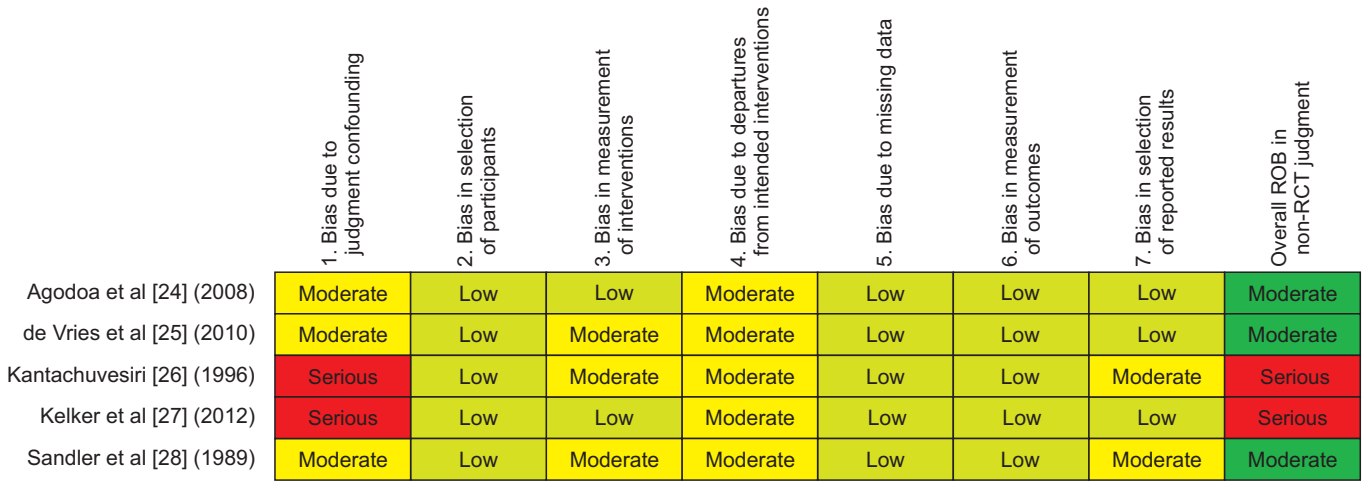
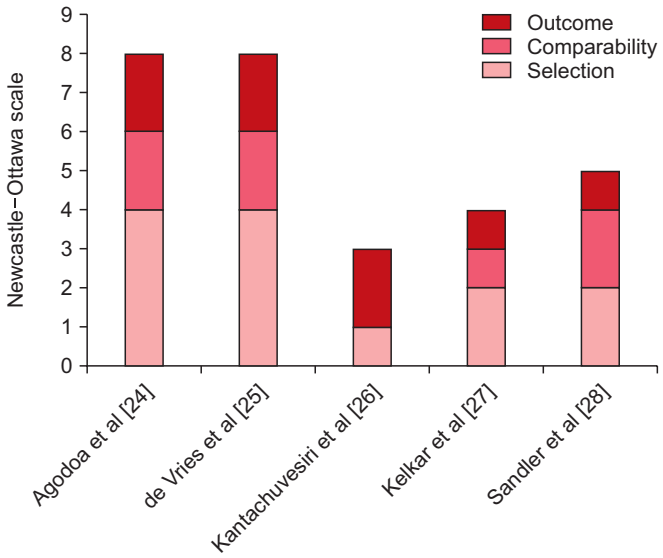
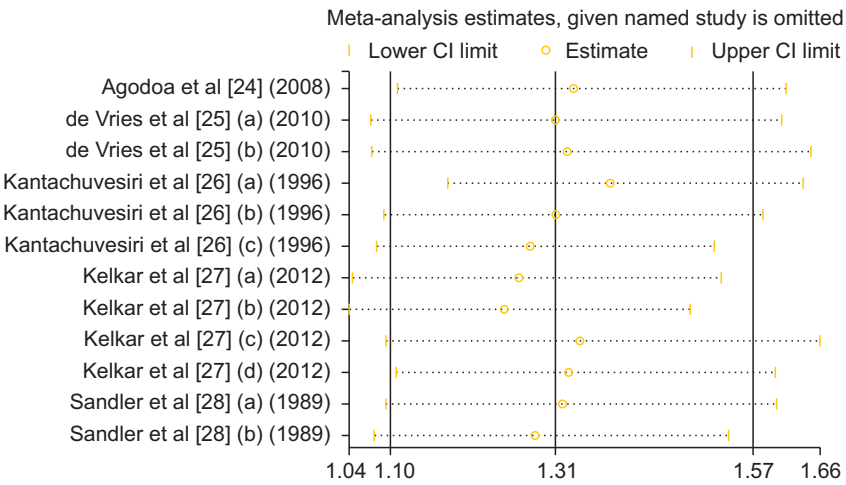


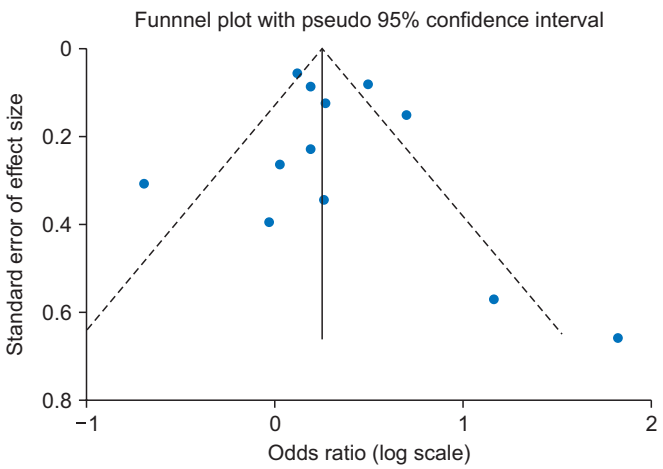
Supplementary Figure 1. Summarized risk of bias of included studies using ROBINS-I tool.
RCT, randomized controlled trial.



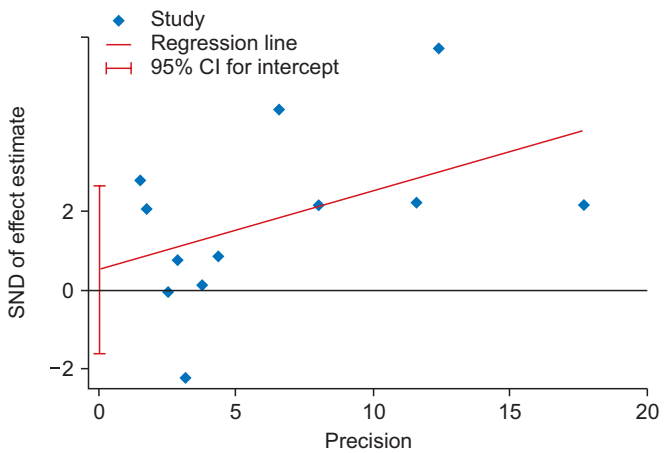
Supplementary Figure 2. Summarized risk of bias of included studies using Newcastle–Ottawa Scale.



Supplementary Figure 3. The graph from Influence plot of included studies in the meta-analysis.
CI, confidence interval.



Supplementary Figure 4. The funnel plot of included studies in the meta-analysis.



Supplementary Figure 5. The graph from Egger's test of included studies in the meta-analysis.
CI, confidence interval; SND, standard normal deviate.

Supplementary Table 1. Search algorithms

Database	No.	Step search algorithm	Items found
PubMed	#1	Search acetaminophen	22958
	#2	Search analgesics	560007
	#3	Search kidney diseases	540991
	#4	Search renal insufficiency	173623
	#5	Search (acetaminophen) AND kidney diseases	689
	#6	Search (acetaminophen) AND renal insufficiency	328
	#7	Search (analgesics) AND kidney diseases	11980
	#8	Search (analgesics) AND renal insufficiency	3796
	#9	Search ((acetaminophen) OR analgesics) AND renal insufficiency	3829
	#10	Search ((acetaminophen) OR analgesics) AND kidney diseases	12046
	#11	Search (acetaminophen) OR analgesics	564176
	#12	Search (kidney diseases) OR renal insufficiency	551032
	#13	Search (((acetaminophen) OR analgesics)) AND ((kidney diseases) OR renal insufficiency)	12325
Cochrane Library	#1	(acetaminophen) (Word variations have been searched)	5469
	#2	(analgesics) (Word variations have been searched)	34417
	#3	(renal insufficiency) (Word variations have been searched)	6524
	#4	(kidney diseases) (Word variations have been searched)	21699
	#5	#1 or #2	22898
	#6	#3 or #4	12876
	#7	#5 and #6	199
Embase	#1	Acetaminophen	21499
	#2	Analgesics	44813
	#3	Kidney AND diseases	160452
	#4	Renal AND insufficiency	38374
	#5	#1 or #2	64313
	#6	#3 or #4	193988
	#7	#5 and #6	573

Supplementary Table 2. Excluded studies

Reference	Reason for exclusion
Alkhuja et al (2001)	Case report
Ammenti et al (1999)	Case report
Asao et al (2008)	Case report
Barnes and Prichard (1972)	Case report
Barrett (1996)	Systematic review
Bengtsson and Lindholm (1977)	No full-text
Boutis and Shannon (2001)	Comparison inappropriate
Boyer and Rouff (1971)	Case report
Brown (1968)	Editorial
Campo (2002)	Editorial
Chen et al (2015)	Comparison inappropriate
Choueiri et al (2014)	Systematic review
Cooper et al (2017)	Systematic review
Curhan et al (2002)	Not interesting outcome
Curry et al (2015)	Not interesting outcome
Denison et al (1991)	No full-text
Drenth et al (1994)	Case report
Edwards et al (1971)	Comparison inappropriate
Eguia and Materson (1997)	Case series
Evans et al (2009)	Participant has renal failure
Fored et al (2001) [7]	Participant has renal failure
Ganry et al (2001)	No full-text
Hauser et al (1991)	Not interesting outcome
Helldén et al (2019)	Comparison inappropriate
Karami et al (2016)	Systematic review
Koppert et al (2006)	Not interesting outcome
Kuo et al (2010)	Participant has renal failure
Kurth et al (2003)	Not interesting outcome
Lipworth et al (2003)	Not interesting outcome
Martín et al (2016)	Case report
Master (1973)	Editorial
Mour et al (2005)	Not interesting outcome
Naess (1973)	No full-text
Nderitu et al (2014)	Not interesting outcome
O'Riordan et al (2011)	Not interesting outcome
Patanwala et al (2018)	Not interesting outcome
Perneger et al (1994)	Participant has renal failure
Pommer et al (1989) [6]	Participant has renal failure
Roberts et al (2016) [8]	Systematic review
Sakallıoğlu (2014)	Letter
Stollings et al (2016)	Not interesting outcome
Thurlow (2002)	Editorial
Tujios et al (2015)	Comparison inappropriate
Urrunaga et al (2016)	Not interesting outcome
von Mach et al (2005)	Case series
Wise (2015)	Letter
Yaxley (2016)	Review
Zhang (2001)	Systematic review

Supplementary Table 3. Description of included studies

Author, year	Study design	Location	Duration of study	Types of participants	Number of participants		Con-founder adjust	Exposures	Outcomes	
					Interventions	Comparators				
Agodoa et al (2008) [24]	Cohorts	National Health and Nutrition Examination Survey in USA	3 years (1999–2002)	Healthy volunteers ≥ 20 years old	245	6,191	Yes	- Habitual analgesic (HA) use is defined if intake of at least 1 of the listed products nearly every day for as long as a month ever occurred - Non-HA use identifies all other analgesic consumption, ranging from none at all to intakes less frequently than every day for a month	Prevalence Of reducing eGFR (< 60 mL/min/1.73 m^2) Odds ratio = 1.03 (95% CI 0.6–1.7)	
de Vries et al (2010) [25]	Cohorts	The UK General Practice Research Database (GPRD)	20 years (1987–2007)	Patients aged 18 years or over who were prescribed paracetamol alone	First Rx. 66 (current exposure) Long gap 142 (current exposure)	First Rx. 66 (past exposure) Long gap 142 (past exposure)	Yes	The total period of follow-up was using the following definitions: current exposure, the period from date of the prescription to 3 months after the estimated end of the prescription; recent exposure, the period 3–6 months after the estimated end of the prescription; past exposure, the period ≥6 months after the estimated end of the prescription. Current users were classified based on the exposure characteristics: 1) first prescription (Rx.), patients who received their first paracetamol prescription at least 12 months after the start data collection; 2) long gap, patients with at least 6 months between a preceding prescription for paracetamol.	Adjusted relative risks of acute renal failure during current exposure compared with past exposure (of same medication class) First Rx. = 1.31 (95% CI 1.03, 1.68) Long gap = 1.21 (95% CI 1.02, 1.43)	Adjusted relative risks of acute renal failure during current exposure compared with past exposure (of same medication class) overall = 1.20 (95% CI 1.14, 1.27)

Supplementary Table 3. Continued

Author, year	Study design	Location	Duration of study	Types of participants	Number of participants		Con-founder adjust	Exposures	Outcomes
					Interventions	Comparators			
Kantachuvesiri et al (1996) [26]	Case control	Thailand	-	Cases were patients aged ≥ 25 years old who had serum creatinine 2 mg/dl or above and newly diagnosed as chronic tubulointerstitial nephritis	0.1–99.9 gm group 202 100-999.9 gm group 81 ≥ 1,000 gm group 12	0 gm group 125	No	The estimated lifetime cumulative dose was calculated using the average amount and frequency and duration in years of regular drug use. Analgesic abuse was defined when estimated lifetime cumulative dose of one or more analgesic drugs is more than 1 kg.	Risk of chronic nephropathy odds ratio (compared with combined controls) of estimated life time use of acetaminophen (grams) - 0.1–99.9 = 0.5 (95% CI 0.3–1.0) - 100–999.9 = 1.3 (95% CI 0.7–2.7) - ≥ 1,000 = 6.2 (95% CI 1.7–22.5)
Kelkar et al (2012) [27]	Case control	IMS LifeLink Health Plans commercial in USA	12 years (1997–2009)	Cases aged ≥ 18 years old who had at least 1 incident claim of renal disease defined by ICD-9-CM codes in the primary diagnosis field.	Acute exposure ≤ 4 gm = 404 > 4 gm = 113 Chronic exposure ≤ 1 kg = 1,351 > 1 kg = 15	Acute exposure ≤ 4 gm = 483 > 4 gm = 116 Chronic exposure ≤ 1 kg = 2,327 >1 kg = 20	Yes	Acute APAP exposure Maximum daily dosage: 30 days pre-index - ≤ 4 grams - > 4 grams Chronic APAP exposure Cumulative dosage in the pre-index year - ≤ 1 kg - > 1 kg	Odds ratio (renal disease) Acute APAP exposure - ≤ 4 grams = 1.64 (95% CI 1.40–1.92) - > 4 grams = 2.01 (95% CI 1.49–2.70) Chronic APAP exposure - ≤ 1 kg = 1.13 (95% CI 1.01–1.26) - > 1 kg = 0.97 (95% CI 0.45–2.12)
Sandler et al (1989) [28]	Case control	North Carolina medical centers in USA	2 years (1980–1982)	Cases were adult aged 30–79 years old with newly diagnosed of chronic kidney disease (serum creatinine ≥ 1.5 mg/dL)	Weekly = 121 Daily = 35	Never use = 857	Yes	- Daily users were defined as persons who had taken one drug for at least 360 consecutive days - Weekly users as those who had taken a drug at least once a week for one year.	Odds ratio (renal diseases) - Weekly = 1.21 (95% CI 0.77–1.89) - Daily = 3.21 (95% CI 1.05–9.80)

APAP, acetaminophen; CI, confidence interval; eGFR, estimated glomerular filtration rate; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; Rx., prescription; UK, United Kingdom; USA, United States of America.

Supplementary Table 4. Description of confounder adjusts of included studies

Author, year	Age	Race/ ethnicity	Sex	Educa-tion level	Income	Specific habitual analgesic use profile	Proximity to the study hospitals	Body mass index	Smoking history or alcohol use	Previous medi cation use[b]	Year report	Number of visits in the previous 6–12 months	Hospital admission in the previous year	Comorbidities[a]							
														1	2	3	4	5	6	7	8	9	10
Agodoa et al (2008) [24]	/	/	/	/		/								/	/	/							
de Vries et al (2010) [25]	/		/					/	/	/	/	/	/										
Kelkar et al (2012) [27]										/				/	/	/					/	/	/
Sandler et al (1989) [28]	/	/	/		/		/																

[a]Comorbidities: 1, hypertension; 2, diabetes; 3, cardiovascular disease; 4, hyperlipidemia; 5, COPD; 6, stroke; 7, alcoholism; 8, kidney infections; 9, substance abuse; 10, cancer. [b]Previous medication use; antibiotics, non-steroidal anti-inflammatory drugs, miscellaneous drugs [carbamazepine, phenobarbital, phenytoin, rifampin, hydralazine, acyclovir, primidone, anti-thyroid drugs, cisplatin, diuretics, ACE inhibitors, corticosteroids, oral anticoagulants].

Supplementary Table 5. Description of participants of included studies

Author, year	Criteria		Age of participants (years old)		Sex of participants			Comorbidity of participants		
	Inclusion	Exclusion	Inter-ventions	Com-parators	Sex	Interventions	Comparators	Diseases	Interventions	Comparators
Agodoa et al (2008) [24]	A total of 10,291 individuals 20 years and older participated in the survey	- Missing information for lifetime analgesic use - Not attending the mobile examination - Missing urinary albumin, urinary creatinine, or serum creatinine measures - Receiving dialysis in the past year - Women who were pregnant or in menses at the time urine specimens were collected.	≥ 20		Male Female	46.0 ± 1.32% 54.0 ± 1.32%	49.7 ± 0.55% 50.3 ± 0.55%	Diabetes High blood pressure Cardiovascular disease	8.5 ± 0.56% 37.6 ± 1.70% 11.5 ± 0.75%	6.0 ± 0.42% 27.5 ± 0.89% 4.2 ± 0.31%
de Vries et al (2010) [25]	Patients aged 18 years or over who were prescribed ibuprofen alone, paracetamol alone or concomitant ibuprofen and paracetamol (tablets or capsules only).		62.5		Male Female	136,324 (36%) 246,080 (64%)		Cancer Heart failure Ischemic heart disease Cerebrovascular disease Depression Diabetes mellitus Substance abuse Osteoarthritis Autoimmune disease Upper gastrointestinal disease	26,492 (7%) 22,940 (6%) 55,383 (14%) 33,316 (9%) 76,287 (20%) 34,634 (9%) 12,442 (3%) 73,922 (19%) 11,411 (3%) 23,664 (6%)	

Supplementary Table 5. Continued

Author, year	Criteria		Age of participants (years old)		Sex of participants			Comorbidity of participants		
	Inclusion	Exclusion	Inter-ventions	Com-parators	Sex	Interventions	Comparators	Diseases	Interventions	Comparators
Kantachuvesiri et al (1996) [26]	- Cass were patients aged 25 years old and over who had serum creatinine 2 mg/dl or above and newly diagnosed as chronic tubulointerstitial nephritis - Controls were subjects who had no condition which was an indication for or contraindication to analgesic use.	Patients, whose etiology of renal disease was known eg diabetic nephropathy, lupus nephritis, amyloidosis, obstructive uropathy, ureterovesical reflux, nephrolithiasis, hereditary kidney disease, renal artery stenonsis	Case = 53.9 (± 3.1)	Visitors controls = 48.1 (± 1.9) Hospital controls = 53.3 (± 2.2)	Male Female	38 46	173 185	-	-	-
Kelkar et al (2012) [27]	- Cases were individuals aged 18 years or older with at least 1 incident primary diagnosis code of acute renal failure; chronic kidney disease; renal failure unspecified; nephritis; nephrotic syndrome; renal sclerosis unspecified; renal osteodystrophy; other specified disorders resulting from impaired renal function; unspecified disorder resulting from impaired renal function; nephrogenic diabetes insipidus; unilateral small kidney; bilateral small kidney; and small kidney unspecified	- Previous diagnosis of renal disease, liver disease, or asthma in 12 months before index date - Previous diagnosis/ procedure code of liver/renal or lung transplant or immunosuppressant prescription at any time before index date - Secondary malignancies, hepatic cancer, respiratory tract cancer, or renal cancer - Previous diagnosis of APAP poisoning in control group	60.8 ± 17.8	60.8 ± 17.8	Male Female	2,485 (52.6%) 2,239 (47.4%)	7,455 (52.6%) 6,717 (47.4%)	Liver disease Heart disease Hypertension Kidney infections Substance abuse Diabetes Metabolic variables Cancer (Comorbidity variables in the 365 days pre-index)	601 (12.7%) 986 (20.9%) 3,058 (64.7%) 1,024 (21.7%) 266 (5.6%) 1,542 (32.6%) 344 (7.3%) 702 (14.9%)	- 1,182 (8.3%) 4,679 (33%) 1,014 (7.2%) 291 (2.0%) 1,655 (11.7%) 344 (2.4%) 1,548 (10.9%)
Sandler et al (1989) [28]	- Cases were adult aged 30–79 years old with newly diagnosed kidney dysfunction or failure (with ICD-9-CM) and serum creatinine ≥ 1.5 mg/dL - Control were matched with sex, race, age (within 5 years range), and proximity to the study hospitals	- Cases had systemic conditions or familial syndromes with known renal manifestations, such as polycystic kidney disease, systemic lupus erythematosus, multiple myeloma, amyloidosis, or hereditary nephritis - Previous renal disease	63	62	-	-	-	-	-	-

APAP, acetaminophen; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

Supplementary Table 6. Description of treatment interventions of included studies

Author, year	Exposure details
Agodoa et al (2008) [24]	Analgesic consumption was ascertained during standardized interviews administered in the home. Participants were shown a card that listed specific prescription and nonprescription analgesics and asked "Have you ever taken any of these prescription or over-the-counter pain relievers nearly every day for as long as a month?" Respondents who replied "yes" were asked to identify each analgesic taken, how many years the product was taken nearly every day for a month during his or her lifetime, and if he or she currently takes the product daily or nearly every day. For purposes of this study, habitual analgesic (HA) use is defined if intake of at least 1 of the listed products nearly every day for as long as a month ever occurred; non-HA use identifies all other analgesic consumption, ranging from none at all to intakes less frequently than every day for a month. For comparison to non-HA users, consumption patterns in HA users were characterized by: 1) number of products (1, 2, and ≥ 3) habitually used; 2) range of product exposure (HA intake of a specific product with and without another reported HA intake); 3) HA exposure duration (< 1, 1 to < 5, and ≥ 5 years); and 4) specific analgesic drug type habitually consumed (aspirin, acetaminophen, ibuprofen, and other listed non-steroidal anti-inflammatory drugs [NSAIDs]).
de Vries et al (2010) [25]	The total period of follow-up was divided into periods of 'current', 'recent' and 'past' exposure using the following definitions: current exposure, the period from date of the prescription to 3 months after the estimated end of the prescription; recent exposure, the period 3–6 months after the estimated end of the prescription; past exposure, the period ≥6 months after the estimated end of the prescription. Current users were classified into seven groups based on the exposure characteristics: (i) first prescription(Rx), patients who received their first ibuprofen or paracetamol prescription at least 12 months after the start of GPRD data collection and who had not previously been prescribed aspirin or other NSAIDs, (ii) long gap, patients with at least 6 months between a preceding prescription for ibuprofen, paracetamol, aspirin or other NSAID and the current prescription for ibuprofen, paracetamol or concomitant ibuprofen and paracetamol, (iii) repeat use with a low medication possession ratio (MPR), for patients who had been prescribed ibuprofen and/or paracetamol in the preceding 6months.The MPR is defined as the ratio of duration of the previous prescription, to the time between that prescription and the current prescription (equal to < 0.40),(iv)repeat use with a medium MPR, as above but with ratio equal to 0.40–0.59,(v) repeat use with a high MPR, as above but with ratio equal to 0.60–0.79, (vi) repeat use with a very high MPR, as above but with ratio equal to > 0.8 and (vii) repeat use with no information on the number of days prescribed, and consequently no information on compliance.
Kantachuvesiri et al (1996) [26]	The estimated lifetime cumulative dose was calculated using the average amount and frequency and duration in years of regular drug use. Analgesic abuse was defined when estimated lifetime cumulative dose of one or more analgesic drugs is more than 1 kg.
Kelkar et al (2012) [27]	Measured any APAP exposure, dosages, and durations of APAP use for acute (7 and 30 days pre-index) and chronic (365 days pre-index) look-back periods dosages were calculated as follows: 1. Potential maximum daily dosage (PMDD) in the 7-day and 30-day pre-index periods: This was the highest potential APAP dosage in any 1 day calculated in the pre-index period using the days supply, strength, and quantity fields in the data. Overlapping prescriptions were identified using fill dates and days supply, and the daily dosages were summed to obtain the potential maximum dosage. 2. Potential average daily dosage (PADD) in the pre-index month: Dosage obtained by summing the APAP dosage contained in all prescriptions in the 30 days pre-index divided by the total days of APAP use. 3. Cumulative dosage in the pre-index year: The sum of APAP dosages from all APAP-containing prescriptions during the pre-index year.
Sandler et al (1989) [28]	Dose of analgesics were estimated on the basis of consumption of the drug taken most often within a given category; thus' the dose estimates tended to be minimal. The patients were classified as daily, weekly, or occasional users or nonusers of analgesics. Daily users were defined as persons who had taken one drug for at least 360 consecutive days, and weekly users as those who had taken a drug at least once a week for one year. A patient's cumulative consumption of aspirin, acetaminophen, and phenacetin in kilograms was approximated on the basis of each drug's pattern of use and the formulation.

Supplementary Table 7. Description of outcomes in studies included in meta-analysis

Author, year	Outcomes
Agodoa et al (2008) [24]	Albuminuria in random urine (albumin-creatinine ratio ≥ 30 mg/g) and reduced estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m^2) using the Modification of Diet in Renal Disease Study equation and the composite of either.
de Vries et al (2010) [25]	Safety outcomes were assessed with OXMIS and Read codes, and included: mortality, upper GI events (gastroduodenal ulcers and complications such as upper GI haemorrhage), myocardial infarction (MI), stroke, acute renal failure, congestive heart failure, overdose (intentional or accidental) and suicidal behaviour. Suicidal behaviour included self-laceration, overdose (irrespective of the type of chemical) or suicidal thoughts. These medical terms are based on those used by Martinez and colleagues in another GPRD study. Adjusted Relative Risks of acute renal failure during current exposure compared with past exposure (of same medication class) and stratified by exposure characteristics.
Kantachuvesiri et al (1996) [26]	Risk factors associated with chronic renal disease. The estimated lifetime cumulative dose was calculated using the average amount and frequency and duration in years of regular drug use. Analgesic abuse was defined when estimated lifetime cumulative dose of one or more analgesic drugs is more than 1 kg.
Kelkar et al (2012) [27]	This study was part of a larger project examining associations between acute and chronic APAP use and hepatic (liver disease) and nonhepatic (renal disease and asthma) outcomes. Renal disease means at least 1 incident primary diagnosis code of acute renal failure (ICD-9-CM codes 584.5–584.9); chronic kidney disease (585. xx); renal failure unspecified (586.xx); nephritis (580.0, 580.4, 580.81, 580.89, 580.9, 582.0–582.2, 582.4, 582.81, 582.89, 582.9, 583.0–583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9); nephrotic syndrome (581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9); renal sclerosis unspecified (587.xx); renal osteodystrophy (588.0); other specified disorders result- ing from impaired renal function (588.8); unspecified disorder resulting from impaired renal function (588.9); nephrogenic diabetes insipidus (588.1); unilateral small kidney (589.0); bilateral small kidney (589.1); and small kidney unspecified (589.9)
Sandler et al (1989) [28]	The role of analgesic use in the risk of renal diseases. The patients' renal disease ranged in severity from minor renal insufficiency to end-stage disease at diagnosis. Serum creatinine values on admission range from 130 μmol/L to more than 1,770 μmol/L (20 mg/dL).

eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GPRD, General Practice Research Database.

Supplementary Table 8. Risk of bias assessment of cohort studies included in the meta-analysis by the Newcastle–Ottawa Scale

Author (year)	Adequacy selection of cohort				Comparability of studies		Outcome assessment			Total NOS score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study control for age and sex	Additional factors; controlled for ≥ 2 variables including DM, HT, CVD, nephrotoxic drug, autoimmune disease, ethnicity race, alcohol use, smoking history	Assessment of outcome	Was follow-up long enough for outcome to occur	Adequacy of follow up of cohorts	
Agodoa et al (2008) [24]	❋	❋	❋	❋	❋	❋	❋	❋	-	8/9
de Vries et al (2010) [25]	❋	❋	❋	❋	❋	❋	❋	❋	-	8/9

CVD, cardiovascular disease; DM, diabetes mellitus; NOS, Newcastle–Ottawa Scale; HT, hypertension.

Supplementary Table 9. Risk of bias assessment of case-control studies included in the meta-analysis by the Newcastle–Ottawa Scale

Author (year)	Adequacy selection of case-control				Comparability of studies		Outcome assessment			Total NOS score
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Study control for age and sex	Additional factors; controlled for ≥ 2 variables including DM, HT, CVD, nephrotoxic drug, autoimmune disease, ethnicity race	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Kantachuvesiri et al (1996) [26]	❋	-	-	-	-	-	❋	❋	-	3/9
Kelkar et al (2012) [27]	-	❋	-	❋	-	❋	-	❋	-	4/9
Sandler et al (1989) [28]	❋	❋	-	-	❋	❋	-	❋	-	5/9

CVD, cardiovascular disease; DM, diabetes mellitus; NOS, Newcastle–Ottawa Scale; HT, hypertension.