OPEN

META-ANALYSIS

Global Burden of Complex Regional Pain Syndrome in At-Risk Populations: Estimates of Prevalence From 35 Countries Between 1993 and 2023

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BACKGROUND: Complex regional pain syndrome (CRPS) is a debilitating and painful condition accompanied by sensory, autonomic, trophic, and/or motor abnormalities. Although CRPS is rare in the general population, the prevalence among individuals at higher risk, particularly post-traumatic and postsurgical patients, remains unknown. This study aims to provide a benchmark that quantifies CRPS prevalence in high-risk groups, and offers insights on potential predictors of developing CRPS.

METHODS: We conducted a systematic review and meta-analysis to identify studies reporting prevalence of CRPS after an inciting event (eg, fracture, surgery), specifically 12-month and 24-month prevalence (primary outcomes), as well as 3-month and 6-month prevalence (secondary outcomes). Estimates from individual studies were transformed using double-arcsine transformation, and the resulting estimates with 95% confidence interval (CI) were pooled in a meta-analysis using a random-effects model.

RESULTS: We included 214 articles with data from 2491,378 participants worldwide (35 countries), of which 16,873 had CRPS. The pooled 12-month and 24-month global prevalence was 3.04% (95% CI, 2.64–3.48) and 6.46% (95% CI, 5.46–7.53), respectively. Subgroup analysis and meta-regression were performed to understand the impact of population-dependent (mechanism of injury, type of CRPS), contextual-dependent (socioeconomic status), and methodological-dependent (study design, publication year) factors. The 12-month prevalence was higher in countries with a high human development index (HDI) compared to those with a medium or very high HDI, was higher in participants with a traumatic inciting injury only versus those with surgical injury only or traumatic/surgical injury, and was higher in prospective versus retrospective studies. Meta-regression analysis showed that publication year was a significant moderator, with more recent articles reporting lower 12-month prevalence.

CONCLUSIONS: This study provides a benchmark of the global prevalence of CRPS, which anesthesiologists and pain specialists can use to prioritize early diagnosis and identify those at the highest risk for CRPS. (Anesth Analg 2025;XXX:00–00)

KEY POINTS

- **Question:** What is the global prevalence of complex regional pain syndrome (CRPS) after an inciting event and how do various factors influence the prevalence?
- **Findings:** The pooled 12-month and 24-month prevalence of CRPS was 3.04% and 6.46%, respectively, with variations influenced by factors such as country, human development index, type of inciting injury, study design, and publication year.
- **Meaning:** These findings establish a global benchmark and potential predictors of CRPS prevalence.

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Complex regional pain syndrome (CRPS) is a chronic debilitating disease that manifests as persistent pain, with features of allodynia and/or hyperalgesia, and extends beyond the expected tissue healing period.[1] Alongside pain, CRPS is accompanied by a combination of sensory, autonomic, trophic, and/or motor changes.[2] Although the exact pathophysiology of CRPS remains incompletely understood, it involves disordered neural inflammatory mechanisms, nociceptive sensitization, vasomotor dysfunction, and maladaptive neuroplasticity.[3] CRPS can be categorized into 2 types, CRPS Type I and CRPS Type II, based on the presence or absence of nerve injury. However, this classification sparks criticism because the majority of conditions classified as CRPS Type I, such as CRPS after bone fracture or surgery, involve some degree of nerve injury.[3]

Currently, the most commonly used diagnostic criteria are the Budapest criteria,[4] followed by The International Association for the Study of Pain (IASP) criteria[5,6] and Veldman criteria.[7] However, due to the complex and variable presentation of CRPS, there is no gold standard test for diagnosis, and clinicians often rely on clinical assessment supported by imaging, such as x-ray evidence of trophic changes, 3-phase (Tc99m) bone scintigraphy, or magnetic resonance imaging.

Owing to its variable manifestation and unknown pathophysiology, CRPS treatment remains challenging.[8] Patients typically require an interdisciplinary and multimodal approach, including conservative treatment (eg, physical therapy, mirror therapy, and acupuncture),[9] multimodal pharmacological therapy,[10,11] and interventional procedures (eg, sympathetic plexus block, spinal cord stimulation, dorsal root ganglion stimulation, peripheral nerve stimulation, and intrathecal drug delivery).[12,13] Despite these efforts, severe cases may progress to the extent of requiring amputation. The multifaceted treatment contributes to the substantial economic burden associated with CRPS. Analysis of the Swiss national database revealed that management of CRPS approximates $86,900 in insurance costs and $23,300 in treatment costs per affected individual over a 5-year period.[14] Moreover, after diagnosis, health care costs double, and prescription costs increase by approximately 2.6-fold from baseline costs annually.[15]

Understanding the prevalence of CRPS is the first step in addressing its widespread social and economic impact. Secondly, it is crucial to evaluate the prevalence of CRPS in the community and variation by geographical region, income, and other variables to reduce health disparities globally. Further, given that there is no specific diagnostic test for CRPS and since diagnosis is based on clinical history and physical examination, there may be a potential for overdiagnosis of this condition.[16] Finally, given the increase in online health seeking and utilization of the Internet in self-diagnosis, the frequency of self-diagnosis of CRPS may also potentially increase.[17]

Based on population studies from the Netherlands, South Korea, and the USA, the reported prevalence of CRPS in the general population varies between 5.4 and 29 per 100,000 individuals.[18–20] However, to date, there is no literature analyzing the global prevalence of CRPS in the at-risk population after an inciting event such as fracture, surgery, or neurological injury. The present meta-analysis aims to address this gap by examining the aggregate global prevalence of CRPS in the at-risk population based on the published literature from 1993 to 2023. This study also explores moderators accounting for potential heterogeneity of the pooled prevalence, including population-dependent (mechanism of injury, type of CRPS), contextual-dependent (socioeconomic status), and methodological-dependent (study design, publication year) factors. Given the implementation of more specific diagnostic criteria over time, we hypothesized that the year of publication would be a significant moderator accounting for potential heterogeneity of CRPS prevalence.

The rationale for conducting this study centers on the need for precise data within at-risk populations, which are currently lacking. While CRPS is rare in the general population,[18–20] the prevalence among individuals at higher risk, particularly posttraumatic and postsurgical patients, remains unknown. This study aims to provide a benchmark that not only quantifies CRPS prevalence in these specific high-risk groups, but also offers insights through subgroup analysis on predictors of higher CRPS risk, helping anesthesiologists and pain specialists identify vulnerable patients early. Additionally, existing research suggests that acute pain management influences the development of chronic pain,[21] especially in the postsurgical context which is a significant focus in the current study's population. By pooling global data, the study offers a clearer picture of CRPS prevalence in at-risk groups, addressing concerns of overdiagnosis particularly with CRPS Type I.[16,22,23] By providing a benchmark of global prevalence data, this study fills a critical knowledge gap and sets the foundation for future research comparisons.

MATERIALS AND METHODS

We adhered to the systematic review and meta-analysis per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines,[24] as well as guidelines for publishing systematic reviews and meta-analyses in pain medicine.[25–28]

The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42024538637).

Search Strategy

A systematic search strategy was developed by a medical librarian experienced in systematic review methods (L.J.P.) with input from the principal investigator (R.S.D.). A comprehensive search was performed on September 11, 2023, identifying relevant studies on the global prevalence and burden of CRPS. No date or language limits were predefined. The searched electronic databases included Ovid MEDLINE and Epub Ahead of Print, Ovid Embase, Web of Science, and Scopus. A controlled vocabulary supplemented with keywords was used. Given that terminology for CRPS has used other terms, including reflex sympathetic dystrophy, Sudek's atrophy, causalgia, algodystrophy, and algoneurodystrophy, the search strategy was constructed to capture these various terms. A preliminary search strategy was completed before protocol registration to determine the type of studies available on this subject. The complete search strategy is described in Supplemental Digital Content 1, Table S1, http://links.lww.com/AA/F208.

Study Selection

Original research publications were considered for inclusion based on the following eligibility criteria:

1. Original studies of any design (randomized clinical trials [RCTs], observational studies, and case series) including abstracts and unpublished articles. In terms of case series, we included any that reported data on at least 10 participants (a priori decision).
2. Studies reporting the prevalence of CRPS or the relative available data (eg, number of cases of CRPS and total number of participants) to calculate the prevalence.
3. Studies that focused on CRPS in the adult population (≥18 years old) after a specific inciting injury located in the upper or lower extremity. The injury type may encompass anything that may potentially lead to CRPS, such as traumatic injury, surgery, and neurological injury. Only studies that documented an inciting injury that may lead to CRPS (eg musculoskeletal [MSK] injury, orthopedic surgery, etc.) were considered for inclusion. Studies that only assessed the general population prevalence without an inciting event were not considered. The rationale for this decision was 2-fold: (1) from a clinician perspective, there is greater interest in knowing the prevalence of CRPS after an inciting event as the development of spontaneous CRPS without an inciting event is extremely rare; and (2) inclusion of normal healthy patients from the general population would falsely lower the pooled prevalence significantly as most patients in the general population without an inciting event are not at risk for CRPS.

We excluded studies that met the following criteria:

1. Studies that did not provide relevant data to calculate prevalence of CRPS.
2. Case series with less than 10 patients in total.
3. Studies that evaluated efficacy of treatment for CRPS, general population-based studies or insurance claims databases that did not focus on at-risk participants, and nonhuman studies.
4. Studies that were based on children and adolescents.
5. Studies that only reported occurrence of CRPS before 3 months.
6. Studies that reported CRPS after stroke or spinal cord injury as these etiologies represent central nervous system injuries.
7. Studies that were published before 1993 (before the introduction of the Veldman and IASP diagnostic criteria).

Studies were not restricted by the mechanism of injury, diagnostic criteria, length of follow-up, or language if the English abstract presented sufficient information. To facilitate a comprehensive capture of studies, we did not mandate for CRPS prevalence to be the primary outcome of included articles.

Study Screening

Each title and abstract were independently screened by 2 of 3 authors (J.K., S.M., and J.S.) using Covidence online software (Covidence systematic review software, Veritas Health Innovation). All potentially eligible citations had their full-text versions independently reviewed by 2 reviewers for final inclusion (S.M. and J.S.). Any discrepancies were adjudicated by another independent author (A.Chi.).

Data Extraction

Data from each included study was extracted into a spreadsheet (Microsoft Excel 2016) by 2 reviewers (A.C. and C.S.). Subsequently, to ensure data accuracy, 2 authors (P.E. and J.K.) verified all extracted data. Any disagreements were resolved by the principal investigator (R.S.D.). The authors extracted the following data from each study: family name of first author, year of publication, country, total population screened in the community, total number of patients with a diagnosis of CRPS or reflex sympathetic dystrophy, duration of study follow-up time during which

diagnosis of CRPS was made, inciting event (eg, MSK injury, surgery, etc.), type of CRPS (eg, Type 1, Type 2, unspecified), diagnostic criteria (eg, Budapest criteria, IASP criteria, Veldman, etc.), study design, and socioeconomic status of country based on human development index (HDI). The studies were classified into 5 groups according to their study follow-up periods, including 3-month prevalence, 6-month prevalence, 12-month prevalence, and 24-month prevalence. Given that the mean follow-up in each study may vary from these exact time points, we defined the following time windows for each time point: 3 months (>2 and <4 months), 6 months (≥4 and <8 months), 12 months (≥8 and <16 months), and 24 months (≥16 and <32 months). HDI is a composite score that consists of variables measuring life expectancy, income per capita, and education. Each of the 3 components is normalized on a scale that ranges between 0 and 1, and subsequently the geometric mean is calculated to yield the composite score (range between 0 and 1). A score of >0.800 signifies a very high HDI, 0.700 to 0.799 signifies a high HDI, 0.550 to 0.699 signifies a medium HDI, and <0.550 signifies a low HDI.

Primary and Secondary Outcomes

The primary outcomes included 12-month and 24-month prevalence of CRPS. Secondary outcomes included 3-month and 6-month prevalence of CRPS. The decision to report prevalence, as opposed to incidence, was because authors abstracted data on participants who had preexisting CRPS as well as newly diagnosed CRPS during the defined time periods.

Statistical Analysis

For each study, the authors recorded the total cases of CRPS and total sample size. We performed a meta-analysis to obtain a pooled estimate of prevalence of CRPS with 95% confidence intervals (CI) using MetaXL software 5.3 (EpiGear International). Prevalence estimates from each study were transformed using the Freeman-Tukey transformation (double-arcsine transformation). Results were pooled in a meta-analysis with a random-effects model and back-transformed estimates were reported with 95% CIs. The rationale for choosing this transformation was 2-fold: (1) to address the problem of confidence intervals laying outside of 0% to 100%; and (2) to address variance instability by minimizing the influence of studies with extreme prevalence estimates (eg 0 or 100%) on the overall prevalence estimate.[29] Further, the variances of the arcsine-based transformation depend only on the sample size which are typically fixed known values, whereas variances of an alternative model (logit transformation) depend additionally on event counts which are random variables.[30] A random-effects model was chosen because of the expected heterogeneity across studies with differing populations and study designs. Statistical significance was set at <0.05.

For assessment of publication bias (eg, small study effects), the traditional funnel plot has been found to have limited sensitivity and may be noninterpretable in meta-analyses of prevalence studies.[31] Therefore, we assessed publication bias using the Doi plot and Luis Furuya-Kanamori asymmetry (LFK) index, which can detect and quantify asymmetry.[32] LFK values beyond ±1 signify asymmetry. The degree of statistical heterogeneity in prevalence estimates among studies was determined using the I^2 statistic with a cutoff of 75% indicating substantial heterogeneity.

Subgroup Analysis and Meta-Regression

Although the decision of subgroup analysis of specific variables was made a priori, the authors made a post hoc decision to only perform subgroup analysis and meta-regression for the primary outcomes of 12-month prevalence and 24-month prevalence. The rationale for this decision was: (1) to limit multiplicity in analyses and the potential for Type I statistical error (eg, false positive result), and (2) to utilize outcomes that had at least 35 included studies as there were 35 total countries represented in our dataset.

Specifically, for studies that reported 12-month prevalence and 24-month prevalence, subgroups were divided according to inciting event (traumatic only, surgical only, or surgical and traumatic injury), type of CRPS (Type I, Type II, unspecified), HDI (very high, high, medium, low), and study design (RCT, prospective observational study, retrospective observational study).

Meta-regression analysis was conducted in IBM SPSS Statistics for Widows, version 29.0 (IBM Corp) to identify if publication year may moderate and contribute to the heterogeneity or observed variations between studies. Further, the authors decided to utilize robust standard errors in the meta-regression model, instead of ordinary least squares (OLS) standard errors, since the former method is meant to generate standard errors for heterogeneous data that are typically heteroskedastic. The OLS residuals tend to underestimate the true errors. To execute this in SPSS, we utilized the HC1 function, which is a degrees-of-freedom adjustment, to incorporate robust standard errors. The regression coefficients, z value, and *P*-values were reported from the meta-regression analysis.

Protocol Deviations

The authors made the following *post hoc* decisions: (1) removed subgroup group analysis based on continent to limit multiplicity of outcomes; (2) stratified prevalence based on defined time periods because pooling

all rates in a crude unadjusted prevalence regardless of time period would be inaccurate; and (3) subgroup analysis and meta-regression was only performed for 12-month and 24-month prevalence (rationale provided above).

Appraisal of Quality and Certainty in Prevalence Estimates

A modified quality appraisal for individual studies was conducted by extracting data on whether diagnostic criteria for CRPS were specified or not, and the specialty of physicians or researchers who diagnosed CRPS. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)[33] criteria were used to appraise the certainty in prevalence estimates for the 2 primary outcomes. We applied domains of risk of bias, inconsistency, indirectness, publication bias, and imprecision. A separate risk of bias assessment was not relevant to this study design, given that this is a prevalence study without comparative assessment of a therapeutic intervention.

RESULTS

Identification of Studies

The search selection process is displayed in the PRISMA diagram (Figure 1). The initial search identified a total of 3056 unique studies from 4 databases. Of these, 531 full-text articles were retrieved and after further screening, 317 articles were excluded. A list of reasons for study exclusions is provided in Supplemental Digital Content 1, Table S2, http://links.lww.com/AA/F208. A total of 214 articles published between 1993 and 2023 qualified for inclusion in the final analysis, comprising a total of 2491,378 participants worldwide (35 countries), of which 16,873 had a diagnosis of CRPS.

Study Characteristics

A summary of key characteristics of all 214 included articles is provided in Supplemental Digital Content 1, Table S3, http://links.lww.com/AA/F208. These articles were conducted across 35 countries, with most articles conducted in the United States (44 articles) and France (42 articles). A total of 23 studies (10.7%) reported data for calculation of 3-month prevalence (n = 222,975), 20 studies (9.3%) reported data for 6-month prevalence (n = 5331), 55 studies (25.7%) reported data for 12-month prevalence (n = 1997,494), and 103 studies (48.1%) reported data 24-month prevalence (n = 261,433). A total of 13 studies (6.1%) reported data for prevalence calculation, although did not specify the time period (n = 4145).

Among included studies, most were retrospective observational studies (156 articles), followed by 49 prospective studies, and 5 RCTs. Four articles did not provide enough information to determine study design. Sample sizes ranged from 10 to 853,186 (median 73; interquartile range 32–198). The type of CRPS described in studies were Type 1 in 86 studies, Type 2 in 2 studies, and both types in 2 studies, although most studies (124 studies) did not specify CRPS type. Most studies reported CRPS in the upper extremity (137 studies), following by the lower extremity (66 studies), and both upper and lower extremity (11 studies). The mechanism of the inciting event was postsurgical in 179 studies, traumatic in 11 studies, both postsurgical and traumatic in 15 studies and unreported mechanism in 9 studies. In terms of HDI, there were 184 studies conducted in countries with very high HDI, 18 studies conducted in countries with high HDI, 10 studies conducted in countries with medium HDI, and 2 studies conducted in countries with low HDI.

Primary Outcomes

The pooled 12-month prevalence estimate of CRPS from 55 studies (n = 1997,494) was 3.04% (95% CI 2.64–3.48) with significant evidence of substantial between-study heterogeneity (I^2 = 99%; P < .01; Figure 2). The pooled 24-month prevalence estimate of CRPS from 103 studies (n = 261,433) was 6.46% (95% CI 5.46–7.53) with significant evidence of substantial between-study heterogeneity (I^2 = 97%; P < .01; Figure 3). Sensitivity analysis using the leave-one-out method did not identify any significant changes in prevalence estimates, suggesting robustness of data in the primary analysis.

Secondary Outcomes

The pooled 3-month prevalence estimate of CRPS from 23 studies (n = 222,975) was 3.77% (95% CI 1.79–6.40) with significant evidence of substantial between-study heterogeneity (I^2=100%; P < .01; Supplemental Digital Content 1, Figure S1, http://links.lww.com/AA/F208). The pooled 6-month prevalence estimate of CRPS from 20 studies (n = 5331) was 6.33% (95% CI 4.26–8.77) with significant evidence of substantial between-study heterogeneity (I^2=89%; P < .01; Supplemental Digital Content 1, Figure S2, http://links.lww.com/AA/F208).

Subgroup Analysis

The prevalence of CRPS varied based on several factors within the subgroups analyzed (Supplemental Digital Content 1, Table S4 and Figures S3-S10, http://links.lww.com/AA/F208). However, despite these subgroup analyses, heterogeneity persisted within each subgroup.

Regarding the inciting event, the 12-month prevalence was 2.15% (95% CI 1.75–2.58) for postsurgical participants and 5.28% (95% CI 3.24–7.54) for participants who experienced both trauma and

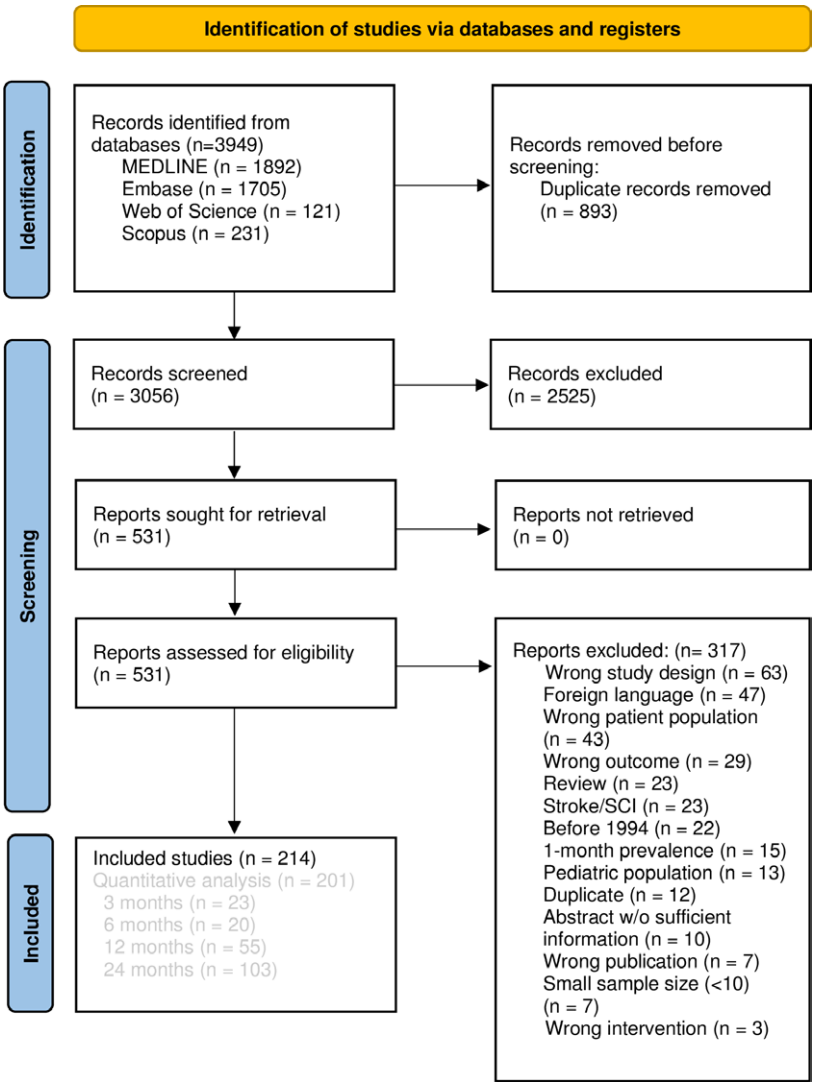

Figure 1. PRISMA diagram. Flowchart demonstrates the study selection process. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

surgery; participants who experienced trauma only reported a higher 12-month prevalence of 24.12% (95% CI 10.42–39.33) compared to postsurgical participants ($P < .001$) and those who experienced both trauma and surgery ($P = .003$) (Supplemental Digital Content 1, Figure S3, http://links.lww.com/AA/F208). The 24-month prevalence was 5.86% (95% CI 4.53–7.30) for postsurgical participants, 12.99% (95% CI 1.18–28.26) for participants who experienced trauma only, and 13.80% (95% CI 0.00–59.08) for participants who experienced both trauma and surgery (Supplemental Digital Content 1, Figure S4, http://links.lww.com/AA/F208); there were no statistical differences in this subgroup analysis.

Regarding the type of CRPS (Supplemental Digital Content 1, Figures S5 and S6, http://links.lww.com/AA/F208), a subgroup analysis was not feasible as there was only 1 study that reported data on CRPS Type II for 12-month prevalence and none for 24-month prevalence.

Regarding the HDI, the pooled 12-month prevalence was 2.58% (95% CI 0.85–4.67) for medium HDI, 15.21% (95% CI 6.79–24.72) for high HDI, and 2.28% (95% CI 1.92–2.67) for very high HDI (Figure S7, http://links.lww.com/AA/F208). The difference was significant when comparing 12-month prevalence between countries with medium versus high HDI ($P = .041$), and countries with high versus very high HDI ($P < .001$). The pooled 24-month prevalence was 8.70% (95% CI 3.51–14.74) for medium HDI, 21.18% (95% CI 4.95–40.34) for high HDI, and 5.40% (95% CI 4.50–6.38) for very high HDI (Figure S8, http://links.lww.com/AA/F208); there were no statistical differences in this subgroup analysis.

Regarding study design, the pooled 12-month prevalence was 2.92% (95% CI 0.62–5.80) for RCTs, 10.32% (95% CI 3.60–18.20) for prospective studies, and 1.04% (95% CI 0.82–1.29) for retrospective studies (Figure S9, http://links.lww.com/AA/F208). The difference was significant when comparing prospective versus retrospective studies ($P < .001$). The pooled

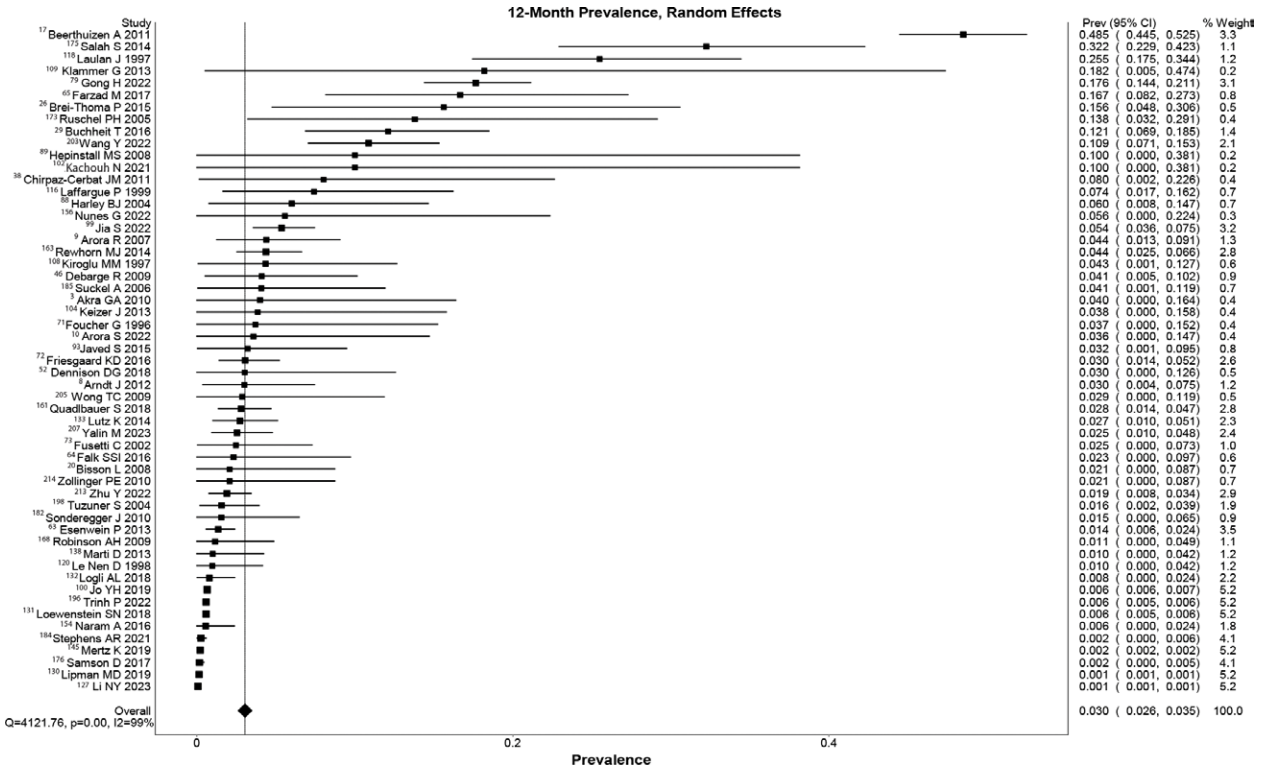

Figure 2. Forest plot displaying 12-month global prevalence of CRPS. Prevalence estimates from each study were transformed using the Freeman-Tukey transformation (double-arcsine transformation). The forest plot displays 12-month prevalence estimates in their back-transformed form as a proportion with 95% confidence intervals from each study and reports the aggregate 12-month global prevalence of CRPS using a random-effects model. The superscript numbers in this figure refer to the numbered supplementary references in Supplemental Digital Content S1, http://links.lww.com/AA/F208. CRPS indicates complex regional pain syndrome.

24-month prevalence was 10.09% (95% CI 3.46–17.90) for prospective studies and 6.00% (95% CI 5.00–7.08) for retrospective studies (Figure S10, http://links.lww.com/AA/F208); there were no statistical differences in this subgroup analysis.

Meta-Regression Analysis

Univariate meta-regression analysis revealed that publication year was a significant moderator (B=-0.017, 95% CI −0.030 to −0.003, t= −2.481, P = .016) that contributed to heterogeneity for the 12-month prevalence (Supplemental Digital Content 1, Table S5; Figure S11, http://links.lww.com/AA/F208); in other words, earlier studies reported higher prevalence rates, and rates declined as time progressed. However, publication year was a nonsignificant moderator (B=0.006, 95% CI −0.002 to 0.014, t=1.411, P = .161) for the 24-month prevalence (Supplemental Digital Content 1, Table S5; Figure S11, http://links.lww.com/AA/F208).

Publication Bias Assessment

For primary outcomes, the Doi plots and LFK indices indicated major asymmetry in favor of studies reporting higher 12-month prevalence (LFK index =10.08; Supplemental Digital Content 1, Figure S12, http://links.lww.com/AA/F208) and higher 24-month prevalence (LFK index =8.55; Supplemental Digital Content 1, Figure S13, http://links.lww.com/AA/F208).

Quality Assessment and Certainty of Prevalence Estimates

Two variables (whether diagnostic criteria were specified or not, and specialty of physician/researcher that diagnosed CRPS) are reported in Supplemental Digital Content 1, Table S3, http://links.lww.com/AA/F208. Although all included studies used current clinical criteria to diagnose CRPS, 169 (78.98%) did not specify the specific name of the criteria. In terms of physician/research specialty that diagnosed CRPS, orthopedics/orthopedic surgery diagnosed CPRS in the vast majority of studies (145 studies [67.75%]), followed by pain management (17 [7.94%]), and general surgery (10 [4.67%]); multiple other specialties were also represented (Supplemental Digital Content 1, Table S3, http://links.lww.com/AA/F208). The Table summarizes the quality assessment per the GRADE criteria, pooled prevalence estimates, and overall certainty in the estimates. The certainty in prevalence estimates at both 12 months and 24 months was judged to be

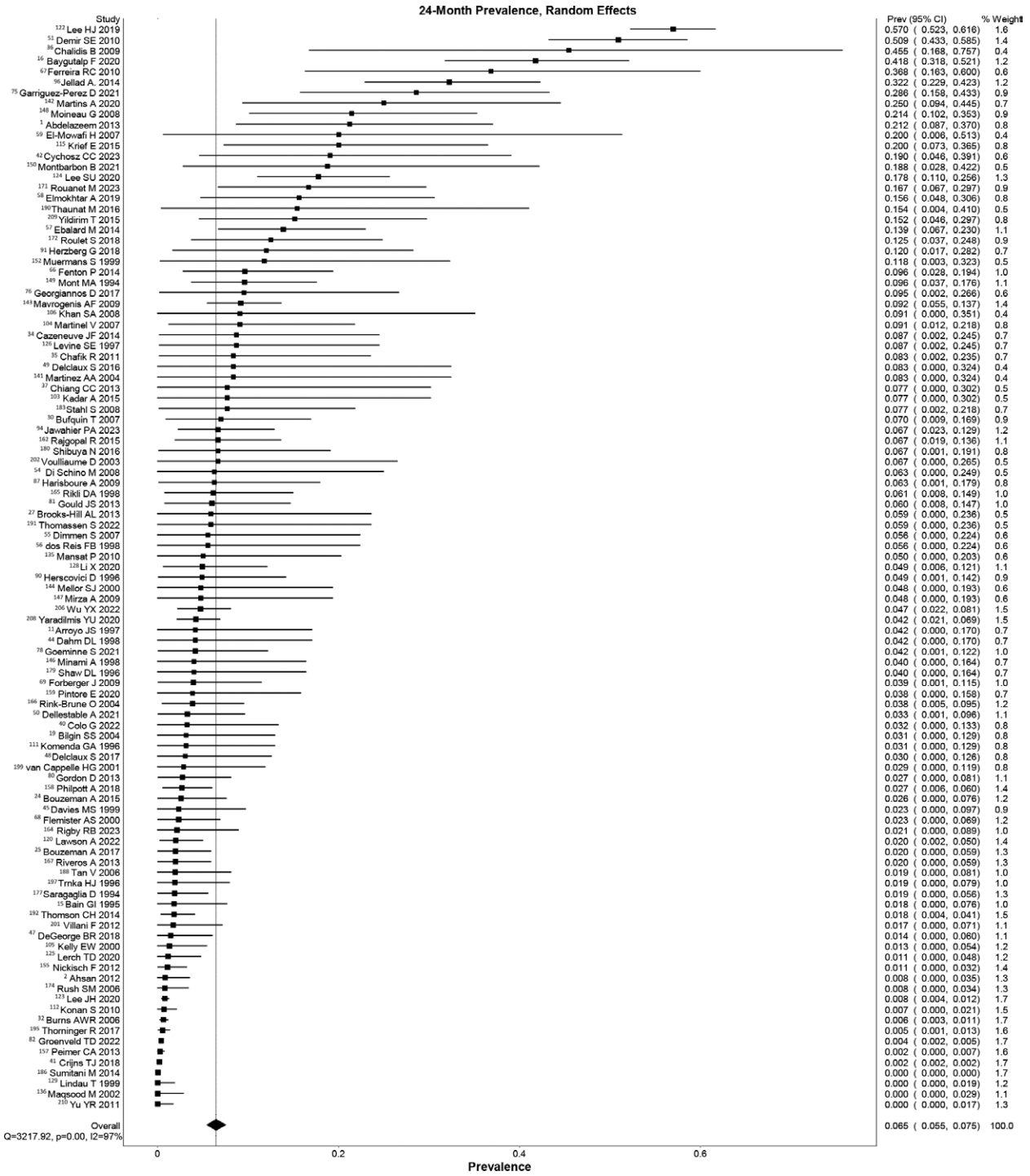

Figure 3. Forest plot displaying 24-month global prevalence of CRPS. Prevalence estimates from each study were transformed using the Freeman-Tukey transformation (double-arcsine transformation). The forest plot displays 24-month prevalence estimates in their back-transformed form as a proportion with 95% confidence intervals from each study and reports the aggregate 24-month global prevalence of CRPS using a random-effects model. The superscript numbers in this figure refer to the numbered supplementary references in Supplemental Digital Content S1, http://links.lww.com/AA/F208. CRPS indicates complex regional pain syndrome.

low, primarily because of inconsistency (high statistical heterogeneity and methodological heterogeneity). Due to the variety of included study designs, the decision was made to not downgrade certainty of evidence based on publication bias.

DISCUSSION

This meta-analysis provided updated estimates of CRPS prevalence among adults by combining data of over 2.4 million participants from 35 countries between 1993 and 2023. We observed that the pooled 12-month

Table 1. GRADE Evidence Profile and Summary of Findings Showing Certainty in Estimates for Primary Outcomes

	GRADE domain					Summary of findings		Certainty in estimates
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Pooled prevalence (95% CI)	No of patients	
12-month prevalence of CRPS	Minimal concerns related to nonresponse bias	Serious concerns (I^2 = 99%, heterogeneity in study design)	No serious concerns	No serious concerns	Undetected	3.04% (2.64–3.48)	1,997,494	Low
24-month prevalence of CRPS	Minimal concerns related to nonresponse bias	Serious concerns (I^2 = 97%, heterogeneity in study design)	No serious concerns	No serious concerns	Undetected	6.46% (5.46–7.53)	261,433	Low

Abbreviations: CI: confidence interval; CRPS: complex regional pain syndrome; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; No: number.

prevalence was 3.04% and the pooled 24-month prevalence was 6.46% in at-risk populations. In our secondary outcome analysis, we observed that the pooled 3-month prevalence was 3.77% and the pooled 6-month prevalence was 6.33% in at-risk populations. Our findings highlight that CRPS is a prevalent health problem in patients who have experienced an inciting event such as musculoskeletal trauma or orthopedic surgery. There are several reasons that may explain the paradoxical higher prevalence at shorter time intervals (eg, 3-, and 6-month) compared to longer time intervals (eg, 12- and 24-month). Recall bias may have led participants to under-report CRPS. In addition, participants with CRPS may experience complete remission of CRPS, especially with institution of early physiotherapy.

A wide range of countries was examined in this meta-analysis and contributed to the substantial heterogeneity in prevalence across studies. Potential factors that may contribute to these differences include sample size, genetic predisposition, socioeconomic status, quality of health care, and risk factor management and preventive services. However, despite comprehensive and sensitive database queries, studies were lacking in most African, Asian, and South American countries, highlighting that the immaturity of research in CRPS may also contribute to potential underestimation of prevalence.

Notably, large population studies that abstracted data from insurance claims or other large national databases were excluded from this meta-analysis because these studies captured prevalence rates in the general population and not those at risk for CRPS. The pathophysiology of CRPS typically requires an inciting noxious event. Although spontaneous cases of CRPS have been described in 3% to 11% of cases,[34] this is highly debated among clinicians and researchers. Therefore, inclusion of studies that abstracted data from the general population and not those at risk for CRPS would not classify as a high clinical or public health priority and would've led to underestimation of aggregate prevalence rates. For instance, a national database study from the United States[35] reported an unadjusted CRPS rate of 0.07% (22,533/33,406,123) between 2007 and 2011 and a national health insurance database study from South Korea[19] reported an unadjusted CRPS rate of 0.1% (74,349/51,529,338) between 2011 and 2015; both rates were several-fold lower than overall pooled rates reported in our meta-analysis.

Subgroup analyses and meta-regression were conducted to explore sources of heterogeneity. We observed that the 12-month prevalence was highest in countries with a high HDI, compared to countries with a medium HDI and countries with a very high HDI. Although this finding is different from other prevalence studies evaluating global burden of disease,[36] it may posit that participants living in high HDI countries (eg, countries that are highly developed in terms of standard of living, life expectancy, and education) may be exposed to additional stressors from higher costs of living, and higher costs of medical treatment compared to medium HDI countries. These factors in addition to social inequalities may contribute to a lesser likelihood of receiving proper medical care for CRPS prevention or treatment. Additionally, our findings indicate that the 12-month prevalence rate of CRPS was higher among individuals with an isolated traumatic injury compared to those who sustained a surgical injury alone or those with both traumatic and surgical injuries. This finding may suggest that patients in surgical settings, including those who initially experienced trauma, may benefit from a more structured and optimized perioperative care environment, particularly concerning acute pain management. Effective acute pain control in perioperative settings has been shown to significantly reduce the risk of chronic postsurgical pain,[37,38] which may in turn also mitigate the risk of CRPS development. Conversely, individuals with isolated traumatic injuries, who may have limited or delayed access to medical or surgical intervention, could be at greater risk of suboptimal acute pain management, potentially

contributing to prolonged recovery periods and a heightened risk of chronic pain and CRPS. Further, we observed that the 12-month prevalence rate was higher in prospective studies compared to retrospective studies, potentially reflecting recall bias and inadequate capture in participants who experienced symptom-free periods in retrospective studies.

Meta-regression analysis revealed that the publication year was a significant moderator for 12-month prevalence with the coefficient in the negative direction. This observation suggests that heterogeneity was greater in earlier studies, and decreased with more recent studies. This finding may also reflect the newer development of more stringent diagnostic criteria, increasing the specificity of CRPS diagnosis.

To the best of our knowledge, this is the first meta-analysis that provides global prevalence estimates of CRPS, thereby addressing a critical gap in the literature. A major strength of the current study is that it includes a large number of studies globally, and incorporates a random-effects model with subgroup and meta-regression analysis. Furthermore, the studies consisted of participants at risk for CRPS in the community, which is of high importance to clinicians, researchers, and public health authorities. These findings are most applicable to pain physicians, neurologists, orthopedic specialists, and public health policymakers in formulating strategies to reduce the burden of CRPS in the community and globally.

This study has several notable limitations. First, the statistical model does not adjust individual study weights based on the population size of each country, increasing the possibility for overrepresentation of under-populated countries and under-representation of heavily populated countries. Second, there was a substantial degree of statistical heterogeneity noted in most pooled outcomes, although this may be the norm rather than an exception in prevalence meta-analyses that pool large numbers of studies globally.[39,40] The substantial heterogeneity and skewed distribution of prevalence rates across studies may limit the reliability and interpretability of pooled results, making it challenging to draw definitive conclusions about the overall rate, potentially leading to misleading interpretations. Third, subgroup analysis was not performed for 3- and 6-month prevalence due to a small number of studies and multiplicity in outcomes. Fourth, there were limited studies in certain subgroups, which may impact reliability of results. Fifth, the diagnosis of CRPS among different studies may potentially not be uniform (eg, per diagnostic criteria) and the primary outcomes and objectives of selected studies were variable, adding a source of clinical and methodological heterogeneity. Sixth, although prevalence rates based on demographic variables such as age, sex, and race are of interest, studies generally reported these data in aggregate for the overall sample without providing granular data. Finally, the prevalence rates and subgroup analyses are derived from data with several limitations, including the accuracy of CRPS diagnosis, variability in sample sizes, and other influencing factors. As a result, the certainty of this study's conclusions is limited, in line with the GRADE criteria's appraisal of low certainty.

CONCLUSIONS

In conclusion, this meta-analysis identified the pooled 3-month, 6-month, 12-month, and 24-month global prevalence of CRPS after an inciting event were 3.77%, 6.33%, 3.04%, and 6.46%, respectively from 1993 to 2023, and the statistical heterogeneity in prevalence was substantial. Subgroup analysis showed that the 12-month prevalence of CRPS was higher in countries with a high HDI (versus medium and very high HDI), was higher in participants who with an isolated traumatic injury (versus a surgical injury alone or those with both traumatic and surgical injuries), and was higher in prospective studies versus retrospective studies. Meta-regression analysis showed that publication year was a determinant of heterogeneity in 12-month CRPS prevalence. Most prevalence estimates were derived from developed countries, and estimates from developing countries are warranted to further refine the global estimate. Overall, this meta-analysis provides a benchmark of the global prevalence of CRPS for past and future comparisons, and provides useful data for health care organizations and public health agencies. ■

DISCLOSURES

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