

SUPPLEMENTARY TABLE S1
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

Ref	First Author (Year)	Journal	Study design	Population characteristics	Sample size	Age range	Sex distribution	Health status	Pain Model/Condition	Hormonal variables	Primary outcomes	Key findings related to sex differences	Authors' conclusions
1	Reja et al. (2020)	Pain	Consensus Statement	International pain experts	N/A	N/A	N/A	N/A	Pain definition	N/A	Revised pain definition	Pain is a personal experience influenced by biological, psychological, and social factors	Biopsychosocial framework essential for understanding pain
2	Bartley et al. (2013)	British Journal of Anaesthesia	Narrative Review	General population	N/A	All ages	Both sexes	Healthy and clinical	Multiple pain conditions	Multiple	Sex differences in pain	Women show greater experimental pain sensitivity and lower pain thresholds	Sex differences in pain are robust but multifactorial
3	Presto et al. (2022)	Neuropharmacology	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Multiple	Neuraxis pain mechanisms	Estrogen, testosterone	Neurobiological mechanisms	Sex differences exist along entire neuraxis from periphery to brain	Sex-specific mechanisms require targeted therapeutic approaches
4	Gobina et al. (2019)	European Journal of Pain	Cross-sectional	Adolescents from 42 countries	219,577	11-15 years	50.4 % female	School-attending	Chronic pain prevalence	N/A	Self-reported chronic pain	Female adolescents report significantly higher chronic pain prevalence	Sex differences in chronic pain emerge early in adolescence
5	Ribeiro-Dasilva et al. (2017)	Journal of Dental Research	Case-Control	Women with and without TMD	18	18-35 years	100 % female	TMD patients vs. controls	Temporomandibular disorder	Estrogen	IL-6 levels, TMD pain	Estrogen-induced monocytic IL-6 response correlates with TMD pain severity	Estrogen modulates inflammatory responses in TMD
6	Bulls et al. (2015)	Journal of Pain Research	Cross-sectional	Healthy adults	48	19-45 years	50 % female	Healthy volunteers	Experimental pain	N/A	Pain sensitivity, CPM	Women show greater pain sensitivity and less efficient endogenous pain inhibition	Sex differences in pain modulation contribute to clinical pain disparities

(Continued on the next page)

SUPPLEMENTARY TABLE S1 (CONT.)
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

Ref	First Author (Year)	Journal	Study design	Population characteristics	Sample size	Age range	Sex distribution	Health status	Pain Model/Condition	Hormonal variables	Primary outcomes	Key findings related to sex differences	Authors' conclusions
7	Farrant et al. (2023)	Journal of Paediatrics and Child Health	Cross-sectional	High school students, New Zealand	7,721	13-18 years	51 % female	School-attending	Chronic pain prevalence	N/A	Chronic pre-pain prevalence, severity, impact	Female students report higher chronic pain prevalence, severity, and functional impact	Sex differences in chronic pain are significant in adolescent populations
8	Zagni et al. (2016)	Neuroscience Journal	Narrative Review	General population	N/A	All ages	Both sexes	Multiple	CNS-related disorders	Estrogen, progesterone, testosterone	CNS disorder prevalence	Sex and gender differences exist across CNS-related disorders including pain	Hormonal and genetic factors contribute to sex differences in CNS disorders
9	Nasser et al. (2019)	Life Sciences	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Multiple	Opioid antinociception	Estrogen, progesterone, testosterone	Opioid analgesia efficacy	Gonadal hormones modulate sex differences in opioid-mediated antinociception	Sex-specific opioid dosing may be warranted
15	Sorge et al. (2017)	Journal of Neuroscience Research	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Multiple	Multiple pain models	Estrogen	IL-6, CGRP expression	Females show greater IL-6 production and CGRP expression influenced by estrogens	Immune mechanisms contribute to sex differences in pain
24	Iyengar et al. (2017)	Pain	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Migraine patients	Migraine, CGRP mechanisms	N/A	CGRP role in pain	CGRP plays a key role in peripheral and central sensitization and in migraine pathophysiology	Blocking CGRP activity appears to be therapeutically relevant in migraine
19	Gupta et al. (2011)	Headache: The Journal of Head and Face Pain	Narrative Review	Women with migraine	N/A	Reproductive age	Female focus	Migraine patients	Migraine	Estrogen, progesterone	Pain modulation mechanisms	Sex hormones modulate migraine through serotonin, CGRP, and opioid pathways	Hormonal fluctuations contribute to migraine prevalence in women

(Continued on the next page)

SUPPLEMENTARY TABLE S1 (CONT.)
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

Ref	First Author (Year)	Journal	Study design	Population characteristics	Sample size	Age range	Sex distribution	Health status	Pain Model/Condition	Hormonal variables	Primary outcomes	Key findings related to sex differences	Authors' conclusions
16	Wang et al. (2014)	Journal of the Neurological Sciences	Experimental (Animal)	Female Sprague-Dawley rats, sham-operated or ovariectomized	66	Adult	100 % female	Ovariectomized	PAG pain modulation	Estrogen, progesterone	PGE2, CGRP levels	Sex hormone deficiency augments PGE2 and CGRP in periaqueductal gray	Female sex hormones have protective effects against pain mediator expression
10	Iacovides et al. (2015)	European Journal of Pain	Systematic Review	Women across menstrual cycle	210 studies reviewed	Reproductive age	100 % female	Healthy and clinical	Menstrual cycle pain	Estrogen, progesterone	Pain threshold, tolerance	Inconsistent evidence for menstrual cycle effects; methodological limitations identified	Standardized methodology needed for menstrual cycle pain research
20	Chen et al. (2021)	Biology of Sex Differences	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Multiple	Estrogen receptor signaling	Estrogen (ER α , ER β , GPER)	Cellular pain mechanisms	Estrogen has concentration-dependent and receptor-specific bidirectional effects on pain	Estrogen receptor subtype determines pro- or antinociceptive effects
21	Maurer et al. (2016)	Pain Management	Narrative Review	General population	N/A	All ages	Both sexes	Multiple	Multiple pain conditions	Estrogen, progesterone, testosterone	Pain perception mechanisms	Sex hormones influence pain through central and peripheral mechanisms	Hormonal factors partially explain sex differences in pain
17	Pavlović et al. (2016)	Neurology	Prospective Cohort	Women with and without migraine	337	35-58 years	100 % female	Perimenopausal	Migraine	Estradiol, progesterone, FSH, LH	Migraine frequency, hormone levels	Women with migraine have distinct hormone profiles compared to controls	Migraine-specific hormonal patterns exist independent of menstrual phase
51	Pieretti et al. (2016)	Annali dell'Istituto Superiore di Sanità	Narrative Review	General population	N/A	All ages	Both sexes	Multiple	Multiple pain conditions	Multiple	Pain perception and relief	Gender differences exist in pain perception, expression, and analgesic response	Personalized pain management should consider sex/gender

(Continued on the next page)

SUPPLEMENTARY TABLE S1 (CONT.)
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

Ref	First Author (Year)	Journal	Study design	Population characteristics	Sample size	Age range	Sex distribution	Health status	Pain Model/Condition	Hormonal variables	Primary outcomes	Key findings related to sex differences	Authors' conclusions
18	De Kraker et al. (2016)	Pain	Population-based Cohort	Community-dwelling elderly women	5,550	≥45 years	100 % female	Community-dwelling	Chronic musculoskeletal pain	Estradiol, testosterone, 17-hydroxyprogesterone, androstenedione	Chronic pain prevalence	Lower sex hormone levels associated with more chronic musculoskeletal pain	Hormonal decline may contribute to increased pain in elderly women
12	Balter et al. (2013)	The Journal of Pain	Experimental (Human)	Women with chronic neck pain	39	21-45 years	100 % female	Chronic neck pain; normally menstruating vs. hormonal contraceptive users	Chronic neck pain	Menstrual cycle phase	Mechanical pain sensitivity	No significant menstrual cycle modulation of pain sensitivity in either group	Menstrual cycle does not significantly affect chronic neck pain
13	Klatzkin et al. (2010)	European Journal of Pain	Experimental (Human)	Healthy women and men	97	18-45 years	50 % female	Healthy volunteers	Experimental pain	Menstrual cycle phase	Pain threshold, tolerance	Menstrual cycle phase does not influence sex differences in experimental pain	Sex differences in pain persist regardless of menstrual phase
49	Lacasse et al. (2023)	BMJ Open	Cohort	Workers with chronic pain, Quebec	2,955	18-50 years	56.1 % female	Chronic pain patients	Healthcare utilization	N/A	Healthcare trajectories	Sex and gender differences exist in healthcare utilization patterns	Gender-sensitive approaches needed in chronic pain management
14	Teepker et al. (2011)	Headache: The Journal of Head and Face Pain	Experimental (Human)	Women with migraine	39	18-45 years	100 % female	Migraine patients	Migraine, oral contraceptives	Estrogen, progesterone (OC use)	Pain thresholds, headache intensity	Oral contraceptives modulate pain thresholds and headache intensity across cycle	Exogenous hormones influence migraine threshold modulation
25	Buse et al. (2013)	Headache: The Journal of Head and Face Pain	Cross-sectional	US population (AMIPP Study)	162,756	≥12 years	Both sexes	Population-based	Migraine prevalence	N/A	Migraine prevalence, symptoms	Women have 3x higher migraine prevalence with distinct symptom profiles	Sex-specific phenotypes exist in migraine presentation

(Continued on the next page)

SUPPLEMENTARY TABLE S1 (CONT.)
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

<i>Ref</i>	<i>First Author (Year)</i>	<i>Journal</i>	<i>Study design</i>	<i>Population characteristics</i>	<i>Sample size</i>	<i>Age range</i>	<i>Sex distribution</i>	<i>Health status</i>	<i>Pain Model/Condition</i>	<i>Hormonal variables</i>	<i>Primary outcomes</i>	<i>Key findings related to sex differences</i>	<i>Authors' conclusions</i>
22	Gupta et al. (2017)	Journal of Neuroscience Research	Neuroimaging (MRI)	Chronic pain patients	182	18-65 years	Both sexes	Multiple chronic pain	Brain morphology	Controlled for hormones	Brain structure and function	Women show unique functional organization of insula and ACC in chronic pain	Sex-specific brain alterations underlie chronic pain differences
23	Reckziegel et al. (2021)	Pain	Neuroimaging (MRI)	Multi-center back-pain cohorts and healthy controls	374	20-70 years	Both sexes	Chronic back pain vs. healthy	Chronic back pain	N/A	Hippocampal morphology	Hippocampal shape deformation is a diagnostic biomarker exclusive to women	Sex-specific neuroimaging biomarkers may improve diagnosis
26	Bartley et al. (2016)	Arthritis Care Research	Cross-sectional	Knee osteoarthritis patients	299	45-85 years	58 % female	Symptomatic knee OA	Knee osteoarthritis	N/A	Pain sensitivity, central sensitization	Women show enhanced pain sensitivity and potential central sensitization	Sex differences in OA pain may reflect central mechanisms
11	Racine et al. (2012a)	Pain	Systematic Review	Experimental pain studies	172 studies	All ages	Both sexes	Healthy and clinical	Experimental pain	Multiple	Pain threshold, tolerance, intensity	Women show greater pain sensitivity; effect sizes small to moderate	Sex differences in experimental pain are consistent but modest
41	Racine et al. (2012b)	Pain	Systematic Review	Biopsychosocial pain studies	172 studies	All ages	Both sexes	Healthy and clinical	Biopsychosocial factors	Multiple	Psychological and social factors	Biopsychosocial factors alter pain sensitivity differently by sex	Integrated biopsychosocial approach essential for understanding sex differences
36	Feng et al. (2012)	Current Drug Targets	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Multiple	Opioid receptor function	N/A	Receptor physiology	Opioid receptors have widespread expression affecting multiple systems	Opioid receptor distribution underlies analgesic and side effects

(Continued on the next page)

SUPPLEMENTARY TABLE S1 (CONT.)
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

Ref	First Author (Year)	Journal	Study design	Population characteristics	Sample size	Age range	Sex distribution	Health status	Pain Model/Condition	Hormonal variables	Primary outcomes	Key findings related to sex differences	Authors' conclusions
37	Al-Hasani et al. (2011)	Anesthesiology	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Multiple	Opioid signaling	N/A	Molecular mechanisms	Opioid receptors interact with mood and reward pathways	Receptor signaling explains dependency potential
38	Bruchas et al. (2010)	Psychopharmacology	Narrative Review	Animal models	N/A	N/A	Both sexes	Multiple	KOR signaling	N/A	Kinase cascades	KOR signaling involves complex kinase cascades with sex differences	KOR-targeted therapies may have sex-specific effects
39	Henriksen et al. (2008)	Brain	Narrative Review	Human neuroimaging studies	N/A	Adults	Both sexes	Multiple	CNS opioid receptors	Sex hormones	Receptor imaging	Sex differences in receptor-ligand binding dynamics influenced by hormones	PET imaging reveals sex-specific opioid receptor patterns
27	Vijay et al. (2016)	American Journal of Nuclear Medicine and Molecular Imaging	PET Imaging	Healthy adults	27	18-45 years	33.3 % female (9/27)	Healthy volunteers	KOR availability	N/A	KOR binding potential	Men show higher KOR expression in gray matter than women	Sex differences in KOR may affect analgesic response
40	Lee et al. (2013)	Molecular Pain	Narrative Review	Human and animal models	N/A	N/A	Both sexes	Multiple	Opioid-estrogen interactions	Estrogen	Receptor interactions	Estrogen receptors modulate opioid receptor expression and function	Estrogen-opioid interactions contribute to sex differences in analgesia
28	Zubieta et al. (1999)	American Journal of Psychiatry	PET Imaging	Healthy adults	66	20-30 years	Both sexes	Healthy volunteers	MOR availability	N/A	MOR binding potential	Women show higher MOR availability across multiple brain regions	Sex and age influence central opioid receptor binding
29	Joe et al. (2016)	Medicine	RCT	Surgical patients	48	20-60 years	50 % female	ASA HI surgical	Remifentanyl requirements	Sex hormones (indirect)	Remifentanyl EC50	Women require lower remifentanyl doses; sex differences in esterase metabolism	Sex-specific opioid dosing may improve clinical outcomes

(Continued on the next page)

SUPPLEMENTARY TABLE S1 (CONT.)
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

Ref	First Author (Year)	Journal	Study design	Population characteristics	Sample size	Age range	Sex distribution	Health status	Pain Model/Condition	Hormonal variables	Primary outcomes	Key findings related to sex differences	Authors' conclusions
31	Schnabel et al. (2012)	Pain	Observational Cohort	Major surgery patients	14,988	18-80 years	43.4 % female	Postoperative	Patient-controlled epidural analgesia	N/A	Opioid consumption, adverse effects	Women use less epidural analgesia but have more adverse effects	Sex-specific adverse effect profiles warrant monitoring
32	Lo et al. (2008)	Acta Anaesthesiologica Taiwanica	Retrospective	Orthopedic surgery patients	320	Adults	Both sexes	Postoperative	PCEA-related vomiting	N/A	Vomiting incidence	Sex is the only significant predictor of vomiting with PCEA	Female sex predicts opioid-related adverse effects
35	Niesters et al. (2010)	Pain	Systematic Review/Meta-analysis	Experimental and clinical studies	50 studies	All ages	Both sexes	Multiple	Opioid analgesia	N/A	Analgesic efficacy	No consistent sex difference in opioid analgesia efficacy	Sex differences in opioid response are inconsistent
33	Triebel et al. (2017)	The Spine Journal	Observational Cohort	Lumbar fusion patients (SWES-PINE)	11,237	Adults	Both sexes	Lumbar spine surgery	Postoperative outcomes	N/A	Pain, quality of life at 2 years	Women show greater improvement in pain and quality of life post-surgery	Women do not fare worse than men after spine surgery
34	Zheng et al. (2017)	PLoS ONE	Prospective Cohort	Surgical patients	890	All ages	Both sexes	Postoperative	Postoperative pain	N/A	Pain scores, opioid use	Age and preoperative pain are major confounders for sex differences	Confounders must be controlled when studying sex differences
30	Li et al. (2016)	Medicine	RCT	General anesthesia patients	223	18-65 years	50 % female	ASA II surgical	Dexmedetomidine morphine-sparing	N/A	Morphine consumption	Sex differences exist in morphine-sparing effects of dexmedetomidine	Alpha-2 agonists have sex-specific opioid-sparing effects
42	Alabas et al. (2013)	European Journal of Pain	Cross-sectional	Healthy adults, cross-cultural	175	18-40 years	50 % female	Healthy volunteers	Experimental pain, gender roles	N/A	Pain threshold, gender role scores	Gender role expectations affect experimental pain responses	Cultural and gender factors influence pain expression

(Continued on the next page)

SUPPLEMENTARY TABLE S1 (CONT.)
DETAILED CHARACTERISTICS OF INDIVIDUAL INCLUDED STUDIES

<i>Ref</i>	<i>First Author (Year)</i>	<i>Journal</i>	<i>Study design</i>	<i>Population characteristics</i>	<i>Sample size</i>	<i>Age range</i>	<i>Sex distribution</i>	<i>Health status</i>	<i>Pain Model/Condition</i>	<i>Hormonal variables</i>	<i>Primary outcomes</i>	<i>Key findings related to sex differences</i>	<i>Authors' conclusions</i>
43	Kröner-Herwig et al. (2012)	GMS Psychosocial-Medicine	Experimental (Human)	Healthy adults	80	18-35 years	50 % female	Healthy volunteers	Pressure pain	N/A	Pain threshold, tolerance, gender role	Sex affects pain threshold but gender role does not significantly affect responses	Biological sex more important than gender role for pain sensitivity
46	Gallach Solano et al. (2020)	Revista de la Sociedad Española del Dolor	Narrative Review	Chronic pain patients	N/A	Adults	Both sexes	Chronic pain	Gender determinants	N/A	Coping strategies, treatment response	Women use more adaptive coping; men prefer physical therapies	Gender-specific treatment approaches may improve outcomes
47	Turk et al. (2002)	Psychological Approaches to Pain Management: A Practitioner's Handbook (Guilford Press)	Book Chapter/ Narrative Review	Chronic pain patients	N/A	All ages	Both sexes	Chronic pain	Biopsychosocial model	N/A	Theoretical framework	Biopsychosocial factors interact bidirectionally with biological systems	Integrated model essential for chronic pain management
48	Mills et al. (2019)	British Journal of Anaesthesia	Narrative Review	Population-based studies	N/A	All ages	Both sexes	Multiple	Chronic pain epidemiology	N/A	Prevalence, associated factors	Women show higher chronic pain prevalence with different associated factors	Sex-specific risk factors exist for chronic pain
45	Sharifzadeh et al. (2017)	Anesthesiology	Retrospective Cohort	Chronic pain patients	1,794	Adults	Both sexes	Chronic pain	Catastrophizing-opioid relationship	N/A	Pain catastrophizing, opioid prescription	Catastrophizing moderates pain-opioid relationship with sex-specific patterns	Psychological factors interact with sex in opioid prescribing
44	Horn et al. (2014)	Pain Research and Treatment	Prospective	Healthy adults	177	18-45 years	70.1 % female	Healthy volunteers	Thermal pain, fear	N/A	Pain sensitivity, fear of pain	Fear of severe pain mediates sex differences in thermal pain sensitivity	Psychological factors explain some sex differences in pain