



Sex differences in pain in 2 large and diverse US databases

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Abstract

Introduction: Sex differences have been recognized as significant influences on disease susceptibility and progression.

Objectives: This study aimed to assess sex differences in pain prevalence using 2 large and diverse US data sources, *All of Us* and *Epic Cosmos*.

Methods: Pain concepts, labels used to describe type, chronicity, and body locations in electronic health records, were identified from 254,639 individuals in *All of Us* and 292,549,808 in *Epic Cosmos* data. Prevalence ratios (PRs) and 95% confidence intervals comparing the prevalence between females and males were computed to determine sex differences in each pain concept, in each data set. Ratios >1 and <1 denoted higher prevalence among females and males, respectively.

Results: The search yielded 195 pain concepts available in both *All of Us* and *Epic Cosmos*. Of these, 72.9% in *All of Us* and 82.6% in *Epic Cosmos* showed higher prevalence among females. Higher prevalence among men was observed in 8.9% (*All of Us*) and 13.3% (*Epic Cosmos*) of pain concepts, mainly involving the chest, lower limbs, and inguinal region. Between 4.1% and 18.2% of the concepts did not show evidence of differences in prevalence by sex. Only one conditions displayed opposing direction in PRs, possibly due to differences in sample composition and/or variation in clinical assignment criteria for pain concepts.

Conclusion: Higher pain prevalence among females in the United States was observed for most pain concepts in 2 large and diverse databases. These results underscore the importance of pain research, prevention, and management approaches stratified by sex.

Keywords: Sex differences, Pain, All of Us, Epic cosmos, Epidemiology

1. Introduction

Pain is a multifaceted, subjective experience influenced by sensory, emotional, cognitive, and social factors.⁵⁴ Evidence has increasingly highlighted the impact of sex differences on the perception, experience, and burden of pain.³⁶

Sex is considered a biological variable and generally categorizes individuals in females and males.³³ Therefore, sex differences can be attributed to biological characteristics, typically based on chromosomal composition, gene expression, and hormonal

profiles.³³ They can be accompanied by differences in physical and phenotypic traits, such as external anatomy, genital structures, and other morphological characteristics. Sex significantly influences disease susceptibility, manifestation, and progression, which highlights the importance of incorporating these factors into health research, disease prevention, and treatment management.^{34,48,69}

Historically, preclinical and clinical research have predominantly focused on male sex, often under the assumption that findings could

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be generalizable to all.^{48,54} However, recent advancements and inclusion of females in research have demonstrated notable sex-based differences such as in responses to pain management strategies, pain modulatory pathways, effectiveness of pain interventions, analgesic efficacy, drug pharmacokinetics, and pharmacodynamics.^{36,55,56,70,71,77} For example, between 1997 and 2000, 80% of drugs withdrawn from the US market were due to adverse effects observed in females, not predicted in male-dominant trials.⁴⁰ Such findings underscore the need to better understand sex-specific factors that drive pain risk and prognosis.

The mechanisms underlying sex-specific differences in pain are complex and multifactorial, including genetic programming, variations in pain processing, neuroimmune, inhibitory and excitatory pathways, hormonal influence, and psychosocial and cultural factors (associated with gender), among others.^{2,17,48,54,64,65,69,78} Sex-related differences in pain start to emerge during puberty, fluctuate throughout menstrual cycles, and drastically shift after menopause, underscoring the influence of gonadal hormones on pain sensitivity.^{16,19,41,86} For example, although testosterone is associated with increased pain thresholds in males, estrogen has variable effects on pain sensitivity in females, producing antinociceptive and enhancing effects depending on context.^{2,16} Moreover, sex-specific differences in immune system activity—which further contribute to pain—are thought to be mediated at least in part by gonadal hormones.^{2,65}

Studies of sex differences in pain have documented a higher female prevalence in several chronic pain conditions,^{36,54} including autoimmune diseases,⁴⁸ headaches,^{9,10,13,69} temporomandibular disorders,⁶⁹ irritable bowel syndrome,³⁷ and fibromyalgia,⁹¹ among others.⁸⁴ Moderate to large effect sizes have also been reported for sex-based differences in pain intensity and interference.⁶⁶ Furthermore, females often experience pain in more bodily locations²⁸ and have higher prevalence of acute postoperative pain.^{82,85} Conversely, males have a higher prevalence of conditions, such as oral cancers,^{29,58} cluster headache,²¹ coronary artery disease,^{48,62} gout,²³ neurodegenerative disorders,⁴⁸ and periodontal disease.^{22,69} Despite these findings, studies exploring sex differences in pain prevalence according to specific body locations are scarce.⁵⁹ Moreover, previous epidemiological studies on sex differences in pain have been subject to selection bias, limited ethnic and racial variability, limited specific geographic populations, or relatively small sample sizes, all of which restrict the generalizability of findings.⁹¹

To overcome these limitations, this study leverages 2 large databases gathering data from millions of individuals across the United States, which specifically include historically underrepresented individuals (*All of Us* and *Epic Cosmos*). In large-scale electronic health record (EHR) databases such as *All of Us* and *Epic Cosmos*, clinical information is captured using standardized terminologies, which classifies medical concepts into structured entries known as *concepts*. These coded concepts may include symptoms, clinical findings, or diagnoses. Therefore, the aim of this study was to explore sex differences in the prevalence of pain concepts, according to their location and chronicity using *All of Us* and *Epic Cosmos* data. We hypothesized that there were distinct patterns of pain prevalence based on sex. The presence of sex difference in pain prevalence and treatment response has practical implications for patient diagnosis, prevention, and management.⁴⁸ These findings will contribute to the development of more targeted and effective strategies accounting for sex-specific insights.^{27,54,78}

2. Methods

This observational study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) guidelines to ensure rigorous and standardized reporting.⁸⁷ The study was considered exempt from institutional review board review, as it did not meet the regulatory definition of human subjects research (45 CFR 46.102). This exemption was granted due to the use of deidentified, aggregate-level data, which eliminated any direct interaction with human subjects or the use of identifiable private data.

2.1. Study design

This was a secondary data analysis of publicly available data conducted over a two-month period, between April and May 2024 and covered the period from the inception of the database to 2024.

2.2. Setting

The *All of Us* Research Program, launched in May 2018,⁶¹ is an initiative led by the National Institutes of Health, which gathers deidentified data from more than 1 million participants across the United States, aiming to foster more diverse medical research.^{46,61,67} At the time of this study, *All of Us* contained genomics data, physical measurements, “Fitbit” tracking, EHR (which include health conditions, drug prescriptions, laboratory measurements, and procedures), and survey responses (including demographics, overall health, lifestyle, healthcare utilization, family health history, COVID-19, and social determinants of health) (<https://databrowser.researchallofus.org>). The *Cosmos* research program, managed by the Epic corporation (Verona, WI), is a large integrated EHR platform.⁸¹ *Epic Cosmos* aggregates EHR data from millions of patients across multiple sites and healthcare systems that use Epic. Data have been prospectively collected since 2018, although data have also been retrospectively added from 2005.⁸¹ The *Epic Cosmos* database is deidentified and provides access to information such as demographics, encounter details, diagnoses, social and family history, procedures, drug prescriptions, allergies, vital signs, laboratory measurements, insurance information, and social determinants of health.⁸¹ Researchers affiliated with healthcare systems contributing data to *Epic Cosmos* can freely query the database through a web application.⁸¹ At the time of this study, *Epic Cosmos* included data from all 50 states in the United States, with a total of 219 participating healthcare systems, representing 1,591 hospitals and 36,300 clinics.⁵²

2.3. Database search and participants

The search included female and male participants with a noncancer pain concept, with no age restriction. We conducted database searches within *All of Us* Research Program using the EHR data feature on the data browser, which provides freely accessible aggregate-level data. Pain concepts across various body locations and chronicity (acute vs chronic) were identified individually in the “EHR Conditions” section (<https://databrowser.researchallofus.org/ehr/conditions>), which—at the time of the search—covered a comprehensive list of 25,638 health conditions. To reflect pain concept use in EHRs, we retained all labels in their original form, despite any anatomical or semantic redundancy. For each pain concept, Systemized Nomenclature of Medicine (SNOMED) labels were documented. To cross-check findings, we then queried the corresponding pain concepts in the *Epic Cosmos* database (https://cosmos.epichosted.com/EpicCareLink_AUTH/common/epic_main.asp) using the “SlicerDicer Explore” feature. Each pain concept was browsed in the “Patient Population” section of *Epic Cosmos*.

At the time of data extraction, the *All of Us* Research Program contained deidentified EHR data for 254,639 total participants, whereas *Epic Cosmos* included records for 292,549,808 participants (**Fig. 1**). However, we included female (*All of Us* $n = 154,454$; *Epic Cosmos* $n = 27,169,438$) and male (*All of Us* $n = 95,083$; *Epic Cosmos* $n = 19,297,460$) participants only (details below), for a total of 249,537 in *All of Us* and 46,466,898 in *Epic Cosmos*.

2.4. Variables by data source

For each pain concept, we extracted the raw count of participants categorized as female and male based on the “sex assigned at birth” variable in both databases. In the *All of Us* Research Program, these data were extracted through the data browser dashboard; in *Epic Cosmos*, it was extracted through the “Patient Demographics” slice. The *All of Us* database also includes “Other” category for sex assigned at birth, and *Epic Cosmos* contains additional categories such as “Choose not to disclose,” “Not recorded on birth certificate,” “Uncertain,” and “Unknown.” These categories were excluded from our analysis to ensure a consistent comparison across both databases.

To protect participant privacy, the *All of Us* Research Program and *Epic Cosmos* do not provide raw counts for EHR concepts with fewer than 20¹ and 11⁸¹ participants, respectively. Thus, we excluded pain concepts with participant counts below these thresholds from our analysis to ensure that sample sizes could be precisely calculated (Supplemental Table 1, <http://links.lww.com/PR9/A361>).

2.5. Pain chronicity

Twenty-five of the pain concepts from each data source had details on chronicity in that they were specifically labelled as

“acute” or “chronic” (as used in original pain concepts, assigned to individuals based on clinical discretion). Pain concepts in *All of Us* and *Epic Cosmos* are included in Supplemental Tables 2 and 3, <http://links.lww.com/PR9/A361>—some of them are labeled as “acute” or “chronic.”

2.6. Statistical analyses

For selected EHR pain concepts in each database, we calculated sex-specific prevalence by determining the proportion of participants reporting that pain concept relative to the total number of participants contained in the database for females and males separately. For each data source, we estimated prevalence ratios (PRs) between female and male proportions with each pain concept, along with the corresponding 95% confidence intervals (CI) using the OpenEpi TwobyTwo module¹⁸ to determine if sex was associated with particular pain concepts in these data (ie, in our study “2 by 2 tables” were used to estimate the associations between sex and each pain concept from counts of subpopulations with and without the pain concept among females and males). A ratio >1 signified greater female prevalence; a ratio <1 signified greater male prevalence, and a ratio = 1 (or when the 95% CI contained 1) was interpreted as no evidence of difference in prevalence between females and males. Results from the 2 databases were then compared qualitatively.

3. Results

The flowchart of **Figure 1** illustrates the total participants with EHR in *All of Us* and *Epic Cosmos*; age, sex, and race/ethnicity distributions by database are available in **Table 1**. Of 249,537

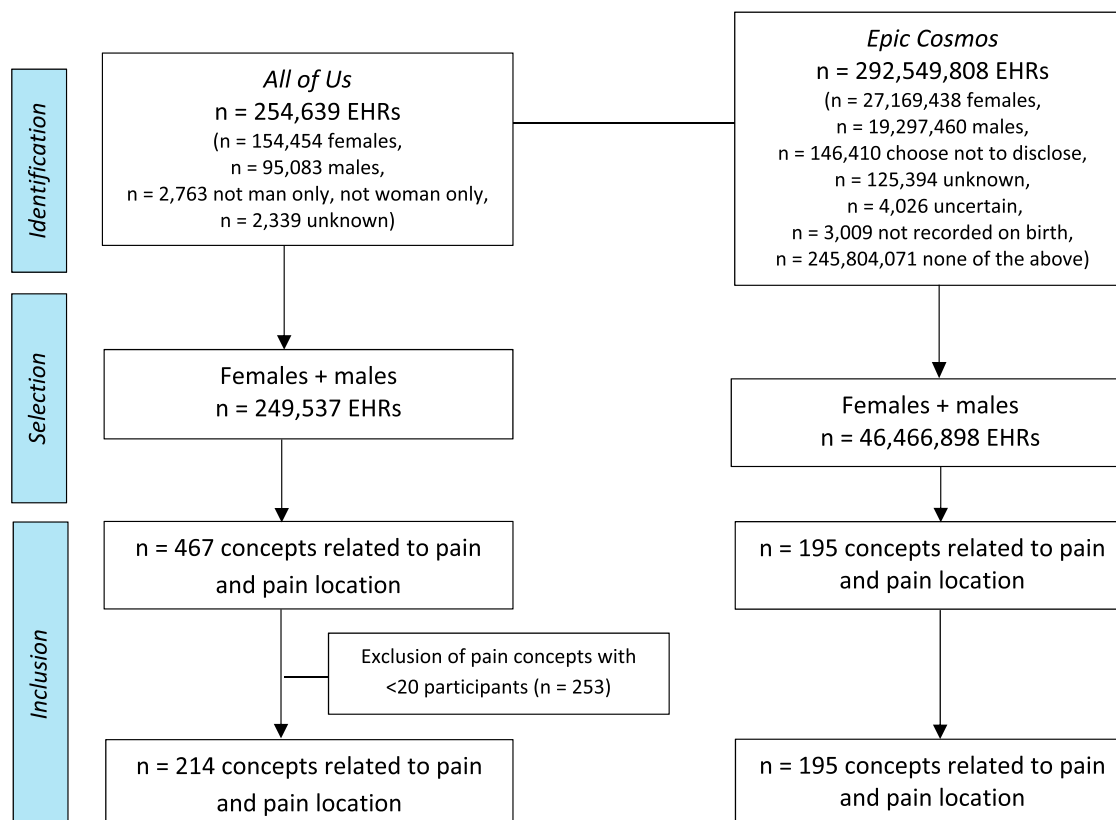


Figure 1. Flow chart diagram for inclusion of pain concepts. EHRs, electronic health records.

female and male participants in *All of Us*, we identified 467 distinctive pain concepts. After excluding those with <20 participants (n = 253), a total of 214 pain concepts were included in the analysis. The concepts with the largest sample size (count of EHRs) included “pain” (n = 201,240), “pain in limb” (n = 143,540), “musculoskeletal pain” (n = 129,120), “joint pain” (n = 121,380), “pain in lower limb” (n = 118,760), “abdominal pain” (n = 102,640), “chest pain” (n = 97,100), “backache” (n = 94,380), “pain in upper limb” (n = 84,000), and “chronic pain” (n = 80,720). Subsequently, we searched the 46,466,898 participants in *Epic Cosmos* for the same 214 pain concepts included from *All of Us*, which yielded a total of 195 pain concepts.

3.1. Sex differences in pain prevalence in All of Us

Supplemental Table 2, <http://links.lww.com/PR9/A361> shows sex-specific prevalence estimates and PRs for sex differences in prevalence for the 214 pain concepts extracted from *All of Us*. Most pain concepts (72.9%) were more prevalent among females, namely (in descending order of magnitude of estimated PRs) “pain of breast” (PR = 1.59, 95% CI 1.58, 1.60), “perineal pain” (PR = 1.48, 95% CI 1.45, 1.50), “pelvic and perineal pain” (PR = 1.44, 95% CI 1.41, 1.47), “pain in pelvis” (PR = 1.39, 95% CI 1.38, 1.40), “myofascial pain” (PR = 1.35, 95% CI 1.32, 1.40), “myofascial pain syndrome” (PR = 1.35, 95% CI 1.29, 1.41), and

“joint pain in the right and left hands” (PR = 1.32, 95% CI 1.24, 1.41). Conversely, a total of 19 pain concepts (8.9%) were more prevalent among males. In descending order, these were “vertebrogenic pain syndrome” (PR = 0.46, 95% CI 0.36, 0.60), “chronic chest pain” (PR = 0.65, 95% CI 0.55, 0.77), “phantom limb pain syndrome” (PR = 0.65, 95% CI 0.56, 0.74), “pain of lower limb due to atherosclerosis” (PR = 0.69, 95% CI 0.57, 0.84), and “inguinal pain” (PR = 0.77, 95% CI 0.70, 0.85). Finally, there was no evidence of sex differences in prevalence in 39 pain concepts (18.2%).

Among the 25 pain concepts with details on the chronicity, 80.0% of the 10 acute pain concepts (including the 3 most common: “acute pain,” “acute postoperative pain,” and “acute low back pain”) and 66.7% of the 15 chronic pain concepts (including the 3 most common: “chronic pain,” “chronic pain syndrome,” and “chronic low back pain”) had higher prevalence among females (PRs ranging from 1.07 to 1.15 among the acute pain concepts, and PRs ranging from 1.09 to 1.27 among the chronic pain concepts).

3.2. Sex differences in pain prevalence in Epic Cosmos

Among the 195 pain concepts included in the analysis of *Epic Cosmos* (Supplemental Table 3, <http://links.lww.com/PR9/A361>), 161 pain concepts (82.6%) were more prevalent among females, namely (in descending order of magnitude of estimated

Table 1

Summary of self-reported age, sex assigned at birth, race, and ethnicity by database.

Variable	All of Us n = 249,537		Epic cosmos n = 46,466,898	
	Categories	%	Categories	%
Age (y)	18–44	30.5	<18	17.0
	45–64	36.5	18–29	14.9
	≥65	33.0	30–39	14.1
			40–49	12.3
			50–64	17.5
			65–74	11.2
			75–84	7.6
≥85 y	5.4			
Sex assigned at birth*	Female	61.9	Female	58.5
	Male	38.1	Male	41.5
Race	Asian	2.8	American Indian or Alaska Native	0.9
	Black or African American	20.3	Asian	4.3
	White	53.6	Black or African American	13.9
	Another single population	0.7	Native Hawaiian or Other Pacific Islander	0.5
	More than 1 population	1.7	White	62.5
	None indicated	18.1	Other Race	11.1
	I prefer not to answer	0.6	None of the above	13.8
Ethnicity	Skip	2.1		
	Hispanic or Latino	19.2	Hispanic or Latino	12.8
	Non-Hispanic	76.9	Non-Hispanic	68.1
	None of these	1.1	None of the above	19.1
	Prefer not to answer	0.6		
Skip	2.1			

* The *All of Us* database also includes “Other” category for sex assigned at birth, and *Epic Cosmos* contains additional categories such as “Choose not to disclose,” “Not recorded on birth certificate,” “Uncertain,” and “Unknown.” These categories were excluded from analysis to ensure a consistent comparison across both databases. Heterogeneity in reported sociodemographic categories and lack of sex-stratified data precluded the use of age, race, and ethnicity in analytic models.

Table 2**Magnitude and direction of differences in sex-specific prevalence of pain concepts in *All of Us* and *Epic Cosmos*.**

Pain concept	All of Us			Epic cosmos		
	PR	95% CI (LL, UL)	Sex-specific prevalence	PR	95% CI (LL, UL)	Sex-specific prevalence
Toothache	0.99	0.90, 1.10	F ~ M	1.03	1.03, 1.03	F > M
Painful swallowing	0.97	0.83, 1.14	F ~ M	1.08	1.07, 1.09	F > M
Shoulder pain	1.01	1.01, 1.02	F > M	1.01	1.00, 1.01	F ~ M
Pain of right forearm	1.08	0.95, 1.22	F ~ M	1.06	1.05, 1.06	F > M
Pain of left upper arm	1.08	0.95, 1.22	F ~ M	1.24	1.23, 1.25	F > M
Pain co-occurrent and due to varicose veins of right leg	0.97	0.93, 1.14	F ~ M	1.24	1.24, 1.25	F > M
Pain in bilateral legs	1.00	0.97, 1.03	F ~ M	1.10	1.10, 1.10	F > M
Pain of left lower leg	1.05	0.98, 1.13	F ~ M	1.10	1.10, 1.11	F > M
Pain of right lower leg	1.02	0.95, 1.10	F ~ M	1.09	1.08, 1.09	F > M
Pain of left calf	1.08	0.97, 1.19	F ~ M	1.12	1.12, 1.13	F > M
Pain of right calf	1.08	0.97, 1.19	F ~ M	1.10	1.10, 1.11	F > M
Pain in right heel	1.08	0.95, 1.22	F ~ M	1.12	1.11, 1.12	F > M
Pain at rest due to peripheral vascular disease	0.81	0.65, 1.01	F ~ M	0.75	0.74, 0.76	M > F
Pain of intercostal space	1.00	0.95, 1.06	F ~ M	1.04	1.03, 1.05	F > M
Angina decubitus	0.97	0.87, 1.09	F ~ M	0.86	0.82, 0.90	M > F
Acute abdominal pain	1.08	0.95, 1.22	F ~ M	1.18	1.18, 1.19	F > M
Right sided chest pain	1.08	0.95, 1.22	F ~ M	1.07	1.06, 1.07	F > M
Chest pain on exertion	0.97	0.83, 1.14	F ~ M	0.78	0.77, 0.78	M > F
Noncardiac chest pain	0.97	0.83, 1.14	F ~ M	1.07	1.07, 10.9	F > M
Chest pain at rest	0.97	0.83, 1.14	F ~ M	0.98	0.98, 0.99	M > F
Renal pain	0.96	0.93, 1.00	F ~ M	0.92	0.91, 0.93	M > F
Thoracic nerve root pain	0.98	0.91, 1.06	F ~ M	1.15	1.12, 1.19	F > M
Neuropathic pain	1.08	1.00, 1.16	F ~ M	1.06	1.05, 1.06	F > M
Pain radiating to right leg	0.97	0.83, 1.14	F ~ M	1.09	1.08, 1.10	F > M
Pain radiating to left leg	0.97	0.83, 1.14	F ~ M	1.08	1.07, 1.09	F > M
Cervical nerve root pain	0.97	0.83, 1.14	F ~ M	1.11	1.10, 1.11	F > M
Low back pain co-occurrent with neuralgia of left sciatic nerve	0.97	0.83, 1.14	F ~ M	1.12	1.11, 1.13	F > M
Peripheral neuropathic pain	0.97	0.83, 1.14	F ~ M	1.02	1.01, 1.03	F > M
Chronic musculoskeletal pain	0.84	0.81, 0.87	M > F	1.00	0.99, 1.00	F ~ M
Pain on left shoulder	1.15	1.04, 1.28	F > M	1.01	1.00, 1.01	F ~ M
Pain in hallux	0.97	0.83, 1.14	F ~ M	0.96	0.95, 0.96	M > F
Scapalgia	1.08	0.95, 1.22	F ~ M	1.12	1.11, 1.13	F > M
Pain in lumbar spine	0.97	0.83, 1.14	F ~ M	1.06	1.06, 1.07	F > M
Tenalgia	0.81	0.65, 1.01	F ~ M	1.05	1.04, 1.06	F > M
Anorectal pain	0.92	0.80, 1.07	F ~ M	0.94	0.93, 0.94	M > F
Anal pain	0.97	0.83, 1.14	F ~ M	0.97	0.96, 0.98	M > F
Acute pain	1.10	1.08, 1.11	F > M	0.86	0.85, 0.86	M > F
Rectal pain	0.90	0.79, 1.02	F ~ M	0.92	0.92, 0.93	M > F
Pain provoked by trauma	0.92	0.88, 0.96	M > F	1.02	1.00, 1.04	F ~ M
Chronic postoperative pain	1.05	0.97, 1.13	F ~ M	1.11	1.10, 1.12	F > M

Bold denotes different directions of higher sex-specific prevalence between the 2 databases.
CI, confidence interval; LL, lower limit; PR, prevalence ratio; UL, upper limit.

PRs) “pelvic and perineal pain” (PR = 1.62, 95% CI 1.62, 1.62), “perineal pain” (PR = 1.60, 95% CI 1.60, 1.60), “scalding pain on urination” (PR = 1.45, 95% CI 1.45, 1.45), “bladder pain” (PR = 1.44, 95% CI 1.43, 1.44), “dysuria” (PR = 1.38, 95% CI 1.38, 1.38), and “referred otalgia” (PR = 1.35, 95% CI 1.33, 1.36). Conversely, 26 pain concepts (13.3%) were more prevalent

among males, such as—in descending order—“painful phantom limb syndrome” (PR = 0.61, 95% CI 0.60, 0.63), “inguinal pain” (PR = 0.65, 95% CI 0.64, 0.65), “chronic chest pain” (PR = 0.69, 95% CI 0.69, 0.70) and “chest pain on exertion” (PR = 0.78, 95% CI 0.77, 0.78), “pain of lower limbs due to atherosclerosis” (PRs between 0.71 in the right lower limb and 0.80 in the left lower

limb), “pain at rest due to peripheral vascular disease” (PR = 0.75, 95% CI 0.74, 0.76), “chronic pain due to injury” (PR = 0.81, 95% CI 0.80, 0.82), “acute postthoracotomy pain syndrome” (PR = 0.83, 95% CI 0.81, 0.86), “angina decubitus” (PR = 0.86, 95% CI 0.82, 0.90), “acute pain” (PR = 0.86, 95% CI 0.85, 0.86), and “acute pain due to injury” (PR = 0.86, 95% CI 0.85, 0.86). No evidence of sex differences in prevalence was observed in 8 pain concepts (4.1%).

When categorizing the subset that had acute and chronic pain labels (25 pain concepts), 70.0% of the 10 acute pain concepts (including the 3 most common: “acute low back pain,” “acute postoperative pain,” and “acute back pain with sciatica”) and 73.3% of the 15 chronic pain concepts (including the 3 most common: “chronic pain,” “chronic low back pain,” and “chronic pain of right upper limb”) had higher prevalence among females (PRs ranging from 1.05 to 1.18 among the acute pain concepts, and PRs ranging from 1.02 to 1.30 among the chronic pain concepts).

Among the 195 pain concepts identified in both databases, 40 (20.5% of pain concepts) displayed inconsistent findings of sex-specific prevalence; ie, evidence of sex-difference in prevalence in one database but not in the other (**Table 2**). Although most PRs suggested minimal differences in prevalence between males and females in the same direction in both databases, 1 pain concept (0.5% of pain concepts included; ie, “acute pain”) demonstrated different PR directions of sex-specific prevalence (higher prevalence among females in *All of Us* and higher prevalence among males in *Epic Cosmos*).

4. Discussion

This study explored sex differences in the prevalence of pain symptoms using data from the *All of Us* and the *Epic Cosmos*. Overcoming limitations of the published literature on sex differences in pain, our 2 large and diverse U.S samples corroborate previous findings of higher pain burden in females.

Our analysis revealed that a notable 73% of pain concepts in these data demonstrated a higher female prevalence, particularly those associated with the breast, pelvis, and myofascial systems. By contrast, a smaller subset of pain concepts (9%–13%) exhibited a higher prevalence in males, such as “vertebrogenic pain syndrome” and “chronic chest pain.” Additionally, for certain pain concepts, there was no evidence of difference in prevalence between females and males.

The observed higher prevalence of pain among females across multiple concepts aligns with the existing literature.^{5,11,15,45,89} This disparity can be attributed to a complex interplay of biological (eg, genetic, molecular, cellular level), psychological, and societal factors.³⁵ Biologically, the distribution of sex hormones and their receptors in key areas of the nervous system involved in pain perception and modulation influence pain sensitivity differently between females and males. Testosterone generally exerts antinociceptive effects,⁷ whereas estradiol and progesterone display both pronociceptive and antinociceptive properties depending on context.⁷⁵ Moreover, sex hormones influence endogenous pain modulation⁶ by altering the sensitivity of serotonergic and dopaminergic receptors⁵⁷ and modulating the expression of endogenous opioid receptors.¹⁴ Fluctuation in female sex hormones across the menstrual cycle and their effects on descending pain modulatory pathways⁶ potentially explains variations in experimental pain sensitivity and increased pain intensity during specific phases.^{42,63,73,74} Nevertheless, other studies have failed to demonstrate significant changes in pain perception across menstrual phases in healthy-females,^{26,38,72,76,93} underscoring the complexity of this

relationship. Because females generally have a higher average age, and some pain conditions are more common with higher age, it is possible that some of the higher female prevalence may be due to older females in our sample. Additionally, males and females exhibit different patterns of activity and functional connectivity in brain areas responsible for pain modulation, emotional processing, and the integration of sensory and emotional inputs.^{6,24,43,88} These regions include the anterior cingulate cortex, insula, prefrontal cortex, amygdala, and periaqueductal gray. Differences in functional connectivity of these areas also appear to be age dependent.⁵⁰

Genetic factors also play a significant role in sex differences in pain sensitivity. For example, genetic variants of the melanocortin-1 receptor (*MC1R*) show sex-dependent effects on analgesia, whereas the A118G single-nucleotide polymorphism of the *OPRM1* gene is associated with pressure pain sensitivity in males but not in females. Decreased catechol-O-Methyltransferase (*COMT*) expression is linked to increased pain perception, particularly among females, due to estrogen-driven downregulation of *COMT* expression. Genetic variants in the transient receptor potential cation channel (*TRPV1*) have also been implicated in greater pain sensitivity among females.^{5,49}

However, it is notable that psychological and social factors may further influence pain perception and coping strategies differently by sex and gender.^{5,51} Women are often reported to exhibit greater levels of catastrophizing,^{20,39} depression,³⁰ kinesiophobia,⁸ pain-related anxiety and fear,^{12,92} and lower level of self-efficacy,³² all of which are thought to be mediators of sex and gender differences in pain.⁸² Moreover, gender roles and societal expectations significantly influence how pain is expressed and tolerated.^{5,82,83} The data ultimately come from men and women who recognized their symptoms, sought care, communicated their symptoms to their clinicians, and had those symptoms recorded by those clinicians. These processes are deeply shaped by gendered social norms and behaviors, not just biology. Although the available analytical variable is “sex assigned at birth,” observed findings likely reflect a combination of both sex- and gender-related processes. Women are often perceived as more likely to express pain and seek treatment, whereas men may face societal pressure to tolerate and underreport pain.^{60,90} Substantial evidence has shown that women are often treated with less effective pain management strategies compared with man for similar complaints, and their pain is likely to be attributed to psychological causes a phenomenon sometimes referred to as “psychologizing” of women’s pain.^{31,68}

An increased prevalence among females was found in specific anatomical sites, especially in the breast, perineum, pelvis, myofascial structures, and hands. In addition to the contributing factors presented above, certain anatomical considerations can further explain differences in pain location. For example, unique anatomical structure and changes in breast tissue during hormonal cycles can predispose females to localized pain.^{4,80} Similarly, differences in pelvic structures, such as wider pelvis and the presence of organs such as the uterus and ovaries, may increase the likelihood of pain from gynecological or urological conditions.⁵³ Conversely, the higher prevalence among males for certain pain symptoms, such as “vertebrogenic pain syndrome” and “chronic chest pain,” may be attributed to biological, hormone-specific, and lifestyle factors.⁴⁷ For instance, a higher prevalence of cardiovascular disease and related conditions among males is well documented, which have often been associated to higher rates of smoking, obesity, and differences in physical activity (although these differences by sex may have been shrinking over the years).^{3,44} Additionally, predominantly

male occupations involving heavy physical labor and military combat might contribute to an increased incidence of musculoskeletal conditions like “vertebrogenic pain syndrome,” “acute postthoracotomy pain syndrome,” and “phantom limb syndrome with pain.” Intriguingly, “chronic musculoskeletal pain” had a higher prevalence among males in the *All of Us* data, contrary to the existing literature.⁸⁹ This discrepancy may be attributed to higher rates of localized or injury-induced musculoskeletal pain in these data, or differences in how chronic musculoskeletal pain was defined or reported in *All of Us* relative to other studies. Our findings that 3 acute pain concepts (ie, “acute postthoracotomy pain syndrome,” “acute pain, and “acute pain due to injury”) were overrepresented in males according to *Epic Cosmos* despite sex and gender differences in care seeking behavior and reporting may be interpreted in light of emerging evidence of sex-specific vulnerability to acute pain hypersensitivity. Martin and colleagues found that only males—both in mice and humans—developed pain hypersensitivity in contexts associated with prior aversive pain, which was linked to stress, testosterone, and memory-related mechanisms involving the hypothalamic–pituitary–adrenal axis and protein kinases.⁴⁷

Mostly similar results were derived from the 2 databases, except for 1 pain concept, which displayed discrepant findings. Possible explanations could be attributed to differences in use of coding in the 2 data sources given the redundancy in pain concepts (eg, acute pain vs acute pain due to injury). Opposite directions could also potentially be attributed to differences in population demographics of healthcare systems and individuals providing data to the databases. Although *All of Us* intentionally oversamples historically underrepresented groups in biomedical research derived from various healthcare settings, *Epic Cosmos* aggregates EHR data from patients who actively sought care at sites using Epic EHR. Conversely, some other pain concepts showed different results in one database the condition did not exhibit any significant difference between females and males, whereas in the second database, there was a clear sex-specific prevalence. Much of these discrepancies could be attributed to instability of estimates due to smaller sample sizes and broader confidence intervals in *All of Us*. Given notable sex differences in the prevalence of pain concepts, these findings highlight the importance of continuing to integrate sex into pain research and clinical management. This knowledge is essential to inform personalized preventive, screening, and treatment strategies to enhance the effectiveness of pain care for all.

4.1. Strengths and limitations

Strengths of this study include the large national sample across the United States, and the use of 2 independent data sources for triangulation of findings, with strong agreement between them. Limitations include that studies such as the present one, using large national databases, rely on correct and complete EHR documentation.⁸¹ This study was exploratory in nature and did not involve formal hypothesis testing but rather relied on PRs and 95% CIs to estimate the magnitude and direction of sex-related differences in pain prevalence. Caution is warranted to prevent overinterpretation of findings due to the absence of correction for multiple comparisons. Moreover, this study examined only differences in prevalence of pain symptoms between females and males, not accounting for other categories reported “unknown,” “not man only, not woman only,” “not recorded on birth,” and “uncertain.” Although best practices suggest measuring sex and gender separately,²⁹ only “sex assigned at birth” was available in these data. Additionally, these findings only reflect

data from the US population who received health care during the study period. Although some institutions may contribute data to both *All of Us* and *Epic Cosmos*, any overlap of participants across the 2 databases—if present—cannot be excluded because data are deidentified. Although pain concepts were documented in internationally, standardized clinical terminology to represent medical terms in EHRs (SNOMED), no data were present on diagnostic criteria used nor final diagnoses given.⁹¹ Labels of acute vs chronic included in certain pain concepts were maintained from the original pain concepts in the databases applied without standard criteria by clinicians assigning concepts to individuals (SNOMED lacks an explicit time-based definition of acute vs chronic). Finally, although age, race and ethnicity have been suggested to influence sex differences in pain prevalence,^{25,45} current analyses could not adjust for these factors due to absence of sex-stratified data by age groups (ie, age distribution was only available at the aggregate-level for total counts by pain concept) and unavailability of all race and ethnicity information at the general-access level of these databases.

Findings from 2 large nationwide databases indicate a higher pain prevalence among females receiving health care in the United States. This study provides robust evidence for sex differences in pain, underscoring the need for enhanced use of pain prevention and management approaches in this population.

Disclosures

The authors have no conflict of interest to declare.

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Data availability: Data subject to third party restrictions. The data that support the findings of this study are available from *All of Us* and *Epic Cosmos* research programs. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at <https://allofus.nih.gov/> and <https://cosmos.epic.com/> with the permission of *All of Us* and *Epic Cosmos* research programs, respectively.

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References

- [1] All of Us Research Program Investigators, Denny JC, Rutter JL, Goldstein DB, Philippakis A, Smoller JW, Jenkins G, Dishman E. The “All of Us” research program. *N Engl J Med* 2019;381:668–76.
- [2] All of Us Research Program, U.S. Department of Health and Human Services. Data and statistics dissemination policy, 2020. Available at: https://supportresearchallofus.org/hc/en-us/article_attachments/22307203778836. Accessed November 6, 2024.

- [3] Athnaiel O, Cantillo S, Paredes S, Knezevic NN. The role of sex hormones in pain-related conditions. *Int J Mol Sci* 2023;24:1866.
- [4] Bakhtiyari M, Kazemian E, Kabir K, Hadaegh F, Aghajanian S, Mardi P, Ghahfarokhi NT, Ghanbari A, Mansournia MA, Azizi F. Contribution of obesity and cardiometabolic risk factors in developing cardiovascular disease: a population-based cohort study. *Sci Rep* 2022;12:1544.
- [5] Balleyguier C, Arfi-Rouche J, Haddag L, Canale S, Delalogue S, Dromain C. Breast pain and imaging. *Diagn Interv Imaging* 2015;96:1009–16.
- [6] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth* 2013;111:52–8.
- [7] Bernal SA, Morgan MM, Craft RM. PAG mu opioid receptor activation underlies sex differences in morphine antinociception. *Behav Brain Res* 2007;177:126–33.
- [8] Bianchi VE. The anti-inflammatory effects of testosterone. *J Endocr Soc* 2018;3:91–107.
- [9] Botta AFB, de Cássia Pinto da Silva J, dos Santos Lopes H, Boling MC, Briani RV, de Azevedo FM. Group- and sex-related differences in psychological and pain processing factors in people with and without patellofemoral pain: correlation with clinical outcomes. *BMC Musculoskelet Disord* 2023;24:397.
- [10] Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. *Headache* 2018;58:496–505.
- [11] Burch RC, Buse DC, Lipton RB. Migraine: epidemiology, burden, and comorbidity. *Neurol Clin* 2019;37:631–49.
- [12] Casale R, Atzeni F, Bazzichi L, Beretta G, Costantini E, Sacerdote P, Tassorelli C. Pain in women: a perspective review on a relevant clinical issue that deserves prioritization. *Pain Ther* 2021;10:287–314.
- [13] Chen Q, Zhang W, Sadana N, Chen X. Estrogen receptors in pain modulation: cellular signaling. *Biol Sex Differ* 2021;12:22.
- [14] Chen L, Zhang S, Tan Y, Zheng Y, Fang S, Yi Y, Xiong X. Anxiety mediates association between sex and jaw function limitation in temporomandibular disorder patients from China. *Front Neurol* 2024; 15:1398788.
- [15] Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. *Eur J Pain* 2004;8:397–411.
- [16] Craft RM. Modulation of pain by estrogens. *PAIN* 2007;132(suppl 1): S3–12.
- [17] Dao TT, LeResche L. Gender differences in pain. *J Orofac Pain* 2000;14: 169–95.
- [18] Dean AG, Sullivan KM, Soe MM. OpenEpi: Open source epidemiologic statistics for public health, version 3. 01. OpenEpi, 2013. Available at: https://www.openepi.com/Menu/OE_Menu.htm. Accessed December 1, 2024.
- [19] Dugan SA, Powell LH, Kravitz HM, Everson Rose SA, Karavolos K, Luborsky J. Musculoskeletal pain and menopausal status. *Clin J Pain* 2006;22:325–31.
- [20] 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.
- [21] Ekbohm K, Ahlberg B, Schéle R. Prevalence of migraine and cluster headache in Swedish men of 18. *Headache* 1978;18:9–19.
- [22] Eke PI, Borgnakke WS, Genco RJ. Recent epidemiologic trends in periodontitis in the USA. *Periodontol* 2000 2020;82:257–67.
- [23] Evans PL, Prior JA, Belcher J, Hay CA, Mallen CD, Roddy E. Gender-specific risk factors for gout: a systematic review of cohort studies. *Adv Rheumatol* 2019;59:24.
- [24] Failla MD, Beach PA, Atalla S, Dietrich MS, Bruehl S, Cowan RL, Monroe TB. Gender differences in pain threshold, unpleasantness, and descending pain modulatory activation across the adult life span: a cross sectional study. *J Pain* 2024;25:1059–69.
- [25] Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open* 2016;6:e010364.
- [26] Fillingim RB, Maixner W, Girdler SS, Light KC, Harris MB, Sheps DS, Mason GA. Ischemic but not thermal pain sensitivity varies across the menstrual cycle. *Psychosomatic Med* 1997;59:512–20.
- [27] Fillingim RB. Sex, gender and pain: women and men really are different. *Curr Rev Pain* 2000;4:24–30.
- [28] Girard-Tremblay L, Auclair V, Daigle K, Léonard G, Whittingstall K, Goffaux P. Sex differences in the neural representation of pain unpleasantness. *J Pain* 2014;15:867–77.
- [29] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahan B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park EK, Catalá-López F, deVeber G, Gotay C, Khan G, Hosgood HD III, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Sanabria J, Beardesley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrimo MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad SM, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Orjuela C, van Gool CH, Violante F, Oh IH, Deribe K, Soriede K, Knibbs L, Kerselesidze M, Green M, Cardenas R, Roy N, Tillmann T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M, Naghavi M. The Global Burden of Cancer 2013. *JAMA Oncol* 2015;1:505–27.
- [30] Heidari S, Babor TF, De Castro P, Tort S, Curmo M. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016;1:2.
- [31] Hirsh AT, Waxenberg LB, Atchison JW, Gremillion HA, Robinson ME. Evidence for sex differences in the relationships of pain, mood, and disability. *J Pain* 2006;7:592–601.
- [32] Hoffmann DE, Tarzian AJ. The girl who cried pain: a bias against women in the treatment of pain. *J Law Med Ethics* 2001;29:13–27.
- [33] Jackson T, Iezzi T, Gunderson J, Nagasaka T, Fritch A. Gender differences in pain perception: the mediating role of self-efficacy beliefs. *Sex Roles* 2002;47:561–8.
- [34] Joel D, Fine C. Who is a woman: sex, gender and policy making. *J Controversial Ideas* 2022;2:1.
- [35] Johnson JL, Repta R. Sex and gender: beyond the binaries. In: Oliffe JL, Greaves L, eds. *Designing and conducting gender, sex, and health research*. Thousand Oaks: SAGE; 2011.
- [36] Kapos FP, Craig KD, Anderson SR, Bernardes SF, Hirsh AT, Karos K, Keogh E, Reynolds Losin EA, McParland JL, Moore DJ, Ashton-James CE. Social determinants and consequences of pain: toward multilevel, intersectional, and life course perspectives. *J Pain* 2024; 25:104608.
- [37] Keogh E. Sex differences in pain. *Rev Pain* 2008;2:4–7.
- [38] Kim YS, Kim N. Sex-gender differences in irritable bowel syndrome. *J Neurogastroenterol Motil* 2018;24:544–58.
- [39] Klatzkin RR, Mechlin B, Girdler SS. Menstrual cycle phase does not influence gender differences in experimental pain sensitivity. *Eur J Pain* 2010;14:77–82.
- [40] Le LHL, Brown VAV, Mol S, Aziji K, Kuijper MM, Becker L, Koopman SSHA. Sex differences in pain catastrophizing and its relation to the transition from acute pain to chronic pain. *BMC Anesthesiol* 2024;24: 25.
- [41] Lee SK. Sex as an important biological variable in biomedical research. *BMB Rep* 2018;51:167–73.
- [42] Lenert ME, Avona A, Garner KM, Barron LR, Burton MD. Sensory neurons, neuroimmunity, and pain modulation by sex hormones. *Endocrinology* 2021;162:bqab109.
- [43] LeResche L, Mancl L, Sherman JJ, Gandara B, Dworkin SF. Changes in temporomandibular pain and other symptoms across the menstrual cycle. *PAIN* 2003;106:253–61.
- [44] Linnman C, Beucke J-C, Jensen KB, Gollub RL, Kong J. Sex similarities and differences in pain-related periaqueductal gray connectivity. *PAIN* 2012;153:444–54.
- [45] Maas AH, Appelman YEA. Gender differences in coronary heart disease. *Neth Heart J* 2010;18:598–603.
- [46] Mansfield KE, Sim J, Jordan JL, Jordan KP. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. *PAIN* 2016;157:55–64.
- [47] Mapes BM, Foster CS, Kusnoor SV, Epelbaum MI, AuYoung M, Jenkins G, Lopez-Class M, Richardson-Heron D, Elmi A, Surkan K, Cronin RM, Wilkins CH, Pérez-Stable EJ, Dishman E, Denny JC, Rutter JL. Diversity and inclusion for the All of Us research program: a scoping review. *PLoS One* 2020;15:e0234962.
- [48] Martin LJ, Acland EL, Cho C, Gandhi W, Chen D, Corley E, Kadoura B, Levy T, Mirali S, Tohyama S, Khan S, MacIntyre LC, Carlson EN, Schweinhart P, Mogil JS. Male-specific conditioned pain hypersensitivity in mice and humans. *Curr Biol* 2019;29:192–201.e4.
- [49] Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, De Vries GJ, Epperson CN, Govindan R, Klein SL, Lonardo A, Maki PM, McCullough LD, Regitz-Zagrosek V, Regensteiner JG, Rubin

- JB, Sandberg K, Suzuki A. Sex and gender: modifiers of health, disease, and medicine. *Lancet* 2020;396:565–82.
- [50] Meloto CB, Bortsov AV, Bair E, Helgeson E, Ostrom C, Smith SB, Dubner R, Slade GD, Fillingim RB, Greenspan JD, Ohrbach R, Maixner W, McLean SA, Diatchenko L. Modification of COMT-dependent pain sensitivity by psychological stress and sex. *PAIN* 2016;157:858–67.
- [51] Mogil JS. Qualitative sex differences in pain processing: emerging evidence of a biased literature. *Nat Rev Neurosci* 2020;21:353–65.
- [52] Monroe TB, Fillingim RB, Bruehl SP, Rogers BP, Dietrich MS, Gore JC, Atalla SW, Cowan RL. Sex differences in brain regions modulating pain among older adults: a cross-sectional resting state functional connectivity study. *Pain Med* 2018;19:1737–47.
- [53] Noel A, Bartelt K. Cosmos: real-world data powered by the healthcare community. *J Soc Clin Data Manag.* 2023;3. doi:10.47912/jscdm.246.
- [54] Origoni M, Leone Roberti Maggiore U, Salvatore S, Candiani M. Neurobiological mechanisms of pelvic pain. *Biomed Res Int* 2014;2014:903848.
- [55] Osborne NR, Davis KD. Sex and gender differences in pain. *Int Rev Neurobiol* 2022;164:277–307.
- [56] Paller CJ, Campbell CM, Edwards RR, Dobs AS. Sex-based differences in pain perception and treatment. *Pain Med* 2009;10:289–99.
- [57] Palmeira CC, Ashmawi HA, Posso IDP. Sex and pain perception and analgesia. *Braz J Anesthesiol* 2011;61:814–28.
- [58] Paredes S, Cantillo S, Candido KD, Knezevic NN. An association of serotonin with pain disorders and its modulation by estrogens. *Int J Mol Sci* 2019;20:5729.
- [59] Park J-O, Nam I-C, Kim C-S, Park S-J, Lee D-H, Kim H-B, Han K-D, Joo Y-H. Sex differences in the prevalence of head and neck cancers: a 10-year follow-up study of 10 million healthy people. *Cancers* 2022;14:2521.
- [60] Racine M, Tousignant-Lafamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. 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? *PAIN* 2012;153:602–18.
- [61] Racine M, Tousignant-Lafamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and pain perception—part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? *PAIN* 2012;153:619–35.
- [62] Ramirez AH, Sulleman L, Schlueter DJ, Halvorson A, Qian J, Ratsimbazafy F, Loperena R, Mayo K, Basford M, Deflaux N, Muthuraman KN, Natarajan K, Kho A, Xu H, Wilkins C, Anton-Culver H, Boerwinkle E, Cicek M, Clark CR, Cohn E, Ohno-Machado L, Schully SD, Ahmedani BK, Argos M, Cronin RM, O'Donnell C, Fouad M, Goldstein DB, Greenland P, Hebring SJ, Karlson EW, Khatri P, Korf B, Smoller JW, Sodeke S, Wilbanks J, Hentges J, Mockrin S, Lunt C, Devaney SA, Gebo K, Denny JC, Carroll RJ, Glazer D, Harris PA, Hripscak G, Philippakis A, Roden DM, Ahmedani B, Cole Johnson CD, Ahsan H, Antoine-LaVigne D, Singleton G, Anton-Culver H, Topol E, Baca-Motes K, Steinhubl S, Wade J, Begale M, Jain P, Sutherland S, Lewis B, Korf B, Behringer M, Gharavi AG, Goldstein DB, Hripscak G, Bier L, Boerwinkle E, Brilliant MK, Murali N, Hebring SJ, Farrar-Edwards D, Burnside E, Drezner MH, Taylor A, Channamsetty V, Montalvo W, Sharma Y, Chinae C, Jenks N, Cicek M, Thibodeau S, Holmes BW, Schlueter E, Collier E, Winkler J, Corcoran J, D'Addezio N, Daviglius M, Winn R, Wilkins C, Roden D, Denny J, Doheny K, Nickerson D, Eichler E, Jarvik G, Funk G, Philippakis A, Rehm H, Lennon N, Kathiresan S, Gabriel S, Gibbs R, Gil Rico EM, Glazer D, Grand J, Greenland P, Harris P, Shenkman E, Hogan WR, Igho-Pemu P, Pollan C, Jorge M, Okun S, Karlson EW, Smoller J, Murphy SN, Ross ME, Kaushal R, Winford E, Wallace F, Khatri P, Kheterpal V, Ojo A, Moreno FA, Kron I, Peterson R, Menon U, Lattimore PW, Leviner N, Obedin-Maliver J, Lunn M, Malik-Gagnon L, Mangravite L, Marallo A, Marroquin O, Visweswaran S, Reis S, Marshall G Jr, McGovern P, Mignucci D, Moore J, Munoz F, Talavera G, O'Connor GT, O'Donnell C, Ohno-Machado L, Orr G, Randal F, Theodorou AA, Reiman E, Roxas-Murray M, Stark L, Tepp R, Zhou A, Topper S, Trousdale R, Tsao P, Weidman L, Weiss ST, Wellis D, Whittle J, Wilson A, Zuchner S, Zwick ME. The All of Us Research Program: data quality, utility, and diversity. *Patterns (N Y)* 2022;3:100570.
- [63] Reis SE, Holubkov R, Smith AJC, Kelsey SF, Sharaf BL, Reichel N, Rogers WJ, Merz CN, Sopko G, Pepine CJ, WISE Investigators. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J* 2001;141:735–41.
- [64] Rezaei T, Hirschberg AL, Carlström K, Ernberg M. The influence of menstrual phases on pain modulation in healthy women. *J Pain* 2012;13:646–55.
- [65] Riley JL III, 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.
- [66] Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. *J Neurosci Res* 2017;95:500–8.
- [67] Rosseland LA, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. *PAIN* 2004;112:248–53.
- [68] Samulowitz A, Gremyr I, Eriksson E, Hensing G. "Brave Men" and "Emotional women": a theory-guided literature review on gender bias in health care and gendered norms towards patients with chronic pain. *Pain Res Manag* 2018;2018:6358624.
- [69] Sangalli L, Souza LC, Letra A, Shaddox L, Ioannidou E. Sex as a biological variable in oral diseases: evidence and future prospects. *J Dent Res* 2023;102:1395–416.
- [70] Sangalli L, Herreo Babiloni A, Thomas DC, Alessandri-Bonetti A. Musculoskeletal pain is associated with poor sleep quality and increased daytime sleepiness in dental students: a cross-sectional pilot study. *Quintessence Int* 2025;56:60–73.
- [71] Sangalli L, West-Pelak E, Knecht-Sabres L, Yanez-Regonesi F, Madhu N, Alabsy M, Kohli D, Alessandri-Bonetti A. Sex and academic stage differences in work-related musculoskeletal disorders pain among dental students. A cross-center cross-sectional study. *Cranio.* 2025;1–17. doi:10.1080/08869634.2025.2451272.
- [72] Sherman JJ, LeResche L. Does experimental pain response vary across the menstrual cycle? A methodological review. *Am J Physiol Regulat Integr Comp Physiol* 2006;291:R245–56.
- [73] Sherman JJ, LeResche L, Mancil LA, Huggins K, Sage JC, Dworkin SF. Cyclical effects on experimental pain response in women with temporomandibular disorders. *J Orofac Pain* 2005;19:133–43.
- [74] Silberstein SD, Merriam GR. Sex hormones and headache. *J Pain Symptom Manage* 1993;8:98–114.
- [75] Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppel RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. *J Neurosci* 2006;26:5777–85.
- [76] Söderberg K, Sundström Poromaa I, Nyberg S, Bäckström T, Nordh E. Psychophysically determined thresholds for thermal perception and pain perception in healthy women across the menstrual cycle. *Clin J Pain* 2006;22:610–6.
- [77] Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2009;48:143–57.
- [78] Sorge RE, Totsch SK. Sex differences in pain. *J Neurosci Res* 2017;95:1271–81.
- [79] Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, Ansha MG, Barac A, Bensenor IM, Doan LP, Edessa D, Endres M, Foreman KJ, Gankpe FG, Gopalkrishna G, Goulart AC, Gupta R, Hankey GJ, Hay SI, Hegazy MI, Hilawe EH, Kasaieian A, Kassa DH, Khalil I, Khang YH, Khubchandani J, Kim YJ, Kokubo Y, Mohammed MA, Mokdad AH, Moradi-Lakeh M, Nguyen HLT, Nirayo YL, Qorbani M, Ranta A, Roba KT, Safiri S, Santos IS, Satpathy M, Sawhney M, Shiferaw MS, Shiu I, Smith M, Szeoek CEI, Truong NT, Venketasubramanian N, Weldegewergs KG, Westerman R, Wijeratne T, Tran BX, Yonemoto N, Feigin VL, Vos T, Murray CJL. Global Burden of Disease 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17:954–76.
- [80] Tahir MT, Vadakekut ES, Shamsudeen S. Mastalgia. *StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; https://www.ncbi.nlm.nih.gov/sites/books/NBK562195/2024 (2022, Accessed December 1, 2024).*
- [81] Tarabichi Y, Frees A, Honeywell S, Huang C, Naidech AM, Moore JH, Kaelber DC. The cosmos collaborative: a vendor-facilitated electronic health record data aggregation platform. *ACI Open* 2021;05:e36–46.
- [82] Templeton KJ. Sex and gender issues in pain management. *J Bone Joint Surg* 2020;102(suppl 1):32–5.
- [83] 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.
- [84] Unruh AM. Gender variations in clinical pain experience. *PAIN* 1996;65:123–67.
- [85] Vina ER, Ran D, Ashbeck EL, Kwok CK. Widespread pain is associated with increased risk of no clinical improvement after TKA in women. *Clin Orthop Relat Res* 2019;478:1453.
- [86] Vincent K, Tracey I. Hormones and their interaction with the pain experience. *Rev Pain* 2008;2:20–24.
- [87] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, Initiative STROBE. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. *PLoS Med* 2007;4:e296.

- [88] Wang G, Erpelding N, Davis KD. Sex differences in connectivity of the subgenual anterior cingulate cortex. *PAIN* 2014;155:755–63.
- [89] Wijnhoven HA, de Vet HC, Picavet HS. Prevalence of musculoskeletal disorders is systematically higher in women than in men. *Clin J Pain* 2006; 22:717–24.
- [90] 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.
- [91] Wolfe F, Walitt B, Perrot S, Rasker JJ, Häuser W. Fibromyalgia diagnosis and biased assessment: sex, prevalence and bias. *PLoS One* 2018;13:e0203755.
- [92] Zhang H, Bi Y, Hou X, Lu X, Tu Y, Hu L. The role of negative emotions in sex differences in pain sensitivity. *Neuroimage* 2021;245:118685.
- [93] Zhang L, Zhao Y, Liu X, Chen J, Sun M, Zhang J, Zhang W. Changes in sex hormones and their interactions are related to pain perception between different menstrual subphases. *Am J Physiol Regul Integr Comp Physiol* 2023;325:R280–9.