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The prevalence of pain among patients with chronic kidney disease using systematic review and meta-analysis

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Pain is a common but often undertreated symptom in patients with chronic kidney disease (CKD) with a much higher prevalence than in the general population. The aim of this systematic review was to synthesize all available quantitative evidence, in order to gain a better understanding of pain prevalence and pain types in patients with CKD. Four databases and the grey literature were searched until 15th January 2021. Random-effect meta-analyses were conducted with multiple subgroup analyses and meta-regressions to further explore the between-study heterogeneity. The quality of studies included was assessed using the Newcastle-Ottawa scale and the level of evidence was determined using the GRADE approach. One hundred sixteen studies reported data on 40,678 individuals. Results from meta-analyses yielded an overall prevalence of 60% (95% confidence interval 56-64) for pain, 48% (42-55) for chronic pain and 10% (6-15) for neuropathic pain. The prevalence of pain was lower among kidney transplant recipients 46% (37-56) compared with patients undergoing dialysis 63% (57-68) and those with non-dialysis CKD 63% (55-70). Musculoskeletal pain appeared to be the most common pain symptom among patients with CKD managed conservatively 42% (28-56) or receiving dialysis 45% (36-55) whilst abdominal pain was most prevalent in kidney transplant recipients 41% (7-86). Thus, all subgroups of patients with CKD suffer from a high burden of pain. Hence, greater awareness and recognition of this issue is vital to inform policy and service provision in this area.

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There is a growing body of evidence showing that pain is among the most common symptoms experienced by individuals with chronic kidney disease (CKD), but little is known about the specific types of pain in this population.[1] Moreover, in clinical practice, there is a lack of recognition by health care providers leading to under-reporting and undertreatment of pain in this population.[2] Chronic pain results in a further reduction in quality of life[3] with associated insomnia, depression,[4] decrease in daily activities and social interactions, isolation, reduced survival, and higher use of other medical resources leading to major health care costs and risk of dialysis withdrawal. Overall, prevalence of pain in patients undergoing kidney replacement therapy is thought to range between 40% and 60%.[5] However, there are currently no reliable overall prevalence estimates of the different types of pain in the various CKD subgroups as quantitative syntheses of chronic pain are scarce, especially among kidney transplant recipients (KTRs) and patients managed conservatively. Moreover, the recent increasing number of publications in this field report highly variable pain prevalence measures.[6] Almutary *et al.*[7] reviewed the burden of symptoms experienced by patients with CKD grades 4 and 5, including dialysis and conservative management. They identified pain as one of the most common symptoms along with fatigue, pruritus, dry skin, and drowsiness, with prevalence measures ranging from 38% to 90% and a weighted mean of 65%. Brkovic *et al.*[6] examined prevalence and severity of pain in a systematic review of patients undergoing hemodialysis, with measurements ranging between 33% and 82% for chronic pain and 21% and 92% for acute pain. However neither meta-analysis nor meta-regression were conducted.[6] They acknowledged important heterogeneity in their results, recommending further exploration of the factors underlying this diversity. These inconclusive findings are likely to be explained by the large variation in pain types and sites studied, the lack of standardization in pain definitions and assessment scales, and heterogeneity of the CKD population with regard to their treatment options (conservative management with or without palliative care, dialysis, kidney transplantation).

The aims of this systematic review are to obtain up-to-date population-based estimates of the prevalence of various pain types in the different subgroups constituting the population

of patients with CKD (CKD nondialysis, dialysis, KTRs, palliative care) and to better understand the heterogeneity reported in previous systematic reviews, via stratified meta-analyses and meta-regressions.

METHODS

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered and published on PROSPERO (CRD42019156491).[8] This article reports the first outcome out of the 3 stated in the protocol.

Data sources and searches

Electronic searches (from inception to January 15, 2021) of MEDLINE/PubMed, Embase, Cochrane Register for Controlled Trials (CENTRAL), and Cumulative Index of Nursing and Allied Health (CINAHL) were conducted. The search strategies combined free text words and medical subject heading (MeSH) terms (Supplementary Table S1). Only articles available in French or English languages were considered. Reference lists of systematic reviews and short-listed studies were manually searched to identify additional citations that could have been missed. The gray literature also supplemented the results in order to cover the topic as extensively as possible. Contact was made with the authors when additional details were required to ensure the suitability of the study or to gather supplementary data.

Study selection

All records were screened on the basis of their title and abstract by 2 different reviewers (EL and GB) who were blinded to each other, using the online platform Rayyan.[9] Conflict was resolved by a third author (SB). Reviewers then proceeded to full-text assessment of potentially relevant articles against the following predefined inclusion/exclusion criteria.

Inclusion criteria. Studies in French or English language that reported (or allowed for calculation of) a prevalence of general or site-specific pain in participants with CKD aged 18 years or older were included. Patients with CKD were defined as individuals with an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2 (or eGFR categories G3 to G5 in the CGA staging [i.e., identify cause of CKD {C}, assign GFR category {G}, assign albuminuria category {A}]) for over 3 months or more, irrespective of cause, in accordance with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) definition.[10,11] Studies investigating pain among KTRs, irrespective of their eGFR measurement, and patients undergoing dialysis (hemodialysis or peritoneal dialysis) were also included. Observational studies were included without any restriction on their design (cross-sectional, case-control, or cohort studies). Clinical trials were also included if a baseline prevalence of pain in the sample before the implementation of any intervention could be retrieved. Data from the gray literature such as conference abstracts and posters were also included to limit the risk of publication bias.

Exclusion criteria. Studies were excluded if they met any of the following criteria: studies investigating acute pain related to specific procedures, such as postoperative or intradialytic pain; studies reporting on individuals <18 years old; and those including patients with an eGFR $>$ 60 ml/min per 1.73 m^2. Case reports, case-series, book chapters, reviews, and personal opinions were also systematically excluded.

Pain definitions. Studies reporting a prevalence of pain without any specification (not qualified as chronic, neuropathic, or site-specific) were included in the "pain" category, independently of the recall period assessed (e.g., current pain, pain over the past 3 days, past week, past month). Studies labeling their outcome "chronic pain" or investigating pain lasting >3 months were categorized as "chronic pain," in accordance with the new International Classification of Diseases–11th Revision classification.[12] Studies labeling their outcome "neuropathic pain," "neuralgia," "neuropathic cause of pain," or "painful peripheral neuropathy" were classified in the neuropathic pain category. Studies on peripheral neuropathy such as diabetic neuropathy were excluded if it was not clearly specified as painful. The musculoskeletal pain category included studies reporting pain affecting the bones, joints, muscles, or related soft tissues. The headache category included pain in the head but also in the back of the upper neck. Abdominal pain and chest pain were differentiated and reported in 2 different categories. Abdominal pain included upper and lower abdominal pain, uncomfortable bloating, stomach pain, pain or burning sensations related to gastroesophageal reflux disease, and discomfort related to constipation or diarrhea. Chest pain included pain related to pulmonary or cardiovascular conditions such as angina but also benign musculoskeletal pain localized specifically in the chest wall area.

Data extraction

Data were extracted on a standardized Microsoft Excel spreadsheet specifically designed for the study and piloted beforehand on a small sample of the selected studies. The spreadsheet contained key characteristics of studies, selected according to the Population Intervention Comparison Outcome Study type (PICOS) principle.[13,14] The detailed list of relevant items collected in the data extraction spreadsheet is available in Supplementary Material S1.

Data were fully extracted by 1 author (EL). However, for outcome data an independent duplicate extraction was performed by another reviewer (KM), as recommended in the Cochrane handbook.[15] Disagreement was resolved by discussion and consensus with a third reviewer (SB).

Risk of bias assessment

Two reviewers (EL and KM) working independently evaluated the risk of bias at study-level using the Newcastle-Ottawa scale,[16] a tool specifically designed to assess the quality of nonrandomized studies. Its "star system" enables us to assign an overall study quality (low, moderate, or high) after evaluating risk of bias across 3 domains: selection bias, confounding, and outcome measurement bias. Prior to performing quality appraisal, the scale was customized to specifically assess studies measuring a prevalence of pain in the CKD population. This adaptation was based on the team's knowledge in the fields of pain and nephrology, as well as on published guidelines for prevalence studies evaluation.[17] Details of the scale are provided in Supplementary Material S2. Exclusion of low-quality studies only took place when performing sensitivity analyses in an objective to explore the result's heterogeneity. Otherwise, following Glass's approach,[18] all studies were retained, independently of their quality.

Publication bias

Funnel plots specifically adapted to proportion data were built to detect "small-study effect." They represent the logit-transformed prevalence, for its better statistical properties, against a measure of precision chosen here as the standard error. Their asymmetry was tested using Egger's (linear regression method) and Begg's (rank

correlation method) tests. However, it should be kept in mind that traditional publication bias assessment tools are designed for comparative studies reporting effect size results along with a significance level and not for observational studies reporting single proportions.[19]

Data synthesis and analysis

Multiple meta-analyses were conducted according to pain types with 3 different outcomes for general pain—pain, chronic pain, neuropathic pain—and 5 supplementary outcomes for pain affecting specific body sites—headache, chest pain, musculoskeletal pain, abdominal pain, and fibromyalgia. Meta-regressions investigating the role of patients' baseline characteristics and meta-analyses stratified by CKD management strategies, risk of bias, and geographic location were planned *a priori*. Meta-analyses stratified by pain assessment scales, dialysis modality, and CKD stages were data-driven.

When a single study simultaneously reported a prevalence of pain in groups of patients characterized by different CKD management strategies, they were included in a same stratified meta-analysis as separate estimates. Between-study heterogeneity was assessed by Higgin and Thompson I^2. I^2 can compare the heterogeneity between subgroups and between meta-analyses of different sizes, suiting the stratified design of our analyses. It is considered that an I^2 value above the 75% threshold describes a high level of heterogeneity.[20] To explore the heterogeneity, uni- and multivariate meta-regressions were conducted with various patients' baseline characteristics as predictors. Specifically, the influence of sex, age, ethnicity, body mass index (BMI), diabetes and hypertension were investigated on prevalence estimates.

Sensitivity analyses

Several sensitivity analyses were also performed to further investigate the observed heterogeneity in results. Specifically, we explored the influence of geographic area and pain assessment scales. The methods and results of those analyses are described in Supplementary Material S3.

Statistical analysis

All statistical analyses were conducted using R software version 3.5.2 (R Foundation). Meta-analyses pooling prevalence data were performed using the metaprop function from R package "meta"[21] and the results obtained were displayed in forest plots. All meta-analyses were undertaken using random-effect models, as assumption was made that pain prevalence would vary between sample populations arising from different countries, health care centers, and socioeconomic areas. A generalized linear mixed model approach was adopted. This method, considered as a promising alternative to the Freeman-Tukey double arcsine transformation, has recently been recommended for meta-analyses of single proportions.[22] The model was built with a maximum likelihood estimator and the Q-profile to estimate tau and its confidence interval (CI), as recommended by Veroniki. The Hartung-Knapp method was systematically implemented to adjust the confidence interval of the overall estimate.[23]

Level of evidence

As recommended by Cochrane, the certainty of available evidence was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. Using the online software GradePro,[24] the assessment was based on study design, consistency, directness, risk of bias, precision, and publication bias. For each outcome, the level of evidence was characterized as high, moderate, low, or very low.

RESULTS

Characteristics of studies included

Our electronic search of MEDLINE, Embase, CENTRAL, and CINAHL yielded 7754 articles, complemented by 34 records from the gray literature. A total of 116 studies met our inclusion criteria, including a total of 40,678 participants in 38 different countries across the 5 continents. The United States and the United Kingdom were the highest data providers with 30 articles arising from those 2 countries (United States: $n = 18$; United Kingdom: $n = 12$). Overall, there were 30% ($n = 35$) investigating pain on <100 patients and only 9% ($n = 10$) assessing pain on >1000 patients. A flow diagram details the selection process (Figure 1) while the precise number of studies and participants by outcome is available in Supplementary Table S2. Baseline characteristics of the 71 studies investigating pain, chronic pain, or neuropathic pain are presented in Supplementary Tables S3, S4, and S5, respectively. Supplementary Tables S6–S10 present the main characteristics of the 45 additional studies focusing on pain in specific body sites.

Pain

Figure 2 displays the forest-plot pooling 57 studies reporting a prevalence of pain among a total of nearly 20,000 participants, stratified by CKD management strategy. Fifty-eight studies were eligible, but 1 was excluded from meta-analyses[25] due to the high threshold chosen by the authors to determine a clinically significant pain (score ≤50 on the 36-Item Short Form Survey), excluding all patients experiencing mild pain and a large part of those with moderate pain. Prevalence estimates ranged from 29% in a sample of KTRs in the United Kingdom to 90% among patients with CKD G5 treated conservatively in a palliative care unit. The mean prevalence of pain was 60% (95% CI: 56%–64%), $I^2 = 96\%$. The dialysis group was the most widely investigated and displayed the highest prevalence of pain, estimated at 63% (95% CI: 57%–68%). Although the burden of pain remained substantial among KTRs, we observed a significantly lower prevalence (46%; 95% CI: 37%–56%) compared with patients with CKD nondialysis (63%; 95% CI: 55%–70%) and those undergoing dialysis (63%; 95% CI: 57%–68%), χ^2 test for subgroup differences $P < 0.01$.

Prevalence of pain was further stratified by dialysis modality (hemodialysis or peritoneal dialysis) in the dialysis subgroup and by CKD stage (3, 4, or 5) in the CKD nondialysis subgroup.

Our random-effect pooled estimates showed similar prevalence of pain (χ^2 test for subgroup difference: $P = 0.42$) among patients undergoing hemodialysis (65%; 95% CI: 58%–72%) or peritoneal dialysis (58%; 95% CI: 30%–81%) (Figure 3). Among patients with CKD managed conservatively, the forest plot stratified by CKD stages considerably decreased the between-study heterogeneity with an I^2 down to 0% in the CKD stage 3 and CKD stage 4 subgroups, and to 17% in the CKD stages 4–5 subgroup. Surprisingly, a lower prevalence of pain was associated with later CKD stages (Figure 4a). However, we hypothesized that this could be

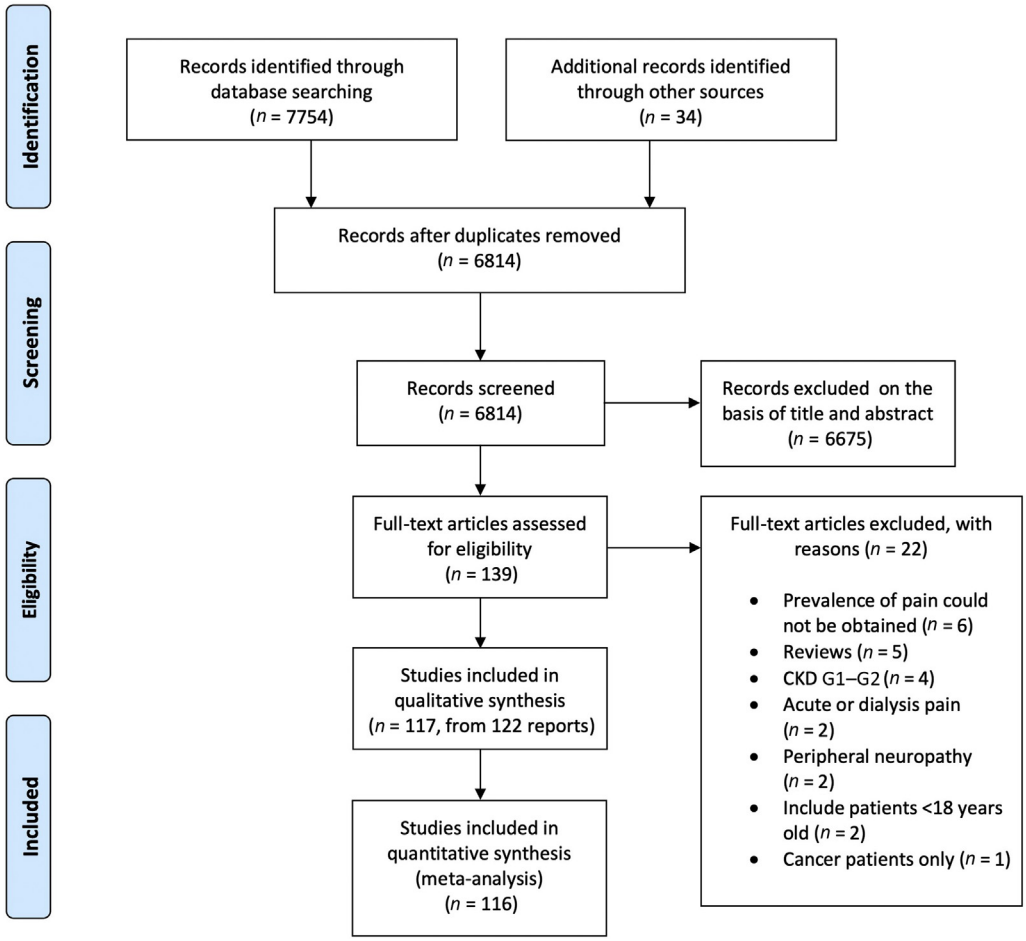

Figure 1 | Flow diagram. CKD, chronic kidney disease; G1, grade 1.

related to the fact that the CKD stage 5 subgroup was mainly constituted of studies conducted in palliative care settings where pain is the main focus and its symptoms are more likely to be treated. Confirming our hypotheses, after removing palliative care studies of the CKD stage 5 subgroup, the pain prevalence increased from 58% to 70% with no more difference across the various CKD stages (Figure 4b). However, this suggests that patients with CKD stage 3 or 4 are just as likely to suffer from pain as those with kidney failure managed conservatively.

Meta-regression models were fitted to further explore the heterogeneity. None of the tested covariates showed significance in the univariate analysis. However, age became significant ($P = 0.018$; $I^2 = 89\%$) in the multivariate model accounting for sex, ethnicity, and the geographical area the study was from (Supplementary Table S11).

Chronic pain

Nineteen studies including 3859 participants were pooled (Figure 5), resulting in an overall random-effect prevalence of 48% (95% CI: 42%–55%). Once again, the largest number of studies ($n = 14$) was in the dialysis subgroup, while the CKD nondialysis and palliative care subgroups only composed a single study. Four studies assessed pain prevalence among KTRs, with estimates showing a relatively good consistency ($I^2 = 53\%$).

Two outlying studies were identified: a particularly low prevalence of chronic pain (21%) was reported in the only study conducted in palliative care settings.[26] However, this is unsurprising as palliative care teams are likely to focus more on pain issues and their management. The other outlying prevalence measurement driving part of the heterogeneity was found in the dialysis subgroup.[27] This study, conducted in a single clinic in Brazil, reported a very low prevalence of chronic pain (16%) among a sample of relatively young patients (mean age: 46.6 ± 12.3 years). As age was found to be significantly associated with pain in our multivariate model (see previous section), the exclusion of patients >65 years old could explain the lower prevalence of pain obtained by the authors. The I^2 value was down to 77% in the dialysis subgroup and to 89% overall, after exclusion of this study (Supplementary Figure S1). Meta-regression analyses did not uncover any significant association with the covariates tested (Supplementary Table S11).

Neuropathic pain

Twelve studies including a total of 3384 individuals were grouped to obtain a global prevalence of neuropathic pain of

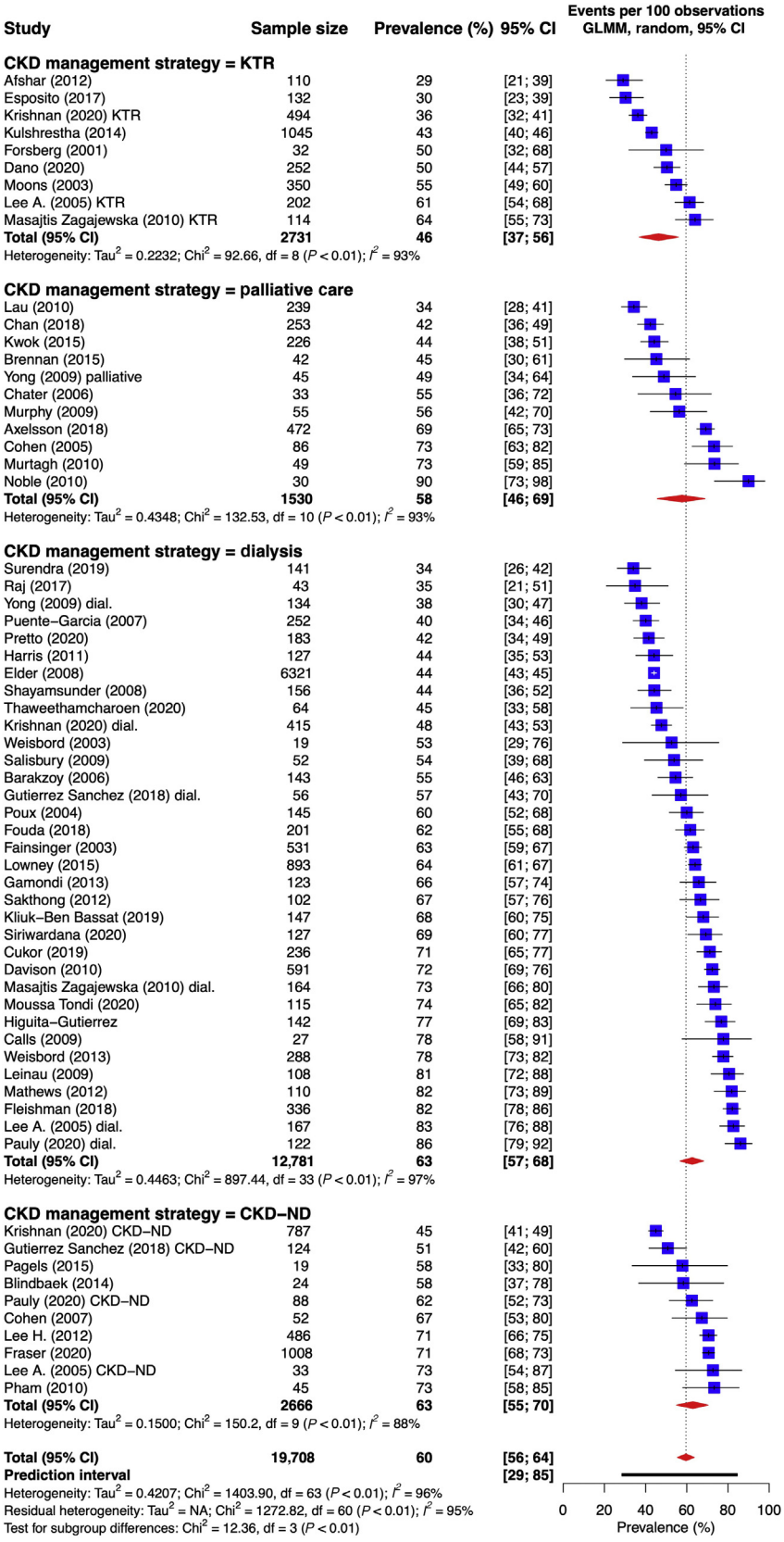

Figure 2 | Forest plot of pain prevalence stratified by chronic kidney disease (CKD) management strategy. CI, confidence interval; df, degrees of freedom; dial., dialysis; GLMM, generalized linear mixed model; KTR, kidney transplant recipient; NA, not available; ND, nondialysis.

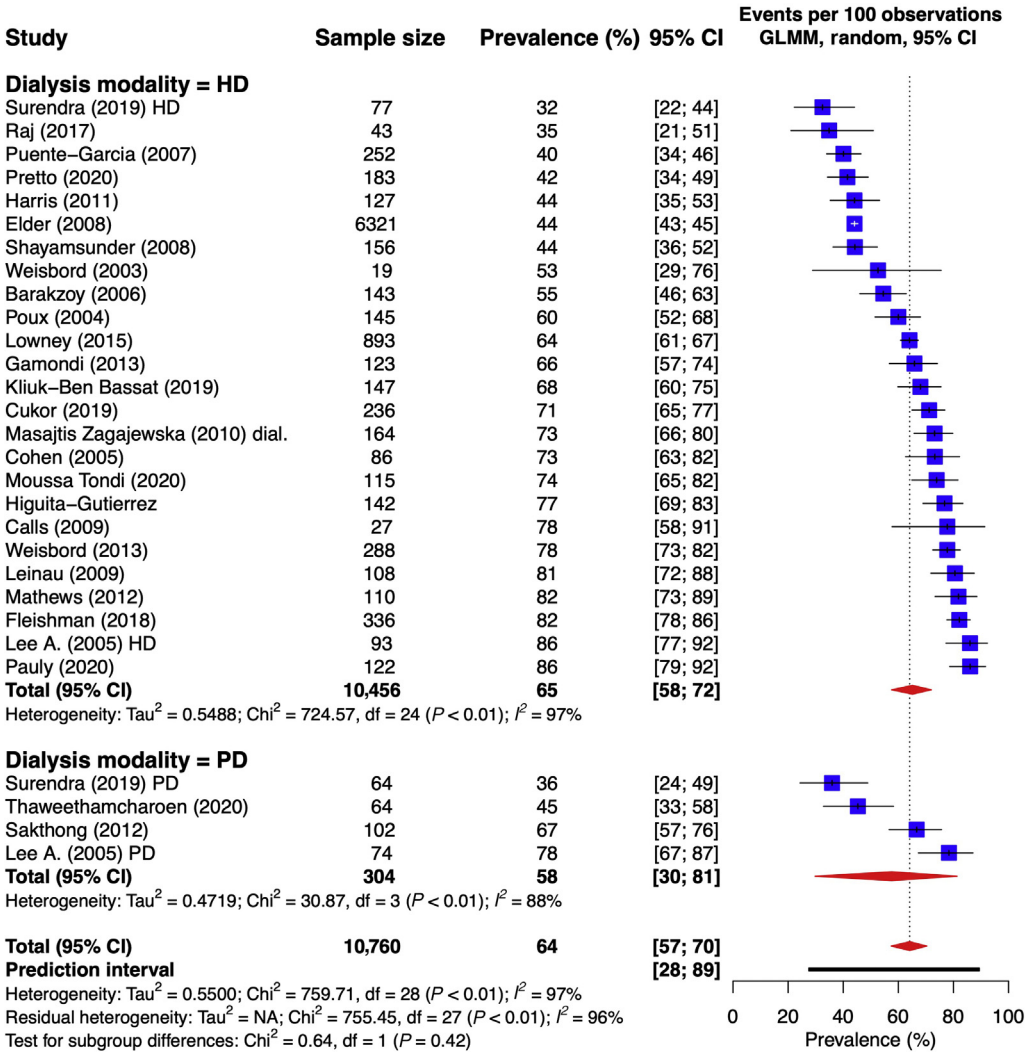

Figure 3 | Forest plot of pain prevalence stratified by dialysis (dial.) modality. CI, confidence interval; df, degrees of freedom; GLMM, generalized linear mixed model; HD, hemodialysis; NA, not available; PD, peritoneal dialysis.

10% (95% CI: 6%–15%) (Figure 6) with no significant difference between subgroups defined by CKD management strategies ($P = 0.51$). Heterogeneity was globally high ($I^2 =$ 95%) except in the KTRs subgroup that contained 2 studies with very consistent estimates ($I^2 = 0\%$).

Meta-regression showed that a higher percentage of participants affected by hypertension in the sample and a higher mean BMI were both associated with a higher prevalence of neuropathic pain (Supplementary Figure S2A and B; $P = 0.002$ and $P <$ 0.0001, respectively). Univariate models with hypertension and BMI as predictors only left 14% and 0% of unaccounted heterogeneity, respectively, suggesting strong relationships (Supplementary Table S11). Those associations remained in the multivariate models controlling for age, sex, and geographic area. The multivariate model also uncovered another significant covariate: the percentage of patients with diabetes in the sample became positively correlated with the prevalence of neuropathic pain after controlling for age, sex, and geographic area (Supplementary Table S11; $P = 0.03$; $I^2 = 61\%$).

Finally, univariate meta-regression demonstrated that the proportion of female subjects in the study sample was negatively associated with the prevalence of neuropathic pain (Supplementary Table S11 and Supplementary Figure S2C).

Pain affecting specific body sites

Supplementary Table S12 summarizes the pooled prevalence obtained for several body sites and fibromyalgia, overall and stratified by CKD management strategy. Musculoskeletal pain appeared to be the most common pain symptom in patients with nondialysis CKD (42%; 95% CI: 28%–56%) as well as in those undergoing dialysis (45%; 95% CI: 36%–55%), but it was of lesser importance among KTRs (18%; 95% CI: 6%–44%). It is worth noting the very high prevalence of fibromyalgia observed in patients with CKD (11%; 95% CI: 8%–14%), much higher than the 1.78% (95% CI: 1.65%–1.92%) estimated prevalence among the general population reported in a previous meta-analysis, but more

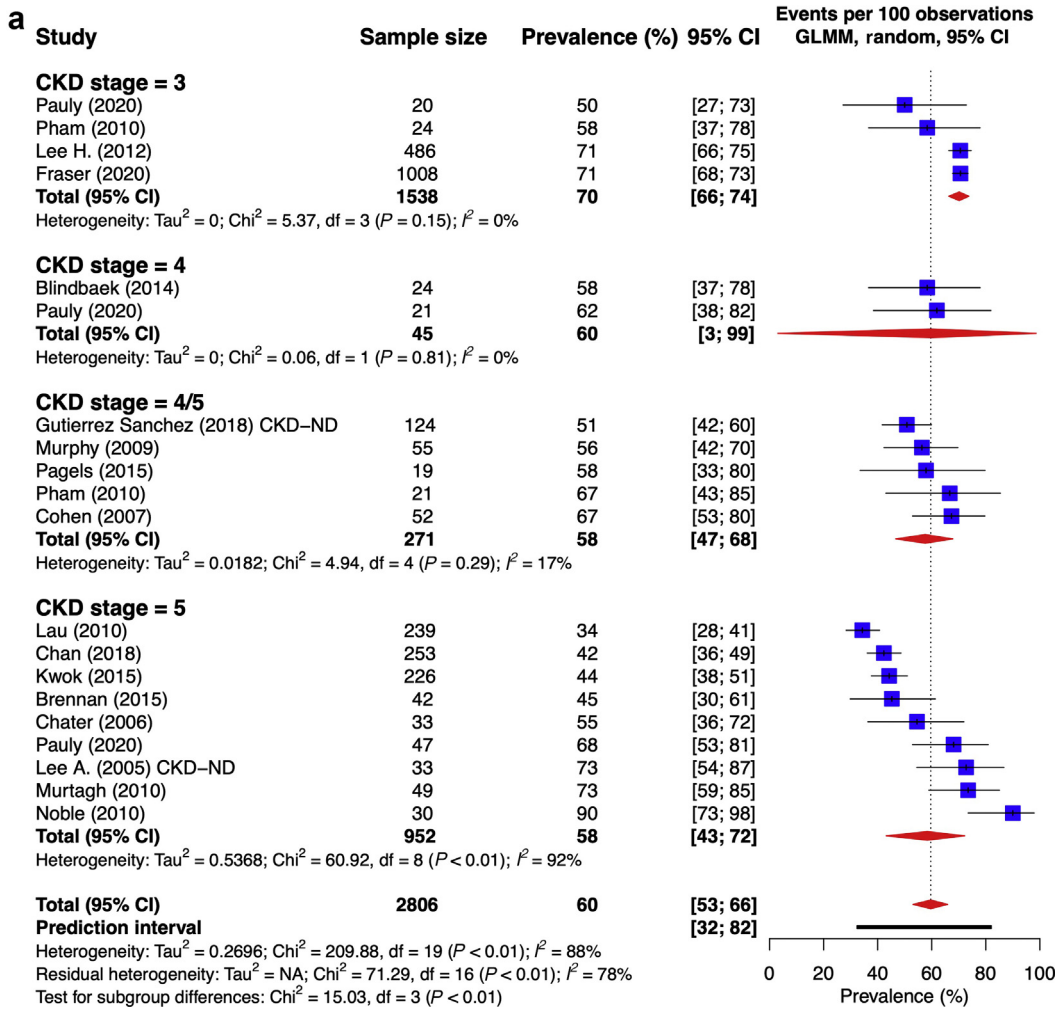

Figure 4| Forest plot of pain prevalence stratified by chronic kidney disease (CKD) stage, before (a) and after (b) exclusion of studies conducted in palliative care settings. CI, confidence interval; df, degrees of freedom; GLMM, generalized linear mixed model; NA, not available; ND, nondialysis. (Continued)

in line with the 6.30% (95% CI: 4.60%–7.90%) prevalence they observed among patients treated with hemodialysis.[28]

Among KTRs, the most prevalent symptom appeared to be abdominal pain (41%; 95% CI: 7%–86%) with a prevalence significantly higher than in the CKD nondialysis (15%; 95% CI: 2%–63%) and dialysis (16%; 95% CI: 10%–24%) subgroups. Regarding the impact of dialysis modalities, 3 studies investigating abdominal pain among patients treated with hemodialysis or peritoneal dialysis were identified. Two of them[29,30] found a higher prevalence among patients treated with hemodialysis while the third[31] found no significant difference. After pooling these 3 studies together, our random-effect meta-analysis did not show any difference between the 2 modalities (χ^2 test for subgroup difference: $P = 0.7$) (Figure 7).

Regarding other site-specific pains, 2 studies[7,31] reported a similar prevalence of headache among patients treated with hemodialysis and peritoneal dialysis. In studies investigating fibromyalgia, Berber *et al.*[32] found no significant difference between dialysis modalities while Sargin *et al.*[33] reported a higher prevalence among patients receiving hemodialysis. Meta-regression analyses showed that an older mean age was associated with a higher prevalence of fibromyalgia (Supplementary Figure S3, $P = 0.05$; $I^2 = 58\%$).

Study quality

Supplementary Tables S13 and S14 show quality assessments at study-level for each item of the 3 domains (selection bias, confounding, and outcome measurement bias) evaluated by the Newcastle-Ottawa scale (see Supplementary Material S2). A majority of studies (51%) were of moderate quality, while 24% and 25% were of low and high quality, respectively. The large proportion of moderate quality studies can be explained by an overall low risk of outcome measurement bias but higher risk of selection bias. Indeed, most studies (54%) sampled participants from a single center, therefore only representing patients attending this specific facility and the practices implemented at that particular unit. In one-half of the studies, a response rate was not identifiable, and among the 22 studies reporting a response rate <80%, only 5

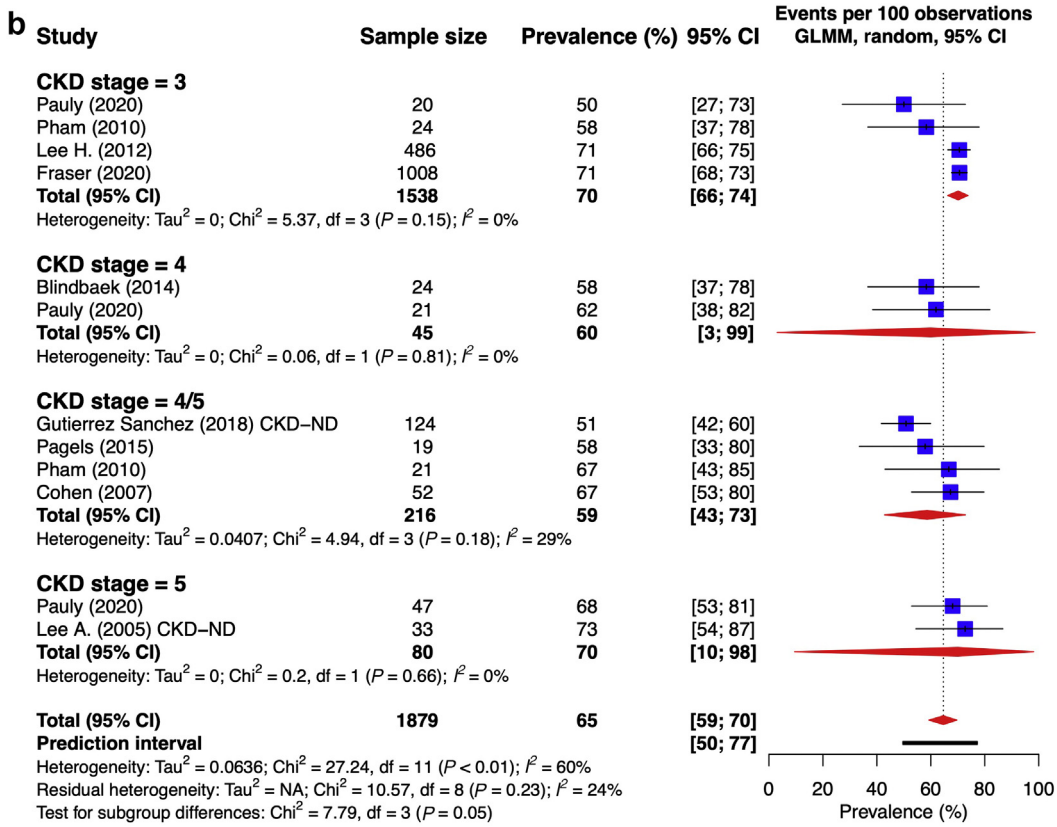

Figure 4 | (Continued)

demonstrated the representativeness of their responders either by showing they were no different from nonresponders or by comparing them to the larger population they were sampled from. Finally, random sampling was only used in a minority of articles (12%). Consecutive sampling was predominant, probably to obtain a larger sample size, especially for studies recruiting patients from a single center. In nearly one-half of the studies included ($n = 48$) the impact of confounding related to variables such as the age, sex, CKD stage, or dialysis modality was not considered. Regarding outcome measurement bias, the quality was satisfactory as self-reported pain assessments, which is considered the gold standard, was chosen by most investigators (89%). Only 4 used a proxy-assessment by a health care professional[34,35] or a caregiver,[36,37] 5 retrieved pain diagnosis via medical records,[38–42] and 2 used a combination of both methods.[43,44] In studies investigating general pain, 43 based their assessment on interviews while 32 relied on self-administered questionnaires. It should be noted that only 1 study used a specific tool to assess neuropathic pain (Leeds Assessment of Neuropathic Symptoms and Signs, S-LANSS).[45] Other studies relied on scales that were not specifically designed for this type of pain such as the Brief Pain Inventory or McGill Pain Questionnaire, report from medical records,[38,46] or determination by a physician[26,47] or neurologist.[41] Most of the time investigators did not mention precisely how the diagnosis of neuropathic pain was made.[48–53] When using nonspecific pain scales, it may have been inferred by the words of the questionnaires chosen by patients to describe the type of pain experienced, as numbness/tingling/burning symptoms are sometimes used to approximate a diagnosis of neuropathic pain.[54] Meta-analyses stratified by study quality did not suggest any difference in pain prevalence estimates among studies of low, moderate, or high quality (Supplementary Table S15; χ^2 test for subgroup difference: $P = 0.2$ for pain; $P = 0.09$ for chronic pain; $P = 0.13$, for neuropathic pain). Likewise, for all outcomes investigated, prevalence estimates remained unchanged after excluding studies of low quality (Supplementary Table S15), suggesting again that despite some concerns regarding the overall quality of studies included, this did not seem to impact the cumulative level of evidence of our pooled estimates.

Publication bias

Begg's test did not find any evidence for publication bias while Egger's test only did for meta-analyses of pain and neuropathic pain but not for chronic pain. When stratifying recent pain by CKD subgroup, asymmetry only remained within the dialysis group (Supplementary Figures S4 and S5).

In this context and knowing the lack of pertinence of publication bias assessment in prevalence studies, we believe it is quite unlikely that our results would be affected by a high level of publication bias.

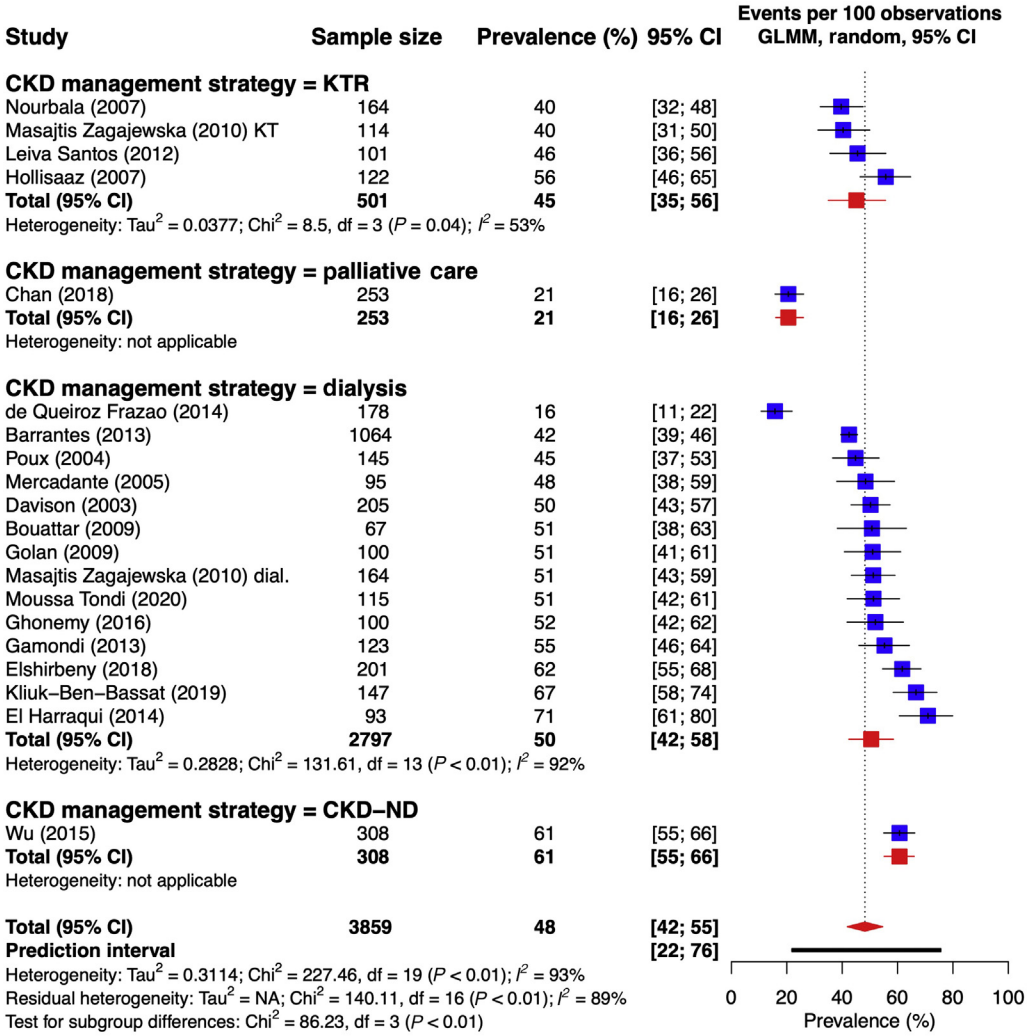

Figure 5 | Forest plot of chronic pain prevalence stratified by chronic kidney disease (CKD) management strategy. CI, confidence interval; df, degrees of freedom; dial., dialysis; GLMM, generalized linear mixed model; KT, kidney transplant; KTR, kidney transplant recipient; NA, not available; ND, nondialysis.

Level of evidence

The certainty in the overall prevalence estimates was considered as low for pain (due to inconsistency and risk of bias), moderate for chronic pain (due to risk of bias), and very low for neuropathic pain (due to inconsistency, risk of bias, and indirectness). Even though sensitivity analyses demonstrated that the inclusion of studies of low or moderate quality—according to the Newcastle-Ottawa scale—did not influence our pooled estimate or the heterogeneity level, all studies were downgraded by 1 level due to serious concerns regarding the risk of selection bias. Indeed, participants were too often sampled from a population that could not be deemed representative of the broader CKD population due to recruitment from single centers and rare use of random sampling. Downgrading also resulted from the high heterogeneity levels observed across studies investigating pain and neuropathic pain. Indirect assessments of neuropathic pain via nonspecific tools also lowered our level of confidence in the pooled estimate for this outcome. Regarding site-specific pain, as heterogeneity and risk of bias limited again our confidence in prevalence estimates, all outcomes except fibromyalgia were assigned a low level of evidence. Due to a lower I^2 (74% overall, 0% among KTRs, 64% in dialysis subgroup), the certainty was considered as moderate for fibromyalgia. GRADE tables are available in Supplementary Table S16 for general pain outcomes and Supplementary Table S17 for site-specific pain outcomes.

Sensitivity analyses

Results of sensitivity analyses exploring the influence of geographic area and pain scales are available in Supplementary Material S3, Supplementary Table S18, and Supplementary Figures S6–S8.

DISCUSSION

A high burden of pain was observed in patients with CKD with an overall estimated prevalence of 60% for acute pain, 48% for chronic pain, and 10% for neuropathic pain. KTRs

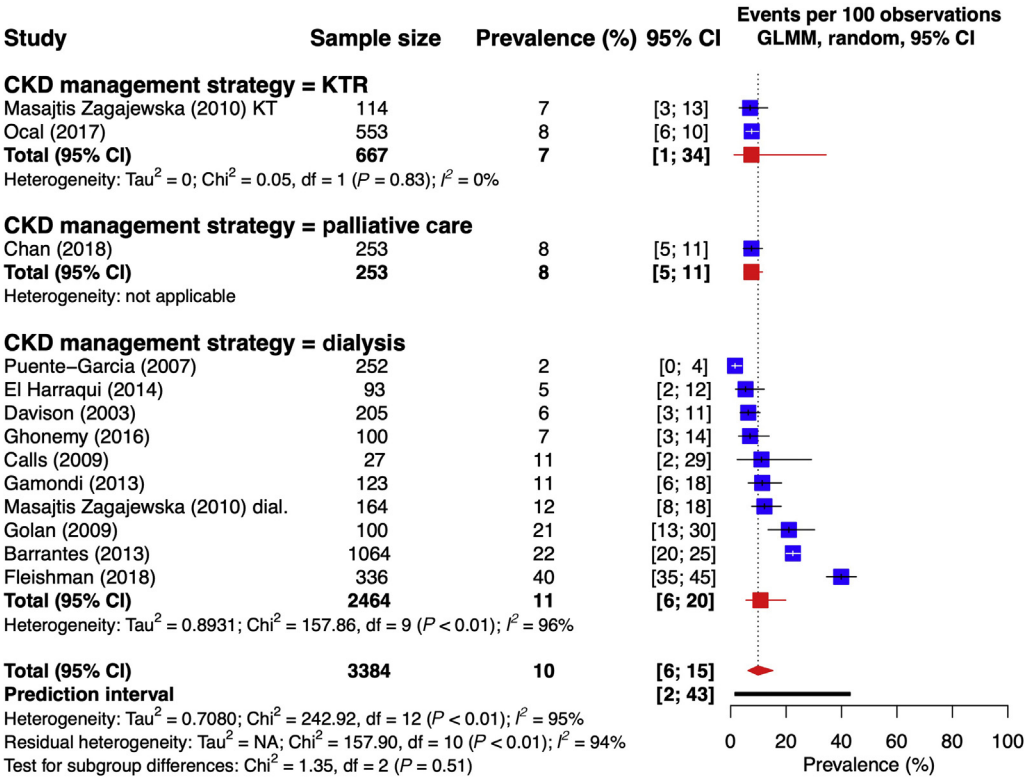

Figure 6 | Forest plot of neuropathic pain prevalence stratified by chronic kidney disease (CKD) management strategy. CI, confidence interval; df, degrees of freedom; dial., dialysis; GLMM, generalized linear mixed model; KT, kidney transplant; KTR, kidney transplant recipient; NA, not available.

appeared to experience less pain (46%; 95% CI: 37%–56%) than did patients receiving dialysis (63%; 95% CI: 57%–68%) and those with CKD nondialysis (63%; 95% CI: 55%–70%), but high levels of abdominal pain were found specifically in this subgroup (41%; 95% CI: 7%–86%). Among patients undergoing dialysis or being managed conservatively, we observed a predominance of musculoskeletal pain, with a similar prevalence in both groups (45% and 42%, respectively).

The benefits of kidney transplantation over dialysis treatment has been highlighted in a previous systematic review where the investigators reported an overall lower mortality

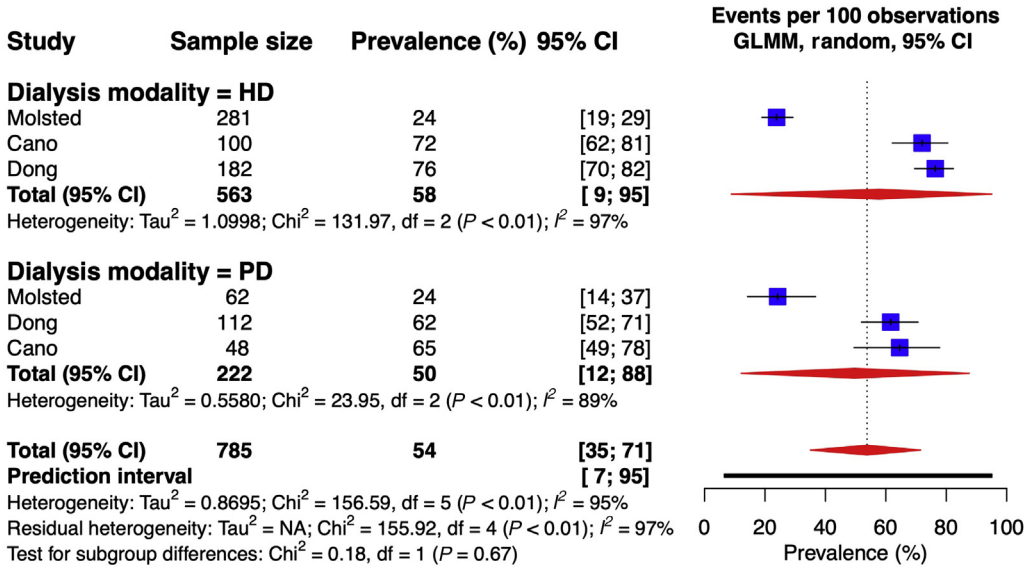

Figure 7 | Forest plot of abdominal pain prevalence stratified by dialysis modality. CI, confidence interval; df, degrees of freedom; GLMM, generalized linear mixed model; HD, hemodialysis; NA, not available; PD, peritoneal dialysis.

and better quality of life.[55] Several studies also reported better pain scores in the KTR group compared with the CKD nondialysis[56] and hemodialysis groups.[56,57] However, it should be stressed that nearly one-half of KTRs still report some form of pain, a substantial prevalence that remains higher than what is observed in the general population. We also observed prevalence of long-term pain, with nearly one-half of the CKD population suffering with chronic pain and 10% with neuropathic pain. As a point of comparison, chronic pain is estimated to affect 20% of the general population worldwide,[58] according to the International Association for the Study of Pain, and neuropathic pain ranges between 6.9% and 10%, placing our CKD population at the upper end of general population estimates.[59]

Our results suggest that the prevalence of pain in patients undergoing hemodialysis or peritoneal dialysis is similar. The prevalence of site-specific pain such as abdominal pain or headache are also likely to be the same. Stratification by CKD stages showed that patients with CKD stages 3 and 4 could suffer just as much as those with kidney failure managed conservatively. The implementation of palliative care adapted to patients with CKD stage 5 managed conservatively seemed to slightly decrease the burden of pain within this subgroup. Even though the large number of different scales used did not enable large subgroups, stratifying by pain assessment tool successfully explained part of the observed between-studies heterogeneity. We believe that the different wording (e.g., pain other than these everyday kinds of pain for the Brief Pain Inventory Short Form, pain or discomfort in the EuroQol 5 dimensions) and various recall periods (e.g., past 24 hours for the Edmonton Symptom Assessment System, past 3 or 7 days for the Palliative Care Outcome Scale-Symptoms Renal) used across the large variety of pain tools are likely to explain a substantial part of the observed heterogeneity. Although most investigators used validated scales when investigating pain or chronic pain, this was not the case when assessing neuropathic pain. Indeed, only 1 of the 12 studies included relied on an appropriate tool, defined as a tool specifically designed to investigate neuropathic pain, such as the S-LANSS, Neuropathic Pain Questionnaire, or Douleur Neuropathique 4 Questions.

Hypertension as well as a higher BMI were both significantly associated with a higher prevalence of neuropathic pain. In multivariate analyses, we also found evidence for an association between percentage of patients with diabetes and prevalence of neuropathic pain. This finding is unsurprising as diabetic neuropathy is a common complication of diabetes. Previous work conducted in groups of patient with type 1 diabetes found that hypertension also contributed to neuropathic pain,[60] by impairing nerve conduction.[61] The association with BMI is in line with previous evidence suggesting that obesity increases the risk[62] and the intensity[63] of neuropathic pain, probably via a mechanism of systemic inflammation inducing nerve damage. Previous studies reported musculoskeletal pain as the most frequent pain symptom among patients treated with hemodialysis.[64] In our analysis, it is the most common pain type in both the CKD nondialysis and dialysis subgroups. As musculoskeletal includes bone/joint pain, this could be related to CKD-Mineral and Bone Disorder, a common complication of CKD leading to disturbances in calcium and phosphorus homeostasis, triggering secondary hyperparathyroidism. Consequences include bone and joint pain and a higher risk of fracture (up to 4 times higher among KTRs compared with the general population) related to changes to bone structure and metabolism.[65] Symptoms of CKD-Mineral and Bone Disorder often appear at an advanced stage of CKD, which could explain the high prevalence of bone/joint pain in the studies we included.[66] Assessing and recognizing this type of pain is vital as it may require specific treatment—different from conventional analgesic therapy—with recent evidence showing that bone pain after kidney transplantation could respond to bisphosphonate.[65]

The predominance and high prevalence of abdominal pain observed among KTRs is likely to be related to well-known side effects of immunosuppression therapies and could be particularly frequent among patients treated with mycophenolate mofetil[67] and sirolimus.[68] Potential underlying mechanisms responsible for these high levels of abdominal pain include persistent post-surgical pain; visceral hyperalgesia; the inherent toxicity of immunosuppressant drugs leading to mucosal injury, ulceration, diverticular disease, and in the worst case perforation;[69] or the high daily number of medications.[67]

To our knowledge, this is the first systematic review and meta-analysis including all pain phenotypes and CKD management strategies. The thorough search for published and unpublished data along with the use of wide inclusion criteria permitted us to cover the topic as extensively as possible and achieve a high statistical power. Furthermore, we were also able to show that excluding studies at high risk of bias left our overall prevalence estimates unchanged. The transparent methodology used and the number of sensitivity analyses conducted ensured the consistency and reliability of our prevalence estimates.

However, some limitations should be noted. A large variety of studies were included, some specifically investigate the prevalence of pain in patients with CKD while others report a range of symptoms and do not strictly focus on pain, often leading to a less precise and less standardized reporting. The lack of standardization in pain assessment methods with a wide variety of pain definitions, recall periods, and pain assessment scales are likely to be responsible for the substantial heterogeneity that remains unexplained. Meta-regression could not always be conducted due to the lack of reported characteristics in some studies. Even though it did not seem to affect our prevalence estimates, it should be noted that the quality of studies was inconsistent. Many were conducted in single centers, and very few investigators (13%) used random sampling and compared characteristics of responders and nonresponders leading to high sampling bias in general. Outcome measurement bias may also have impacted our results as self-administered questionnaires may not be filled by more unwell patients experiencing high levels of pain

while interviews may lead to social desirability bias. It has been shown that dialysis studies restricting their survey to patients able to complete a questionnaire without any assistance may lead to inaccurate results, and assessment by means of interview was recommended by the investigators.[70] According to GRADE scoring, all our pooled estimates were assigned a level of evidence ranging from very low to moderate for the reasons mentioned herein; therefore, if the true prevalence of chronic pain is likely to be close to our estimate, it is probably markedly different for neuropathic pain. Further evidence, which is conducted among representative samples, using tools specifically designed to assess neuropathic pain is therefore required.

The burden of pain is high in patients with CKD, especially among the CKD nondialysis subgroup and those treated with dialysis, reinforcing the benefit of kidney transplantation on quality of life. However, the burden of pain among kidney transplant recipients is not insignificant. Comprehensive pain assessments must rely on validated scales. A greater awareness of this common symptom is vital to reduce its prevalence and prevent unnecessary suffering in a group of patients whose quality of life is already altered by CKD.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. MEDLINE search strategy.
Supplementary Material S1. List of items included in the data extraction spreadsheet.
Supplementary Material S2. Newcastle-Ottawa scale adapted to cross-sectional studies.
Supplementary Material S3. Methods and results of sensitivity analyses.
Table S2. Number of studies and participants included in each outcome for general pain (**A**) and site-specific pain (**B**).
Table S3. Overview of studies included in the meta-analysis on pain.
Table S4. Overview of studies included in the meta-analysis on chronic pain.
Table S5. Overview of studies included in the meta-analysis of neuropathic pain.
Table S6. Overview of studies included in the meta-analysis of musculoskeletal pain.
Table S7. Overview of studies included in the meta-analysis of headache.
Table S8. Overview of studies included in the meta-analysis of abdominal pain.
Table S9. Overview of studies included in the meta-analysis of chest pain.
Table S10. Overview of studies included in the meta-analysis of fibromyalgia.
Table S11. Meta-regression showing results of univariate and multivariate models for pain, chronic pain, and neuropathic pain.
Figure S1. Forest plot of chronic pain stratified by CKD management strategy after removing outlying study by Frazao *et al.*
Figure S2: Bubble plots of neuropathic pain prevalence by percentage of patients affected by (**A**) hypertension, (**B**) mean BMI, and (**C**) percentage of females in the study sample.
Table S12. Summary of forest-plots for pain affecting specific body sites and fibromyalgia.
Figure S3. Bubble plots of fibromyalgia prevalence by mean age of participants in the study sample.
Table S13. Summary Risk of Bias assessment with overall study-level risk of bias—studies investigating general pain.
Table S14. Summary Risk of Bias assessment with overall study-level risk of bias—studies investigating site-specific pain.
Table S15. Summary of meta-analyses (forest-plots) of pain, chronic pain, and neuropathic pain stratified by study quality (risk of bias).
Figure S4. Funnel plot for pain (**A**), chronic pain (**B**), and neuropathic pain (**C**) logit transformed prevalence.
Figure S5. Funnel plots of studies reporting pain prevalence stratified by CKD subgroups.
Table S16. GRADE table displaying level of evidence for general pain outcomes.
Table S17. GRADE table displaying level of evidence for site-specific pain outcomes.
Table S18. Summary of meta-analyses (forest-plots) of pain, chronic pain, and neuropathic pain stratified by geographic location.
Figure S6. Forest plot pooling studies reporting prevalence of pain in patients with CKD-ND, stratified by pain assessment tool.
Figure S7. Forest plot pooling studies reporting prevalence of pain in patients undergoing dialysis, stratified by pain assessment tool.
Figure S8. Forest plot pooling studies reporting prevalence of chronic pain (independently of CKD management strategy) stratified by pain assessment tool.

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