

Non-steroidal anti-inflammatory drugs: what is the actual risk of chronic kidney disease? A systematic review and meta-analysis

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Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are common cause of acute kidney injury, but chronic kidney disease (CKD) risk of NSAIDs is controversial. Prior systematic reviews are outdated with some methodological flaws. We conducted this systematic review to clarify the association between chronic NSAIDs use and occurrence and/or progression of CKD.

Methods: MEDLINE, Cochrane Library, Web of Science and Science direct were searched for observational and interventional studies from inception to May 2023. Qualitative synthesis was performed. The meta-analysis used pooled odds ratios (OR) and hazard ratios (HR) to estimate the association between chronic NSAID use and CKD occurrence or progression.

Results: Forty studies with a total of 1757118 participants were included in the systematic review; of them 39 studies were suitable for meta-analysis. 56% of our included studies were recent, published within the last 10 years. The meta-analysis revealed a significant association between chronic NSAIDs use and CKD occurrence and progression. The pooled odds ratio was 1.24 (95% CI: 1.11–1.39, $p < 0.001$, $I^2 = 91.21\%$), and the pooled hazard ratio was 1.50 (95% CI: 1.31–1.7, $p < 0.001$, $I^2 = 90.77\%$). The pooled hazard ratio (HR) for individuals with no CKD at baseline was 1.31 (95% CI, 1.26–1.40), while for those with preexisting CKD, the HR was significantly higher at 1.67 (95% CI, 1.38–2.02). The HR for individuals with no specific chronic disease was 1.6 (95% CI, 1.32–1.94). For populations with diabetes mellitus (DM) and/or hypertension (HTN), the HR was 1.35 (95% CI, 1.27–1.43), and for those with rheumatic disease, the HR was 1.36 (95% CI, 0.88–2.10).

Conclusions: Long-term NSAID use increases the risk of chronic kidney disease (CKD) occurrence and progression, especially in individuals with pre-existing CKD, who have a 67% risk compared to the general population's 60%. A patient-centered approach for safe and effective pain management is crucial, with special caution for those with pre-existing CKD.

Keywords: Non-steroidal anti-inflammatory drugs; analgesics; chronic kidney disease; renal disease; pain.

What is new? What is important?

- 1 – Our meta-analysis stands out due to the limited availability of studies examining the link between NSAIDs and the occurrence or progression of chronic kidney disease (CKD). Conclusions derived from prior meta-analyses exhibit inconsistencies and are susceptible to biases and methodological limitations, leaving a knowledge gap to be addressed. Given the dynamic nature of medical research, an updated meta-analysis is urgently warranted. Such an analysis will deepen our comprehension of the relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and the occurrence or progression of chronic kidney disease (CKD).
- 2 – Our findings highlight the importance of cautious NSAID prescribing practices in managing patients.

INTRODUCTION

Around 30 million people worldwide use non-steroidal anti-inflammatory drug (NSAIDs) every day [1]. NSAIDs are available over the counter at

an affordable price which facilitates its use and unawareness of NSAID-related side-effects from the patients' side causes these medications to be taken even without physician's consultation for the appropriate dose or duration which suit their clinical

conditions [2,3]. NSAIDs are very helpful to control pain and to decrease inflammation but these medicines are linked to both acute kidney injury (AKI) and chronic kidney disease (CKD).

Chronic Kidney Disease is considered one of the leading causes of death and disability in the world nowadays. It affects more than 800 million people worldwide [4]. Two distinct groups of NSAIDs users face increased risk of occurrence and or progression of CKD. Patients with chronic inflammatory diseases are often prescribed large doses of NSAIDs typically for prolonged periods [5]. People with apparent normal kidney function or with early stages of CKD (stage 1 & 2) may use these drugs freely and in combinations without monitoring of their kidney function [6].

There is a scarcity in meta-analyses that are conducted on the association between NSAIDs and CKD occurrence or progression. The most recent systematic review and meta-analysis on this topic dates back to 2013. [7] Moreover, conclusions drawn from previous research are inconsistent and suffer from some biases and methodological flaws leaving a gap of knowledge to be covered through. The given evolving landscape of medical research, there is compelling need for an updated meta-analysis. Such analysis will enhance understanding of the association between NSAIDs and CKD occurrence and /or progression.

MATERIAL AND METHODS

We conducted a systematic review and meta-analysis of observational and interventional studies that examine the association between chronic, regular NSAIDs use and CKD occurrence and/or progression. The protocol of this systematic review and meta-analysis was registered on PROSPERO (PROSPERO 2023 CRD42023418146) [8] and the results reported following the PRISMA guidelines [9].

SEARCH STRATEGY

An initial limited search of PUBMED was undertaken to identify articles on the topic [9]. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy (Additional file 1). The search strategy, including all identified keywords and index terms, was adapted for each included database and/or information source. Studies published in either English or other languages (with English abstract) were included. There were no date limitations

on the search. We searched the following electronic databases from inception to May 2023: MEDLINE, Cochrane Library, Web of Science and Science direct. We also hand-searched the reference lists of relevant articles and contacted experts in the field for additional studies or retrieval of full text of studies.

STUDY SELECTION

Inclusion criteria: We included studies that meet the following criteria:

(1) participants are adult general populations or CKD patients of any stage or cause;

(2) exposure is chronic use of any selective or non-selective NSAIDs, defined as regular or daily use for at least three months (Regular Use of NSAIDs is typically refers to taking these medications on a consistent, scheduled basis. This could mean nearly daily or several times per week over a prolonged period more than 90 days, often for managing chronic pain or inflammation);

(3) comparator is non-use or less frequent use of NSAIDs (Less frequent use of NSAIDs refers to short term occasional, sporadic or as-needed consumption, typically in response to acute pain for example a few times a month or only during specific episodes of pain for just a few days or weeks for temporary relief);

(4) outcome is CKD occurrence and/or progression, measured by decline in estimated glomerular filtration rate (eGFR), persistent elevation of serum creatinine, development of albuminuria or entering dialysis (all of them are parameters of CKD);

and (5) study design is cohort, case-control, cross-sectional or randomized controlled clinical trials (RCTs).

Exclusion criteria: We excluded studies that are case reports, case series, reviews, editorials, or commentaries.

Two reviewers independently screened the titles and abstracts of the identified records, and then full texts of the potentially eligible studies, using predefined eligibility criteria for study selection. Any disagreement was resolved by discussion or consultation with a third senior reviewer.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

Data extraction was performed by one reviewer using a standardized data extraction form and checked by another reviewer. The extracted data included: study information; (name, journal name,

year, authors, title, country), study design, aim, setting, participants description (inclusion, exclusion, total number and number per group), exposure description and measurements, outcome (CKD description and measurements), results summary, number and percentage of NSAIDs users with CKD and non NSAIDs users with CKD and reported main effect size measure.

Another form was used to assess the risk of bias of included studies using JBI's critical appraisal tools for observational [10]. The risk of bias assessment was conducted independently by two reviewers. Both reviewers evaluated the studies separately and were blinded to each other's assessments. Each potential risk of bias was judged as high, low and no information. Any discrepancies between the two reviewers were resolved through discussion, and when necessary, a third reviewer was consulted to reach a consensus. We used Robvis online tool for data visualization to summarize the risk of bias for each included study [11].

ASSESSMENT OF HETEROGENEITY

We assessed included studies for clinical and methodological heterogeneity by inspecting all studies for setting or participants that are clearly different from other studies and methodological outliers were discussed, possible sources were considered in the analysis.

DATA ANALYSIS

Out of the 40 included studies, 39 were meta-analyzable. We used the generic inverse variance method to pool log Odds ratios and log Hazard ratios and their standard error for binary, and time-to-event effect measures, respectively. Methodological heterogeneity in measurement of exposures and outcomes necessitated the use of a random-effects model. We assessed the statistical heterogeneity among the studies (heterogeneity in effect size variance) by visual inspection of the results to examine the statistical heterogeneity and by using the I-squared statistic and the Cochran's Q test. We explored the sources of heterogeneity using subgroup analysis and meta-regression based on the study characteristics, such as study design, setting (hospital, outpatient, community and secondary data), quality, population (comorbidities, age groups, gender), exposure definition (Duration and type of NSAIDs use) and outcome definition. We assessed studies included in meta-analysis for publication

bias using funnel plots for studies reporting Odds ratio and HR separately (Additional file 2). Stata software (version 18) native suite of commands, "meta", was used to perform meta-analysis. The suite is broad and simple. "meta set" command was used for meta-analysis setup, followed by "meta summarize" and "meta forest" commands. These commands allow for subgroup analyses. We used the "leave one out" command to test the effect of deleting each study on the pooled effect size.

RESULTS

SEARCH RESULTS AND STUDY CHARACTERISTICS

We identified 4108 publications from electronic and hand-searches from inception to May 2023 for screening. After excluding studies failing to meet our inclusion criteria and duplicates, 260 full-text studies were assessed for eligibility. Of these, 40 studies met the inclusion criteria were included. The PRISMA flow chart is provided in Figure (1).

This systematic review included **40 studies**, 19 cohort, 11 cross sectional, and 10 case control studies reviewing a total of 1,757,118 participants. All the included 40 studies were available in a full-text format and were in English or with English abstract except for Yarger et al study [12] which was published as abstract only, but we found enough data to include it in our systematic review and meta-analysis.

Although the included studies were between 1986 and 2023, more than half of them (56%) were recent (23 studies out of the 40 were in the last 10 years between 2013–2023). Main characteristics of included 40 studies, settings and populations' characteristics are shown in Table (1).

Thirty-nine studies out of 40 studies were meta-analyzable (18 cohort, 11 cross sectionals, and 10 case control) studies reviewing a total of 1,756,934 participants. A study on CKD patients found that COX-2 inhibitors significantly reduced eGFR after three and six months, with no notable change post withdrawal at one and two years [13]. This study was excluded from our meta-analysis as it was the only one using means and standard deviations for continuous variables to estimate effect size.

Over all 14 studies were from United States and 2 from Canada, 14 from Asia, 9 from Europe and 1 from Africa. The map in Fig (2) represents the geographical distribution of studied populations.

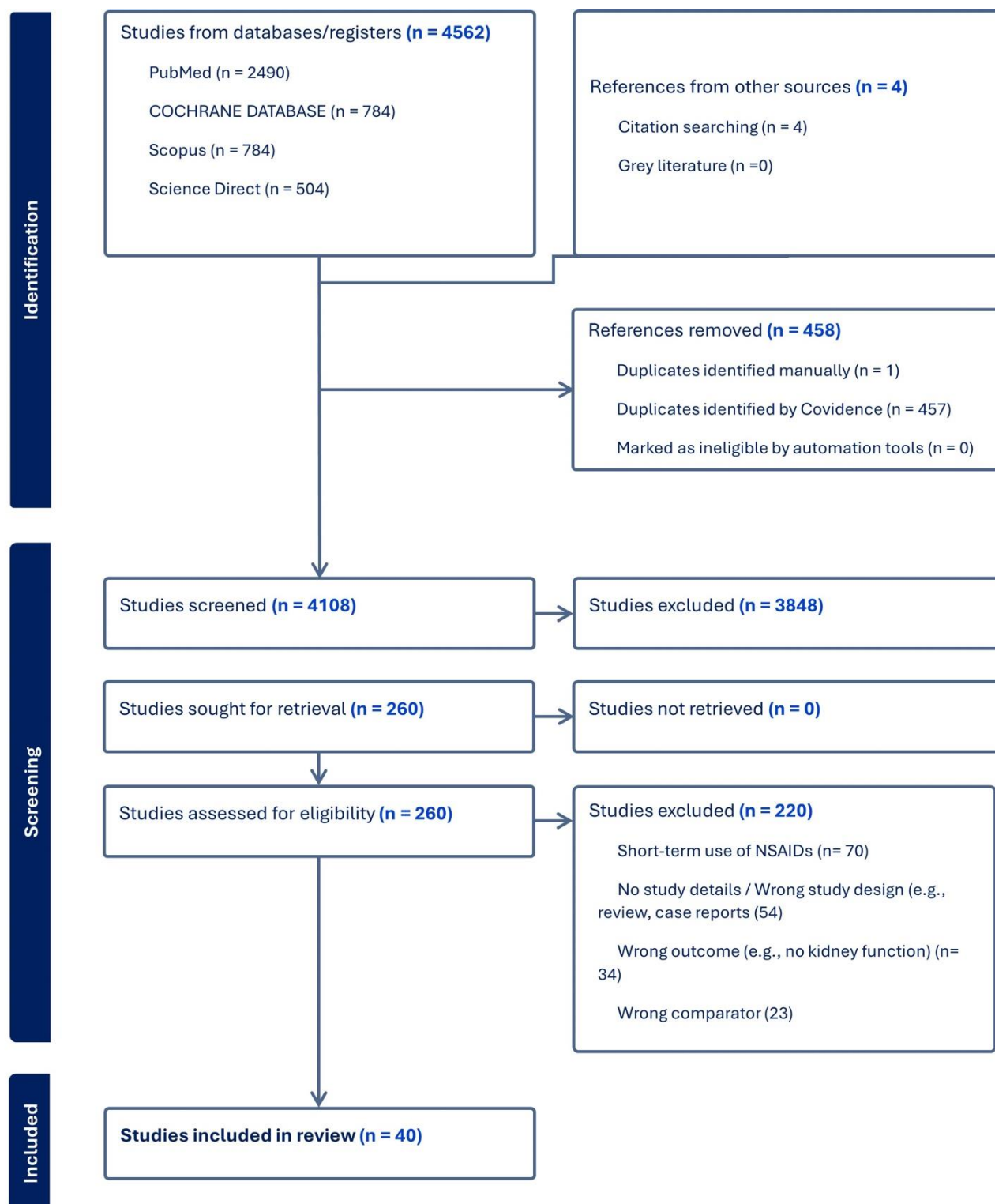


Figure 1. PRISMA flowchart of study selection.

Table 1

Characteristics of included studies

Study ID	Population numbers	Country	Year of publication	Aim of study: to determine	Setting	Study design	Start date-End date of the study	Population characteristics	How NSAIDs exposure was assessed	Outcome	Outcome assessment methods
Agodoa ⁴⁵ 2008	996	United States	2008	Habitual analgesic use with decreased kidney function	community based	Cross sectional	1999–2002	civilian population 20 years or older	standardized interview	ACR $\geq$ 30 mg/g and/or eGFR < 60 mL/min/1.73 m ²	Creatinine, eGFR (MDRD), ACR
Amatruda ¹⁴ 2021	2999	United States	2021	NSAID use with kidney damage in older adults	community based	Cross sectional	1997–1998	older adults 70–79 years with preserved physical function	structured interview	ACR $\geq$ 30 mg/g and/or eGFR < 60 mL/min/1.73 m ²	cysC-based CKD-EPI equation; ACR
Battelli ⁴⁴ 2015	33227	Republic of San Marino	2015	prevalence of NSAID use in patients with kidney damage in year 2013 compared to the general population	community based	Case-control	2013–2013	whole population under national health care	Medical records	Non severe renal damage Vs severe	Creatinine; e GFR (CKD-EPI)
Chiu ²² 2015	17376	Taiwan	2015	concomitant drugs of psoriasis and the risk of CKD	community based	Cohort	2001–2005	newly diagnosed with psoriasis and psoriatic arthritis	Health Insurance Database	new-onset CKD, ESRD	secondary claim data
Chiu ²³ 2015	50316	Taiwan	2015	Risk of developing CKD in patients with RA	community based	Cohort	2001–2005	newly diagnosed with RA	Health Insurance Database	new-onset CKD, ESRD	secondary claim data
Curhan ¹⁹ 2004	1697	United States	2004	association between lifetime use of aspirin, and NSAIDs and renal function	community based	Cohort	1989–2000	Female aged 30–55 years with high life-time use of analgesic	a mailed questionnaire	change in eGFR in 11 years	Estimated creatinine clearance(Cockcroft-Gault formula); e GFR (MDRD)
Field ¹⁵ 1999	4999	United States	1999	NSAIDs use in older people and kidney function	community based	Cross sectional	1981–1989	older adults aged 70 y or more	by interview	Increased BUN and creatinine	Creatinine, BUN BUN:creatinine ratio
Flores ⁴⁶ 2017	121	United States	2017	associations to CKD in an urban adult population	A population-based	Cross sectional	2015–2015	adult urban residents	questionnaire	Low eGFR	e GFR (MDRD), spot proteinuria (semiquantitative reagent strip)
Gooch ¹⁶ 2007	13523	Canada	2007	NSAID use and the progression of CKD in an elderly people	community based	Cross sectional	2001–2003	older adults aged 66 years with ≥ 2 serum creatinine measurements	healthcare database	decrease in eGFR of 15 mL/min/1.732	Creatinine; e GFR (MDRD)

Table 1 (continued)

Study ID	Population numbers	Country	Year of publication	Aim of study: to determine	Setting	Study design	Start date-End date of the study	Population characteristics	How NSAIDs exposure was assessed	Outcome	Outcome assessment methods
Guh ⁴¹ 2007	1740	Taiwan	2007	Herbal Vs NSAIDs therapy and CKD	community based	Cross sectional	1993–1996	adults in Nutrition and Health Survey in Taiwan	by interview	eGFR< 60 mL/min/1.73 m ²	e GFR(Cockcroft-Gault)
Hanaoka ²⁴ 2022	423	Japan	2022	CKD in patients with RA and factors that influence CKD progression	community based	Cross sectional	2000–2016	patients diagnosed with RA who treated with one bDMARD for >5 years	medical records	eGFR< 60 mL/min/1.73 m ² or >25% decrease in eGFR from baseline	e GFR(MDRD)
Hemmelgarn ¹⁷ 2007	10148	Canada	2007	predict rapid progression of kidney dysfunction in elderly	community based	Cohort	2001–2003	elderly ≥66 years with ≥2 serum creatinine measurements	provincial administrative data	≥25% decrease in eGFR from baseline	Creatinine, e GFR (MDRD)
Hsu ³¹ 2015	94541	Taiwan	2015	NSAID use on the development of CKD in hypertensive patients	community based	Cohort	2007–2011	Hypertensive patients aged 20 or more, had 1 admission or 2 outpatient visits and free of CKD	Health Insurance Database	newly diagnosed CKD	medical claims data
Hsu ³⁷ 2019	456	Taiwan	2019	chronic pain and CKD progression in pre-dialysis CKD	community based	Cohort	2006–2007	18–80 y with stable CKD	by interview	CKD stage progression	BUN, Creatinine; eGFR(CKD-EPI) and Proteinuria
IBAÁ' NEZ ³² 2005	1302	Spain	2005	risk of ESRD associated with the chronic use of NSAID	community based	Case-control	1995–1997	advanced CKD patients	by interview using a standardized questionnaire	Entering dialysis	Unclear
Ingrasciotta ⁴² 2015	10034	Italy	2015	NSAIDs and risk of CKD in a general population	community based	Case-control	2006 to 2011	general populations who were registered in the Arianna database	healthcare database	Incident CKD	By using ICD9-CM codes
Kaewput ¹³ 2016	184	Thailand	2016	COX-2 inhibitors and CKD progression	community based	Cohort	2009–2014	>18 years with a diagnosis of CKD	Medical records	Any decrease in eGFR	Creatinine, e GFR (CKD-EPI), spot proteinuria (semiquantitative reagent strip)

Table 1 (continued)

Study ID	Population numbers	Country	Year of publication	Aim of study: to determine	Setting	Study design	Start date-End date of the study	Population characteristics	How NSAIDs exposure was assessed	Outcome	Outcome assessment methods
Kang ¹⁸ 2019	24219	Korea	2019	polypharmacy and kidney dysfunction among older patients.	community based	Case-control	2009–2013	older adults 65–84	medical records	decline rate of $\geq 10\%$ compared to the baseline eGFR	e GFR (CKD-EPI)
Kuo ³⁸ 2010	19163	Taiwan	2010	Analgesic use in CKD patients	hospital based	Cohort	1997–2006	newly diagnosed CKD	healthcare database	increased risk for ESRD	By using ICD9-CM codes
Kurth ²¹ 2003	4494	United States	2003	aspirin and chronic kidney disease	community based	Cohort	1982–1996	apparently healthy males	questionnaire	Increase creatinine ≥ 0.3 mg/dl or decrease in eGFR of 29 mL/min/1.732	Creatinine, e GFR (MDRD)
Mackinnon ⁵⁰ 2003	7827	UK	2003	the rate of decline in renal function and risk of death or dialysis	hospital based	Cohort	1989–2003	Patients diagnosed with AAN	by interview	rate of change of ECC per year	ESTIMATED Creatinine clearance (ECC)
Möller ²⁵ 2015	4101	Switzerland	2013	prolonged NSAID exposure on renal function in (RA) patient	community based	Cohort	1996–2007	RA patients	annual visit & phone calls	change of eGFR	e GFR(Cockcroft–Gault formula)
Mori ²⁶ 2017	1908	Japan	2017	prevalence of renal dysfunction in rheumatoid arthritis patients	hospital based	Cross sectional	2014–2015	Patients with RA	medical records	change of eGFR	e GFR(Cockcroft–Gault formula)
Morlans ²⁰ 1990	1305	Spain	1990	risk of ESRD with the regular use of analgesics	Hospital based	Case-control	1980–1983	female patients on dialysis	by interview	ESRD	Unclear
Murray ⁴⁰ 1990	1908	United States	1990	incidence of renal impairment among patients NSAIDs	community based	Cohort	1975–1986	general population	medical records	>10% increase of BUN, Creatinine	BUN, Creatinine
Nderitu ⁴⁷ 2014	3566	UK	2014	the effect of different dose NSAIDs on eGFR decline	community based	Cohort	2009–2010	general population	healthcare database	>5mL/min/1.73 m ² /year eGFR decrease	e GFR(MDRD)
Nelson ⁴⁹ 2019	764228	United States	2019	NSAIDs and incident chronic kidney disease	community based	Cohort	2011–2014	active-duty US Army soldiers	medical records	Incident CKD	By using ICD9-CM codes
Pan ⁴⁸ 2014	50316	China	2014	NSAIDs intake and presence of (CKD)	community based	Cross sectional	2009–2010	general population	by questionnaire	eGFR < 60 mL/min per 1.73 m ²	e GFR (Cockcroft–Gault formula), ACR
Perneger ³³ 1994	1900	United States	1994	cumulative intake (in pills) with ESRD	community based	Case-control	1991–1991	20 to 64 y. with advanced CKD	by telephone interview	ESRD	unclear

Table 1 (continued)

Study ID	Population numbers	Country	Year of publication	Aim of study: to determine	Setting	Study design	Start date-End date of the study	Population characteristics	How NSAIDs exposure was assessed	Outcome	Outcome assessment methods
Plantinga ⁴³ 2011	12065	United States	2011	patterns of NSAID use in CKD patients	community based	Cross sectional	1999–2004	adult aged 20 years or older	by questionnaire	eGFR< 60 mL/min per 1.73 m ²	e GFR (MDRD)
Sandler ³⁴ 1989	1070	United States	1989	analgesics and chronic renal disease	community based	Case-control	1980–1982	age 30–70 y with newly diagnosed CKD and matched controls	By telephone interview	Renal disease	ICD9-CM codes
Sandler ³⁵ 1991	1070	United States	1991	risk for CKD with regular use of (NSAIDs).	hospital based	Case-control	1980–1982	newly diagnosed CKD and matched controls	by telephone interview	Renal disease	ICD9-CM codes
Shigidi ²⁹ 2021	736	Sudan	2021	factors that promote the development and progression of DKD	hospital based	Case-control	2019–2019	aged 35 years or above, with T2DM for more than 10 years	Direct interview	eGFR< 60 mL/min per 1.73 m ²	e GFR
Sturmer ²⁷ 2001	802	Germany	2001	effects of NSAID half-life and dosing intervals on renal function	hospital based	Cross sectional	1995–1996	patients undergoing total joint replacement because of osteoarthritis under the age of 76 years	Standardized interview	eGFR< 60 mL/min per 1.73 m ²	Creatinine, estimate creatinine clearance
Tokoroyama ²⁸ 2017	107746	Japan	2017	prevalence of CKD	hospital based	Cohort	2004–2014	RA patients	medical records	eGFR< 60 mL/min per 1.73 m ²	Proteinuria $\geq$ +1, e GFR (Cockcroft–Gault formula)
Tsai ³⁰ 2015	48715	Taiwan	2015	relationship between NSAIDs and the development of CKD in people with Type 2 diabetes mellitus	hospital based	Cohort	2007–2011	adult population with Type 2 diabetes	Healthcare database	CKD development	ICD9-CM codes
vanderWoude ³⁶ 2007	3286	Germany	2007	relation between phenacetin-free analgesics and nephropathy	community based	Case-control	2001–2004	advanced CKD under the age of 50	by Standardized interview	ESRD	unclear
WanEYF ⁵¹ 2021	419506	Hong kong	2021	NSAIDs exposure and eGFR	hospital based	Cohort	not mentioned	All individuals with eGFR above or equal 60 mL/min	by interview	incident eGFR, 60 mL/min per 1.73 m ² ; eGFR decline $\geq$ 30%	e GFR (MDRD)

Table 1 (continued)

Study ID	Population numbers	Country	Year of publication	Aim of study: to determine	Setting	Study design	Start date-End date of the study	Population characteristics	How NSAIDs exposure was assessed	Outcome	Outcome assessment methods
Yarger ¹² 2011	34,295	United States	2011	NSAID use and CKD progression in elderly	community based	Cohort	2006–2008	CKD stage 2 or 3 who were elderly (67 years of age) received treatment at a military facility	Healthcare database	CKD progression of stage 2 or 3	e GFR
Zhan ³⁹ 2020	3939	United States	2020	opioid and NSAID use in patients with CKD	hospital based	Cohort	2003–2006	21–74 years of age with eGFR 20–70 mL/min	by interview	50% reduction of baseline eGFR or requiring kidney replacement therapy	e GFR(MDRD)

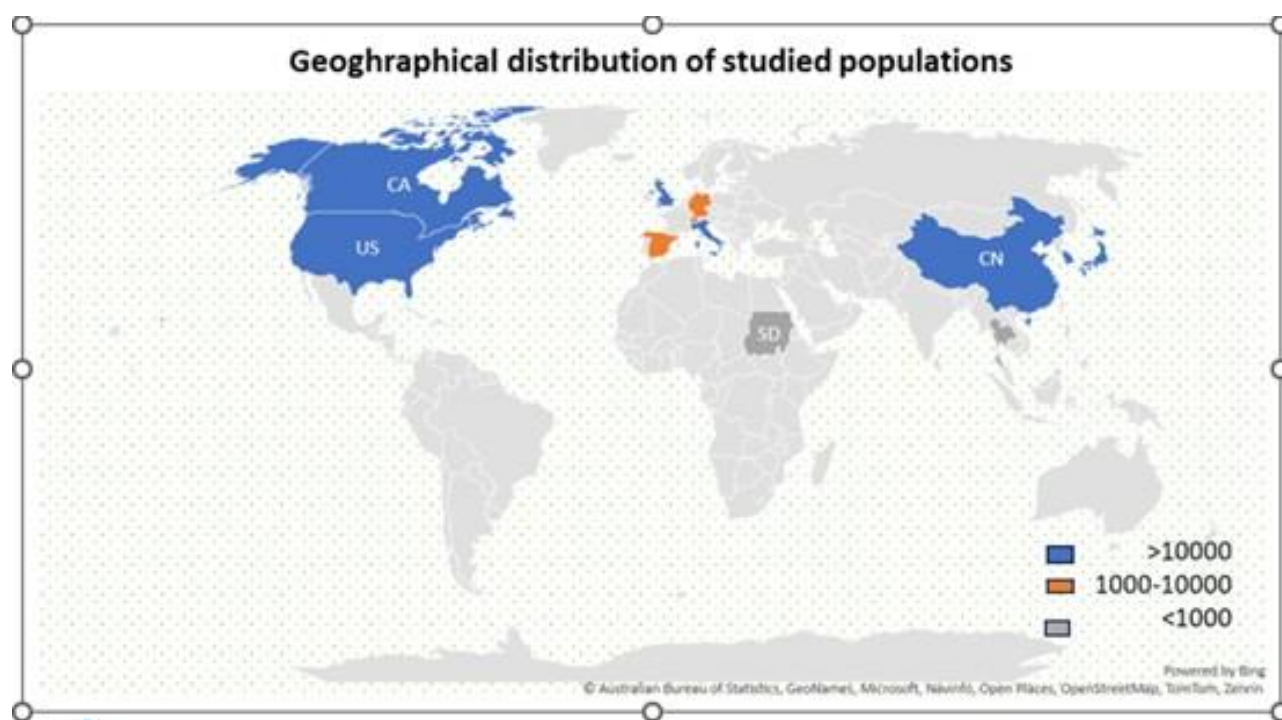


Figure 2. Geographical distribution of studied populations.

POPULATION CHARACTERISTICS

Although all studies included population aged 18 years or older, six studies were limited to populations older than 60 years [12,14–18]. Two studies included only female population [19,20] and *one* study include only male population [21].

Seven studies dealt with patients diagnosed with musculoskeletal diseases [22–28], two on people with diabetes [29,30] and 1 for hypertensive patients [31]. Despite cancer patients are considered as frequent and chronic users of NSAIDs but they are considered as exclusion criteria in most of studies enrolled in our meta-analysis.

At baseline, eleven studies enrolled CKD patients (of those, seven studies compared the CKD patients to matched non-CKD [13,20–32–36] controls while four studies compared CKD patients within different stages [12,37–39].

OUTCOME MEASURE

CKD occurrence or progression was assessed by eGFR in most of studies and serum creatinine, ACR, spot proteinuria. Different definitions used for eGFR decline are shown in table (1). Out of 40 studies, 17 studies included an eGFR < 60 mL/min/1.73 m², 4 studies included any change in eGFR. 1 study for each of the following outcome: decrease of 29 mL, 15 mL/min/1.732, >5mL/min/1.73 m² /year, ≥ 10%, 25%, 50% from baseline to measure the occurrence or progression

of CKD. Eleven studies estimated the GFR using the four-variable MDRD equation, 6 studies used Cockcroft–Gault formula, 5 studies used CKD-EPI, 6 studies By using ICD9-CM codes whereas eGFR method was unclear in 6 studies [12,20,29,32,33, 36].

Creatinine, BUN used in 2 studies [15,40] to assess the outcome. The other 3 studies used secondary claim data for their outcome assessment [22,23,31]. However, these diverse outcome measurements collectively contribute to defining the occurrence or progression of chronic kidney disease (CKD).

EXPOSURE ASSESSMENT

In 22 studies, information regarding chronic NSAIDs exposure was obtained through interviews (either direct or telephone) or questionnaires. In the remaining studies, assessment relied on healthcare databases and medical records (Table 1).

EFFECT SIZE ASSOCIATED WITH CKD OCCURRENCE AND PROGRESSION

Estimation of the effect size was done by HR in 11 studies, by OR in 35 studies and by mean eGFR difference in one study. We extracted the adjusted measure if available otherwise we used the crude (univariate measure).

Among 35 studies that measure the OR as effect size, [15,16,20,22,23,24,29,35,41,42,43] reported hazardous effect, [14,26,44,45] reported

protective effect while [12,16,17,18,19,21,25,27, 32,33,34,36,40,46,47,48] reported no effect. Some of these studies provided inconsistent effect in different subsets of their populations [16,33,45,47].

Among 11 studies that measure the HR as effect size [37] reported protective effect, [39,49] reported no effect and [28,30,31,38,50,51] reported hazardous effect. One study provided different effect in subsets of its population [38].

META-ANALYSIS

Odds ratios were extracted or calculated from 35 studies or subpopulations within studies. Figure

3 forest plot showed significant association between chronic NSAIDs use and CKD (occurrence and progression); pooled odds ratio was 1.24 (95% CI: 1.11–1.39, $p < 0.001$, $I^2 = 91.21\%$), (May represent substantial between studies statistical heterogeneity).

Hazard ratios were extracted or calculated from 11 studies or subpopulations within studies. Figure 4 forest plot showed significant association between chronic NSAIDs use and CKD (occurrence and progression); pooled Hazard ratio=1.50 (95thCI:1.31:1.7), $P < 0.001$, $I^2=90.77\%$ (considerable statistical heterogeneity).

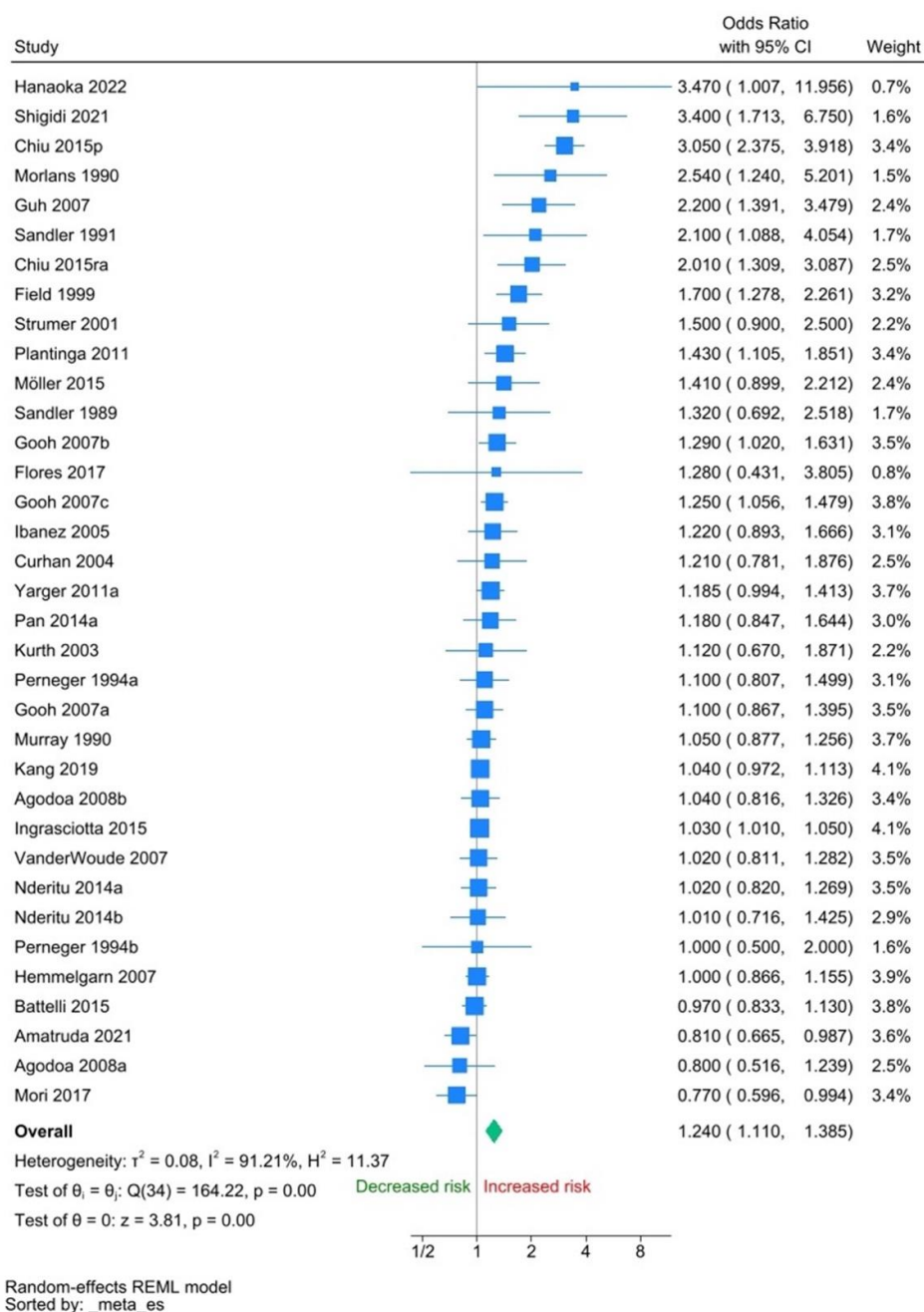


Figure 3. Forest plot of pooled ORs.

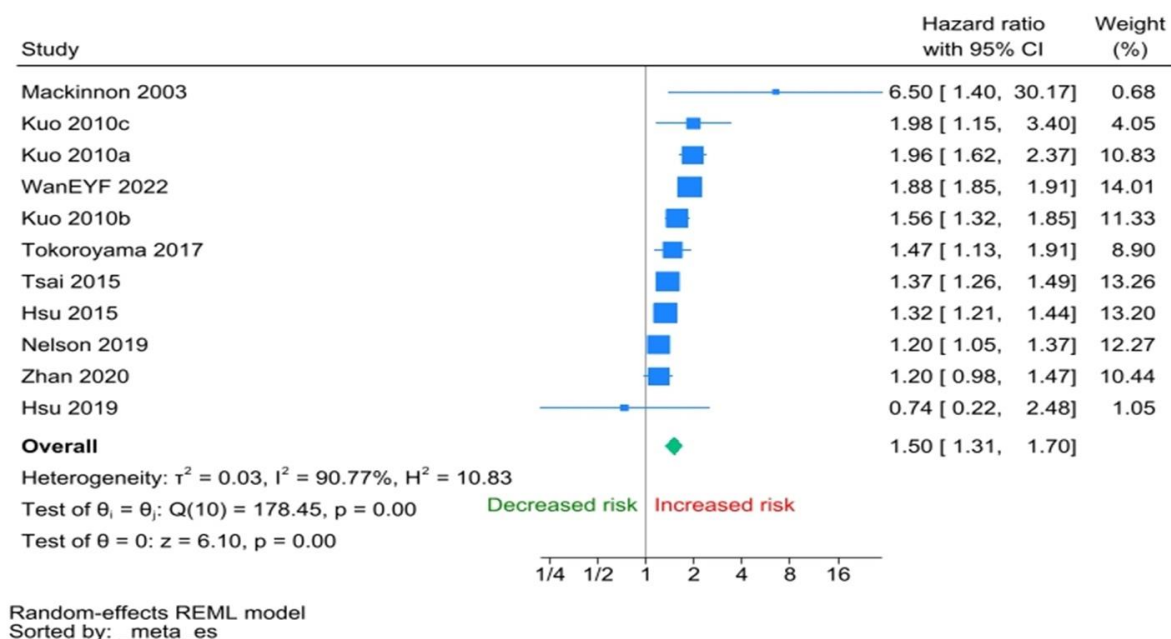


Figure 4. Forest plot of pooled HRs.

SUBGROUP ANALYSES

Subgroup analyses

As our reported heterogeneity was high, we investigated possible sources by subgroup analysis of pooled studies by population parameters (whether they were older population or general population, and if they have preexisting CKD at baseline and other chronic disease, namely Diabetes, Hypertension and/or rheumatic disease), exposure measurement (whether it was by interview, questionnaire or through medical record/unclear) and outcome measure (eGFR, create, or medical record data). The subgroup analyses modestly reduced heterogeneity.

Subgroup analyses of studies reporting OR

- 1 – Age of participants, 6 studies were exclusively conducted on older people. Subgroup analysis showed that the pooled OR shows no association between NSAIDs exposure and CKD pooled OR= 1.109 (95th CI: 0.92:1.30) while the pooled OR of studies conducted on adults of any age remained significant pooled OR= 1.29 (95th CI: 1.13 :1.47) as shown in figure 5.
- 2 – Chronic kidney disease measurement methods: there was marked decrease in heterogeneity among studies that measured CKD outcome by serum creatinine followed by eGFR, however, heterogeneity remained high among studies relied on ICD diagnosis for assessment of the outcome as shown in figure 6.

- 3 – Method of NSAID assessment: Heterogeneity was the least in studies assessing NSAIDs use by interview followed by questionnaire. Marked heterogeneity remained among studies relied on claims data, questionnaire and unclear methods. The pooled OR of “interview” subgroup was 1.18 (95th CI: 1.08: 1.29) as shown in figure 7.

Subgroup analyses of studies reporting HR

- 1 – Preexisting CKD: The pooled hazard ratio (HR) from six studies was calculated for two groups (figure 8):
 - No CKD at baseline: HR 1.31 (1.26–1.40)
 - Preexisting CKD: HR 1.67 (1.38–2.02)
- 2 – Disease status of the population other than CKD: The pooled hazard ratio (HR) from six studies was calculated for three groups (figure 9):
 - No specific chronic disease: HR 1.6 (95% CI, 1.32–1.94)
 - Population with diabetes mellitus (DM) and/or hypertension (HTN): HR 1.35 (95% CI, 1.27–1.43)
 - Population with rheumatic disease: HR 1.36 (95% CI, 0.88–2.10)
- 3 – Method of NSAID assessment: The pooled hazard ratio (HR) varied based on the assessment method (figure 10):
 - Interview: HR 1.56 (95% CI 1.00, 2.44)
 - Unclear / Medical record or claim: HR 1.56 (95% CI 1.46, 1.67).

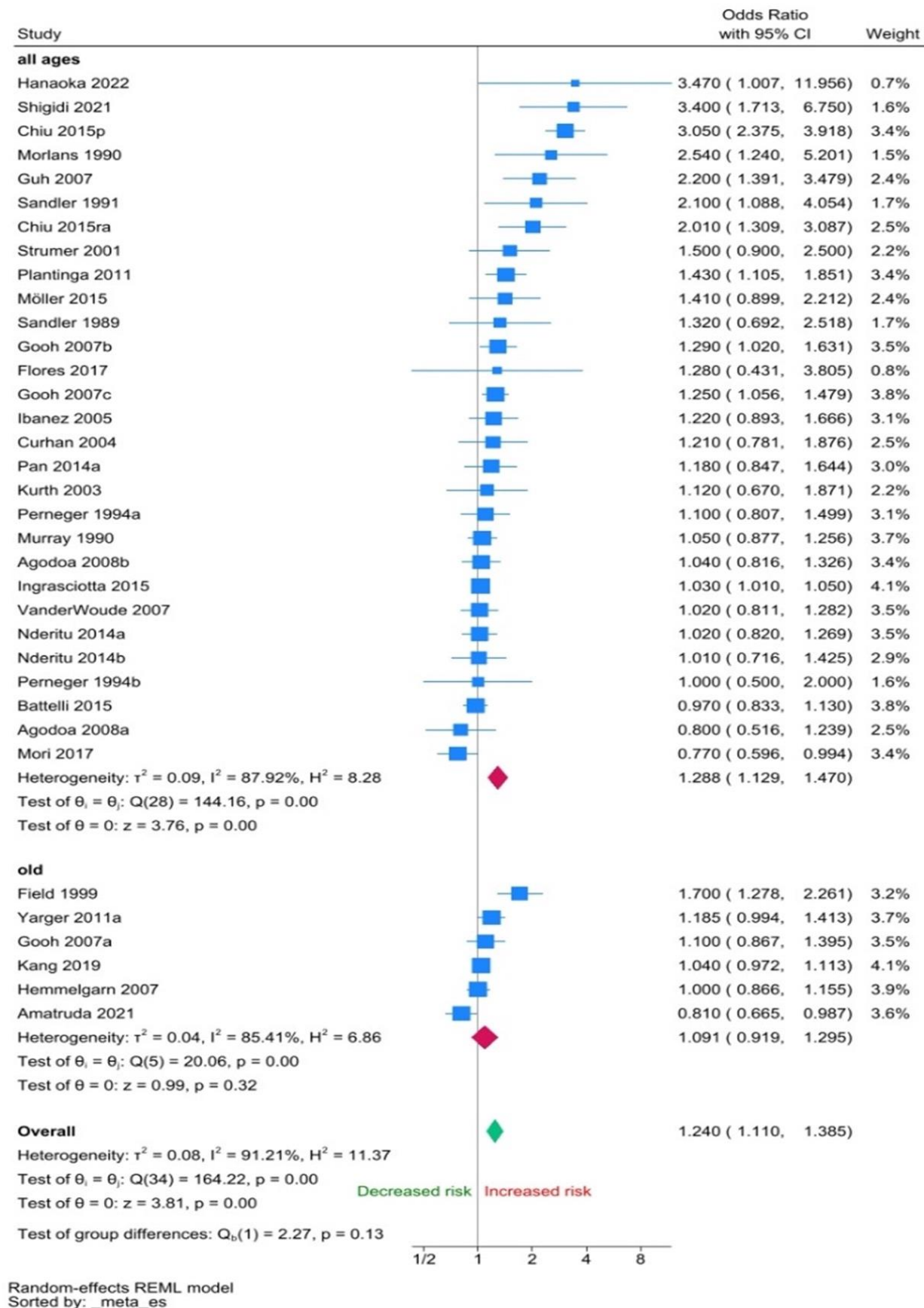


Figure 5. Forest plot of pooled ORs with subgroup analysis by age.

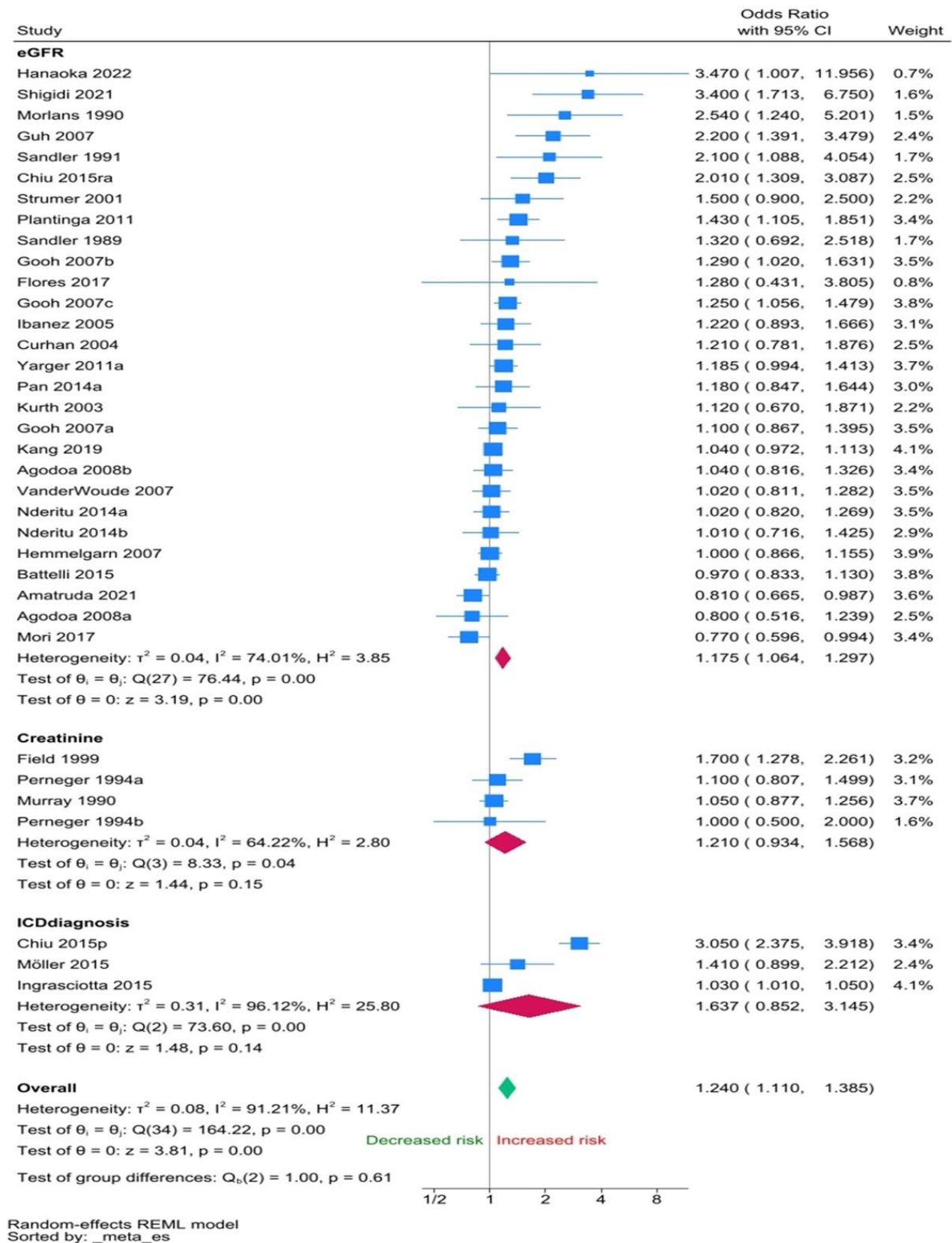


Figure 6. Forest plot of pooled ORs with subgroup analysis by chronic kidney disease outcome measurement methods.

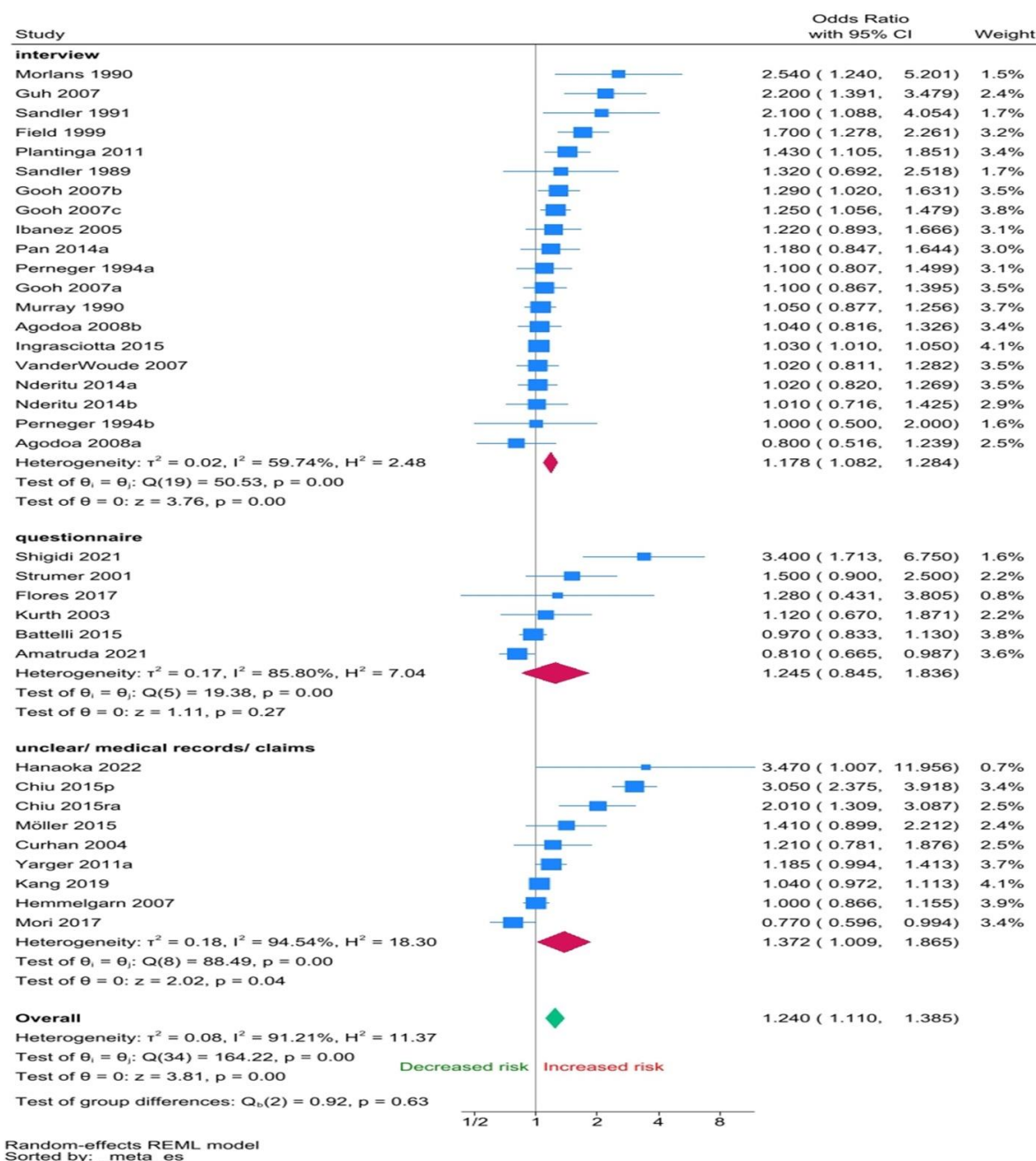


Figure 7. Forest plot of pooled ORs with subgroup analysis by method of NSAID assessment.

RISK OF BIAS IN INCLUDED STUDIES

The review authors' judgement about each risk of bias item for each included study is summarized in figure 11 (by study and by domain) and additional file 3 (by domain).

In most of the cohort studies included, the risk of bias was generally low regarding participant recruitment, confounder identification, follow-up duration, and statistical methods used. Specifically, the risk of bias for the measurement of exposure was low in 10 studies. Concerning incomplete

follow-up and the strategies used to address it, the risk of bias was low in 7 and 6 out of the 18 studies, respectively.

In most of the case-control studies, the risk of bias was low across all domains, except for strategies to deal with confounders, where only 5 out of 10 studies had a low risk of bias. Similarly, in the majority of cross-sectional studies, the risk of bias was low for all domains except for the measurement of exposure, with only 5 out of 11 studies demonstrating a low risk of bias in this area.

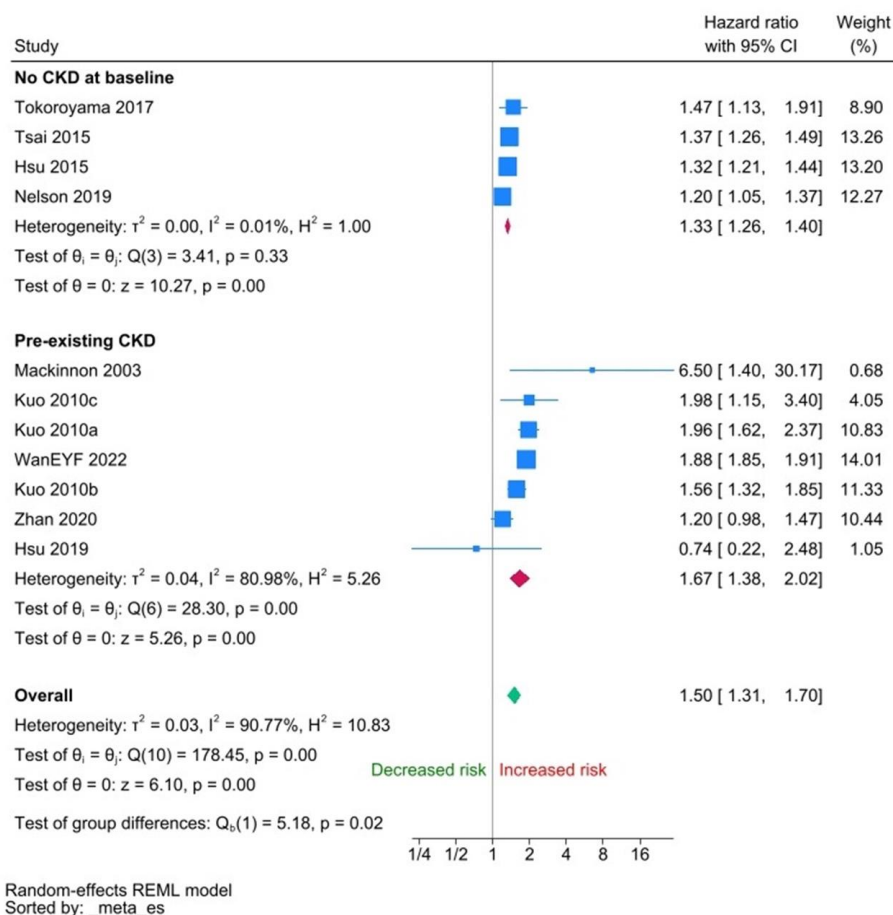


Figure 8. Forest plot of pooled HRs with subgroup analysis by chronic kidney disease status.

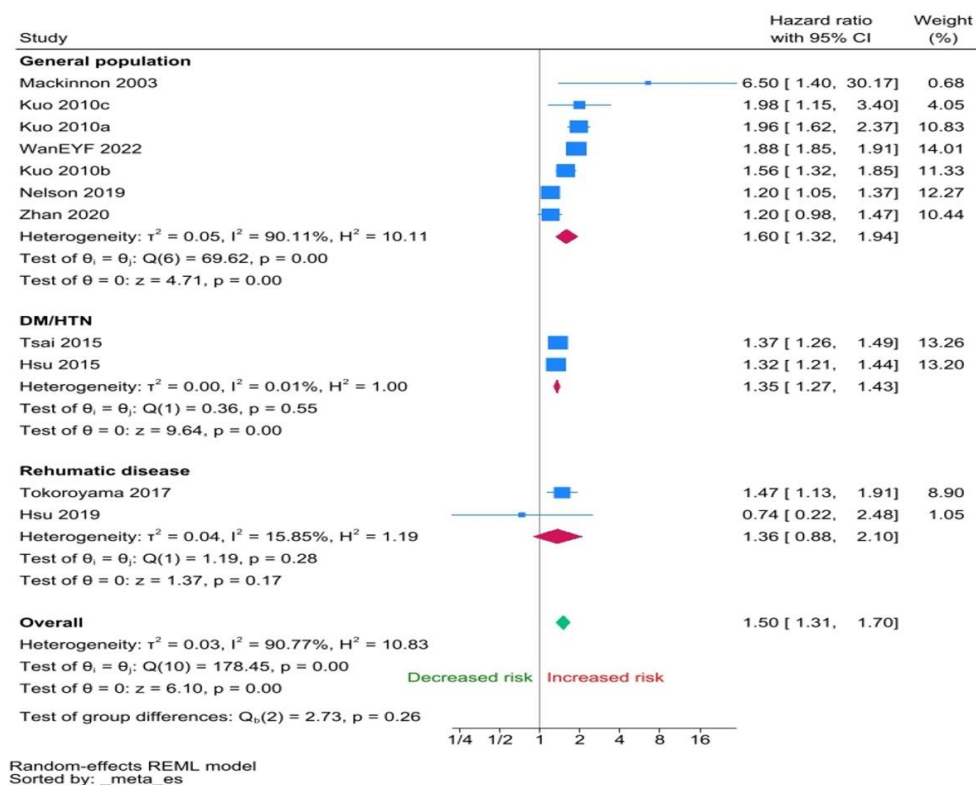


Figure 9. Forest plot for studies with HR by subgrouping by chronic disease other than CKD.

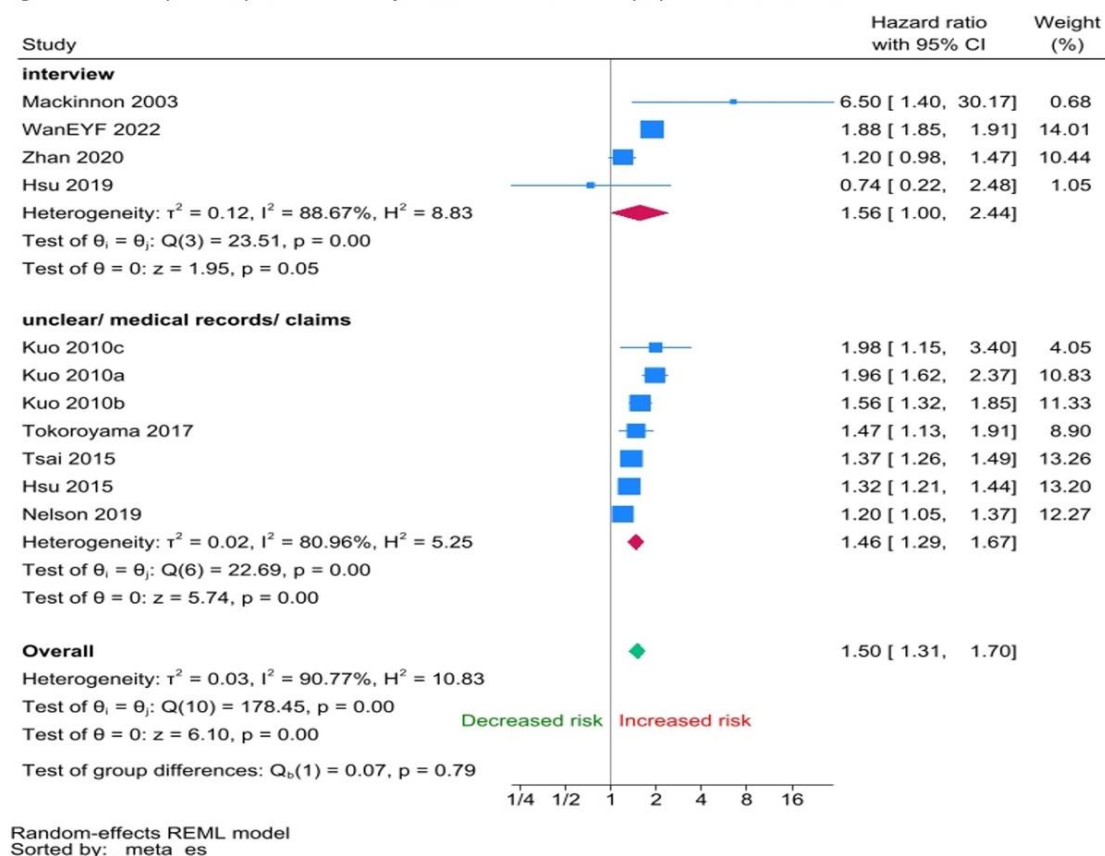


Figure 10. Forest plot for studies with HR by subgrouping with Method of NSAID assessment.

DISCUSSION

Our systematic review and meta-analysis is the most updated comprehensive study dealt with recent large numbers of studies with different clinical situations and broader definition for kidney outcome to clarify the association between chronic NSAIDs use and CKD occurrence and/or progression. This meta-analysis showed regular and chronic NSAID users had a hazard ratio of 1.50 (95% CI: 1.30–1.70) for CKD occurrence/progression, which means a 50% higher risk of CKD outcomes compared to non-users. Additionally, chronic NSAID users had modestly but significantly higher odds (OR: 1.24, 95% CI: 1.11–1.39) for CKD outcomes compared to non-users.

The statistical heterogeneity observed in our meta-analysis can be attributed to clinical heterogeneity among the included studies and the use of broader eligibility criteria. To ensure comprehensive applicability across various patient populations and diagnoses, we incorporated a large number of studies. Given this context, encountering high heterogeneity is natural. To address this issue, we conducted subgroup analyses to explore and explain the sources of variation as mentioned earlier. Subgroup analyses suggest that the method

of CKD outcome measurement, the age of participants, and the method of NSAID assessment influence the heterogeneity and strength of the association. Therefore, it's essential to approach this information thoughtfully.

Our review encompasses an analysis of 40 studies without age restrictions. Among these, 17 studies reported a hazardous effect while 23 reported either no effect or a protective effect on the kidneys of chronic NSAID users. This includes the most recent studies up to May 2023. In contrast, the latest similar meta-analysis conducted 11 years ago was based on only three studies. These studies were limited to patients aged 45 or older and included research from the years 2001 to 2011 [7]. Another recent meta-analysis in 2022 by Emilie Lambourg et al [52] is concerned mainly with the prevalence of analgesic use and its related adverse events in CKD population. It includes only two studies to explore the effect of chronic NSAIDs use and CKD progression and one for kidney transplant patients [52]. In addition, the methodological design of our work makes our findings to be suitable for general physicians and for the concerned patients in the general population as our review includes different outcomes in different clinical conditions.

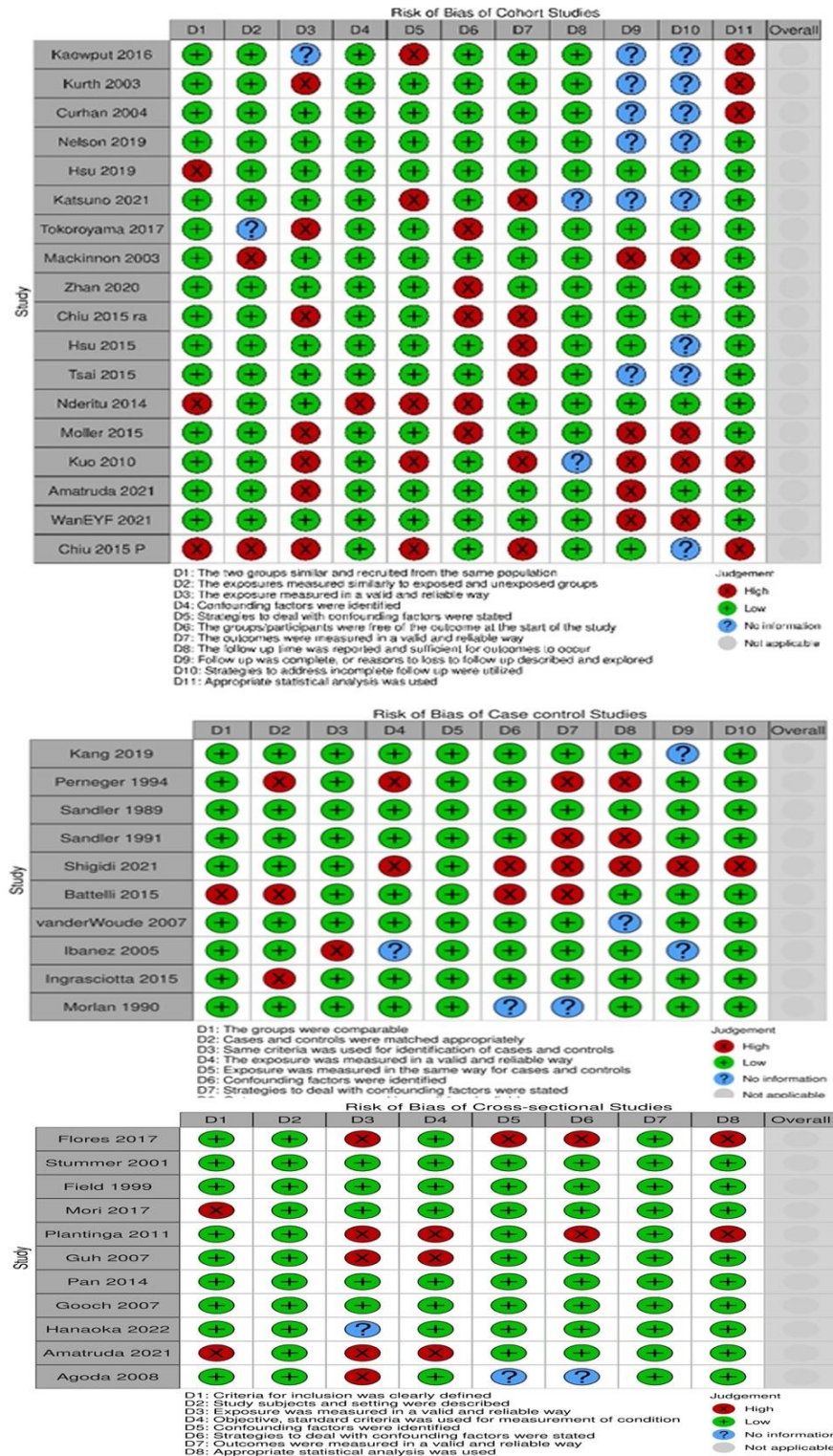


Figure 11. Risk of bias (by study and by domain).

In our work, individuals with pre-existing CKD are the most affected group, with a significantly higher risk rate of 67%, compared to the general population risk of 60%. Other groups, such as individuals with no CKD at baseline (31%), patients with diabetes mellitus (DM) or hypertension (HTN)

(35%), and patients with musculoskeletal disease (36%), exhibit lower risk rates. Our findings partially concur with those of Paul Nderitu *et al.*, who concluded that regular NSAID use did not correlate with accelerated CKD progression or a heightened risk of developing moderate to severe CKD.

However, they found that high-dose NSAID use was associated with a 26% increased risk of such outcomes, as reported in their meta-analysis [7]. However, their meta-analysis, which was limited to three cohort studies and focused on a narrower outcome definition (specifically assessing accelerated eGFR decline of ≥ 15 ml/min/1.73 m² in stage 3 CKD patients). The 2013 study by Nderitu et al. addressed whether chronic NSAID use increases the risk of CKD progression and the risk of developing moderate to severe CKD, focusing exclusively on CKD patients and excluding general populations, studies with only male or female participants, those with stages 1–2 CKD, participants under 45 years, and studies involving phenacetin or using ESRD as the primary outcome. Their findings indicated that accelerated CKD progression occurred in 10.9–13.3% of participants. In contrast, our broader meta-analysis encompasses a wider range of outcomes, despite reaching similar conclusions.

The quality assessment of studies reporting either a protective or no effect [12,14,16–19,21,25–27,32–34,36,40,44–48] revealed several methodological limitations. These include inaccurate outcome estimation, exposure assessment bias, and suboptimal handling of confounders. Such issues could complicate the generalization of these results.

Regarding the limitations of this work, we must acknowledge the potential for publication bias. Despite that our eligibility criteria included RCTs, we encountered only observational studies. These studies inherently carry various measured and unmeasured confounders that could influence the results. Additionally, there was a notable scarcity of data regarding specific NSAID classes and their dosages. Furthermore, our review was constrained by the inclusion of studies and abstracts published solely in English, which may omit relevant findings published in other languages. For many studies, NSAID exposure was determined using medical records or health insurance database. However, the widespread availability of these agents over the counter means that prescriptions and medical

records likely underestimate their use. NSAIDs are commonly combined with PPIs to mitigate GI adverse effects. However, recent evidence suggests an increased risk of chronic kidney disease (CKD) with PPI use. The potential synergetic role of PPI-induced CKD and complex interplay between PPIs, and CKD occurrence or progression particularly in patients received NSAIDs needs further analysis.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Given the result of this systematic review and meta-analysis, clinicians should monitor the renal function of their patients periodically. Policy makers should consider implementing guidelines and regulations to limit the over-the-counter availability and prescription of NSAIDs, especially for high-risk populations. Further research should aim to determine the most appropriate NSAID type and dosage for varying pain and clinical scenarios, as well as to evaluate if intervals without NSAID use could facilitate renal recovery and the reestablishment of prostaglandin levels.

CONCLUSION

Long-term use of NSAIDs is associated with an increased risk of chronic kidney disease (CKD) occurrence and progression. Individuals with pre-existing CKD are the most affected group, with a significantly higher risk rate of 67%, compared to the general population risk of 60%. Other groups, such as individuals with no CKD at baseline (31%), patients with diabetes mellitus (DM) or hypertension (HTN) (35%), and patients with musculoskeletal disease (36%), exhibit lower risk rates. Therefore, a patient-centered approach prioritizing safe and effective pain management is crucial. Special caution should be exercised when prescribing NSAIDs to patients with pre-existing CKD due to their heightened vulnerability. Further research is essential to define safe patterns of NSAID prescription and consumption.

Introducere: Medicamentele antiinflamatorii nesteroidiene (AINS) sunt o cauză frecventă a leziunilor renale acute, dar riscul de boală renală cronică (CKD) dat de AINS este controversat. Sintezele sistematice anterioare sunt depășite cu unele deficiențe metodologice. Am efectuat această sinteză sistematică pentru a clarifica asocierea dintre utilizarea și apariția și/sau progresia CKD.

Metode: Medline, Cochrane Library, Web of Science și Science Direct Direct au fost căutate pentru studii observaționale și intervenționale de la începutul indexării până în mai 2023. S-a efectuat sinteză calitativă. Meta-analiza a utilizat raportul cotelor (OR) și

raportul hazardului (HR) pentru a estima asocierea dintre utilizarea cronică a AINS și apariția sau progresia CKD.

Rezultate: Patruzeci de studii cu un total de 1757118 participanți au fost incluse în sinteza sistematică; dintre ele, 39 de studii au fost potrivite pentru meta-analiză. 56% din studiile noastre incluse au fost recente, publicate în ultimii 10 ani. Metaanaliza a evidențiat o asociere semnificativă între utilizarea cronică a AINS și apariția și progresia CKD. OR combinat a fost de 1,24 (IC 95%: 1,11–1,39, $p < 0,001$, $I^2 = 91,21\%$), iar HR combinat a fost de 1,50 (IC 95%: 1,31–1,7, $p < 0,001$, $I^2 = 90,77\%$). HR pentru persoanele fără CKD inițial a fost de 1,31 (IC 95%, 1,26–1,40), în timp ce pentru cei cu CKD preexistent, HR-ul a fost semnificativ mai mare la 1,67 (IC 95%, 1,38–2,02). HR-ul pentru persoanele fără boală cronică specifică a fost de 1,6 (IC 95%, 1,32–1,94). Pentru populațiile cu diabet zaharat (DM) și/sau hipertensiune arterială (HTN), HR-ul a fost de 1,35 (IC 95%, 1,27–1,43), iar pentru cei cu boală reumatică, HR-ul a fost de 1,36 (IC 95%, 0,88–2,10).

Concluzii: Utilizarea AINS pe termen lung crește riscul de apariție și progresie a bolilor renale cronice (CKD), în special la persoanele cu CKD preexistente, care au un risc de 67% în comparație cu 60% din populația generală. O abordare centrată pe pacient pentru o gestionare sigură și eficientă a durerii este crucială, cu precauție specială pentru cei cu CKD preexistent.

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Abbreviations: ACR: albumin creatinine ratio; AKI: Acute kidney injury; CI: BUN: blood urea nitrogen; CI: Confidence interval; CKD: Chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration Equation; COX-2 inhibitors: cyclooxygenase-2 enzyme inhibitors; Cr Cl: Creatinine clearance; GFR: Glomerular filtration rate; HR: Hazard ratio; ICD: International Classification of Diseases; KDIGO: Kidney Disease Improving Global Outcomes; NSAIDs: Non-steroidal anti-inflammatory drugs; OR: Odds ratio; RCT: randomized controlled clinical trials; RR: Relative risk; SCr: Serum creatinine; UK: United Kingdom; US: United States

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ADDITIONAL FILES

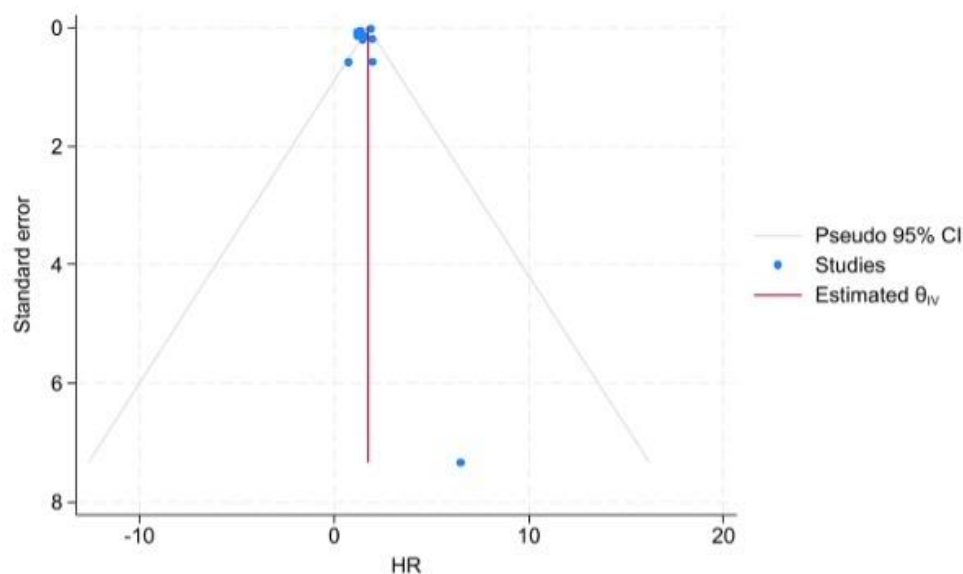
ADDITIONAL FILE 1: SEARCH STRATEGY

Keywords

1. NSAID use
2. CKD
3. eGFR

Source/database	Search term 1: NSAIDs Use	Search Term 2: (AND)	Search TERM 3: (OR)	Number of entries found
Pubmed	((((NSAID*[Title/Abstract]) OR (non-steroidal[Title/Abstract] AND anti-inflammatory[Title/Abstract] AND drugs[Title/Abstract])) OR (nonsteroidal[Title/Abstract] AND antiinflammatory[Title/Abstract] AND drugs[Title/Abstract])) OR (((ANTI-INFLAMMATORY AGENT [Title/Abstract]) OR (ANTI-INFLAMMATORY AGENTS[Title/Abstract])) OR (ANALGESICS[Title/Abstract]))	(((((CKD[Title/Abstract]) OR (Chronic[Title/Abstract] AND Kidney[Title/Abstract] AND Disease[Title/Abstract])) OR (KIDNEY DISEASES[Title/Abstract])) OR (KIDNEY FAILURE[Title/Abstract])) OR (Nephropathy[Title/Abstract]) OR		2490
Chocrane database	(nonsteroidal OR non-steroidal OR NSAID*):ti,ab,kw AND (((Long-term OR Chronic OR prolonged OR extended OR continuous) AND use) OR "Long-term effect" OR "long-term toxicity" OR "drug toxicity"OR "adverse effect"):ti,ab,kw	("Renal function" OR "kidney function" OR "glomerular filtration rate" OR creatinine OR albuminuria OR proteinuria OR EGFR):ti,ab,kw)		784
Scopus through Egyptian Knowledge bank	((((((AB=(CKD)) OR AB=(chronic kidney disease)) OR AB=(chronic renal)) OR AB=(e-GFR)) OR AB=(eGFR)) OR AB=(glomerular AND filtration)) OR AB=(nephropathy)	(((AB=(nsaid*)) OR AB=(non-steroidal OR nonsteroidal)) OR AB=(anti-inflammatory)) OR AB=(anti-inflammatory)		784
Science direct	(nsaids OR non-steroidal OR nonsteroidal OR analgesics	(((((CKD) OR (Chronic AND Kidney AND Disease)) OR (KIDNEY DISEASES)) OR (KIDNEY FAILURE))		504

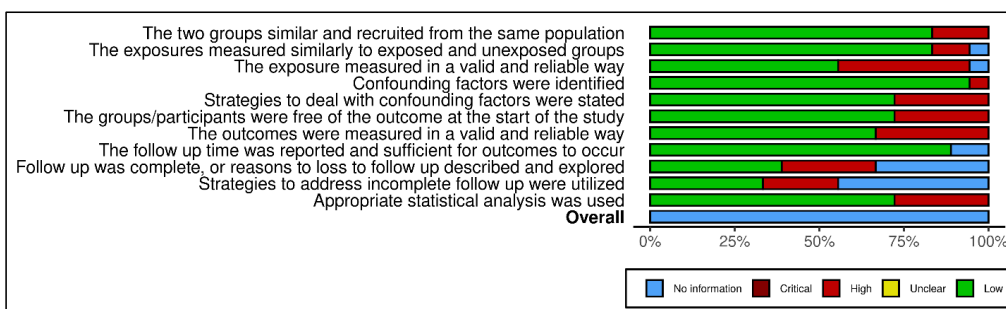
ADDITIONAL FILE 2: PUBLICATION BIAS ASSESSMENT



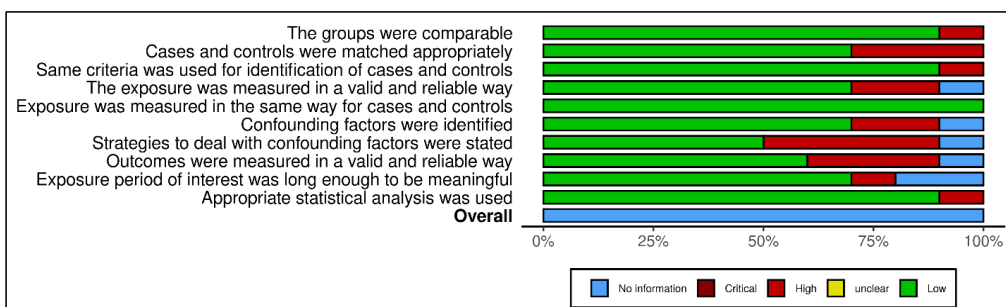
ADDITIONAL FILE 3: RISK OF BIAS ASSESSMENT (BY DOMAIN)

Review authors' judgement about each risk of bias item presented as percentages across all included studies.

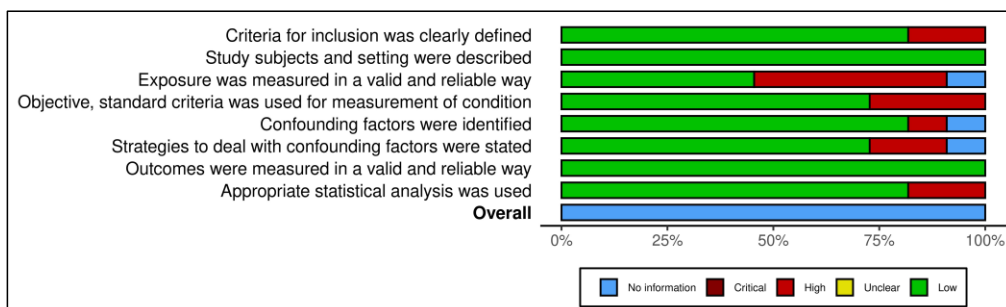
Risk of bias in cohort studies



Risk of bias in case-control studies



Risk of bias in cross-sectional studies



ADDITIONAL FILE 4: FOREST PLOT OF POOLED ORS WITH SUBGROUP ANALYSIS BY CKD STATUS

