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Acetaminophen use and risk of renal impairment: A systematic review and meta-analysis

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Background: Acetaminophen is commonly used for the relief of pain and fever. Advocacy organizations recommend acetaminophen as the drug of choice in patients with kidney disease. Although some studies have suggested a risk of renal impairment after the use of acetaminophen, the effect of acetaminophen on the risk of renal impairment is unclear. The purpose of this research was to demonstrate any correlation linking acetaminophen treatment and renal impairment.

Methods: We performed a systematic review and meta-analysis of the association between acetaminophen and renal impairment in adults by searching Cochrane Library, PubMed, and Embase databases from initiation to June 16, 2019.

Results: Of 13,097 articles identified, 5 studies (2 cohort studies and 3 case-control studies) with a total of 13,114 participants were included. In the random-effects meta-analysis of the cohort study, acetaminophen use was shown to have statistically significant effects on the increased risk of renal impairment (adjusted odds ratio 1.23; 95% confidence interval, 1.07–1.40). The results of sensitivity and subgroup analyses also suggested that acetaminophen use increases the risk of renal impairment. The Egger's test (P = 0.607) and Begg's test (P = 0.732) revealed no apparent publication bias.

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Conclusion: Acetaminophen is associated with a significantly increased risk of newly developing renal impairment in adults. Physicians who prescribe acetaminophen should be aware of potential adverse renal effects. A longitudinal study that further explores this association is warranted.

Keywords: Acetaminophen, Acute kidney injury, Kidney disease, Renal insufficiency

Introduction

Acetaminophen, also known as paracetamol, is a commonly used antipyretic and analgesic that can be obtained over the counter or by prescription in many countries. It is available in combination with other analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, or as a single-entity formula [1]. Its popularity as an antipyretic or analgesic is largely due to evidence supporting its safety in patients of all ages. Consequently, acetaminophen is generally considered to be safer than other widely used analgesics, including NSAIDs and opiates [2].

Although acetaminophen has a superior side-effect profile when compared with other commonly used analgesics, this medication has one well-recognized adverse effect associated with its use: hepatotoxicity [3]. Not as well-known are case reports and case series that have found an association between renal impairment and acetaminophen use in adults. In addition, observational studies and a systematic review suggest a correlation between acetaminophen use and renal impairment [4–8]. In contrast, advocacy groups such as the National Kidney Foundation and numerous pain guidelines recommend acetaminophen as a drug of choice for pain management in patients with kidney disease [9–11], partly because the association between acetaminophen exposure and renal impairment is unclear. Renal impairment is defined as acute kidney injury or chronic kidney disease by the Kidney Disease Improving Global Outcome (KDIGO) foundation [12,13].

A previous systematic review suggested that patients who use acetaminophen are at increased risk of renal impairment. However, the study had several methodological limitations. Screenings of titles, abstracts, and full-text publications were conducted by a single reviewer and searches were performed using only 2 databases and with a language restriction. In addition, renal impairment as an outcome was found in only a single study [8]. The purpose of this meta-analysis was to assess the possible association between acetaminophen use and the incidence of renal impairment in adults.

Methods

This systematic review and meta-analysis was carried out and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. This research was registered in PROSPERO (registration number: CRD42019120923).

Data sources and search strategy

Embase, PubMed, and Cochrane Library databases were systematically searched from their beginning until June 16, 2019. Medical Subject Headings were applied as applicable. Bibliographic lists of related articles were explored. The search strategy was carried out with the following keywords: "acetaminophen," "analgesics," "kidney diseases," and "renal insufficiency," with slight adjustments depended on the database. There was no study design and language restriction.

Study selection

We included studies: 1) that were performed in patients without a history of renal failure and aged ≥ 18 years old; 2) that presented the results as odds ratio (OR), risk ratio (RR), hazard ratio (HR), or the number of renal failures, and with a 95% confidence interval (CI) or *P* value; 3) in which patients received acetaminophen as the exposure group; 4) in which patients received a placebo or did not receive acetaminophen as a comparator; and 5) that examined the effect of acetaminophen on the new diagnosis of renal impairment (in the form of acute kidney injury or chronic kidney disease). Animal studies and those studies not presented as original research, such as reviews, comments, editorials, expert opinions, surveys,

letters, conference meeting abstracts, case reports, case series, systematic reviews and meta-analyses, were excluded. Studies with the same participants that did not include effect estimates or had insufficient data to measure effect estimates were also eliminated.

Outcome measures

The primary outcome was a new diagnosis of renal impairment in patients exposed to acetaminophen. The term "renal impairment" includes both acute kidney injury (stage 1 and above) and chronic kidney disease (stage 3a and above) with a diagnosis based on physical examinations and implicated laboratory values, United Kingdom (UK) Read codes, or international classification of diseases (ICD) codes, as diagnosed by physician. Acute kidney injury stage 1 was defined according to the following criteria: 1) an increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; 2) an increase in serum creatinine to ≥ 1.5 times the baseline known or presumed to have occurred within the prior 7 days; or 3) urine volume < 0.5 mL/kg/h for 6 to 12 hours [12]. Chronic kidney disease stage 3a was defined as: 1) abnormalities of kidney structure for longer than 3 months (albuminuria, urine sediment abnormalities, electrolyte abnormalities due to tubular disorders, structural abnormalities detected by imaging, or history of kidney transplantation); or 2) abnormalities of kidney function for longer than 3 months defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 [13].

Data extraction and quality assessment

Two investigators (S.K. and A.A.) independently screened each title, abstract, and full-text article for potentially eligible studies. Discrepancies were resolved by discussion between with a third investigator (S.S.). Data extractions from all potentially relevant articles were conducted by the same investigators. The following information was extracted from each study: setting, region, design, duration, sample size, characteristics of participants (such as age, sex, and comorbidity), details of intervention/exposure (such as treatment regimens, dose and treatment durations), details of outcome (such as type of renal impairment and renal impairment ascertainment), number of renal impairment or effect size (such as OR, RR, or HR) and their 95% CI or standard error. We contacted study authors when outcome information was missing. If the authors did not answer within a month, the study was excluded. All extracted data were independently reviewed by two investigators (S.S. and W.S.).

The quality of individual studies was appraised independently by S.K. and A.A. using the Cochrane Collaboration's tool for randomized controlled trials. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [15] and the Newcastle–Ottawa Scale (NOS) [16] were used for observational studies. The NOS assigns a maximum of 9 points, with studies having a total score of > 7 defined as high quality. In addition, we confirmed the quality of the included studies by the Downs and Black score [17]. Discrepancies were resolved by discussion.

Data synthesis and statistical analysis

To define the correlation between acetaminophen exposure and renal impairment, overall ORs and 95% CIs were analyzed by the DerSimonian–Laird random-effects models [18]. We selected adjusted OR if the adjusted OR was reported. Heterogeneity was investigated using Cochran's Q statistic. An alpha value of 0.10 was chosen to designate heterogeneity amid trials for each analysis. The degree of heterogeneity was presented with I^2 values. I^2 values greater than 75%, 25% to 75%, and lower than 25% indicate high, moderate, and low heterogeneity, respectively [19]. In the case where heterogeneity existed, an attempt to explore possible sources of heterogeneity was made. Publication bias was appraised using Begg's test, Egger's test, and funnel plot [20–22]. A P value < 0.05 in publication bias tests was suggestive of publication bias. In addition, the trim-and-fill method was carried out to calibrate for publication bias [23].

Sensitivity and subgroup analysis

To appraise the robustness of our analysis, sensitivity and subgroup analyses were conducted by pooling model (random effect vs. fixed effect), study design, the dose of acetaminophen, duration of acetaminophen use, type of toxic dose, type of renal impairment, comorbidity, exposure to other nephrotoxic drugs, and quality of the

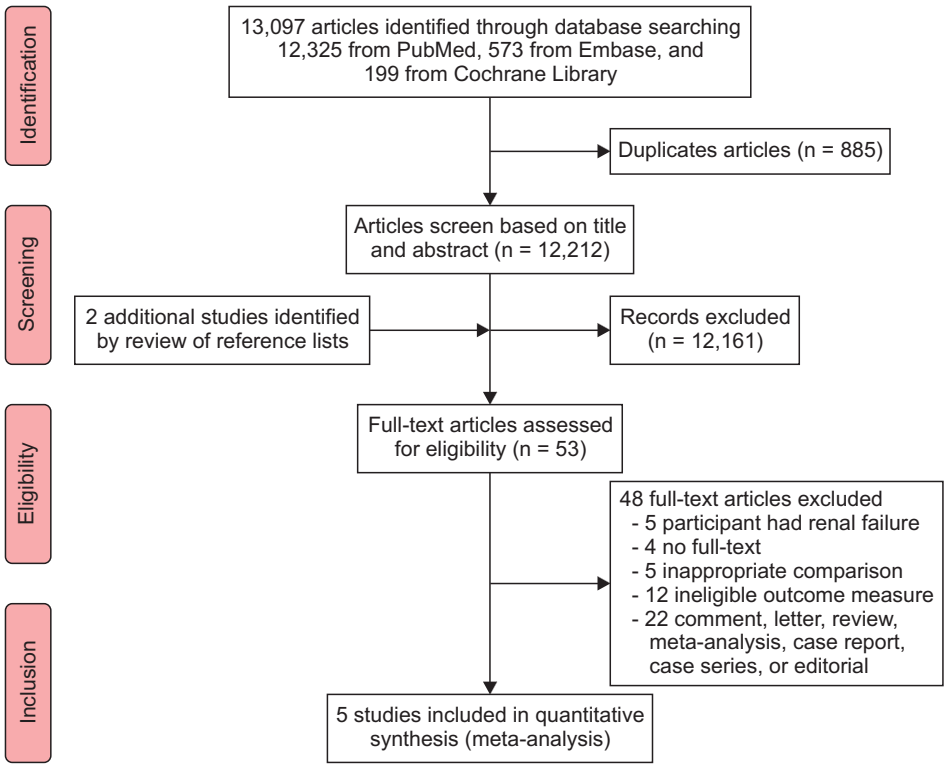

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizes the study selection process.

studies. Articles with unadjusted ORs were omitted and not included in our analysis.

Results

Search results and included study characteristics

A PRISMA flow diagram is illustrated in Fig. 1. A total of 13,097 articles were retrieved from 3 scientific databases. The full details of our literature search are provided in Supplementary Table 1 (available online). Duplicated and unrelated studies were removed via screening of titles and abstracts. Consequently, 53 likely appropriate articles (51 plus 2 additional articles identified by reviewing bibliographies) were recovered for more detailed assessment. Forty-eight studies were excluded. Of these, 22 were comments, reviews, letters, case reports, case series, editorials, or meta-analyses. In addition, 12 studies used ineligible outcome measures, 4 were not full-text, 5 involved an inappropriate comparison, and 5 included participants with renal failure. Finally, 5 full-text articles were included for synthesis of this systematic review and meta-analysis [24–28]. Factors leading to article elimination are presented in detail in Supplementary Table 2 [6–8].

Important characteristics and outcomes of the included articles are aggregated in Table 1 [24–28]. Among 5 articles that included 13,114 participants, 2 were cohort studies [24,25] while the other 3 were case-control studies [26–28]. Of the 5 studies, 3 were performed in the United States (US) [24,27,28], 1 in the UK [25], and 1 in Thailand [26]. All were observational. The mean age of the patients in the included studies was 60 years (range from 43.0–78.6) and most were female. Only Agodoa et al [24] and Sandler et al [28] did not supply the mean age and sex ratios of patients, respectively. Of the 5 included articles, 3 focused on the association between acetaminophen use and chronic kidney disease [24,26,28]; 1 article reported an association between acetaminophen use and acute kidney injury [25]; and in the final article, the primary outcome was acetaminophen-related renal impairment, which was defined as acute kidney injury or chronic kidney disease [27].

The measurement of acute kidney injury or chronic kidney disease varied across the studies. Three articles used ICD-9 or OXMIS and Read codes [25,27,28]; 1 used serum creatinine levels [28]; 1 identified renal impairment as characterized by a diagnosis of chronic tubulointerstitial nephritis or serum creatinine level [26]; and 1 used

Table 1. Characteristics of studies included in the meta-analysis

Characteristic	Author (year)				
	Sandler et al (1989) [28]	Kantachuvesiri et al (1996) [26]	Agodoa et al (2008) [24]	de Vries et al (2010) [25]	Kelkar et al (2012) [27]
Setting	North Carolina medical centers	Ramathibodi Hospital, Srinagarind Hospital, Maharat Nakhon Ratchasima Hospital	National Health and Nutrition Examination Survey	The UK General Practice Research Database (GPRD)	IMS Life Link Health Plans commercial
Region	USA	Thailand	USA	UK	USA
Study design	Case-control study	Case-control study	Cohort study	Cohort study	Case-control study
Duration of study	2 years	N/A	3 years	20 years	12 years
Sample size	1,013	420	6,436	416	4,829
Characteristics of participants	Adult aged 30 to 79 years old with first diagnosed of CKD (SCr ≥ 130 μmol/L)	Adult (≥ 25 yr) with SCr 176.8 μmol/L or above and newly diagnosed as chronic tubulointerstitial nephritis	Healthy volunteers aged ≥ 20 yr with had no history of renal failure	Patients (≥ 18 yr) got a prescription for acetaminophen	Adult (≥ 18 yr) who had ≥ 1 incident of renal disease in the primary diagnosis field
Comorbidity of participants	N/A	N/A	Diabetes mellitus Hypertension Cardiovascular disease	Cancer Heart failure Ischemic heart disease Cerebrovascular disease Depression Diabetes mellitus Substance abuse Osteoarthritis Autoimmune disease Upper gastrointestinal disease	Liver disease Heart disease Hypertension Kidney infections Substance abuse Diabetes mellitus Metabolic variables Cancer
Interventions/ exposure (no-use versus)	Daily users were defined as persons who had taken APAP for at least 360 consecutive days Weekly users as those who had taken APAP at least once a week for 1 year	Used APAP cumulative dose were 0.1–99.9 g, 100–999.9 g, and ≥ 1,000 g	Used APAP nearly every day for as long as a month	First prescription, patients who received their first APAP prescription ≥ 12 months after the start data collection Long gap, patients with ≥ 6 months between a preceding prescription for APAP	Acute APAP exposure MDD: 30 days pre-index - ≤ 4 g - > 4 g Chronic APAP exposure Cumulative dosage in the pre-index year - ≤ 1 kg - > 1 kg
Type of renal impairment	CKD	CKD	CKD	AKI	AKI or CKD
Renal impairment ascertainment	ICD-9-CM codes and SCr level	newly diagnosed as chronic tubulointerstitial nephritis or SCr level	reduced eGFR and ACR	assessed with OXMIS and Read codes	ICD-9-CM codes

Table 1. Continued

Characteristic	Author (year)				
	Sandler et al (1989) [28]	Kantachuvesiri et al (1996) [26]	Agodoa et al (2008) [24]	de Vries et al (2010) [25]	Kelkar et al (2012) [27]
Effect size (95% CI)	Weekly = 1.21 (0.77–1.89) Daily = 3.21 (1.05–9.80)	0.1–99.9 g = 0.50 (0.30–1.00) 100–999.9 g = 1.30 (0.70–2.70) ≥ 1,000 g = 6.20 (1.70–22.5)	1.03 (0.60–1.70)	First prescription = 1.31 (1.03–1.68) Long gap = 1.21 (1.02–1.43)	(a)[c] = 1.64 (1.40–1.92) (b)[c] = 2.01 (1.49–2.70) (c)[c] = 1.13 (1.01–1.26) (d)[c] = 0.97 (0.45–2.12)
Confounders adjusted	Age, race, sex, income, proximity to the study hospitals	N/A	Age, race, sex, education level, specific habitual analgesic use, comorbidities	Age, sex, body mass index, smoking history or alcohol use, year report, number of visit, hospital admission, previous medication use	Previous medication use, comorbidities
Age of exposure group (year)	63[b]	53.9 (±3.1)[a]	N/A	62.5[b]	60.8 (± 17.8)[a]
Female (%)	N/A	54.76	54.0	64.0	47.4
Down and black score	15	14	19	19	14

ACR, albumin-creatinine ratio; AKI, Acute kidney injury; APAP, acetaminophen; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; MDD, maximum daily dosage; N/A, not available; SCr, serum creatinine; UK, United Kingdom; USA, United States of America.

[a]Mean (SD); [b]Mean age (yr); [c](a), acute exposure 30 day maximum daily dosage ≤ 4 g; (b), acute exposure 30 day maximum daily dosage > 4 g; (c), chronic cumulative dose ≤ 1 kg; (d), chronic cumulative dose > 1 kg.

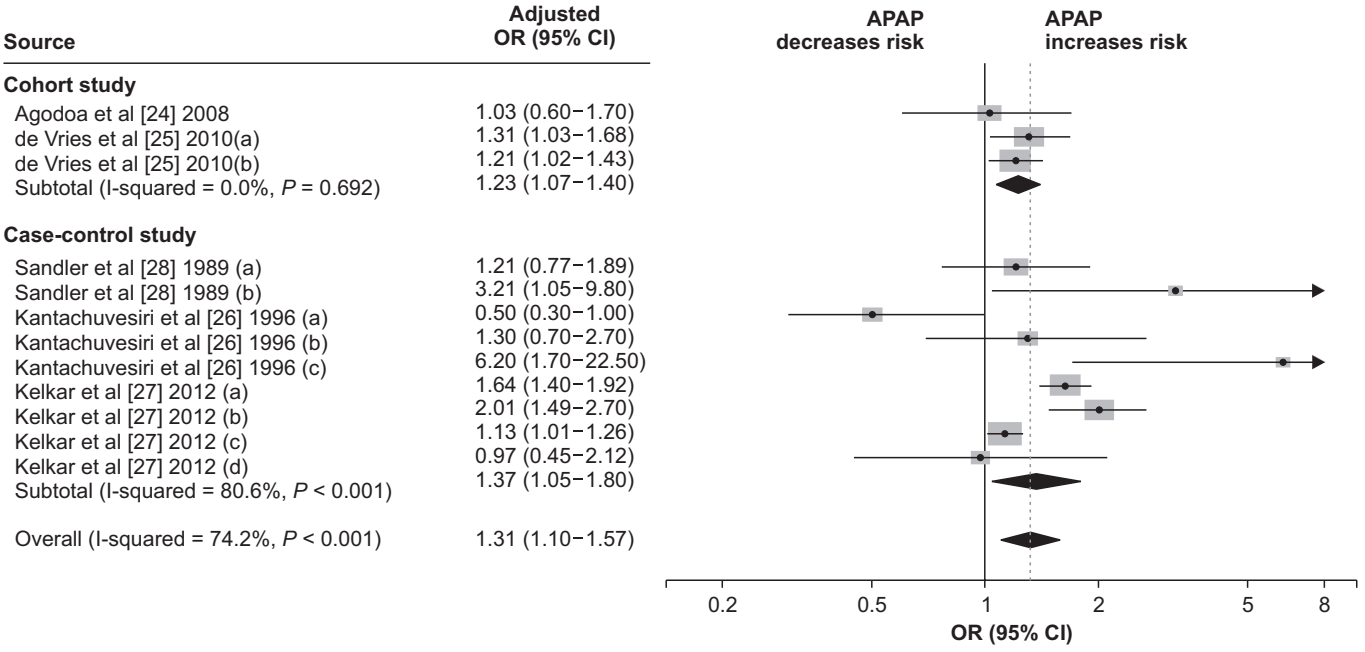

Figure 2. Effect of acetaminophen on the risk of renal impairment. de Vries (a), first prescription; de Vries (b), long gap; Sandler (a), weekly use; Sandler (b), daily use; Kantachuvesiri (a), lifetime cumulative dose of APAP = 0.1–99.9 g; Kantachuvesiri (b), lifetime cumulative dose of APAP = 100–999.9 g; Kantachuvesiri (c), lifetime cumulative dose of APAP > 1,000 g; Kelkar (a), acute exposure 30 day maximum daily dosage ≤ 4 g; Kelkar (b), acute exposure 30 day maximum daily dosage > 4 g; Kelkar (c), chronic cumulative dose ≤ 1 kg; Kelkar (d), chronic cumulative dose > 1 kg.
APAP, acetaminophen; CI, confidence interval; OR, odds ratio.

estimated GFR and the albumin-creatinine ratio [24] Of the studies, 4 reported separate results for an association of acetaminophen use with renal impairment for a total of 12 events [25–28]. All articles adjusted for confounding factors, except Kantachuvesiri et al [26] Full details of the study characteristics are supplied in Supplementary Tables 3 to 7 [24–28].

Quality assessment

The methodological quality assessments of the five studies were revealed with the ROBIN-I tool, NOS, and the Downs and Black score. In terms of quality assessment by the ROBIN-I tool, 3 studies had a moderate risk of bias [24,25,28], while the other 2 exhibited a serious risk of bias [26,27]. For quality evaluation through NOS, studies were considered high quality if they received a score of 7 stars or more. In this analysis, 2 studies [24,25] received 8 stars, with the remaining 3 [26–28] receiving fewer than 7 stars (Supplementary Tables 8 and 9) [24–28]. Details of the quality assessment by ROBIN-I tool and NOS are presented in Supplementary Fig. 1 and 2, respectively [24–28]. Furthermore, the average Downs and Black score was 16.2 (range from 14 to 19), and the score for each study can be found in Table 1.

Renal impairment

Fig. 2 and Fig. 3 shows the effect of acetaminophen on the risk of renal impairment [24–28]. Before data analysis, heterogeneity of renal impairment among all articles was assessed. Evidence of heterogeneity among these articles was found to be moderate (I^2 = 74.2%; P < 0.001). The results of this study suggest a significantly increased risk of renal impairment in participants who used acetaminophen, as evidenced by a pooled adjusted OR of 1.31 (95% CI, 1.10–1.57). In the cohort studies, 3 events led us to conclude acetaminophen use was significantly corre-

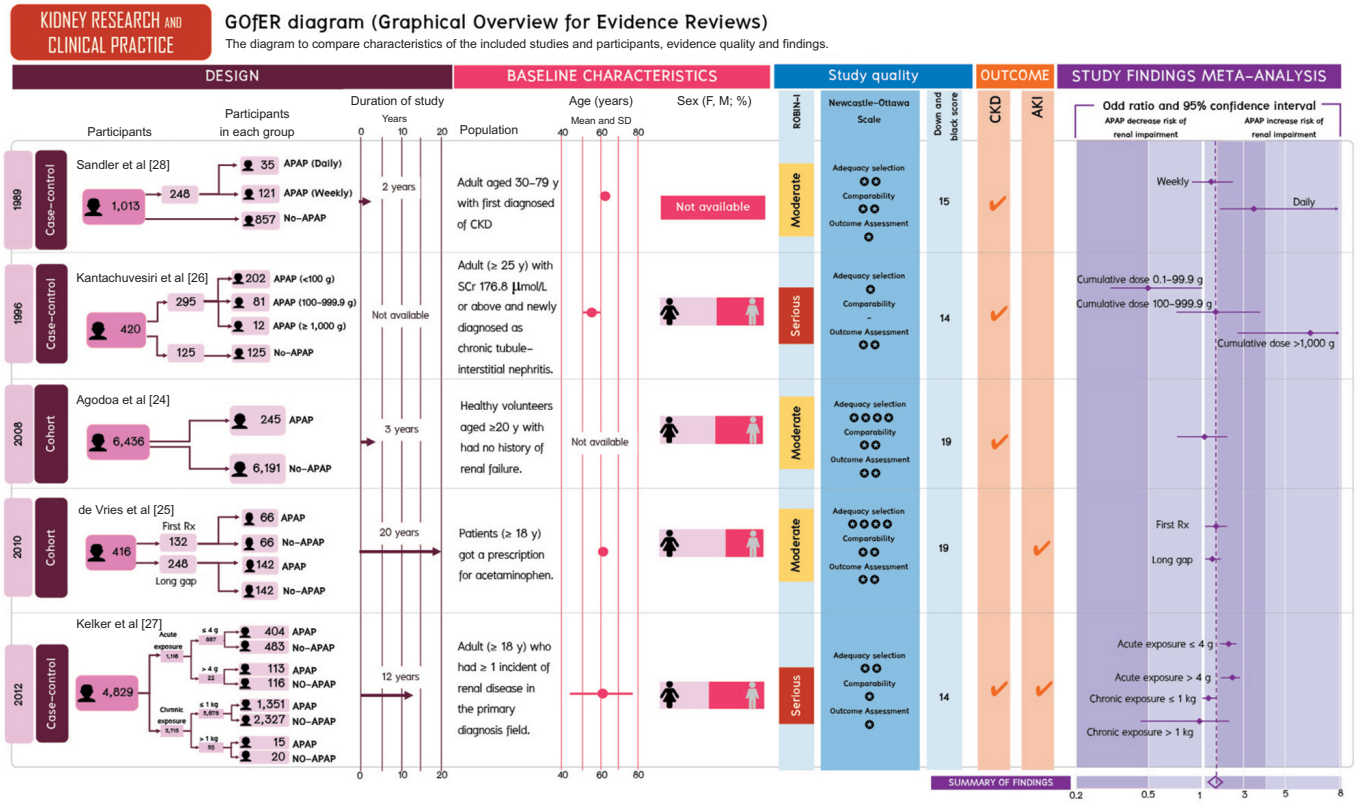

Figure 3. Graphical overview of evidence reviews.
AKI, acute kidney injury; APAP, acetaminophen; CKD, chronic kidney disease; F, female; first Rx., patients who received their first APAP prescription ≥ 12 months after the start data collection; Long gap, patients with ≥ 6 months between a preceding prescription for APAP AKI; M, male; SD, standard deviation.

Table 2. Sensitivity and subgroup analyses

Characteristic	All studies			Cohort studies			Case-control studies		
	Adjusted OR (95% CI)	Heterogeneity I^2 value (%)	Heterogeneity *P* value	Adjusted OR (95% CI)	Heterogeneity I^2 value (%)	Heterogeneity *P* value	Adjusted OR (95% CI)	Heterogeneity I^2 value (%)	Heterogeneity *P* value
Models									
Fixed-effects model	1.29 (1.20–1.38)	74.2	< 0.001	1.23 (1.07–1.44)	0.0	0.692	1.31 (1.20–1.42)	80.6	< 0.001
Random-effects model	1.31 (1.10–1.57)	74.2	< 0.001	1.23 (1.07–1.40)	0.0	0.692	1.37 (1.05–1.80)	80.6	< 0.001
Omitted Kantachuvesiri et al [26] (a) and Kelkar et al [27] (b) in the analysis of case-control study[a]									
Before omitted	1.31 (1.10–1.57)	74.2	< 0.001	1.23 (1.07–1.40)	0.0	0.692	1.37 (1.05–1.80)	80.6	< 0.001
After omitted	1.31 (1.12–1.54)	63.0	0.004	1.23 (1.07–1.40)	0.0	0.692	1.42 (1.08–1.87)	74.2	< 0.001
Omitted Kantachuvesiri et al [26] (a)–(b) and (c) in the analysis of case-control study[b]									
Before omitted	1.31 (1.10–1.57)	74.2	< 0.001	1.23 (1.07–1.40)	0.0	0.692	1.37 (1.05–1.80)	80.6	< 0.001
After omitted	1.36 (1.15–1.60)	70.8	0.001	1.23 (1.07–1.40)	0.0	0.692	1.46 (1.12–1.91)	80.6	< 0.001
Dose of acetaminophen									
Usual therapeutic dose[c]	1.23 (1.03–1.46)	70.4	0.001	1.23 (1.07–1.40)	0.0	0.692	1.22 (0.91–1.64)	80.9	< 0.001
Toxic dose[d]	1.98 (0.94–4.17)	67.9	0.044	N/A	N/A	N/A	1.98 (0.94–4.17)	67.9	0.044
Duration use of acetaminophen									
Short-term use[e]	1.21 (0.95–1.55)	78.0	0.001	1.24 (1.08–1.43)	0.0	0.601	1.06 (0.57–1.95)	86.6	0.001
Long-term use[f]	1.17 (0.95–1.45)	17.0	0.306	1.03 (0.61–1.73)	N/A	N/A	1.32 (0.87–1.99)	42.3	0.177
Type of toxic dose									
Acute toxic ingestion[g]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chronic toxic ingestion[h]	1.98 (0.94–4.17)	67.9	0.044	N/A	N/A	N/A	1.98 (0.94–4.17)	67.9	0.044
Type of renal impairment[i]									
Acute kidney injury	1.24 (1.08–1.43)	0.0	0.601	1.24 (1.08–1.43)	0.0	0.601	N/A	N/A	N/A
Chronic kidney disease	1.32 (0.78–2.23)	71.4	0.004	1.03 (0.61–1.73)	N/A	N/A	1.47 (0.74–2.92)	76.9	0.002
Acute kidney injury or Chronic kidney disease	1.45 (1.06–1.97)	87.0	< 0.001	N/A	N/A	N/A	1.45 (1.06–1.97)	87.0	< 0.001
Exposure to other potentially nephrotoxic drugs preceding the index date									
Yes	1.37 (1.14–1.65)	79.2	< 0.001	1.24 (1.08–1.43)	0.0	0.601	1.45 (1.06–1.97)	87.0	< 0.001
No	1.32 (0.78–2.23)	71.4	0.004	1.03 (0.61–1.73)	N/A	N/A	1.47 (0.74–2.92)	76.9	0.002
Comorbidity									
Cardiovascular disease									
Yes	1.34 (1.13–1.60)	75.7	< 0.001	1.23 (1.07–1.40)	0.0	0.692	1.45 (1.06–1.97)	87.0	< 0.001
No	1.47 (0.74–2.92)	76.9	0.002	N/A	N/A	N/A	1.47 (0.74–2.92)	76.9	0.002
Hypertension									
Yes	1.34 (1.13–1.60)	75.7	< 0.001	1.23 (1.07–1.40)	0.0	0.692	1.45 (1.06–1.97)	87.0	< 0.001
No	1.47 (0.74–2.92)	76.9	0.002	N/A	N/A	N/A	1.47 (0.74–2.92)	76.9	0.002
Diabetes mellitus									
Yes	1.34 (1.13–1.60)	75.7	< 0.001	1.23 (1.07–1.40)	0.0	0.692	1.45 (1.06–1.97)	87.0	< 0.001
No	1.47 (0.74–2.92)	76.9	0.002	N/A	N/A	N/A	1.47 (0.74–2.92)	76.9	0.002
Quality of the study (ROBIN-I)									
Low	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Moderate	1.24 (1.09–1.41)	0.0	0.469	1.23 (1.07–1.40)	0.0	0.692	1.71 (0.69–4.29)	60.4	0.112
Serious	1.34 (0.98–1.82)	84.4	< 0.001	N/A	N/A	N/A	1.34 (0.98–1.82)	84.4	< 0.001
Quality of the study (NOS)									
Star > 7	1.23 (1.07–1.40)	0.0	0.692	1.23 (1.07–1.40)	0.0	0.692	N/A	N/A	N/A
Star ≤ 7	1.37 (1.05–1.80)	80.6	< 0.001	N/A	N/A	N/A	1.37 (1.05–1.80)	80.6	< 0.001
Quality of the study (Downs and Black score)									
Score > 20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Score ≤ 20	1.31 (1.10–1.57)	74.2	< 0.001	1.23 (1.07–1.40)	0.0	0.692	1.37 (1.05–1.80)	80.6	< 0.001

APAP, acetaminophen; CI, confidence interval; N/A, not available; NOS, Newcastle–Ottawa Scale. [a]Selected from influence plot (Supplementary Fig. 3); [b]Study unadjusted results; [c]Dose of APAP ≤ 4 g in 24 hours; [d]Including acute toxic dose and chronic toxic dose; [e]Use usual therapeutic doses continuously ≤ 30 days or use < 15 dose/month or lifetime cumulative dose 0.1–99.9 g; [f]Use usual therapeutic doses continuously > 30 days or use ≥ 15 dose/month or lifetime cumulative dose 100–999.9 g; [g]Single ingestion of > 4 g in period of < 1 hour; [h]Ingestion > 4 g in 24 hours for a long time 3–4 days or lifetime cumulative dose > 1,000 g; [i]Following definition by Kidney Disease Improving Global Outcomes (KDIGO) [12,13].

lated with a 23% increase in the risk of renal impairment (adjusted OR, 1.23; 95% CI, 1.07–1.40), without heterogeneity (I^2 = 0.0%; P = 0.692). The 3 case-control studies yielded 9 events and suggest the use of acetaminophen increases the risk of renal impairment by 37% compared with non-use (adjusted OR, 1.37; 95% CI, 1.05–1.80), with a high level of heterogeneity (I^2 = 80.6%; P < 0.001).

Sensitivity and subgroup analysis

Results of sensitivity and subgroup analyses are displayed in Table 2 [12,13,24–28]. In the sensitivity analysis, the analysis model was stratified by study design. For the cohort study, the adjusted ORs were 1.23 (95% CI, 1.07–1.40) for the random-effects model and 1.23 (95% CI, 1.07–1.44) for the fixed-effect model. While in the case-control study, adjusted ORs were 1.37 (95% CI, 1.05–1.80) and 1.31 (95% CI, 1.20–1.42) for the random-effects model and fixed-effect model, respectively. A sensitivity analysis was then carried out after removing studies that may have affected the influence plot (Supplementary Fig. 3) [24–28]. After removal, the results showed statistical significance and were associated with a 31% increased risk of renal impairment (adjusted ORs, 1.31; 95% CI, 1.12–1.54). Finally, we eliminated the study by Kantachuvesiri et al [26] because the authors did not report an unadjusted OR. After the omission, our results found acetaminophen use was associated with a significantly increased risk of renal impairment (adjusted OR, 1.36; 95% CI, 1.15–1.60). We found that the effect estimates of such analysis still exhibited a trend toward increased risk of renal impairment in patients who use acetaminophen.

In the subgroup analysis, the results were stratified by dose of acetaminophen (usual therapeutic dose: dose of acetaminophen ≤ 4 g in 24 hours vs. toxic dose, including acute toxic dose and chronic toxic dose), duration of acetaminophen use (short term use = use usual therapeutic doses continuously ≤ 30 days or use < 15 dose/month or lifetime cumulative dose 0.1–99.9 g vs. long-term use = use of usual therapeutic doses continuously > 30 days or use ≥ 15 doses/month or a lifetime cumulative dose 100–999.9 g), type of toxic dose (acute toxic = single ingestion of > 4 g in period of < 1 hour vs. chronic toxic = ingestion > 4 g in 24 hours for an extended time [3–4 days] or a lifetime cumulative dose > 1,000 g), type of renal impairment (acute kidney injury, chronic kidney disease, or both), exposure to other potentially nephrotoxic drugs, comorbidity (e.g., cardiovascular disease, hypertension, and diabetes mellitus), and quality of studies (determined by ROBIN-I tool, NOS, Downs and Black score). The effects of acetaminophen use on renal impairment were consistent across all subgroups.

Publication bias of included studies

An appraisal of publication bias using acetaminophen-use data and risk of renal impairment was conducted. There was no apparent publication bias as determined by a symmetric funnel plot (Supplementary Fig. 4). In addition, Begg's and Egger's tests reveal no significant difference; P = 0.732, and 0.607, respectively (Supplementary Fig. 5).

Discussion

We performed a systematic review and meta-analysis to assess the possible association between acetaminophen use and appearance of renal impairment. We found that participants without a history of renal impairment who used acetaminophen were at a 23% higher risk of renal impairment compared with no use (the adjusted OR was 1.23, 95% CI, 1.07–1.40). However, a great degree of heterogeneity was observed. The most likely mechanism for the potential increase in new renal impairment associated with acetaminophen use is acute tubular necrosis. Approximately 5% of acetaminophen is metabolized through phase I metabolism (cytochrome P-450 pathway) to form *N*-acetyl-*p*-benzoquinone imine. The cytochrome P-450 pathway can be detected in both the kidney and liver, although they vary moderately in each organ. This process produces lipid peroxidation that leading to cell apoptosis and initiates programmed cell death. For this reason, tissue necrosis and organ dysfunction occur [29,30]. Furthermore, a previous *in vitro* study revealed acetaminophen-induced apoptosis in proximal tubular epithelial cells and induced endoplasmic reticulum stress in tubular cells [31]. Accordingly, the results of this study support the hypothesis that acute tubular necrosis is one of the most likely mechanisms responsible for renal impairment in people who use acetaminophen. The risk factors associated with acetaminophen use for renal impairment were the toxic dose of acetaminophen,

comorbidity (such as diabetes mellitus, liver failure), alcohol ingestion, and concomitant use nephrotoxic drugs (such as NSAIDs) [32,33]. Patients with these risk factors taking acetaminophen may be at increased risk of renal impairment.

The findings of this study are similar to those of a previous systematic review [8] that examined the association between acetaminophen use and a number of adverse events (i.e., mortality, cardiovascular, gastrointestinal, and renal). As it relates to renal adverse events, there was a trend toward elevated serum creatinine and reduced estimated GFR in patients who use acetaminophen. However, the utility of the previous review was limited because the authors included studies of low quality and the dose of acetaminophen was unclear. Moreover, the previous review was not a meta-analysis. To our knowledge, this study is the first meta-analysis to assess the potential association between patients who use acetaminophen and risk of renal impairment.

Strengths and limitations

The strengths of this study should be highlighted. First, we performed a comprehensive search of three major databases (Embase, PubMed, and Cochrane Library), which is a standard method for conducting a systematic review. Second, we employed a comprehensive search strategy with no restrictions on language and study design. Third, because there is currently no gold standard appraisal tool for evaluating the risk of bias in the observational study [34–36], we performed a rigorous evaluation of the methodological quality of included studies determined by 3 commonly used tools (ROBIN-I tool, NOS, and Downs and Black score). The results have shown consistency in terms of the quality of the included studies. Fourth, this meta-analysis adheres to the standard methodology of systematic reviews and meta-analyses as required by the PRISMA checklist. Finally, our study covered updated evidence and was conducted using the appropriate statistical methods for analyses.

Limitations of this research should be highlighted. First, all included studies were observational study. However, observational study is the most appropriate study design to use when evaluating the risk of renal impairment in patients who use acetaminophen. Second, although we searched 3 major databases, some specific databases (e.g., the public website of the US Food and Drug Administration) were not searched due to accessibility limitations. Nonetheless, after applying Begg's test, Egger's test, and a funnel plot, we found no evidence of publication bias. Third, the definition of renal impairment in each study was not described. If a definition was different, it could have led to a distortion of the overall effects of acetaminophen use on renal impairment. The correlation between acetaminophen use and renal impairment in this study therefore may not be obvious, and caution should be used in interpreting and implementing the results. However, this study was designed only to inform physicians who prescribe acetaminophen about a possible side effect. Finally, it is possible the moderate degree of heterogeneity found in this study could be a limitation. Sensitivity and subgroup analyses revealed that the quality of the included study, type of renal impairment, and study design were probable factors contributing to heterogeneity. Furthermore, the results of the sensitivity and subgroup analysis indicated that acetaminophen use is associated with an increased risk of renal impairment, but only after omitting two studies — one with unadjusted results and one that impacted the influence plot.

Suggestions for practice and future research

One of the main clinical merits associated with acetaminophen use in analgesia and fever is its well-established efficacy and safety profile when regular doses of the drug are ingested, as compared with other analgesics, such as NSAIDs. Moreover, acetaminophen has a low potential for drug-drug interactions. Another inherent benefit is that acetaminophen can be used in special populations, e.g., pregnant women, patients with dengue fever, and those who have allergies to other analgesics. Nonetheless, acetaminophen is still associated with noteworthy adverse effects, such as hepatotoxicity and nephrotoxicity, and this study supports previous findings that acetaminophen is associated with renal impairment as a rare but severe adverse effect. This is association is particularly prevalent in patients taking higher doses of the drug, consuming alcohol, or experiencing liver failure.

Physicians who anticipate prescribing acetaminophen should consider limiting those prescriptions to the shortest practical time and at lowest effective dosage (the maximum quantity of drug should be restricted to 325

to 650 mg per dose and should not to exceed 3.25 g per day or more than 5 days of use) [37]. Moreover, physicians should assess and monitor renal and liver function in patients who regularly use acetaminophen or take it at higher doses. Furthermore, physicians should advise patients to avoid drinking alcohol while taking acetaminophen, and caution should be applied when treating patients with existing renal impairment.

Future research in this area to better elucidate the association between the risk of renal impairment and acetaminophen use could include: 1) assessment of time-to-occurrence of renal impairment, 2) a new, high-quality study in the future (e.g., randomized control trial), and 3) assessment of the relationship between renal impairment and acetaminophen use stratified by age, sex, and risk of renal impairment.

In conclusion, this systematic review and meta-analysis suggest that acetaminophen is associated with a significantly increased risk of new renal impairment in adults. Physicians who recommend or prescribe acetaminophen should be concerned about this side effect. The overall results were limited by the heterogeneity of the included studies, and our finding should be interpreted with caution.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

Sukrit Kanchanasurakit, Aimusa Arsu, Wuttikorn Siriplabpla, and Surasak Saokaew contributed to the research idea and design. Sukrit Kanchanasurakit and Aimusa Arsu created the search strategy. Sukrit Kanchanasurakit and Aimusa Arsu screened titles, abstracts, and full texts. Sukrit Kanchanasurakit, Aimusa Arsu, and Surasak Saokaew contributed to data extraction and quality assessment. Sukrit Kanchanasurakit and Surasak Saokaew contributed to statistical analysis and interpretation of data. Sukrit Kanchanasurakit wrote the first draft of the manuscript. Wuttikorn Siriplabpla, Acharaporn Duangjai, and Surasak Saokaew edited the draft of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content, approved and reviewed the final manuscript.

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