Systematic Review and Meta-Analysis

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Sex differences in pain expressed by patients across diverse disease states: individual patient data meta-analysis of 33,957 participants in 10 randomized controlled trials

Jessica X.L. Li[a], Xia Wang[b], Amanda Henry[b,c], Craig S. Anderson[b,d,e], Naomi Hammond[a,b,f], Katie Harris[b], Hueiming Liu[b,g], Kelly Loffler[h], John Myburgh[a,b,i], Jeyaraj Pandian[j], Brendan Smyth[b,k,l], Balasubramanian Venkatesh[a,b], Cheryl Carcel[b,g,*], Mark Woodward[b,m]

Abstract

The experience of pain is determined by many factors and has a significant impact on quality of life. This study aimed to determine sex differences in pain prevalence and intensity reported by participants with diverse disease states in several large international clinical trials. Individual participant data meta-analysis was conducted using EuroQol-5 Dimension (EQ-5D) questionnaire pain data from randomised controlled trials published between January 2000 and January 2020 and undertaken by investigators at the George Institute for Global Health. Proportional odds logistic regression models, comparing pain scores between females and males and fitted with adjustments for age and randomized treatment, were pooled in a random-effects meta-analysis. In 10 trials involving 33,957 participants (38% females) with EQ-5D pain score data, the mean age ranged between 50 and 74. Pain was reported more frequently by females than males (47% vs 37%; $P < 0.001$). Females also reported greater levels of pain than males (adjusted odds ratio 1.41, 95% CI 1.24-1.61; $P < 0.001$). In stratified analyses, there were differences in pain by disease group (P for heterogeneity <0.001), but not by age group or region of recruitment. Females were more likely to report pain, and at a higher level, compared with males across diverse diseases, all ages, and geographical regions. This study reinforces the importance of reporting sex-disaggregated analysis to identify similarities and differences between females and males that reflect variable biology and may affect disease profiles and have implications for management.

Keywords: Sex differences, Pain, Meta-analysis

1. Introduction

Although pain can be a useful response when it deters further injury and protects injured tissue during healing, progression to chronic pain may reflect abnormal functioning of the nervous system.[27] Chronic pain is associated with a number of factors, including older age, female sex, lower socioeconomic status, and various comorbidities.[49] It can diminish function and overall quality of life by altering mood, disturbing sleep, and impairing sexual function.[23]

Females are particularly overrepresented in specific pain conditions, such as low back pain,[48] fibromyalgia,[17] osteoarthritis,[25] temporomandibular joint dysfunction, migraine, and irritable bowel syndrome.[22] Moreover, the literature pertaining to biological pathways,[51,59,64] psychosocial influences,[29,38,63] and behavioral factors[41,68] is highly suggestive of sex differences in underlying pain mechanisms. This supports a basis for a sex difference in pain across many diseases, but the presence and magnitude of these differences in noncommunicable diseases are not known. Knowledge of the presence and magnitude of sex differences in

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[a] *University of New South Wales, Sydney, Australia,* [b] *The George Institute for Global Health, University of New South Wales, Sydney, Australia,* [c] *Discipline of Women's Health, School of Clinical Medicine, University of New South Wales, Sydney, Australia,* [d] *The George Institute China at Peking University Health Sciences Centre, Beijing, P.R. China,* [e] *Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, Australia,* [f] *Malcolm Fisher Department of Intensive Care, Royal North Shore Hospital, Sydney, Australia,* [g] *Sydney School of Public Health, Sydney Medical School, The University of Sydney, Sydney, Australia,* [h] *Adelaide Institute for Sleep Health, Flinders Health and Medical Research, Flinders University, Bedford Park, Australia,* [i] *Department of Intensive Care Medicine, St George Hospital, Sydney, Australia,* [j] *Department of Neurology, Christian Medical College, Ludhiana, India,* [k] *Department of Renal Medicine, St George Hospital, Kogarah, Australia,* [l] *National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Camperdown, Australia,* [m] *School of Public Health, Imperial College London, The George Institute for Global Health, London, United Kingdom*

**Corresponding author. Address: The George Institute for Global Health, University of New South Wales, Sydney 2042, New South Wales, Australia. Tel.: +61 2 8052 4508; fax: +61 2 8052 4301. E-mail address: ccarcel@georgeinstitute.org.au (C. Carcel).*

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pain may direct further study of underlying pain mechanisms and improve the diagnosis and management of pain for all patients.

We hypothesized that more females experience pain and at a higher intensity than males across common noncommunicable diseases (NCDs), including critical illness and chronic disease states, and undertook a study to obtain reliable estimates of sex differences in the prevalence and intensity of pain through a pooled analysis of large data sets from high-quality clinical trials of NCDs.

2. Methods

2.1. Design

This study is a pooled individual participant data (IPD) meta-analysis of randomized controlled trials (RCTs) in noncommunicable diseases led by investigators at the George Institute for Global Health (TGI), performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[55] Ethical approval was granted by the Human Research Advisory Panel (HC200009) of the University of New South Wales, and data-sharing conditions were reviewed by the TGI Data Sharing Committee. The George Institute for Global Health held data may be made available for sharing externally by request from the corresponding author, subject to legal agreement.

Trials were eligible for inclusion if they were RCTs registered in the TGI Global Projects Database as of the 10th of February 2020, published between January 2000 and January 2020, and applied the EuroQol-5 Dimension (EQ-5D) health-related quality of life (HRQoL) measure. This is a valid, widely accepted, generic measure of HRQoL across various populations and conditions,[13,26,28,32,34,35,54,69,73] enabling the comparison of pain and discomfort across many cultures and diseases. The EQ-5D records self-assessed health status in mobility, self-care, usual activities, pain or discomfort, and anxiety or depression domains, with 3 (EQ-5D-3L) or 5 (EQ-5D-5L) ratings of severity. Participants select a rating that best describes their health on the day. In the EQ-5D-3L, the pain or discomfort domain ratings are "I have no pain or discomfort," "I have moderate pain or discomfort," and "I have extreme pain or discomfort." In the EQ-5D-5L, pain or discomfort domain ratings are "none," "slight," "moderate," "severe," and "extreme."[21]

Abstracts of the main publications were reviewed for projects with RCT study design before review of full texts for use of the EQ-5D instrument. Data custodians of eligible trials were contacted and conditions for sharing data were agreed upon. Participant information statements and consent forms of each trial were reviewed for clauses relating to secondary use of data. Trials were excluded if the trial participant information sheet or consent forms forbade use of trial data for secondary research purposes.

2.2. Variables

The following baseline characteristics, when collected for trials, were extracted: age, country of recruitment, baseline clinical observations (blood pressure [BP], heart rate [HR], and body mass index), medical history (cardiovascular disease, stroke, hypertension, hypercholesterolaemia, diabetes mellitus, obesity, smoking status, and alcohol consumption), medications at time of admission, and randomized treatment group (Appendix 1, available as supplemental digital content at http://links.lww.com/PAIN/B791).

Preliminary analysis was performed to match baseline characteristics and outcomes with results reported in the main publication of each trial to verify receipt of correct trial data. This was not possible in 1 study based in a First Nations population, for which permission was granted to access data from only patients recruited by general practitioners, due to ethical barriers.[57]

In 1 trial consisting of 2 partially overlapping cohorts in a factorial design,[5,7] the larger cohort was included to avoid participant overlap.[7] Another trial[4] had the same design and treatment as its pilot trial[6]; the data sets were combined and treated as 1 trial to increase precision. In trials that administered the EQ-5D-5L version of the EQ-5D tool,[70] the EQ-5D-5L pain categories were summarized as "no pain," "moderate pain" (including slight and moderate pain), and "extreme pain" (including severe and extreme pain), matching the EQ-5D-3L categories, which were scored as 0, 1, and 2, respectively.

Outcomes were the relative frequency of self-reported pain levels and intensity of self-reported pain levels between females and males, as measured by the EQ-5D at the end of each study.

2.3. Risk of bias assessment

One reviewer assessed risk of bias in each trial guided by the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[33] Each domain was assessed as having low, high, or unclear risk of bias for each trial.

2.4. Statistical analysis

Baseline characteristics were summarized by sex and trial and by pain group and trial. Summary statistics were mean (standard deviation) or median (interquartile range) for continuous data and number and percentage for categorical data. Comparisons of baseline characteristics were undertaken using *t*-tests or Wilcoxon tests for continuous variables and χ^2 tests for categorical variables.

The full range of EQ-5D scores (no pain, moderate pain, and extreme pain) at study end points was used to determine the common odds ratio (OR) of better outcomes with females vs males, using proportional odds logistic regression models, and included adjustment for random cluster effects for the single study that had a cluster randomized design.[3] This approach was repeated for each dichotomy of EQ-5D score, namely, no pain vs any pain and no or moderate pain vs extreme pain, and these IPD were analyzed using the 2-stage method for meta-analyses.[67] In the first stage, study-specific crude models, minimally adjusted for age and randomized allocation and then fully adjusted models, were built to estimate sex differences in pain. The following rules were applied a priori to determine the covariates for inclusion in the study-specific multivariable models: the covariate was (1) missing in less than 10% of cases, (2) associated with sex ($P < 0.1$), and (3) associated with pain in unadjusted analysis ($P < 0.1$), shown in Appendix 2, available as supplemental digital content at http://links.lww.com/PAIN/B791. Multivariable analyses were only performed on studies with >200 available measurements of pain.[19] Two studies were only minimally adjusted.[36,57] The covariates selected are listed in Appendix 3, available as supplemental digital content at http://links.lww.com/PAIN/B791. The second stage of analyses pooled the study-specific estimates using random effects in an inverse-variance–weighted meta-analysis.

Because of the heterogeneity of variables collected from different studies, age and randomized treatment minimally adjusted models were used for the primary analysis and fully adjusted models as sensitivity analysis. Subgroup analyses included age, region, and disease groups. Disease groups were stroke, critical care, kidney failure, diabetes mellitus, cardiovascular, and obstructive sleep apnea. Sensitivity analysis using all

possible dichotomisations of EQ-5D score was also performed. All data harmonization and analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc, Cary, NC).

3. Results

Of 79 identified trials, 10 were included (**Fig. 1**) and these related to stroke,[3,4,6,7,42] critical care,[52,70] kidney failure,[36] diabetes mellitus,[56] cardiovascular disease risk,[57] and obstructive sleep apnea.[47]

Table 1 describes the characteristics of the 10 trials, including 43,565 participants (16,723, 38% female), where end of study EQ-5D data collection ranged from 51%[57] to 91%.[36] Overall, 33,957 participants had EQ-5D data, which represented 78% of total IPD-recorded outcomes. The percentage of end of study EQ-5D data from females (n = 13,004, 38%) mirrored the total percentage of females in the trials (n = 16,723, 38%). There was the same percentage of missing data (22%) on EQ-5D between females and males overall, and similar percentages in each individual trial (Appendix 4, available as supplemental digital content at http://links.lww.com/PAIN/B791). Of 9608 missing EQ-5D data, death accounted for 4820 (50%) leaving 4788 (50%) missing EQ-5D data due to unspecified reasons. For each covariate analysed that had greater than 10% missing values, and thus was not adjusted for, there was a similar percentage of missing values between the sexes (Appendix 5, available as supplemental digital content at http://links.lww.com/PAIN/B791). Performance bias was the only risk of bias domain identified as high because of an open-label study design in 8 trials.[3,4,6,7,36,42,47,57,70]

Females were generally older and more likely to have lower diastolic BP, a faster HR, and a history of hypertension compared with males (Appendix 6, available as supplemental digital content at http://links.lww.com/PAIN/B791). Males were more likely to be current cigarette smokers and females had poorer baseline disease severity indicators in 3 of 4 stroke trials (National Institutes of Health Stroke Scale [NIHSS])[3,4,6,7] and in the cardiovascular trial (total cholesterol)[57] while males had poorer baseline disease severity indicators in the kidney failure trial (serum creatinine),[36] a critical care trial (Acute Physiology And Chronic Health Evaluation II [APACHE II]),[70] and the sleep apnea trial (apnea–hypopnea index).[47] There were no significant differences between females and males in disease severity in the remaining trials.[42,52,56]

A summary of baseline characteristics stratified by pain group, either pain or no pain, and by trial is provided in Appendix 7, available as supplemental digital content at http://links.lww.com/PAIN/B791. The group with pain was generally older, female, and nonsmokers. They also had more diabetes mellitus, hypercholesterolaemia, hypertension, acute coronary syndrome, and atrial fibrillation, as well as higher disease severity scores in the 5 stroke trials (NIHSS)[3,4,6,7,42] and cardiovascular trial (total cholesterol).[57] The group with no pain was generally younger, male, and more likely to be smokers. They also had higher disease severity scores in a critical care study (APACHE II)[52] and the obstructive sleep apnea study (apnea–hypopnea index).[47] In the group with no pain, there was a lower rate of almost all medical history and comorbidity variables, except for stroke, and there were no consistent differences between the pain groups for BP, HR, or history of previous stroke.

Forty-seven percent of females reported experiencing pain (either moderate or extreme), compared with 37% of males (**Fig. 2**) ($P < 0.001$). Of participants reporting pain, a higher proportion of females reported extreme pain (12% in females and 10% in males; $P = 0.004$).

Figure 3 shows that, in all the trials, higher pain scores were reported in females compared with males; the OR adjusted for age and randomized treatment was 1.41 (95% CI 1.24-1.61; $P < 0.001$). The fully adjusted model had a similar result (OR 1.47, 95% CI 1.26-1.71; $P < 0.001$) (Appendix 8, available as supplemental digital content at http://links.lww.com/PAIN/B791). Sensitivity analysis of all possible dichotomisations (Appendix 9, available as supplemental digital content at http://links.lww.com/PAIN/B791) showed the same direction and consistent magnitude of differences to the ordinal analysis. Only 1 study[70] had both EQ-5D-3L and EQ-5D-5L results, in which the age and randomized treatment-adjusted ORs were 1.22 (95% CI 1.04-1.43) and 1.13 (95% CI 0.96-1.34), respectively.

Females were significantly more likely to report a higher pain score than males, which was consistent within each trial when considered stratified by age, region, or disease study population with one exception across the 68 subgroup analyses (Appendix 10, available as supplemental digital content at http://links.lww.com/PAIN/B791). Regarding the pooled stratified analyses (**Fig. 4**), there was no evidence of a difference in the female to male ORs by age group or region of recruitment, but the ORs by disease group were heterogeneous ($P < 0.001$) with lower ORs in the critical illness population (OR 1.17) compared with other diseases.

4. Discussion

In this study of 33,957 participants in several NCD populations, females consistently reported pain more often than males (47% vs 37%) and females were approximately 1.4 times as likely as males to report a higher pain level. Female participants reported more pain in all individual trials, regardless of age, region of recruitment, and disease group.

Females were 30% more likely than males to report a higher pain score after stroke in our study and this extends findings from earlier studies of pain in NCDs. An ischaemic stroke study of 1370 (46.3% females) participants found approximately 45% of females, vs 35% of males, reported having pain or discomfort 3 months poststroke.[14] This suggests that females may experience more painful sequelae after ischaemic stroke, are more sensitive to stroke sequelae, or may experience less pain relief from pain management than males. Similarly, a large study of 15,745 participants (34.3% females) found female sex predicted pain after stroke.[53] Other research has also shown sex differences in characteristics of chest pain in acute myocardial infarction.[60]

Our findings of pronounced sex differences in pain in the diabetes mellitus and obstructive sleep apnea trials[47,56] are also consistent with previous literature. In diabetes mellitus, females have been found to experience a higher prevalence of neuropathic pain than males[1] and, despite diabetic sensorimotor polyneuropathy being more frequent in males, females with the complication report higher pain intensities.[16] This may be attributed to increased proinflammatory markers causing the greater glycaemic variability, dyslipidaemia, and nephropathy observed in the female cohort of this study. Although there is little evidence that directly links obstructive sleep apnea and pain, obstructive sleep apnea is known to disrupt sleep quality, and female sex plus insomnia is associated with higher pain scores than insomnia alone.[75] Interestingly, our study found less marked sex differences in self-reported pain in the critical care studies compared with the other studies. A possible explanation is that because the critical illness populations included both patients with acute disease alone and patients with a background of chronic disease, acute pain mechanisms may be less sexually

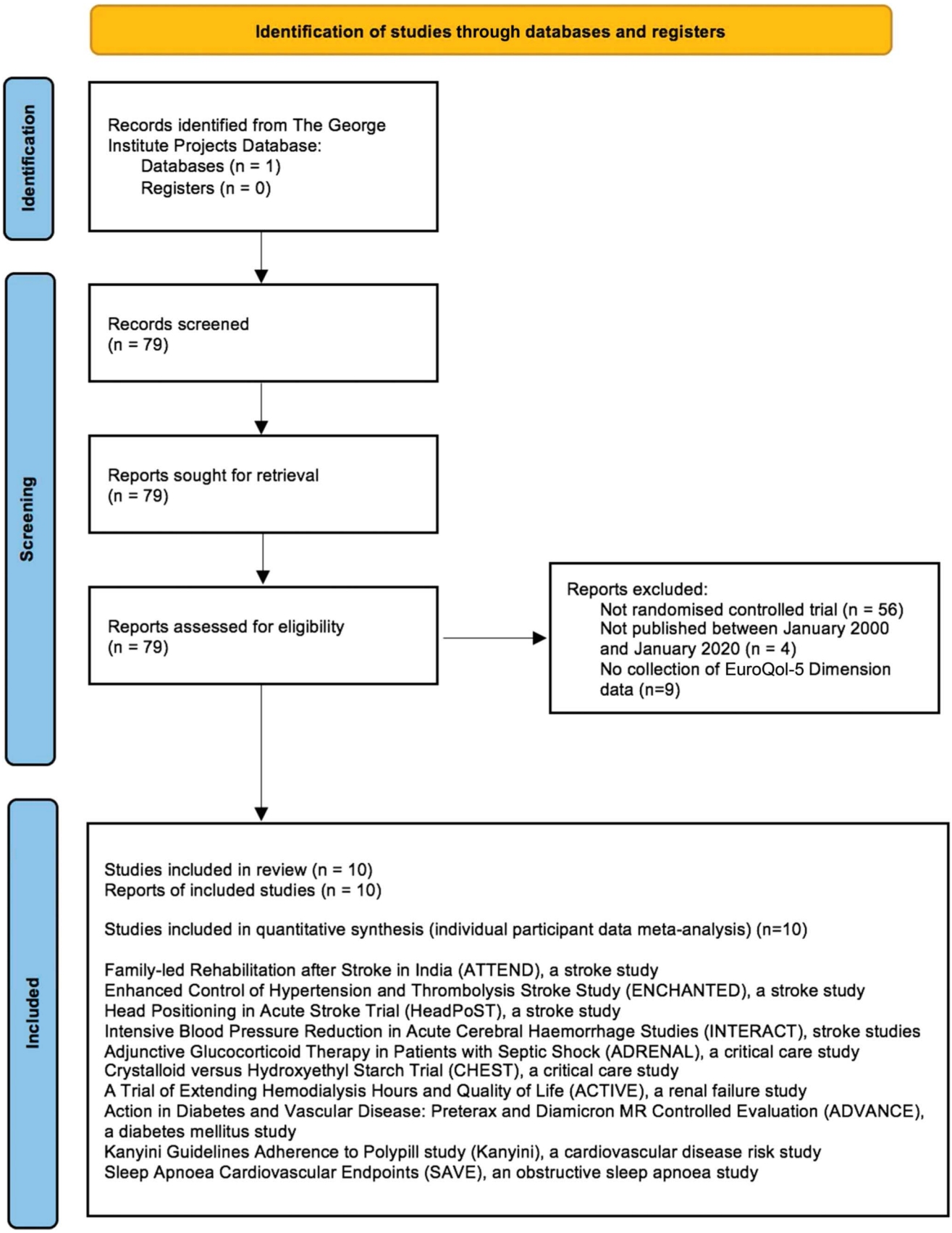

Figure 1. Database search and trial identification strategy.

Table 1

Characteristics of included trials.

Trial	Setting	Population of interest	Females, n (% total n)	Females with EQ-5D, n (% total EQ-5D)	Mean age (SD)		Intervention	Primary outcome	End of study EQ-5D timing
					Females	Males			
ATTEND[38]	India (14 hospitals)	Patients who had a stroke in the past month and residual disability requiring help for daily activities	413/1250 (33)	339/1039 (33)	57.5 (13)	56.2 (13)	Usual care vs rehabilitation training for family members	Modified Rankin Score 3-6	6 mo
ENCHANTED[28]	International (13 countries and 111 hospitals)	Patients who had an acute ischaemic stroke and met guideline criteria for treatment with intravenous alteplase	1248/3297 (38)	1083/2882 (38)	68.1 (13)	64.1 (12)	Low-dose intravenous alteplase vs standard dose	Modified Rankin Score 2-6	90 d
HeadPoST[34]	International (9 countries and 114 hospitals)	Patients diagnosed with acute stroke	4429/11,093 (40)	3463/8930 (39)	70.1 (14)	65.4 (13)	Lying flat vs sitting up position	Modified Rankin Score 3-6	90 d
INTERACT studies[30,31]	International (21 countries and 188 hospitals)	Patients who had an intracerebral haemorrhage and systolic blood pressure between 150 and 220 mm Hg	1191/3233 (37)	1047/2769 (38)	64.9 (13)	62.5 (13)	Intensive vs guideline recommended blood pressure control	Modified Rankin Score 3-6	90 d
ADRENAL[32]	International (5 countries and 69 intensive care units)	Intensive care unit patients undergoing mechanical ventilation who had documented or strong clinical suspicion of infection	1454/3713 (39)	852/2155 (40)	61.8 (15)	63.0 (15)	Intravenous infusions of hydrocortisone vs matched placebo	90-d mortality	6 mo
CHEST[39]	Australia and New Zealand (32 hospitals)	Intensive care unit patients who were judged by clinicians to require fluid resuscitation	2580/6651 (39)	1784/4479 (40)	64.2 (17)	62.3 (17)	Hydroxyethyl starch with sodium chloride vs saline	90-d mortality	90 d
ACTIVE[37]	International (4 countries and 40 dialysis centres)	Patients on haemodialysis therapy for end-stage kidney disease	61/200 (31)	58/181 (32)	50.7 (12)	50.7 (12)	Extended weekly vs standard haemodialysis hours for 12 mo	Change in EQ-5D score	12 mo
ADVANCE[40]	International (20 countries and 215 institutions)	Patients diagnosed with type 2 diabetes at age 30 y or older, at least aged 55 y and with at least 1 cardiovascular risk factor	4735/11,140 (43)	3869/8970 (43)	65.1 (6)	65.4 (6)	Fixed combination of perindopril and indapamide vs matched placebo and intensive vs standard glycaemic control	Major macrovascular or microvascular event	Mean of 4.3 y
Kanyini[27]	Australia (12 general practices)	Patients, including Aboriginal and Torres Strait Islanders, with cardiovascular disease (coronary, ischaemic cerebrovascular or peripheral vascular disease) or a high estimated 5-year cardiovascular disease risk	231/623 (37) 99/301* (33)	— 55/153 (36)	— 74.0 (8)	— 69.4 (9)	Polypill containing aspirin, simvastatin, lisinopril, and either atenolol or hydrochlorothiazide vs usual care	Adherence to the polypill	Median of 18 mo

(*continued on next page*)

Table 1 (*continued*)

Trial	Setting	Population of interest	Females, n (% total n)	Females with EQ-5D, n (% total EQ-5D)	Mean age (SD)		Intervention	Primary outcome	End of study EQ-5D timing
					Females	Males			
SAVE[41]	International (7 countries and 89 clinical centres)	Patients aged 45-75 diagnosed with coronary artery disease or cerebrovascular disease and moderate-to-severe obstructive sleep apnea	513/2687 (19)	454/2399 (19)	63.2 (7)	60.8 (8)	Continuous positive airway pressure treatment plus usual care vs usual care alone	Major macrovascular event	Mean of 3.7 y
Overall accessed data			16,723/43,565 (38)	13,004/33,957 (38)					

* Remaining participant data after patients recruited through Aboriginal Community Controlled Health Services were excluded because of ethical barriers

ACTIVE, a trial of extending hemodialysis hours and quality of life; ADRENAL, adjunctive glucocorticoid therapy in patients with septic shock; ADVANCE, action in diabetes and vascular disease: Preterax and Diamicron MR controlled evaluation; ATTEND, family-led rehabilitation after stroke in India; CHEST, hydroxyethyl starch or saline for fluid resuscitation in intensive care; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; EQ-5D, EuroQol-5 Dimension; HeadPoST, Head Positioning in Acute Stroke Trial; INTERACT, intensive blood pressure reduction in acute cerebral haemorrhage; Kanyini, Kanyini Guidelines Adherence to Polypill study; SAVE, Sleep Apnea Cardiovascular End Points.

divergent than pain mechanisms secondary to chronic disease. This could involve changes in the hypothalamic–pituitary–adrenal axis secondary to the stress response in critical illness leading to altered sex hormone–regulated pain mechanisms and responses. Furthermore, critically ill patients receive sedation and analgesia and can acquire physical, cognitive, and mental deficits[71] that may mask sex differences in pain.

Previous studies suggest females and males have inherent differences in pain processing at genome and neuroimmune levels, increasing women's vulnerability to experiencing pain. Females demonstrate specific enzyme activity involved in inflammatory pain modulation associated with higher pain sensitivity; for example, gene polymorphisms coding for GTP cyclohydrolase are associated with sickle cell anaemia pain crises only in females.[20] Sophisticated animal models have shown sexually dimorphic pain sensitivity processing pathways[51,64] and sex hormone links with receptor expression, macrophage phagocytosis activity,[62] and chemokine signalling.[39] In a study of 6636 children aged up to 18 years, girls had a marked increase in chronic pain reporting after puberty.[58] This is consistent with our finding that females self-reported higher levels of pain and also implicates hormonal mechanisms underlying chronic pain. Although the literature detailing biological mechanisms of sex differences in pain is extensive, few results have been replicated. Furthermore, psychosocial factors can significantly amplify or moderate the sensation and perception of pain.[10,29] Sex roles have been shown to influence pain perception and reporting[2,46] and may be important in attitudes towards pain and recovery goals.[43] Thus, a complex interplay between biological and psychosocial factors contributes to the challenge of elucidating mechanisms of sex differences in pain. Our findings may thus reflect both biological and psychosocial sex differences.

It is well established that more females report experiencing chronic pain and at higher pain levels than males.[11,61,65] In a population of participants with chronic pain, females experienced a higher disease burden for chronic and pain-related conditions such as osteoarthritis, fibromyalgia, and osteoporosis while males experienced more angina pectoris.[61] Sex differences exist in modifiable risk factors of chronic disease, which may account for a level of the sex difference in disease burdens. Cigarette smoking remains more common in males in some countries and is associated with a higher chronic disease burden.[44] Although smoking can provide temporary pain relief, the behavior has been linked with poorer pain and quality of life outcomes over time.[37] Physical activity is a protective factor for chronic disease,[45] and males are more likely to be sufficiently physically active compared with females,[9,31] which possibly reduces their risk of severe pain.[24] Pain treatment may also differ between each sex; 1 study

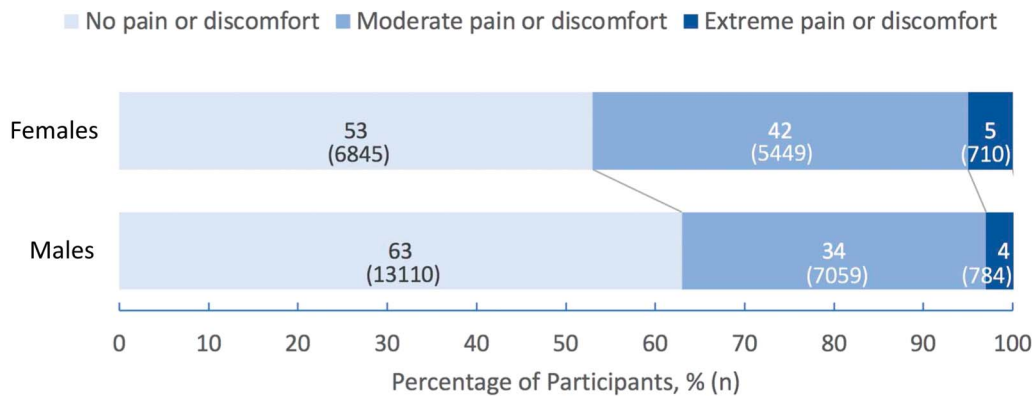

Figure 2. Patient EuroQol-5 Dimension pain or discomfort scores. Pain reported at end of trial by all participants according to sex. Pain is reported as EuroQol-5 Dimension-3L categories or the equivalent simplification from EuroQol-5 Dimension-5L. Sum of percentages for men do not add to 100 because of rounding (62.6%, 33.7%, and 3.7%).

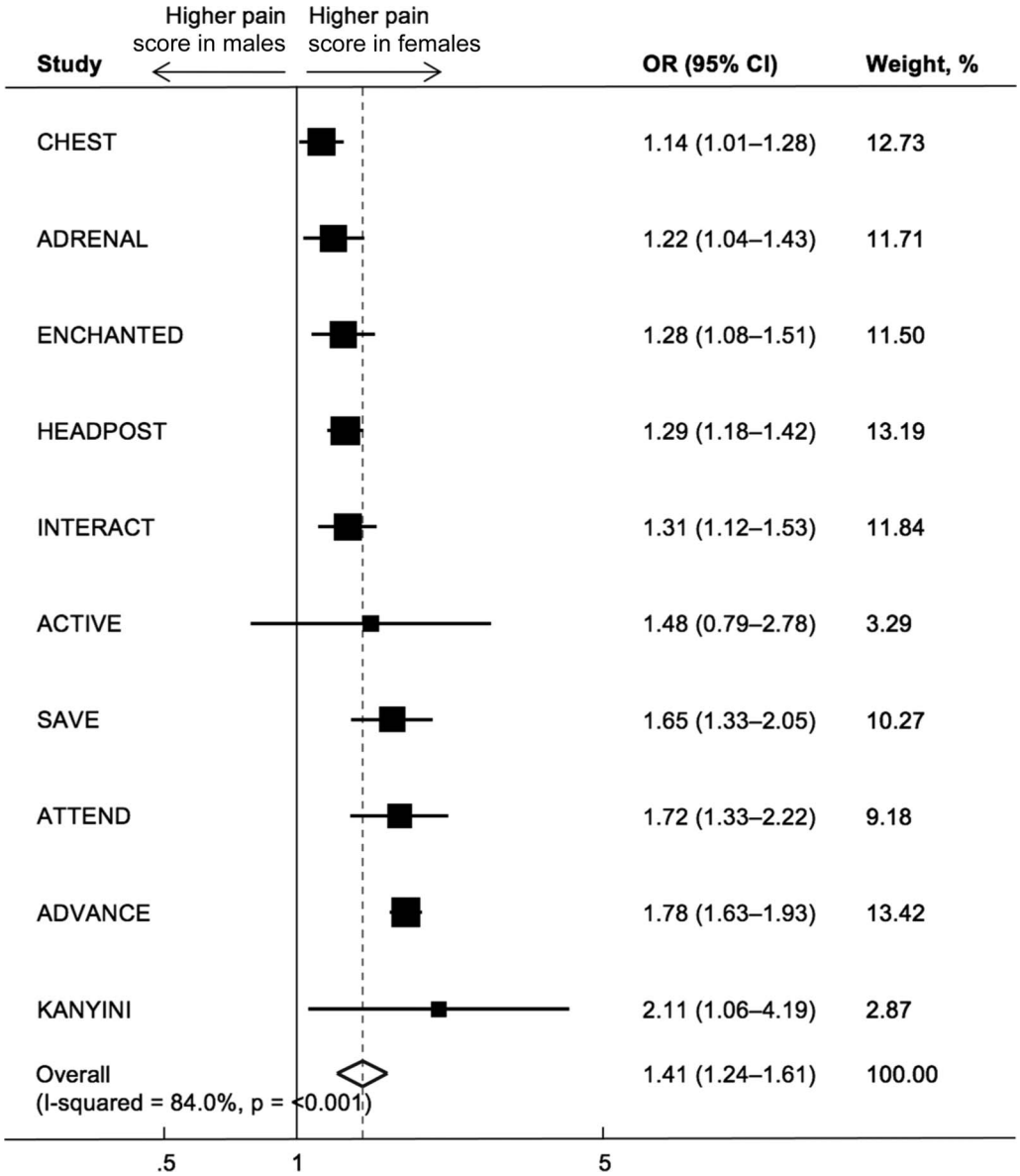

Figure 3. Age and randomized treatment-adjusted ordinal analysis of self-reported pain scores comparing females with males. Black square sizes indicate trial weighting based on sample size. Extremities of horizontal lines indicate 95% confidence intervals. The diamond is the overall adjusted odds ratio and its horizontal points indicate the overall 95% confidence interval. The vertical dotted line indicates the overall adjusted odds ratio. Covariates adjusted for in each trial are age and randomisation group. ACTIVE, a trial of extending hemodialysis hours and quality of life; ADRENAL, adjunctive glucocorticoid therapy in patients with septic shock; ADVANCE, action in diabetes and vascular disease: Preterax and Diamicron MR controlled evaluation; ATTEND, family-led rehabilitation after stroke in India; CHEST, hydroxyethyl starch or saline for fluid resuscitation in intensive care; CI, confidence interval; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; HeadPoST, Head Positioning in Acute Stroke Trial; INTERACT, intensive blood pressure reduction in acute cerebral haemorrhage; KANYINI, Kanyini Guidelines Adherence to Polypill study; OR, odds ratio; SAVE, Sleep Apnea Cardiovascular End Points.

showed that females were more likely to receive analgesia and physiotherapy while more males received no treatment for pain and reported less satisfaction with their level of independence.[61] Interestingly, another study showed that although females received more prescriptions, the average cost of each prescription was 14% to 26% more expensive for males than for females. This occurred with antidiabetic medications, suggesting that males received newer and more expensive insulin preparations than females.[66] As pain experiences differ between females and males, clinicians and researchers must also recognize that disease and disease management experiences can likewise differ. Historically, the study of only male samples resulted in knowledge bias towards male biological mechanisms and disease presentations.[50] Recent studies in various noncommunicable disease groups show that sex differences exist in disease symptom presentation,[8,40] pathogenesis,[12,74] diagnosis,[8] management,[15] treatment response,[40] and outcomes.[72] This calls for sex-disaggregated analysis in noncommunicable disease research to identify sex similarities and differences and guide treatment to improve both female and male outcomes.

Data-driven analysis on sociocultural and environmental factors affecting chronic pain, such as race, marital status, education, income, and early life stress, may be valuable in creating a risk factor profile or a risk assessment tool for chronic pain. A chronic pain risk assessment tool can help identify people at risk of developing chronic pain and most likely to benefit from timely intervention.[18]

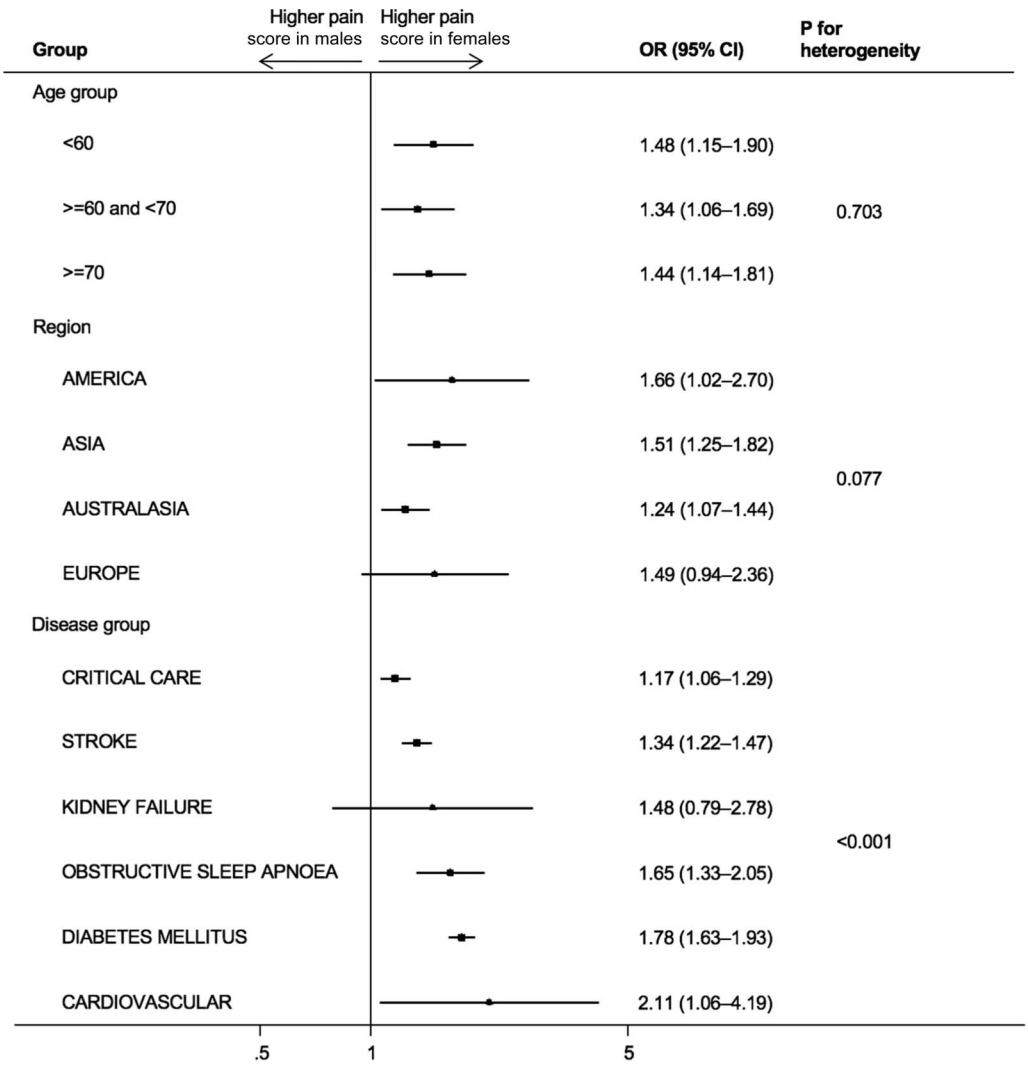

Figure 4. Stratified analysis by age, region, and disease group. Black square sizes indicate group weighting based on sample size. Extremities of horizontal lines indicate 95% confidence intervals. The stroke disease group included ATTEND, ENCHANTED, HeadPoST, and INTERACT, the critical care studies included ADRENAL and CHEST, and the other studies were ACTIVE (kidney failure), ADVANCE (diabetes mellitus), Kanyini (cardiovascular disease risk), and SAVE (obstructive sleep apnea). ATTEND, family-led rehabilitation after stroke in India; CHEST, hydroxyethyl starch or saline for fluid resuscitation in intensive care; CI, confidence interval; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; HeadPoST, Head Positioning in Acute Stroke Trial; INTERACT, intensive blood pressure reduction in acute cerebral haemorrhage; KANYINI, Kanyini Guidelines Adherence to Polypill study; OR, odds ratio; SAVE, Sleep Apnea Cardiovascular End Points.

A major strength of these data is that each trial showed the same direction of association despite different patient populations and geographic regions. Strengths of this study included the large sample size of participants across a range of international settings and disease conditions, which improves the generalizability of the findings, and the use of IPD meta-analysis, the first in this topic, which enabled the incorporation of previously unreported data. Pain measurement instruments are heterogeneous and often inadequately described in pain-related literature, but in this study, the consistent use of the validated EQ-5D instrument across included trials enabled comparisons between diverse populations. Although the EQ-5D is validated in both acute and chronic pain states,[34,35,54,69] the measure does not capture the temporal variation of pain intensity in chronic pain. The EQ-5D pain measure is more likely to pick up participants who experience pain frequently and may overrate or underrate pain scores of participants who experience pain variably day-to-day. A sex difference in the temporal nature of pain would bias our result; however, whether this difference exists requires further study. Key limitations include potential incomplete adjustment for confounders in the relationship between pain scores and sex, such as pain-related conditions unrelated to the disease under trial investigation and pain-related behaviors, eg, engagement with psychological or pharmacological management. Analysis of sociocultural covariates and specific medical history components with pain were limited because few trials collected socioeconomic information, and when collected, there were heterogeneous definitions for these variables, a difficulty inherent in pooling data. By searching for studies from TGI Projects Database, rather than international databases, such as the World Health Organization International Clinical Trials Registry Platform, we have by no means captured all trials that collected EQ-5D data. Nevertheless, our data pool is diverse, both in medical specialization and patient geography. Death accounted for a large proportion of missing data that represent an unclear attrition bias because it is possible that there are more or less pronounced sex differences in pain in participants with more serious illness that resulted in death. However, given the similarity between the sexes in

missingness of both covariates and EQ-5D pain data, there is unlikely to be any appreciable bias in our sex comparisons because of missing data. Moreover, because the mean age of participants in each trial ranged from 50 to 74 years, sex differences in pain in younger age groups were not captured in this study. The generalizability of the results is predominantly limited by the advanced age of most participants in our studies and the incomplete coverage of medical specialties. The use of end of study EQ-5D, due to greater availability, meant that pain scores may have indicated health states different to the health states captured at baseline. Finally, our findings may reflect both biological and psychosocial sex differences, but our pooled data did not allow a distinction to be made between biological sex and gender.

In summary, this pooled individual participant data meta-analysis of 33,957 participants found that females in NCD trials were more likely to report pain and at higher levels compared with their age-matched male counterparts. Sex differences in central pain processing mechanisms that increase the risk of females experiencing pain may contribute to this finding. Research in pain, disease, and treatment must therefore report sex-disaggregated results to determine both similarities and differences between females and males. This will enhance our understanding of sex differences in pain and disease, and enable improved therapy and outcomes.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B791.

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