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Stone Prevalence in Autosomal Dominant Polycystic Kidney Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: It is uncertain how often patients with autosomal dominant polycystic kidney disease (ADPKD) develop kidney stones.
Objective: To review English-language studies reporting the incidence and prevalence of stones and stone interventions in adults with ADPKD.
Design: Systematic review and meta-analysis.
Setting: Any country of origin.
Patients: Adult patients with ADPKD.
Measurements: Incidence or prevalence of kidney stones and stone interventions.
Methods: We reviewed 1812 citations from bibliographic databases, abstracted data from 49 eligible studies, and assessed methodological quality in duplicate. In some studies, the proportion of adults with ADPKD with the outcome were compared to adults without ADPKD; for these studies, prevalence risk ratios were calculated and pooled using a random effects model.
Results: We identified 49 articles that met our review criteria. The methodological quality of many studies was limited (scores ranging from 2 to 14 out of 22, with a higher score indicating higher quality). No study clearly reported stone incidence, and in the cross-sectional studies, the definition of stones was often unclear. The prevalence of stones ranged from 3% to 59%, and a prevalence of stone interventions ranged from 1% to 8%; the average patient age at the time of assessment ranged from 26 to 61 years across the studies. Two studies reported a nonstatistically significant higher stone prevalence in patients with ADPKD compared to unaffected family members. Compared to unaffected family members, patients with ADPKD had a higher prevalence of kidney stones (6 cross-sectional studies; unadjusted prevalence ratio: 1.8; 95% confidence interval: 1.3 to 2.6; $P = .0007$; test for heterogeneity: $I^2 = 0\%$, $P = .8$).
Limitations: Studies were limited to articles published in English.
Conclusions: The prevalence of kidney stones and stone interventions in adults with ADPKD remains uncertain. Future studies of higher methodological quality are needed to better characterize the incidence and prevalence of kidney stones in patients with ADPKD.
Trial registration: We did not register the protocol for this systematic review.

Abrégé

Contexte: La prévalence du développement de calculs rénaux chez les patients atteints de polykystose rénale autosomique dominante (ADPKD) est mal connue.
Objectif: Examiner les études publiées en anglais portant sur l'incidence et la prévalence des calculs rénaux et des interventions liées à ces derniers chez les adultes atteints d'ADPKD.
Type d'étude: Revue systématique et méta-analyze.
Cadre: Tous les pays d'origine.
Sujets: Des adultes atteints d'ADPKD.
Mesures: L'incidence ou la prévalence des calculs rénaux et des interventions sur ceux-ci.
Méthodologie: Nous avons examiné 1 812 citations issues des bases de données bibliographiques, extrait les données des 49 études admissibles et analysé leur qualité méthodologique en duplicata. Dans certaines études, la proportion d'adultes

atteints d'ADPKD présentant le résultat d'intérêt avait été comparée à celle de sujets non atteints d'ADPKD; dans ces études, les rapports de risque de la prévalence ont été calculés et regroupés à l'aide d'un modèle à effets aléatoires.
Résultats: Nous avons repéré 49 articles satisfaisant nos critères, dont plusieurs étaient de qualité méthodologique limitée (scores entre 2 et 14 sur une possibilité de 22, une note élevée indiquant une meilleure qualité). Aucune étude ne faisait clairement état d'une incidence de calculs rénaux. De plus, la définition des calculs rénaux n'était souvent pas très claire dans les études transversales. La prévalence des calculs rénaux variait entre 3 % et 59 % et celle des interventions liées variait de 1 % à 8 %. L'âge moyen des patients au moment de l'évaluation allait de 26 à 61 ans selon les études. Deux études faisaient état d'une prévalence plus élevée, quoique non statistiquement significative, chez les patients atteints d'ADPKD par rapport aux membres de leurs familles non atteints. De même, six études transversales rapportaient une prévalence plus élevée de calculs rénaux chez les patients atteints d'ADPKD comparé aux membres de leurs familles non atteints (rapport de prévalence non corrigé: 1,8; IC 95 %: 1,3 à 2,6; p=0,0007; test d'hétérogénéité: I^2=0 %; p=0,8).
Limites: L'étude ne porte que sur des articles publiés en anglais.
Conclusion: La prévalence des calculs rénaux et des interventions relatives à ces derniers demeure mal connue chez les adultes atteints d'ADPKD. Des études supplémentaires et de meilleure qualité méthodologique sont nécessaires afin de mieux caractériser l'incidence et la prévalence des calculs rénaux dans cette population.
Enregistrement de l'essai: Le protocole de cette revue systématique n'a pas été enregistré.

Keywords
polycystic kidney disease, prevalence, kidney stones, stone intervention, epidemiology, observational study, systematic review

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What was known before

It is uncertain how often patients with autosomal dominant polycystic kidney disease (ADPKD) develop kidney stones.

What this adds

This review summarized the results of 49 studies. The prevalence of kidney stones reported in the literature ranged between 3 and 59%, and the prevalence of stone intervention ranged from 1 to 8% in patients with ADPKD. The quality of published literature was poor, and no study clearly reported stone incidence in ADPKD. This review calls for better studies to be conducted in the future.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease and is characterized by focal cyst development in both kidneys.[1] In early stages of ADPKD, the cysts cause structural deformation to the kidney and damage adjacent nephrons, but overall kidney function is maintained by compensatory hyperfiltration of functioning nephrons.[2,3] As the number and size of cysts increase progressively, more nephrons become damaged, and overall kidney function starts to decline.[4] By the age of 55 years, about half of the patients reach end-stage kidney disease (ESKD) and require kidney transplantation or dialysis to sustain life.[5,6]

End-stage kidney disease is not the only kidney manifestation of ADPKD. Previous studies suggest that kidney stones are more prevalent in patients with ADPKD compared to the general population; however, there remains uncertainty about the incidence and prevalence of kidney stone in patients with ADPKD.[7-12] Kidney stones in patients with ADPKD are associated with significant morbidity. For example, stones are a significant determinant of pain and may accelerate disease progression to ESKD in patients with ADPKD.[13,14]

We conducted this systematic review to critically appraise and summarize studies which reported the incidence and prevalence of kidney stones and stone interventions in patients with ADPKD. This encompassed studies which also included patients without ADPKD as a comparator.

Methods

Design and Study Selection

We conducted this systematic review using a pre-specified protocol not previously published but detailed below and report this review according to the Preferred Reporting Items

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for Systematic Review and Meta-Analysis (PRISMA) statement (Supplementary Table S1).[15]

The following studies met our eligibility criteria for review: (1) published English full-text articles and conference proceedings; (2) any study design (eg, cross-sectional or cohort study); (3) mean age of studied population 18 years or older; (4) study populations not solely restricted to patients with ESKD; (5) reported prevalence or incidence of stones; and (6) studies published any time after 1970 (the resolution of imaging modalities in older studies would be different from current ones). In some studies, patients without ADPKD were included as a comparator to patients with ADPKD, and in such cases, we abstracted information on both groups of patients.

Identifying Relevant Articles

We performed a comprehensive search of bibliographic databases from 1970 to February 2019 (MEDLINE, EMBASE, Web of Science, BIOSIS Preview, and CINAHL) to identify all relevant journal articles and conference proceedings (detailed in Supplementary Table S2). To identify further relevant articles, we also used the "cited by" function on Web of Science and Google Scholar and "related article" function on Google Scholar and "similar article" function on PubMed to identify other relevant articles. We also reviewed the reference lists of all relevant articles.

Two reviewers (V.K. and G.G.) independently removed duplicates and rated the title and abstract of each citation as "relevant," "possibly relevant" or "not relevant." We then retrieved the full text of "relevant" and "possibly relevant" articles to assess study eligibility. The 2 reviewers resolved any disagreement through discussion and consensus.

Data Abstraction

Two reviewers (V.K. and G.G.) independently abstracted data from all included articles, recorded the data on the standardized abstraction form (Supplementary Table S3), and resolved any disagreements through discussion, or with the help of a third reviewer (D.M.N.). We collected data on study characteristics, patient characteristics, incidence or prevalence of stones, and stone characteristics. We abstracted the prevalence of stone intervention from the included studies that reported it.

We assessed the methodological quality of included studies using a modified Downs and Black checklist (Supplementary Table S4). We assigned all included studies a score between 0 and 22 based on our modified checklist with a higher score indicating a greater quality.[16]

Data Analysis

We used a Fischer Exact test for studies with controls that did not statistically compare the prevalence of stones between patients with ADPKD and controls. We also calculated the prevalence ratio of kidney stones for each of the studies with controls using Cochrane Review Manager 5.3. We assessed for heterogeneity across all studies using the I^2 test. I^2 values below 25%, between 25% and 75%, and above 75% correspond to low, moderate, and high levels of heterogeneity, respectively. We conducted a meta-analysis to combine the results if I^2 was less than 75%. We calculated the meta-analyzed prevalence ratio estimates for kidney stones using a random effects model and Cochrane Review Manager 5.3.

Results

Study Selection

A schematic diagram of the study selection process is presented in Figure 1. Our search yielded 1812 citations, and we identified 29 eligible articles that met our eligibility criteria. We identified an additional 20 eligible articles through our further search strategy described above, which resulted in a total of 49 eligible articles (a total of 9396 patients with ADPKD).[7-12,14,17-58] The chance-corrected agreement between 2 independent reviewers for full-text eligibility was excellent ($\kappa = 0.86$).

Description of Included Studies

The characteristics of included studies are summarized in Table 1. The 49 eligible studies were published between 1977 and 2019, and the majority of the studies were conducted in Turkey (7 studies) followed by the United States (6 studies), Albania (5 studies), Brazil (3 studies), India (3 studies), Spain (3 studies), Canada (2 studies), Italy (2 studies), and Japan (2 studies). A single study was conducted in Bulgaria, China, Cyprus, Greece, Ireland, Korea, Pakistan, Philippines, Republic of Macedonia, Saudi Arabia, Senegal, Taiwan, Tunisia, and the United Kingdom, and one was a multinational study. The country where the study was conducted was unknown for one study. The number of centers participating in a study was unclear in 19 of 49 studies; of the remainder, 21 studies were single center and 9 were multicenter. Among the 49 included studies, 12 were cohort studies, 33 were cross-sectional studies, and the study design was unclear for 4 studies.

Patient Population

The sample size of patients with ADPKD ranged from 30 to 1139 (Table 2). The mean age of patients with ADPKD ranged from 26 to 61 years, 35% to 71% of the patients with ADPKD were male, up to 51% developed end-stage renal disease (ESRD), 5% to 88% were hypertensive, and 1% to 73% experienced at least one prior urinary tract infection (UTI; Table 2).

Six studies compared the prevalence of stones in patients with ADPKD to unaffected family members as controls.[7-12]

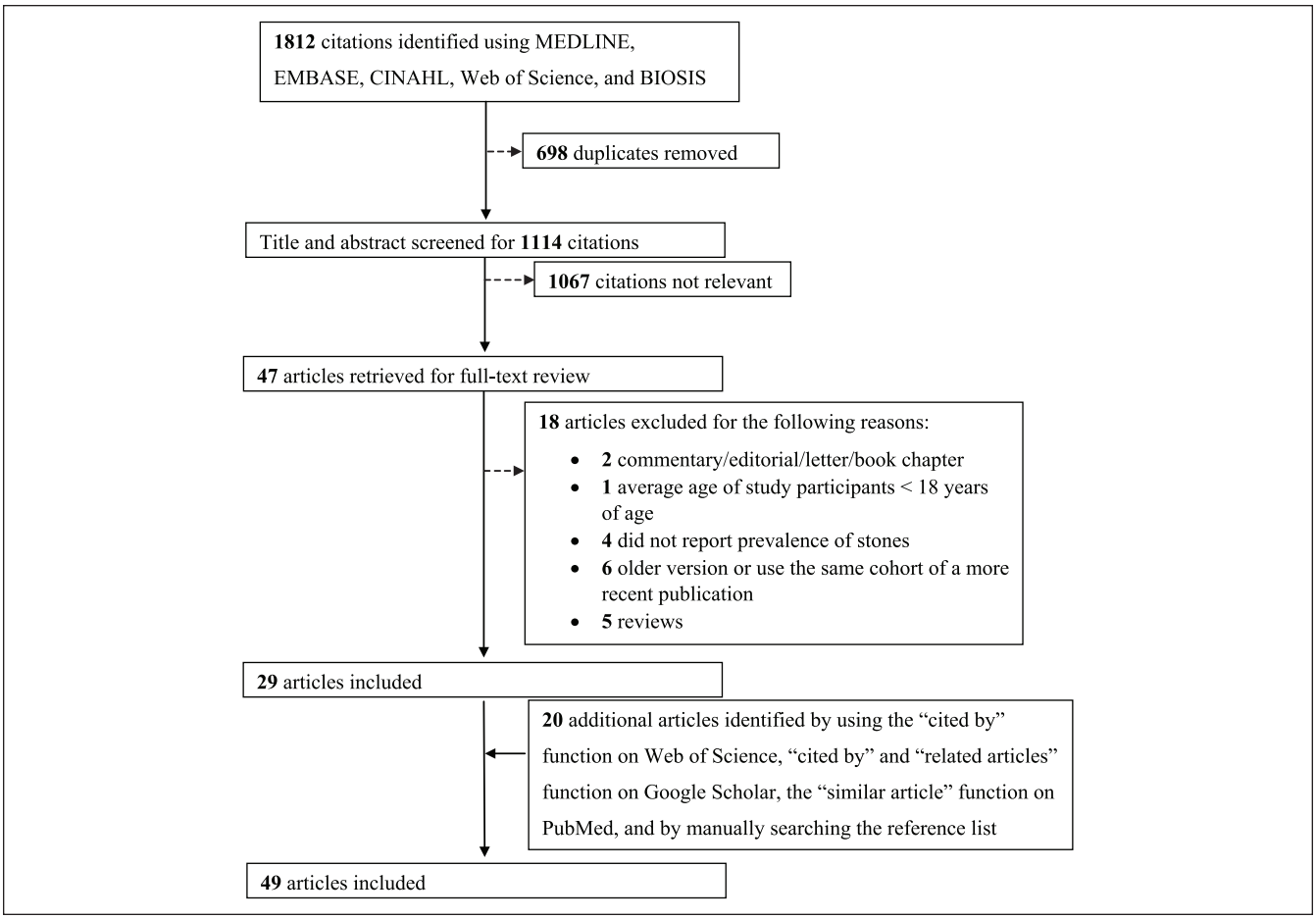

Figure 1. Study selection.

The mean age of controls ranged from 35 to 60 years, 36% to 48% of the controls were male, 4% to 36% were hypertensive, and 2% to 36% experienced a prior UTI (Table 2).

Quality Assessment of Studies

The methodological quality of the studies was limited as the methods quality score ranged from 2 to 14 out of 22 (where higher scores indicate higher methodological quality).

The internal validity of studies' results is affected by the definition of the exposure being investigated and the outcome of interest. Of the 49 studies, 29 specified the definition for ADPKD. Patients with ADPKD were identified using Ravine criteria in 6 studies, Ravine criteria or another additional criterion such as family history and liver cysts in 3 studies, Pei criteria in 3 studies, Pei criteria and an additional criterion in 2 studies, at least 5 cysts in each kidney in 3 studies, and other criteria in the remaining 13 studies; the definition for ADPKD was unclear or not reported in the remaining 19 studies. Ravine and Pei criteria to diagnose ADPKD are summarized in Supplementary Table S5 *and Table S6*, respectively.[59,60] Some studies used a definition different from the most accepted diagnostic criteria at the time the study was published. For example, Ekin et al[45] and Kazancioglu et al[28] defined patients with at least 5 cysts in each kidney as patients with ADPKD, although Pei criteria were the most commonly used diagnostic criteria for ADPKD during the time period in which the studies were conducted.[28,45]

Thirty of the 49 studies described how they identified patients with stones, while the remaining 19 studies did not. Among the 30 studies that specified how the stones were detected, 3 studies relied on patient self-report of a history of stones, 14 solely relied on radiological evidence of stone, and 13 studies relied on combination of radiological evidence of stone and at least one other criterion (ie, stone passage and recovery, surgical removal of stone and self-report of stone). Among the 27 of the 30 studies that used radiological evidence of stones as one of their diagnostic criteria, 9 reviewed historic imaging, 10 reviewed recent imaging, and the nature of considered imaging was unclear in 8 studies. Eight of the 27 studies thoroughly described what they were looking for on the radiological image to identify stones. Among the 5 studies that reported asymptomatic stones, the percentage of patients ranged between 1% and 68%.[17,18,21,37,48]

Table 1. Study Characteristics.

Author (year), *country*	No. of centers	Eligibility criteria	Recruitment period	Mean (SD) follow-up	ADPKD sample size	ADPKD case definition *(imaging modality)*	Control population *(sample size)*	Quality score[a]
Cross-sectional studies								
Al-Muhanna et al,[25] *Saudi*	1	ADPKD	NR	N/A	30	1. 5+ renal cysts distributed between both kidneys *(U/S, intravenous pyelogram, or CT)*	None	4
Baishya et al,[17] *India*	Unclear	ADPKD	Since 1992	N/A	452	NR *(NR)*	None	6
Bajrami et al,[20] *Albania*	Unclear	ADPKD	2011 to 2014	N/A	100	Ravine criteria *(x-ray or U/S)*	None	9
Chang et al,[44] *Taiwan*	1	ADPKD	October 2008 to May 2011	N/A	46	1. Ravine criteria; *OR* 2. No fam hx + bilateral kidney enlargement + at least 10 cysts in each kidney *(U/S)*	None	9
Corradi et al,[27] *Italy*	Multicenter (unclear)	ADPKD	Since April 2007	N/A	100	Ravine criteria *(U/S)*	None	12
Demetriou et al,[7] *Cyprus*	1	1. Alive 2. Has an affected family member with a *PKD2* mutation	Up to August 1998	N/A	106	1. 1+ cyst in one kidney for patients aged 5 to 14 years; 2. 2+ unilateral cysts or one in each kidney for patients aged 15 to 19 years; 3. 3+ cysts in both kidneys combined for patients aged 20 to 29 years; 4. 2+ cysts in each kidney for patients aged 30 to 59 years; *AND* 5. 4+ cysts in each kidney for patients aged 60 years or above *(U/S)*	Unaffected family members (105)	11
Duli et al,[36] *Albania*	Unclear	ADPKD	NR	N/A	180	Unclear *(NR)*	None	7
Ekin et al,[45] *Turkey*	1	ADPKD	1995 to 2014	N/A	144	1. 5+ renal cysts in both kidneys *(NR)*	None	9
Cornec-Le Gall et al,[35] *France*	22	1. Genkyst study participants 2. 18+ years old 3. Mutation in *PKD2* gene	January 2010 to March 2016	N/A	293	1. Pei criteria; *OR* 2. 10+ cysts in both kidneys combined + no fam hx *(NR)*	None	10
Galliani et al,[47] *Italy*	28	ADPKD	February 2013 to April 2014	N/A	462	NR *(NR)*	None	2
Gonzalo et al,[8] *Spain*	Unclear	1. At risk of ADPKD 2. Asymptomatic 3. 13+ years old	June 1993 to December 1994	N/A	65	1. 1+ cysts in each kidney; *OR* 2. 2+ cysts in one kidney *(U/S)*	unaffected family members (60)	13
Grampsas et al,[23] *United States*	1	1. ADPKD 2. Part of The University of Colorado Health Sciences Center's Research Study Group database	NR	N/A	48	NR *(NR)*	None	7
Ishibashi,[49] *Japan*	1	ADPKD	May 1972 to September 1980	N/A	118	NR *(U/S or CT)*	None	3

(continued)

Table 1. (continued)

Author (year), *country*	No. of centers	Eligibility criteria	Recruitment period	Mean (SD) follow-up	ADPKD sample size	ADPKD case definition *(imaging modality)*	Control population *(sample size)*	Quality score[a]
Fary Ka et al,[39] *Senegal*	1	1. ADPKD 2. Black 3. 16+ years 4. Without acquired simple cyst, angiomyolipoma, tuberous sclerosis, cyst calcification, any alterations suggestive of malignancy	January 1, 1995 to December 31, 2005	N/A	53	Ravine criteria *(U/S)*	None	5
Kaygısız et al,[40] *Turkey*	1	1. Referred and diagnosed with ADPKD at a tertiary care center 2. Not on dialysis 3. eGFR >30 mL/min	2010 to 2016	N/A	118	Pei criteria *(U/S)*	None	11
Kazancioglu et al[28] *Turkey*	12	ADPKD	January 2003 to December 2009	N/A	1139	5+ cysts distributed between both kidneys *(NR)*	None	11
Kim et al,[43] Korea	9	1. Korean 2. ADPKD and CKD 3. Pre-dialysis 4. Part of Korean Cohort Study for Outcomes in Patients with Chronic Kidney Disease cohort 5. Provided written consent 6. Not a transplant recipient 7. Without heart failure, liver cirrhosis, or current or past history of cancer 8. Not pregnant 9. No single kidney due to trauma or kidney donation	April 2011 to February 2016	N/A	364	Pei criteria (*U/S*)	None	11
Kumar et al,[41] *India*	1	ADPKD	November 2011 to October 2012	N/A	41	Unclear *(U/S, intravenous pyelogram, CT)*	None	7
Memili et al,[29] *Turkey*	1	1. ADPKD 2. Referred to nephrology outpatient clinic	January 2003 to December 2006	N/A	136	NR (*NR*)	None	8
Meng et al,[33] *China*	1	1. ADPKD 2. Inpatient 3. Complete medical records	January 2012 to December 2016	N/A	167	Japanese criteria for patients with unknown genotype (*NR*)	None	10

(continued)

Table 1. (continued)

Author (year), *country*	No. of centers	Eligibility criteria	Recruitment period	Mean (SD) follow-up	ADPKD sample size	ADPKD case definition *(imaging modality)*	Control population *(sample size)*	Quality score[a]
Milutinovic et al,[12] *United States*	Unclear	At risk of ADPKD	NR	N/A	140	1. Fam hx + multiple bilateral cysts (*Unclear*)	Unaffected family members (119)	12
Milutinovic et al,[11] *United States*	Unclear	1. Fam hx of ADPKD 2. 50+ years old	NR	N/A	32	1. Bilateral renal cysts + fam hx (Unclear)	Unaffected family members (25)	12
Nikolov et al,[31] *Unclear*	1	ADPKD referred to center	1998 to 2008	N/A	208	NR (*NR*)	None	4
Nishiura et al,[24] *Brazil*	1	1. Referred to PKD unit due to the presence of affected progenitor/sibling with ADPKD 2. ADPKD confirmed using U/S	NR	N/A	125	Ravine criteria (*U/S or CT*)	None	14
Parfrey et al,[10] *Canada*	NR	Family members of index ADPKD cases	NR	N/A	Unclear	1. Reported on autopsy report, surgical report or of a death due to CKD with an ADPKD diagnosis; 2. 1+ in each kidney; *OR* 3. 1+ in one kidney *(excretory urography, CT, U/S)*	Unaffected family members *(Unclear)*	12
Romão et al,[55] *Brazil*	1	ADPKD	January 1985 to December 2003	N/A	92	1. Ravine criteria; *OR* 2. Fam hx + hepatic cyst *(U/S)*	None	9
Roscoe et al,[42,b] *Canada*	Unclear	ADPKD	NR	N/A	80	NR *(NR)*	None	9
Segal et al,[56] *United States*	2	ADPKD	NR	N/A	100	NR *(NR)*	None	3
Strakosha et al,[48] *Albania*	NR	ADPKD	NR	N/A	180	NR *(NR)*	None	5
Torra et al,[9] *Spain*	Unclear	ADPKD or at-risk of ADPKD	NR	N/A	PKD1: 146; PKD2: 20; All: 166	Ravine criteria *(U/S)*	Unaffected family members (150)	13
Torres et al,[18] *United States*	1	1. ADPKD 2. Without any cyst wall calcification, or with poorly localized parenchymal calcification	1976 to 1986	N/A	751	1. Bilateral polycystic kidneys + fam hx; *OR* 2. No fam hx + bilaterally enlarged and polycystic kidneys + exclusion of other disorders associated with renal cysts *(NR)*	None	10
Vikrant and Parashar[32] *India*	1	1. ADPKD 2. Attending renal clinic	April 2009 to March 2015	N/A	208	1. Pei criteria; *OR* 2. Fam hx + hepatic cyst *(U/S)*	None	13

(continued)

Table 1. (continued)

Author (year), *country*	No. of centers	Eligibility criteria	Recruitment period	Mean (SD) follow-up	ADPKD sample size	ADPKD case definition *(imaging modality)*	Control population *(sample size)*	Quality score[a]
Yildiz et al[46] *Turkey*	Unclear	1. ADPKD 2. Not on renal replacement therapy 3. eGFR > 30mL/min 4. In the Turkish Nephrology Society Cystic Kidney Disease Working Group online database	NR	N/A	93	NR *(NR)*	None	3
Cohort Study								
Gonzalo et al,[58] *Spain*	1	ADPKD	June 1977 to June 1988	6 years 3 months (NR)	107	1. 3+ cysts in each kidney + fam hx *(excretory urography or U/S)*	None	
Hajji et al[53] *Tunisia*	Multicenter (unclear)	ADPKD	1969 to 2016	NR	569	NR *(NR)*	None	10
Hateboer et al[30] *The Netherlands, Spain, Bulgaria, and the United Kingdom*	7	ADPKD	NR	NR	624	1. Ravine criteria; 2. Deoxyribonucleic acid linkage test; *OR* 3. Report of ADPKD on medical records *(U/S)*	None	14
Idrizi et al,[37] *Albania*	Unclear	ADPKD	NR	NR	180	NR *(NR)*	None	10
Ozkok et al,[14] *Turkey*	1	ADPKD	January 2000 to January 2012	100 (38) months	323	Pei criteria *(U/S)*	None	13
Papadopoulou et al,[66] *Greece*	Unclear	At-risk of ADPKD	NR	NR	85	1. 2+ cysts in one kidney and one cyst in the other kidney+ fam hx (U/S)	None	10
Rabbani et al,[67] *Pakistan*	1	ADPKD	January 1997 to December 2003	7.6 (4.2) years	56	1. Fam hx + 2+ cysts in either kidney + hypertension or renal insufficiency; 2. Bilateral cysts + no fam hx; *OR* 3. Unilateral polycystic kidney + liver cyst, berry aneurysm, arterio-venous malformation or evidence of prior cerebrovascular accident on MRI/MRA *(U/S)*	None	9
Ristovska et al,[34] *Republic of Macedonia*	Unclear	ADPKD	NR	3 (NR) years	60	Unclear *(echosonography or CT)*	None	5
Senel et al,[54] *Turkey*	Unclear	ADPKD	January 1990 to January 2015	NR	300	NR *(NR)*	None	6

(continued)

Table 1. (continued)

Author (year), *country*	No. of centers	Eligibility criteria	Recruitment period	Mean (SD) follow-up	ADPKD sample size	ADPKD case definition *(imaging modality)*	Control population *(sample size)*	Quality score[a]
Tantoco and Alano,[68] *Philippines*	1	ADPKD	May 1973 to January 1986	3 (NR) years	60	1. Signs and symptoms + fam hx + imaging *(intravenous pyelogram, infusion intravenous pyelogram with tomogram, U/S or CT)*	None	3
Thong and Ong,[38,b] *United Kingdom*	Unclear	1. ADPKD 2. In research database 3. Have at least 5 years of renal function tests at the time of analysis	1978 to 2012	11.3 (5.5) years	210	NR *(NR)*	None	8
Wright et al,[50] *Ireland*	Unclear	Belonging to *PKD1* family	NR	NR	PKD1: 49; non-PKD1: 17; All: 66	ADPKD documented the following ways: (1) by post-mortem examination; (2) by report of a death due to chronic renal failure with a clinical diagnosis of ADPKD; (3) by operative report during abdominal surgery; (4) by excretory urography or CT scan; (5) by unequivocal findings on ultrasonography; *OR* (6) 1+ cyst in at least one kidney *(diagnostic data files or ultrasound)*	None	10
Study design unclear								
Delaney et al,[26] *United States*	1	Symptomatic ADPKD	1947 to 1980	12 (NR) years	53	1. History and physical examination; *OR* 2. Diagnosis confirmed with imaging or autopsy *(intravenous pyelogram with tomograms, sonography, CT with contrast, arteriography, laparotomy)*	None	4
Dimitrakov and Simeonov,[22] *Bulgaria*	Unclear	ADPKD	NR	N/A	82	Unclear *(echography, venous urography, or CT)*	None	5
Higashihara et al,[22] *Japan*	38	ADPKD	January 1988 to December 1988	N/A	316	NR*(U/S or CT)*	None	11
Idrizi et al,[21] *Albania*	Unclear	ADPKD	2002 to 2009	N/A	200	Ravine criteria *(U/S)*	None	7

Note. ADPKD = autosomal dominant polycystic kidney disease; NR = not reported; N/A = not applicable; U/S = ultrasound; CT = computed tomography; Fam Hx = family history; PKD = polycystic kidney disease.
[a]A modified Downs and Black checklist was used to assess the methodological quality of each included study. The methods quality score ranged between 0 and 22 with higher scores indicating higher quality.
[b]Data were abstracted and methodological quality was assessed for the portion of the multicomponent study that reported the prevalence of stones.

Table 2. Patient Characteristics.

Author (year), *country*	Mean age (standard deviation) (years)	No. of male (%)	No. of patients on dialysis (%)	No. of transplant recipient (%)	No. of patients who had ESRD (%)	No. of hypertensive patients (%)	No. of patients with UTI (%)	Serum creatinine (μmol/L)
Al-Muhanna et al,[25] *Saudi*	45 (10)	13 (43)	2 (7)	2 (7)	4 (13)	17 (57)	22 (73)	NR
Baishya et al,[17] *India*	NR	NR	NR	NR	NR	NR	NR	NR
Bajrami et al,[20] *Albania*	NR	42 (42)	NR	NR	NR	NR	NR	NR
Chang et al,[44] *Taiwan*	48 (13)	24 (52)	NR	NR	NR	31 (67)	17 (37)	NR
Corradi et al,[27] *Italy*	48 (NR)	58 (58)	NR	6 (6)	29 (29)	75 (75)	NR	NR
Demetriou et al,[7] *Cyprus*	ADPKD: 38 (NR) CONTROL: NR (NR)	NR	ADPKD: 0 (0) CONTROL: NR (NR)	ADPKD: 1 (1) CONTROL: NR (NR)	NR	ADPKD: 24 (23) CONTROL: 4 (4)	ADPKD: 24 (23) CONTROL: 12 (11)	NR
Duli et al,[36] *Albania*	NR	NR	NR	NR	NR	NR	NR	NR
Ekin et al,[45] *Turkey*	45 (NR)	61 (42)	NR (11)	NR	NR (11)	117 (82)	14 (2)[a]	168 (186)
Cornec-Le Gall et al,[35] *France*	61 (NR)	123 (42)	NR	NR	Unclear	221 (75)	NR	NR
Galliani et al,[47] *Italy*	NR	194 (42)	NR	NR	NR	NR (60)	NR (28)	NR
Gonzalo et al,[8] *Spain*	ADPKD: 33 (NR) CONTROL: NR (NR)	ADPKD: 26 (40) CONTROL: 28 (47)	NR	NR	NR	ADPKD: 19 (29) CONTROL: 3 (5)	ADPKD: 4 (6) CONTROL: 1 (2)	NR
Grampsas et al,[23] *United States*	NR	17 (35)	NR	NR	NR	23 (48)	NR	NR
Ishibashi,[49] *Japan*	44 (NR)	54 (46)	NR	NR	NR	NR	57 (54)[a]	NR
Fary Ka et al,[39] *Senegal*	47 (5)	30 (57)	10 (19)	NR	27 (51)	36 (68)	7 (13)	NR
Kaygısız et al,[40] *Bursa*	NR	54 (46)	0 (0)	NR	0 (0)	72 (61)	29 (25)	NR
Kazancioglu et al,[28] *Turkey*	NR	548 (48)	108 (11)	8 (1)	NR	828 (73)	228 (23)[a]	194 (194)
Kim et al,[43] *Korea*	47 (11)	184 (51)	0 (0)	0 (0)	NR	319 (88)	8 (2)	119 (79)
Kumar et al,[41] *India*	NR	29 (71)	NR	NR	13 (32)	27 (66)	6 (40)	398 (283)
Memili et al,[29] *Turkey*	47 (16)	65 (48)	16 (12)	1 (1)	NR	98 (72)	22 (16)	NR
Meng et al,[33] *China*	49 (NR)	72 (43)	NR	NR	NR	84 (50)	41 (25)	309 (290)
Milutinovic et al,[12] *United States*	ADPKD: 37 (14) CONTROL: 35 (16)	ADPKD: 64 (46) CONTROL: NR (NR)	ADPKD: 25 (18) CONTROLS: 0 (0)	NR	ADPKD: 28 (20) CONTROL: 0 (0)	ADPKD: 73 (52) CONTROLS: 13 (11)	ADPKD: 64 (46) CONTROLS: 33 (28)	NR
Milutinovic et al,[11] *United States*	ADPKD: 58 (7) CONTROL: 60 (7)	ADPKD: 15 (47) CONTROL: 9 (36)	NR	NR	ADPKD: 15 (47) CONTROL: 0 (0)	ADPKD: 22 (69) CONTROL: NR (36)	ADPKD: 13 (41) CONTROL: NR (36)	NR
Nikolov et al,[31] *Unclear*	NR	NR	NR	NR	NR	NR	NR	NR
Nishiura et al,[24] *Brazil*	NR	45 (36)	NR	NR	NR	59 (47)	4 (3)	NR
Parfrey et al,[10] *Canada*	NR	NR	NR	NR	NR	ADPKD: 118 (36) CONTROL: 238 (16)	ADPKD: 24 (22)[a] CONTROL: 35 (17)[a]	NR

(continued)

Table 2. (continued)

Author (year), *country*	Mean age (standard deviation) (years)	No. of male (%)	No. of patients on dialysis (%)	No. of transplant recipient (%)	No. of patients who had ESRD (%)	No. of hypertensive patients (%)	No. of patients with UTI (%)	Serum creatinine (μmol/L)
Romão et al,[55] *Brazil*	35 (15)	34 (37)	NR	NR	27 (29)	61 (63)	33 (36)	212 (247)
Roscoe et al,[42,b] *Canada*	NR	NR	NR	NR	22 (28)	NR	NR	NR
Segal et al,[56] *United States*	NR	NR	NR	NR	NR	NR	NR	NR
Strakosha et al,[48] *Albania*	NR	NR	NR	NR	NR	NR	NR	NR
Torra et al,[9] *Spain*	NR	ADPKD: 72 (43) CONTROL: 72 (48)	NR	NR	ADPKD: 42 (25) CONTROL: NR (NR)	ADPKD: 76 (46) CONTROL: 23 (15)	ADPKD: 57 (34)[a] CONTROL: 26 (17)	NR
Torres et al,[18] *United States*	NR	393 (52)	NR	NR	NR	NR	NR	NR
Vikrant and Parashar,[32] *India*	46 (15)	126 (61)	5 (2)	NR	20 (10)	145 (70)	81 (39)	292 (318)
Yildiz et al,[46] *Turkey*	41 (13)	49 (53)	0 (0)	0 (0)	0 (0)	NR (72)	NR	NR
Gonzalo et al,[58] *Spain*	46 (14)	58 (54)	NR	NR	NR	73 (68)[a]	33 (31)[a]	NR
Hajji et al,[53] *Tunisia*	49 (14)	297 (52)	298 (52)	13 (2)	NR	321 (59)	NR (24)	459 (NR)
Hateboer et al,[30] *The Netherlands, Spain, Bulgaria, and the United Kingdom*	NR	308 (49)	NR	NR	NR	227 (50)[a]	119 (28)[a]	NR
Idrizi et al,[21] *Albania*	NR	97 (49)	NR	NR	NR	NR	108 (54)	NR
Ozkok et al,[14] *Turkey*	53 (15)	149 (46)	46 (14)	NR	48 (14)	255 (79)[a]	64 (21)[a]	NR
Papadopoulou et al,[66] *Greece*	26 (12)	44 (52)	NR	NR	NR	ADPKD: 4 (5)	ADPKD: 1 (1)	NR
Rabbani et al,[67] *Pakistan*	NR	40 (71)	NR	NR	7 (13)	38 (68)	NR	398 (282)
Ristovska et al,[34] *Republic of Macedonia*	43 (13)	NR	NR	NR	NR	NR	NR	NR
Senel et al,[54] *Turkey*	NR	143 (48)	NR	NR	NR	231 (83)[a]	52 (19)[a]	203 (221)
Tantoco and Alano,[68] *Philippines*	44 (NR)	30 (50)	NR	NR	17 (28)	40 (67)	17 (28)	NR
Thong and Ong,[38, b] *United Kingdom*	46 (16)	102 (49)	NR	NR	NR	147 (70)	57 (27.2)	NR
Wright et al,[50] *Ireland*	NR	NR	NR	NR	12 (18)	16 (24)	5 (8)	NR
Delaney et al,[26] *United States*	NR	21 (40)	9 (17)	NR	NR	11 (21)	10 (19)	NR
Dimitrakov and Simeonov,[22] *Bulgaria*	NR	34 (41)	NR	NR	NR	NR	NR	NR
Idrizi et al,[37] *Albania*	NR	NR	NR	NR	NR	NR	108 (60)	NR
Higashihara et al,[22] *Japan*	51 (13)	167 (53)	72 (23)	NR	72 (23)	201 (64)[a]	NR	354 (380)

Note. UTI = urinary tract infection; NR = not reported; ADPKD = autosomal dominant polycystic kidney disease; ESRD = end-stage renal disease.
[a]Denominator includes a subset of the population.
[b]Data were abstracted for the portion of the multicomponent study that reported the prevalence of stones.

The setting and source population from which the samples are recruited affects the study generalizability. For 21 of the studies, the setting or population from which the sample was recruited from was unclear or not reported. Patients were recruited from hospitals in 18 studies, outpatient clinics in 7 studies, solely from an inpatient setting in 1 study, an outpatient ADPKD speciality clinic in 1 study, and from both an inpatient and outpatient setting for 1 study. It is unclear if patients were recruited from an inpatient or outpatient setting for 20 studies and setting was not reported for one study.

Six of the 49 studies compared the prevalence of stones in patients with ADPKD to controls, which were unaffected family members. All of these studies were cross-sectional. Only 2 of the 6 studies statistically compared the prevalence of stones in patients with ADPKD to controls. Both of these studies used univariate analyses and did not adjust for any confounders.

Prevalence and Characteristics of Stones and Prevalence of Stone Intervention

In patients with ADPKD, the prevalence of stones ranged between 3% and 59% (Table 3). Of those patients with stones, 2% to 47% underwent at least one stone intervention. Urinary tract infections and flank pain were the predominant precursor to diagnosis of stones in patients with ADPKD.[17,21,24,37,40,48] In most patients, stones were solely located in the renal calyces.[17,18] Most stones were composed of uric acid according to 6 studies[7,18,20,21,37,48] and oxalate according to 2 studies (Table 4).[22,26]

The prevalence of stones ranged from 3% to 12% in family members confirmed not to be affected with ADPKD (Table 3). None of the studies described the characteristics of stones in unaffected family members. All 6 studies that compared the prevalence of stones in patients with and without ADPKD reported stones were more prevalent in patients with ADPKD; however, 4 studies did not statistically analyze the prevalence of stones between the 2 groups, and the remaining 2 studies found no statistical difference. When we statistically compared the prevalence of stones in patients with ADPKD to unaffected family members in the 4 studies that did not conduct any statistical analyses, we found that only one out of the 4 studies found a significant difference. Meta-analysis of the calculated prevalence ratios across 6 cross-sectional studies show that patients with ADPKD had a higher prevalence of kidney stones compared to unaffected family members (unadjusted prevalence ratio: 1.8, 95% confidence interval: 1.3 to 2.6, $P = .0007$; test for heterogeneity: $I^2 = 0\%$, $P = .8$; Figure 2).

Six studies reported the prevalence of stone intervention in patients with ADPKD, which ranged between 1% and 8% (Table 3). None of the studies with controls reported the prevalence of stone intervention in unaffected family members.

Stone Incidence

No study clearly reported the incidence of kidney stones and the incidence of stone intervention in patients with ADPKD. Most cohort studies included in this review assessed kidney stones at cohort entry and not during follow-up. Whether the reported percentage was a prevalence or incidence estimate was unclear for 3 of the included cohort studies.

Discussion

Many popular educational materials and clinical practice guidelines state that kidney stones are common in patients with ADPKD, and its prevalence may be 5 to 10 times higher than the general population.[61,62] This make clinical sense based on our knowledge of the pathophysiology of ADPKD; the kidney cysts in patients with ADPKD lead to urinary stasis which promotes stone formation.[23] Our review of the literature, however, indicates that the evidence to support these assertions is weak and illuminates several knowledge gaps about the clinical epidemiology of stones in ADPKD. No study has clearly reported the incidence of stones in ADPKD. Prevalence estimates in ADPKD varied widely ranging from 3% to 59% for kidney stones and from 1% to 8% for stone interventions. Urinary tract infections and flank pain were the predominant precursors to diagnosis of stones; however, UTI and flank pain are not specific to stones and are also manifestations of ADPKD independent of stones. It is likely that UTI and flank pain were associated with ADPKD itself rather than stone because most of the stones in ADPKD were located in the renal calyces where they would be less likely to be symptomatic. Uric acid stones are the most prevalent stone composition in patients with ADPKD. The wide-ranging prevalence estimates along with the discovery that no published studies clearly reported stone incidence confirm that how often patients with ADPKD develop kidney stones remains uncertain.

There are several reasons why prevalence estimates of stones varied drastically across studies. These include inconsistent stone definitions, different distributions of stone risk factors, potential recall bias in studies that relied on patient self-report to identify stone events, and relying on past imaging reports done for reasons other than stone identification. Self-report is particularly problematic because the symptoms of flank pain and hematuria are common with ADPKD in the absence of stone disease. Patients with ADPKD may be more likely to undergo renal imaging, which would lead to overdetection of potentially clinically insignificant stones which may also exist undetected in the general population. The variability in imaging modalities used across studies and even between patients in the same study may also explain the variable prevalence estimates across studies. For example, computed tomography (CT) is a more sensitive method of stone detection than ultrasound and would provide a more accurate estimate of stone prevalence.[63,64] There are many in the

Table 3. Prevalence of Stones and Stone Intervention in Patients With ADPKD and Controls.

Author (year), *country*	Stone definition (*modality*)	No. of unique patients with stones (%)	No. of unique patients who underwent stone intervention (%)
Al-Muhanna et al,[25] *Saudi*	NR *(Unclear)*	5 (17)	NR
Baishya et al,[17] *India*	NR *(NR)*	19 (4)	9 (2)
Bajrami et al,[20] *Albania*	Echogenic focus with posterior acoustic shadowing within the kidney[a] *(U/S; or plain abdominal KUB film, intravenous pyelography and noncontrast helical CT in cases where stones were not observed on U/S or KUB film)*	58 (58)	NR
Chang et al,[44] *Taiwan*	NR *(NR)*	19 (41)	NR
Corradi et al,[27] *Italy*	NR *(NR)*	24 (24)	NR
Demetriou et al,[7] *Cyprus*	Passage of stone or presence of stone on a plain KUB film or U/S[b] *(Plain KUB film or U/S)*	ADPKD: 21 (20) CONTROL: 4 (4)	NR
Duli et al,[36] *Albania*	Image of stone within the urinary collecting system[a] *(U/S, renal radiography, CT)*	106 (59)	NR
Ekin et al,[45] *Turkey*	Presence and absence of stone on U/S[b] and/or history of passing stone *(U/S)*	24 (17)	NR
Cornec-Le Gall et al,[35] *France*	NR *(NR)*	57 (20)	NR
Galliani et al,[47] *Italy*	NR *(NR)*	102 (22)	NR
Gonzalo et al,[8] *Spain*	Hyperechogenic image with posterior shadowing[a] *(U/S or plain roentgenogram with tomograms)*	ADPKD: 7 (11) CONTROL: 2 (3)	NR
Grampsas et al,[23] *United States*	Echogenic focus with posterior acoustic shadowing within the kidney but outside an identifiable cyst[a] + with or without a clinical history of stone *(U/S)*	15 (31)	NR
Ishibashi,[49] *Japan*	NR *(NR)*	10 (13)	NR
Fary Ka et al,[39] *Senegal*	NR *(NR)*	6 (11)	NR
Kaygısız et al,[40]*Bursa*	History of stone or positive imaging[a] *(U/S, noncontrast CT)*	28 (24)	10 (8)
Kazancioglu et al,[28] *Turkey*	Presence or absence of urinary tract stones on U/S[c] and/or history of passing stone *(U/S)*	278 (27)[d]	NR
Kim et al,[43] *Korea*	NR *(NR)*	92 (29)[d]	NR
Kumar et al,[41] *India*	NR *(NR)*	6(15)	NR
Memili et al,[29] *Turkey*	Presence and absence of kidney stone[b] *(U/S)*	39 (29)	NR
Meng et al,[33] *China*	NR *(NR)*	65 (39)	NR
Milutinovic et al,[12] *United States*	Stones apparent on radiogram[c] or passed in urine *(radiogram)*	ADPKD: 16 (11) CONTROL: 5 (4)	NR
Milutinovic et al,[11] *United States*	Stone apparent on radiograms[a] or were found in urine *(radiogram)*	ADPKD: 5 (17) CONTROL: 3 (12)	NR
Nikolov et al,[31] *Unclear*	NR *(NR)*	29 (14)	NR
Nishiura et al,[24] *Brazil*	Image of stone within the renal collection system[a] *(U/S and CT)*	35 (28)	NR
Parfrey et al,[10] *Canada*	Self-report history of kidney stones during interview *(NR)*	ADPKD: 16 (15)[d] CONTROL: 20 (10)[d]	NR
Romão et al,[55] *Brazil*	NR *(NR)*	15 (16)	NR
Roscoe et al,[42,e] *Canada*	Acoustic shadowing on radiologic imaging[b] *(NR)*	8 (10)	NR
Segal et al,[56] *United States*	NR *(NR)*	20 (20)	NR
Strakosha et al,[48] *Albania*	Presence on imaging[a] *(ultrasound or abdominal x-ray)*	81 (45)	2 (1)
Torra et al,[9] *Spain*	Passage of stone with recovery of stone or evidence of stone within the collecting system as reported by the radiologist[b] *(unclear)*	ADPKD: 29 (18) CONTROL: 15 (10)[d]	NR
Torres et al,[18] *United States*	Historical evidence of passage, recovery, surgical removal of stone, evidence of stone within the collecting system, or renal papillary tips as reported by radiologist[b] *(excretory urogram for a subset [79 patients]; unclear for remaining patients)*	151 (20)	31 (4)

(continued)

Table 3. (continued)

Author (year), *country*	Stone definition (*modality*)	No. of unique patients with stones (%)	No. of unique patients who underwent stone intervention (%)
Vikrant and Parashar,[32] *India*	History of stone passage, removal of stone or calcific foci/nephrocalcinosis seen on imaging[b] *(unclear)*	81 (39)	NR
Yildiz et al,[46] *Turkey*	Self-reported history of stone *(NR)*	23 (25)	NR
Gonzalo et al,[58] *Spain*	Passage or surgical removal of stones or presence of radio-opaque deposits on X-ray[c] *(X-ray)*	32 (30)[f]	NR
Hajji et al,[53] *Tunisia*	NR *(NR)*	28 (5)[f]	NR
Hateboer et al,[30] *The Netherlands, Spain, Bulgaria, and the United Kingdom*	Radiological evidence of kidney stone[c] *(U/S, plain radiographs, intravenous pyelograms, CT)*	42 (10)[d, g]	NR
Idrizi et al,[37] *Albania*	An echogenic focus with posterior acoustic shadowing within the kidney but outside an identifiable cyst and with or without clinical history of stone[a] *(U/S and X-ray)*	76 (42)[h]	2 (1)
Ozkok et al,[14] *Turkey*	Self-reported hx of passing stone or presence or absence of kidney stone on ultrasound[b] *(U/S)*	101 (33)[h]	NR
Papadopoulou et al,[66] *Greece*	Self-reported history of stone during interview *(NR)*	3 (4)[h]	NR
Rabbani et al,[67] *Pakistan*	Presentation on imaging[b] *(NR)*	6 (11)[h]	NR
Ristovska et al,[34] *Republic of Macedonia*	Evidence on imaging[a] *(echosonography and CT scan)*	22 (37)[h]	NR
Senel et al,[54] *Turkey*	NR *(NR)*	68 (28)[d,h]	NR
Tantoco and Alano,[68] *Philippines*	Presence of radiopaque stone on radiographic ultrasound[c] *(radiograph or U/S)*	18 (30)[f]	NR
Thong and Ong,[38,e] *United Kingdom*	NR *(NR)*	16 (8)[h]	NR
Wright et al,[50] *Ireland*	NR *(NR)*	2 (3)[h]	NR
Delaney et al,[26] *United States*	Passage of stone or surgical removal of stones from urinary tract or presence of radio-opaque deposits on X-ray[c] *(X-ray)*	18 (34)	1 (2)
Dimitrakov and Simeonov,[22] *Bulgaria*	Presence or absence of kidney stone on imaging[c] *(echography, venous urography, CT)*	23 (28)	NR
Higashihara et al,[22] *Japan*	NR *(NR)*	53 (18)d	NR
Idrizi et al,[21] *Albania*	Echogenic focus with posterior acoustic shadowing within the kidney[c] *(U/S; or plain abdominal KUB film, intravenous pyelography and noncontrast helical CT in cases where stones were not observed on U/S or KUB film)*	116 (58)	4 (2)

Note. NR = not reported; U/S = ultrasound; KUB = kidney, ureter, bladder; CT = computed tomography scan; ADPKD = autosomal dominant polycystic kidney disease.

[a]Patients underwent prospective abdominal imaging.

[b]Authors reviewed historic images to ascertain stone event.

[c]Unclear whether investigators prospectively imaged abdomen or reviewed past abdominal images or imaging report to identify stone event.

[d]The denominator only includes a subset of the study population.

[e]Data were abstracted for the portion of the multicomponent study that reported the prevalence of stones.

[f]Unclear whether stone event was ascertained at baseline or during follow-up; therefore, unknown whether the reported percentage was a prevalence or incidence estimate.

[g]Stone was ascertained at baseline and during follow-up; therefore, the percentage is a prevalence estimate.

[h]Stone event was ascertained at baseline; therefore, the percentage is a prevalence estimate.

current literature. Most of the studies published to date on stones in ADPKD were conducted in a single center and are of poor methodological quality. Additionally, only 6 studies compared the prevalence of stones in patients with ADPKD to controls.[7-12] Among these 6 studies, only 2 statistically compared the prevalence of stones between the 2 groups,[9,10] and none of these studies adjusted for confounders.[7-12] Additionally, not all patients with ADPKD were hospitalized; as a result, prevalence estimates obtained from patients recruited from an inpatient setting must be generalized to the

Table 4. Symptoms and Characteristics of Stones.

Author (year), *country*	Symptoms	Location	Composition
Baishya et al,[17] *India*	• Anorexia: 3 (16%) • Fever: 1 (5%) • Fluid Overload: 2 (11%) • Hematuria: 5 (26%) • Pain: 6 (32%) • Vomiting: 3 (16%) • Weakness: 2 (11%)	Location of stones in the 23 kidneys with stones among 19 patients (denominator is 23): • Renal calyces: 10 (28%) • Renal pelvis: 2 (9%) • Both renal pelvis and calyces: 5 (22%) • Ureter: 5 (22%) • Staghorn: 1 (4%)	NR
Bajrami et al,[20] *Albania*	NR	NR	• Calcium oxalate: NR (39%) • Urate: NR (47%) • Other compounds: NR (14%)
Demetriou et al,[7] *Cyprus*	NR	NR	Majority were uric acid
Kaygısız et al,[40] *Bursa*	Lower back pain: 10 (36%)	NR	NR
Nishiura et al,[24] *Brazil*	Low back pain	NR	NR
Strakosha et al,[48] *Albania*	• 40% of patients with stone associated with a history of UTI and flank pain	NR	• Calcium oxalate: NR (39%) • Urate: NR (47%) • Other Compounds: NR (14%)
Torres et al,[18] *United States*	NR	Among the 71 patients where details about stone location is available: • Only renal calyces: 63 (89%) • Renal pelvis/Staghorn: 4 (6%) • Ureter: 4 (6%)	Composition examined in 30 patients: • Calcium carbonate: 3 (10%) • Calcium oxalate: 14 (47%) • Calcium phosphate: 6 (20%) • Struvite: 3 (10%) • Uric acid: 17 (57%)
Idrizi et al,[37] *Albania*	History of UTI and flank pain: NR (40%)	NR	• Calcium oxalate: NR (39%) • Urate: NR (47%) • Other compounds: NR (14%)
Idrizi et al,[21] *Albania*	• UTI and Flank pain: 70 (60%) • Gross Hematuria: 65 (56%)	NR	Among the 63 patients with information on stone composition: • Calcium oxalate: 25 (39%) • Uric acid: 30 (47%) • Other compounds: 8 (14%)
Delaney et al,[26] *United States*	NR	NR	• Calcium oxalate: 3 (50%) • Uric acid stones: 1 (17%) • Calcium oxalate stones in one occasion and uric acid or calcium phosphate stones on the other occasion: 2 (33%)
Dimitrakov and Simeonov,[22] *Bulgaria*	NR	NR	• Oxalate: 12 (52%) • Urate: 6 (26%) • Mixed composition: 5 (22%)

Note. NR = not reported; UTI = urinary tract infection.

broader ADPKD population with caution. Similarly, the prevalence estimates obtained from patients recruited from an outpatient speciality clinic must also be generalized to the broader ADPKD population with caution due to increased surveillance. Also, only 8 of 49 of the included studies described the composition of stones in patients with ADPKD; none of the 8 studies compared the composition of stones in patients with ADPKD to patients without ADPKD.

This review serves as a call to action for better research in this field. We recommend conducting large, multicenter studies that compare the risk of stones and risk of stone intervention between a representative population of ADPKD and controls to better characterize the magnitude of kidney stone and stone intervention risk in patients with ADPKD. We also recommend that such studies adjust for important confounders, such as hypertension, to better characterize the true association between ADPKD and kidney stones and stone intervention. Imaging tests are much more advanced, widespread, and frequent over time; this may lead to the possibility of detecting stones in ADPKD that may not be

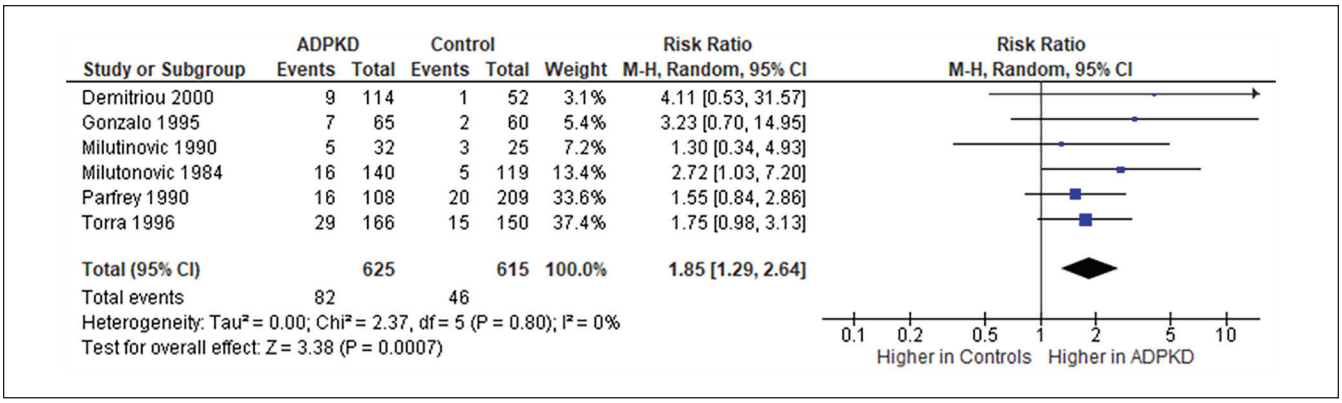

Figure 2. Calculated unadjusted prevalence ratio of stones in patients with autosomal dominant polycystic kidney disease compared to unaffected family members.

Note. The prevalence ratios were calculated using prevalence estimates obtained from studies and Cochrane Review Manager 5.3. CI = confidence interval.

clinically relevant. Examining risk of kidney stone diagnosis and kidney stones that require intervention separately would provide insight into whether there is a potentially higher burden of asymptomatic stone that were detected incidentally on imaging. More reliable estimates of the magnitude of risk of stones and stone intervention would provide insight into clinical management practices and help patients with ADPKD and their physicians better prognosticate. If patients with ADPKD are truly at higher risk for kidney stones, then nephrologists may want to consider preventative measures for kidney stones. For example, if patients with ADPKD are at higher risk of kidney stones and hypocitraturia, then nephrologists may want to screen for hypocitraturia and treat patients with potassium citrate. Nephrologists may also want to consider treating large cysts that obstruct the urinary system and cause urinary stasis. Preventing stone formation would alleviate pain due to kidney stones and potentially slow down disease progression in patients with ADPKD. We also recommend comparing the composition of stones observed in patients with ADPKD compared to patients without ADPKD. New medications used in ADPKD, such as vasopressin receptor 2 antagonists, may alter the urine composition and change the types of renal stones that these patients get. Future ADPKD-specific risk factors, such as mutation type, of kidney stone studies may help identify patients at high risk for stones and provide further insight into the pathophysiology of kidney stones in patients with ADPKD.

Our study is the first to systematically review and summarize the prevalence of stones in patients with ADPKD. Unlike past narrative reviews, we used a comprehensive search strategy across 6 different databases, and 2 reviewers independently screened all citations retrieved from the search strategy to identify all relevant articles. We also conducted this review in accordance with an a priori protocol and published guidelines for systematic reviews. Two independent reviewers abstracted the data to minimize human error and bias.

There are some limitations inherent in our systematic review. First, we only included original journal articles and conference proceedings published in English. However, studies show that language-restricted meta-analysis does not lead to biased estimates.[65] Second, the definitions for ADPKD and stones varied across studies; therefore, the pooled estimate must be interpreted with caution.

Conclusions

Our systematic review highlights that there is poor consensus on the prevalence of stones in patients with ADPKD. A more methodologically robust study is needed to better characterize and understand the magnitude of risk of stones and stone intervention in patients with ADPKD. This information can help patients with ADPKD and physicians with their prognostication and might inform the use of interventions to reduce the risk of stones.

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Ethics Approval and Consent to Participate

Since this systematic review and meta-analysis did not involve human investigation, ethics approval was not required. Consent to participate was not required as our study did not rely on human subjects and reviewed the existing literature.

Consent for Publication

All authors have consented for publication.

Availability of Data and Materials

All data is presented in the original article.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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