2008;140:429–35.
[111] Lautenbacher S, Nielsen J, Andersen T, Arendt-Nielsen L. Spatial summation of heat pain in males and females. Somatosens Mot Res 2001;18:101–5.
[112] Liou JT, Lui PW, Lo YL, Liou L, Wang SS, Yuan HB, Chan KH, Lee TY. Normative data of quantitative thermal and vibratory thresholds in normal subjects in Taiwan: gender and age effect. Zhonghua Yi Xue Za Zhi (Taipei) 1999;62:431–7.
[113] Logan HL, Gedney JJ. Sex differences in the long-term stability of forehead cold pressor pain. J Pain 2004;5:406–12.
[114] Lugo M, Isturiz G, Lara C, Garcia N, Eblen-Zaijur A. Sensory lateralization in pain subjective perception for noxious heat stimulus. Somatosens Mot Res 2002;19:207–12.
[115] Lund I, Lundeberg T, Kowalski J, Svensson E. Gender differences in electrical pain threshold responses to transcutaneous electrical nerve stimulation (TENS). Neurosci Lett 2005;375:75–80.
[116] Lundström JN, Frasnelli J, Larsson M, Hummel T. Sex differentiated responses to intranasal trigeminal stimuli. Int J Psychophysiol 2005;57:181–6.
[117] Maffiuletti NA, Herrero AJ, Jubeau M, Impellizzeri FM, Bizzini M. Differences in electrical stimulation thresholds between men and women. Ann Neurol 2008;63:507–12.
[118] Manchikanti L, Benyamin RM, Helm S, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: part 3: systematic reviews and meta-analyses of randomized trials. Pain Physician 2009;12:35–72.
[119] Manning EL, Fillingim RB. The influence of athletic status and gender on experimental pain responses. J Pain 2002;3:421–8.
[120] Maquet D, Croisier JL, Demoulin C, Crielaard JM. Pressure pain thresholds of tender point sites in patients with fibromyalgia and in healthy controls. Eur J Pain 2004;8:111–7.
[121] Meana M. The meeting of pain and depression: comorbidity in women. Can J Psychiatry 1998;43:893–9.
[122] Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–99.
[123] Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–7.
[124] Millar WJ. La douleur chronique. Rapports sur la santé - Statistiques Canada – 82-003 1996;7:51–8.
[125] Mitchell LA, MacDonald RAR, Brodie EE. Temperature and the cold pressor test. J Pain 2004;5:233–7.
[126] Mogil JS. Sex, gender and pain. In: Cervero F, Jensen TS, editors. Pain: handbook of clinical neurology, vol. 81. Edinburgh: Elsevier; 2006. p. 325–41.
[127] Moulin DE, Clark AJ, Speechley M, Morley-Forster PK. Chronic pain in Canada—prevalence, treatment, impact and the role of opioid analgesia. Pain Res Manag 2002;7:179–84.
[128] Moulton EA, Keaser ML, Gullapalli RP, Maitra R, Greenspan JD. Sex differences in the cerebral BOLD signal response to painful heat stimuli. Am J Physiol Regul Integr Comp Physiol 2006;291:R257–67.
[129] Myers CD, Riley III JL, Robinson ME. Psychosocial contributions to sex-correlated differences in pain. Clin J Pain 2003;19:225–32.
[130] Myers CD, Robinson ME, Riley III JL, Sheffield D. Sex, gender, and blood pressure: contributions to experimental pain report. Psychosom Med 2001;63:545–50.
[131] Mylius V, Kunz M, Schepelmann K, Lautenbacher S. Sex differences in nociceptive withdrawal reflex and pain perception. Somatosens Mot Res 2005;22:207–11.
[132] Nayak S, Shiflette SC, Esheu S, Levine FM. Culture and gender effects in pain beliefs and the prediction of pain tolerance. Cross Cult Res 2000;34:135–51.
[133] Nie H, Arendt-Nielsen L, Andersen H, Graven-Nielsen T. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. J Pain 2005;6:348–55.
[134] Nie H, Arendt-Nielsen L, Kawczynski A, Madeleine P. Gender effects on trapezius surface EMG during delayed onset muscle soreness due to eccentric shoulder exercise. J Electromyogr Kinesiol 2007;17:401–9.
[135] Nie H, Kawczynski A, Madeleine P, Arendt-Nielsen L. Delayed onset muscle soreness in neck/shoulder muscles. Eur J Pain 2005;9:653–60.
[136] Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: measurement, causation, and consequences. J Pain 2009;10:231–7.
[137] Nishino T, Isono S, Ishikawa T, Shinozuka N. Sex differences in the effect of dyspnea on thermal pain threshold in young healthy subjects. Anesthesiology 2008;109:1100–6.
[138] Nordahl S, Kopp S. Pressure pain threshold of the posterior aspect of the temporomandibular joint measured with a semi-spherical probe. J Orofac Pain 2003;17:145–50.
[139] Ogura K, Kimoto S, Yamaguchi H, Kobayashi K. Perception thresholds for electrical stimulation of the palatal mucosa. Int J Prosthodont 2007;20:423–31.
[140] Ohayon MM. Relationship between chronic painful physical condition and insomnia. J Psychiatr Res 2005;39:151–9.
[141] Paulson PE, Minoshima S, Morrow TJ, Casey KL. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. Pain 1998;76:223–9.

[142] Peddireddy A, Wang K, Svensson P, Arendt-Nielsen L. Effect of experimental posterior temporalis muscle pain on human brainstem reflexes. Clin Neurophysiol 2005;116:1611–20.
[143] Pedersen J, Reddy H, Funch-Jensen P, Arendt-Nielsen L, Gregersen H, Drewes AM. Differences between male and female responses to painful thermal and mechanical stimulation of the human esophagus. Dig Dis Sci 2004;49:1065–74.
[144] Pickering G, Jourdan D, Eschalier A, Dubray C. Impact of age, gender and cognitive functioning on pain perception. Gerontology 2002;48:112–8.
[145] Pinerua-Shuhaibar L, Prieto-Rincon D, Ferrer A, Bonilla E, Maixner W, Suarez-Roca H. Reduced tolerance and cardiovascular response to ischemic pain in minor depression. J Affect Disord 1999;56:119–26.
[146] Plesh O, Curtis DA, Hall LJ, Miller A. Gender difference in jaw pain induced by clenching. J Oral Rehabil 1998;25:258–63.
[147] Popescu A, LeResche L, Truelove EL, Drangsholt MT. Gender differences in pain modulation by diffuse noxious inhibitory controls: a systematic review. Pain 2010;150:309–18.
[148] Poudevigne MS, O'Connor PJ, Pasley JD. Lack of both sex differences and influence of resting blood pressure on muscle pain intensity. Clin J Pain 2002;18:386–93.
[149] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17:45–56.
[150] Pud D, Sprecher E, Yarnitsky D. Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. Neurosci Lett 2005;380:209–13.
[151] Quiton RL, Greenspan JD. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. Pain 2007;132:S134–49.
[152] Quiton RL, Greenspan JD. Across- and within-session variability of ratings of painful contact heat stimuli. Pain 2008;137:245–56.
[153] Raak R, Wahren LK. Stress coping strategies in thermal pain sensitive and insensitive healthy subjects. Int J Nurs Pract 2001;7:162–8.
[154] Rainville P, Feine JS, Bushnell MC, Duncan GH. A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. Somatosens Mot Res 1992;9:265–77.
[155] Rhudy JL, Meagher MW. Noise stress and human pain thresholds: divergent effects in men and women. J Pain 2001;2:57–64.
[156] Riley III JL, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998;74:181–7.
[157] Riley III JL, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. Pain 1999;81:225–35.
[158] Robinson ME, Gagnon CM, Riley III JL, Price DD. Altering gender role expectations: effects on pain tolerance, pain threshold, and pain ratings. J Pain 2003;4:284–8.
[159] Rollman GB, Abdel-Shaheed J, Gillespie JM, Jones KS. Does past pain influence current pain: biological and psychosocial models of sex differences. Eur J Pain 2004;8:427–33.
[160] Rollnik JD, Schneider U, Siggelkow S, Schmitz N, Kugler J. Gender differences in cardiovascular responses to sphygmomanometric measurements. J Psychophysiol 2001;15:43–6.
[161] Romaniello A, Valls-Sole J, Iannetti GD, Truini A, Manfredi M, Cruccu G. Nociceptive quality of the laser-evoked blink reflex in humans. J Neurophysiol 2002;87:1386–94.
[162] Rosen A, Feldreich A, Dabirian N, Ernberg M. Effect of heterotopic noxious conditioning stimulation on electrical and pressure pain thresholds in two different anatomical regions. Acta Odontol Scand 2008;66:181–8.
[163] Sanford SD, Kersh BC, Thorn BE, Rich MA, Ward LC. Psychosocial mediators of sex differences in pain responsivity. J Pain 2002;3:58–64.
[164] Sarlani E, Farooq N, Greenspan JD. Gender and laterality differences in thermosensation throughout the perceptible range. Pain 2003;106:9–18.
[165] Sarlani E, Grace EG, Reynolds MA, Greenspan JD. Sex differences in temporal summation of pain and after sensations following repetitive noxious mechanical stimulation. Pain 2004;109:115–23.
[166] Sarlani E, Greenspan JD. Gender differences in temporal summation of mechanically evoked pain. Pain 2002;97:163–9.
[167] Schopflocher D, Borowski H, Harstall C, Juzwishin D, Ospina M, Taenzer P. Chronic pain in Alberta: a portrait from the 1996 National Population Health Survey and the 2001 Canadian Community Health Survey. Edmonton, Alberta. Edmonton, Alberta, Canada: Health Surveillance, Alberta Health; 2003. p. 1–26.
[168] Serrao M, Rossi P, Sandrini G, Parisi L, Amabile GA, Nappi G, Pierelli F. Effects of diffuse noxious inhibitory controls on temporal summation of the RIII reflex in humans. Pain 2004;112:353–60.
[169] Sheffield D, Biles PL, Orom H, Maixner W, Sheps DS. Race and sex differences in cutaneous pain perception. Psychosom Med 2000;62:517–23.
[170] Sherman JJ, LeResche L. Does experimental pain response vary across the menstrual cycle? A methodological review. Am J Physiol Regul Integr Comp Physiol 2006;291:R245–56.
[171] Simone DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. Pain 1989;38:99–107.
[172] Skljarevski V, Ramadan NM. The nociceptive flexion reflex in humans—review article. Pain 2002;96:3–8.
[173] Soetanto AL, Chung JW, Wong TK. Are there gender differences in pain perception? J Neurosci Nurs 2006;38:172–6.
[174] Stening K, Eriksson O, Wahren L, Berg G, Hammar M, Blomqvist A. Pain sensations to the cold pressor test in normally menstruating women: comparison with men and relation to menstrual phase and serum sex steroid levels. Am J Physiol Regul Integr Comp Physiol 2007;293:R1711–6.
[175] Sterling M, Treleaven J, Edwards S, Jull G. Pressure pain thresholds of upper limb peripheral nerve trunks in asymptomatic subjects. Physiother Res Int 2000;5:220–9.
[176] Stohler CS, Kowalski CJ, Lund JP. Muscle pain inhibits cutaneous touch perception. Pain 2001;92:327–33.
[177] Sullivan MJ, Tripp DA, Darcy S. Gender differences in pain and pain behavior: the role of catastrophizing. Cogn Ther Res 2000;24:121–34.
[178] Svensson P, Cairns BE, Wang K, Hu JW, Graven-Nielsen T, Arendt-Nielsen L, Sessle BJ. Glutamate-evoked pain and mechanical allodynia in the human masseter muscle. Pain 2003;101:221–7.
[179] Ter RB. Gender differences in gastroesophageal reflux disease. J Gend Specific Med 2000;3:42–4.
[180] Thorn BE, Clements KL, Ward LC, Dixon KE, Kersh BC, Boothby JL, Chaplin WF. Personality factors in the explanation of sex differences in pain catastrophizing and response to experimental pain. Clin J Pain 2004;20:275–82.
[181] Torisu T, Wang K, Svensson P, De Laat A, Fujii H, Arendt-Nielsen L. Effects of muscle fatigue induced by low-level clenching on experimental muscle pain and resting jaw muscle activity: gender differences. Exp Brain Res 2006;174:566–74.
[182] Tousignant-Laflamme Y, Page S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res 2008;1230:73–9.
[183] Tousignant-Laflamme Y, Rainville P, Marchand S. Establishing a link between heart rate and pain in healthy subjects: a gender effect. J Pain 2005;6:341–7.
[184] Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demytteneare K, de Girolomo G, de Graaf R, Gureje O, Lepine JP, Haro JM, Levinson D, Oakley Browne MA, Posada-Villa J, Seedat S, Watanabe M. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain 2008;9:883–91.
[185] Unruh AM. Gender variations in clinical pain experience. Pain 1996;65:123–67.
[186] Vallerand AH, Polomano RC. The relationship of gender to pain. Pain Manag Nurs 2000;1:8–15.
[187] van Selms MK, Wang K, Lobbezoo F, Svensson P, Arendt-Nielsen L, Naeije M. Effects of masticatory muscle fatigue without and with experimental pain on jaw-stretch reflexes in healthy men and women. Clin Neurophysiol 2005;116:1415–23.
[188] Wiesenfeld-Hallin Z. Sex differences in pain perception. Gend Med 2005;2:137–45.
[189] Wise EA, Price DD, Myers CD, Heft MW, Robinson ME. Gender role expectations of pain: relationship to experimental pain perception. Pain 2002;96:335–42.
[190] Zeichner A, Loftin M, Panopoulos G, Widner S, Allen J. Sex differences in pain indices, exercise, and use of analgesics. Psychol Rep 2000;86:129–33.
[191] Zimmer C, Basler HD, Vedder H, Lautenbacher S. Sex differences in cortisol response to noxious stress. Clin J Pain 2003;19:233–9.