BMJ Open

Does chronic hyperglycaemia increase the risk of kidney stone disease? results from a systematic review and meta-analysis

Robert Geraghty ,[1] Abdihakim Abdi,[2] Bhaskar Somani,[3] Paul Cook,[4] Paul Roderick[5]

To cite: Geraghty R, Abdi A, Somani B, *et al*. Does chronic hyperglycaemia increase the risk of kidney stone disease? results from a systematic review and meta-analysis. *BMJ Open* 2020;**10**:e032094. doi:10.1136/bmjopen-2019-032094

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-032094).

Received 07 June 2019
Revised 02 December 2019
Accepted 19 December 2019

[1]Urology, Freeman Hospital, Newcastle upon Tyne, UK
[2]University of Southampton, Southampton, UK
[3]Urology, University Hospital Southampton NHS Trust, Southampton, UK
[4]Clinical Biochemistry, University Hospital Southampton, Southampton, UK
[5]Health Care Research Unit, University of Southampton, Southampton, UK

Correspondence to
Dr Robert Geraghty;
rob.geraghty@newcastle.ac.uk

ABSTRACT

Design Systematic review and meta-analysis of observational studies was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for studies reporting on diabetes mellitus (DM) or metabolic syndrome (MetS) and kidney stone disease (KSD).

Objective To examine the association between chronic hyperglycaemia, in the form of DM and impaired glucose tolerance (IGT) in the context of MetS and KSD.

Setting Population-based observational studies. Databases searched: Ovid MEDLINE without revisions (1996 to June 2018), Cochrane Library (2018), CINAHL (1990 to June 2018), ClinicalTrials.gov, Google Scholar and individual journals including the Journal of Urology, European Urology and Kidney International.

Participants Patients with and without chronic hyperglycaemic states (DM and MetS).

Main outcome measures English language articles from January 2001 to June 2018 reporting on observational studies. Exclusions: No comparator group or fewer than 100 patients. Unadjusted values were used for meta-analysis, with further meta-regression presented as adjusted values. Bias was assessed using Newcastle-Ottawa scale.

Results 2340 articles were screened with 13 studies included for meta-analysis, 7 DM (three cohort) and 6 MetS. Five of the MetS studies provided data on IGT alone. These included: DM, n=28 329; MetS, n=31 767; IGT, n=12 770. Controls: DM, n=5 89 791; MetS, n=1 78 050; IGT, n=2 93 852 patients. Adjusted risk for DM cohort studies, RR=1.23 (0.94 to 1.51) (p<0.001). Adjusted ORs for: DM cross-sectional/case-control studies, OR=1.32 (1.21 to 1.43) (p<0.001); IGT, OR=1.26 (0.92 to 1.58) (p<0.0001) and MetS, OR=1.35 (1.16 to 1.54) (p<0.0001). There was no significant difference between IGT and DM (cross-sectional/case-control), nor IGT and MetS. There was a moderate risk of publication bias. Statistical heterogeneity remained significant in adjusted DM cohort values and adjusted IGT (cross-sectional/case-control), but non-signficant for adjusted DM (cross-sectional/case-control).

Conclusion Chronic hyperglycaemia increases the risk of developing kidney stone disease. In the context of the diabetes pandemic, this will increase the burden of stone related morbidity and mortality.

Strengths and limitations of this study

- ► Largest systematic review and meta-analysis examining the risk of chronic hyperglycaemic states and kidney stone disease (KSD), with bias analysis.
- ► Meta-analysis of cohort studies examining diabetes mellitus (DM) demonstrates an increased risk of KSD of 1.23 (0.94 to 1.51) (p<0.001) over the general population.
- ► There was a moderate risk of publication bias.
- ► Statistical heterogeneity remained significant in adjusted DM cohort values and adjusted impaired glucose tolerance.
- ► No data on stone type.

PROSPERO registration number CRD42018093382

INTRODUCTION

Kidney stone disease (KSD) is a painful and costly condition[1] where precipitates of normal urinary solutes aggregate to form stones of varying sizes and compositions.[2] Incidence of acute urolithiasis is rising worldwide,[3–6] with corresponding rises in surgical treatment rates[7] and morbidity[8 9] although mortality has declined.[8 10] Five-year recurrence rates have been reported as high as 50%.[11] Long-term problems associated with recurrent KSD are decreased quality of life, missed work days,[12] disabling pain, need for repeated operations, complications including infection and acute kidney injury,[13 14] as well as long-term increased risk of developing chronic kidney disease.[15]

Patients with diabetes mellitus (DM)[16] and metabolic syndrome (MetS)[17] have been identified as carrying a higher risk of developing KSD. The global prevalence of both conditions has risen to pandemic levels[9 18] seemingly in parallel with KSD.[19] There is overlap between the two conditions, with impaired glucose tolerance (IGT), or pre-diabetes

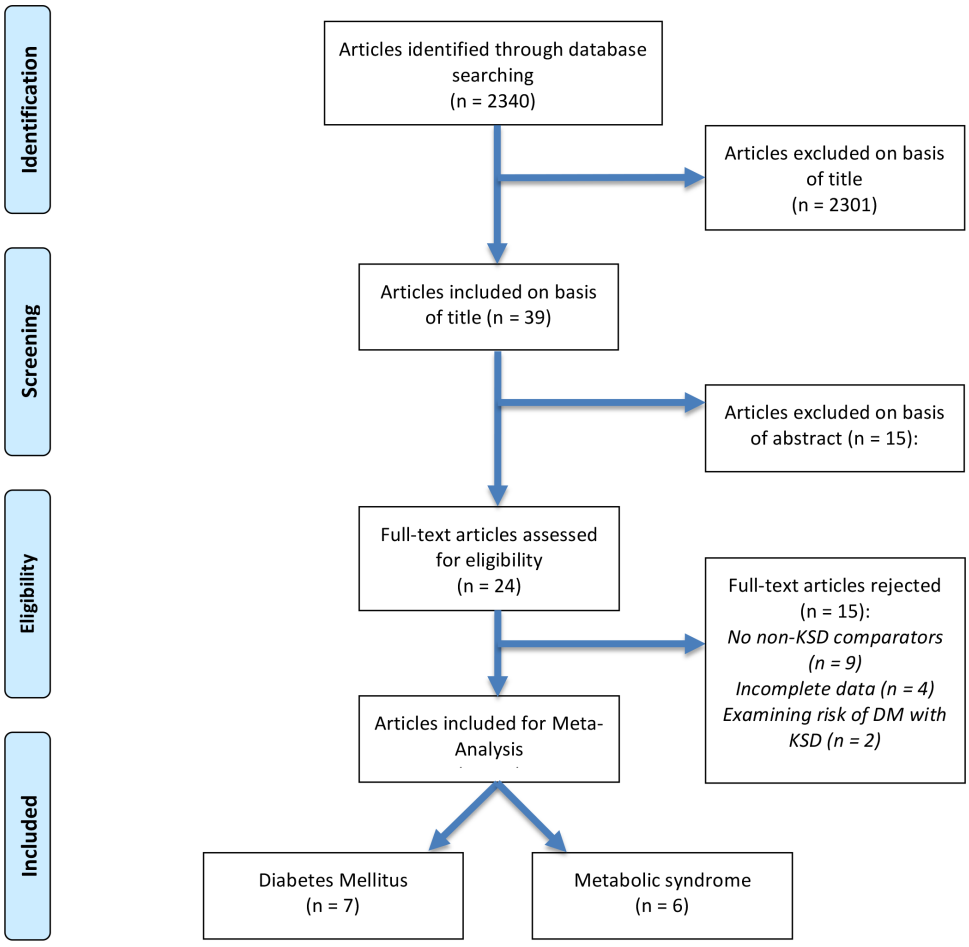

Figure 1 PreferredReporting Items for Systematic Reviews and Meta-Analyses flow diagram for article selection. DM, diabetes mellitus; KSD, kidney stone disease.

being one of the five components of the 'metabolic syndrome'.[20] Although the pathophysiology with respect to KSD is yet to be definitively described, patients with either MetS or DM have been shown to have increased urinary acidification and produce more uric acid stones than controls. Notably, with rising body mass index (BMI) in both diabetic and non-diabetic patients, the incidence of uric acid stones rises, while calcium oxalate stones fall.[21 22]

Previous systematic reviews have examined either DM[16] or MetS[17 23] in isolation. These studies performed either no meta-analysis,[17] or else their heterogeneity/sensitivity analyses were limited.[16 23] Given the overlap between the two conditions we aimed to perform a systematic review and meta-analysis of the existing literature on both DM and MetS with complete sensitivity, bias and heterogeneity analyses.

EVIDENCE ACQUISITION

Search strategy and study selection

Population – Chronic hyperglycaemics (diabetes mellitus, impaired glucose tolerance in the context of metabolic syndrome) and those with metabolic syndrome.

Comparator – Those without hyperglycaemia (DM/IGT) or metabolic syndrome, respectively.

Outcome – KSD – all compositions.

Study design – Systematic review and meta-analysis of published observational studies (cohort, case-control and cross-sectional).

Inclusion criteria

1. All articles written in the English language.
2. Adults (>18 years).
3. All articles reporting on risk of developing kidney stone disease in diabetes mellitus (type 1 and type 2) in comparison to general population.
4. All articles reporting on risk of developing kidney stone disease in patients with metabolic syndrome in comparison to general population.
5. Risk in risk ratio (RR), HR, OR or prevalence ratio (PR) with 95% CIs.

Exclusion criteria

1. Older studies using the same data as a more recent study – longest follow-up used.
2. Studies exclusively using patients with kidney stone disease – unable to calculate risk.

Table 1 Study demographics

DM	Study	Study type	Country	Sample	Controls	Metabolic syndrome definition	Diabetes mellitus ascertainment	KSD ascertainment	M:F (%)	Mean age
Cohort	Taylor *et al*[27]	Prospective cohort	USA	NHS I (1980–2000: 20-year f/u)+II (1991–2001: 20-year f/u) (female nurses), HPFS participants (1986–2000: 14-year f/u) (Health Professionals Follow-up Study - all male) – 'diabetics', those with known KSD excluded	NHS I+II, HPFS participants - non-diabetics	N/A	Biennial health questionnaire with supplementary questionnaire on symptoms, diagnostic tests and treatment - DM diagnosis corroborated by medical record review. T1 (≥2 episodes of ketonuria/ ketoacidosis) and T2 included.	Biennial health questionnaire and medical record review for corroboration - incident stone with pain/haematuria	NHS: Entirely female HPFS: Entirely male	NHS I: 48.6; NHS II: 37.6; HPFS: 60.9
	Chen *et al*[28]	Retrospective cohort	Taiwan	National Health Insurance system database - prospectively maintained - patients with DM (T1+T2) (2000–2007: 7 years f/u). Known KSD excluded at start.	Without DM and excluding patients who developed DM in follow-up period	N/A	At least three outpatient visits for DM from 2000 to 2002 with corresponding health insurance records; ICD-9-CM 250; A-code A181. T1+T2 included	Health insurance records; ICD9-CM 592; A-code A352, excluding bladder stones. Only new stones included	50:50	N/A
	Akoudad *et al*[29]	Prospective cohort	USA	ARIC study participants: Visit 3 (1993–1995) to 2005 with incident KSD (patient reported physician diagnosis of KSD at baseline excluded). F/U – mean 10.8 years.	Without incident KSD	N/A	Receiving diabetic medication, OGTT with FPG>110 mg/dL, FPG>126 mg/dL, patient reported physician diagnosis. Unclear T1/T2 differentiation.	ICD-9 codes: 592, 592.0, 592.1, 592.9, 274.11 on discharge summaries	42:58	60.0±5.7 (calculated)
CaCo	Lieske *et al*[31]	Case-control	USA	Rochester, Olmsted County, Minnesota residents with electronically documented KSD - random sample of results of electronic medical record search of Mayo Clinic and Olmsted Clinic databases (original search n>7000)	Patients without electronic documentation of KSD, matched for age, sex and calendar year of stone	N/A	Electronic medical records using codes: ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0 (gestational DM), 648.8, 790.2, 791.5, 962.3. No clear differentiation between T1+T2.	Electronic medical records using codes: ICD-9-CM 592, 594, 275.11 with case review	62: 38	45.0±18
	Davarci *et al*[32]	Case-control	Turkey	Hospital outpatients with urolithiasis attending single centre between 2008–2009, T1DM excluded	Without urolithiasis	N/A	Receiving diabetic medication, OGTT with FPG>110 mg/dL, FPG>126 mg/dL. T1 excluded	USS, AXR, patient reported	47.5:52.5	49.0±10
XS	Meydan *et al*[30]	Cross-sectional with matching	Turkey	Diabetic hospital attendees, unclear if inpatients or outpatients	Non-diabetic hospital attendees, unclear if inpatients or outpatients - matched for age	N/A	Unclear how defined. Included both T1 and T2.	History of KSD, XR/USS – if any positive confirmed with IVU	Cases: 30:70 Controls: 21:79	Cases: 57±10 Controls: 56±9
	Taylor *et al*[27]	Cross-sectional	USA	Baseline characteristics: NHS I (1980) + II (1991) (female nurses), HFPS participants (1986) (male health professionals) - diabetics	Baseline characteristics: NHS I+II, HFPS participants - non-diabetics	N/A	Biennial health questionnaire with supplementary questionnaire on symptoms, diagnostic tests and treatment - DM diagnosis corroborated by medical record review	Biennial health questionnaire and medical record review for corroboration - kidney stone history	22:78	NHS I: 48.6; NHS II: 37.6; HFPS: 60.9

Continued

Table 1 Continued

DM	Study	Study type	Country	Sample	Controls	Metabolic syndrome definition	Diabetes mellitus ascertainment	KSD ascertainment	M:F (%)	Mean age
	Akoudad *et al*[29]	Cross-sectional	USA	ARIC study participants: Visit 3 (1993–1995), patient reported physician diagnosis of KSD	Without KSD	N/A	Receiving diabetic medication, OGTT with FPG>110 mg/dL, FPG>126 mg/dL, patient reported physician diagnosis	Patient reported physician diagnosis	44:56 (calculated)	60.0±5.7 (calculated)
	Weinberg *et al*[33]	Cross-sectional	USA	NHANES participants 2007–2010 with T2DM	Without DM	N/A	Self- reported history of DM, use of glucose-lowering medications (insulin or oral hypoglycemics), and self-reported diabetic comorbidities. T2 only.	Patient reported answer to: 'have you ever had a kidney stone?'	N/A	N/A
MetS								**IGT/DM ascertainment**		
XS	Rendina *et al*[34]	Cross-sectional	Italy	Single centre inpatients between 2004–2005 - those with MetS or IGT. Exclusions: acute/ chronic renal failure, abnormal renal anatomy, hyperthyroidism, hyperparathyroidism, treatment for osteoporosis, metabolic bone disorders, neoplasia	Those without MetS or IGT	American Heart Association; National Heart, Lung, and Blood Institute: three or more of: (1) Waist circumference >102 cm in men, >88 cm in women. (2) fasting serum triglycerides >1.7 mmol/L or treatment. (3) fasting serum HDL <1.03 mmol/L in men,<1.30 mmol/L in women or treatment. (4) systolic >130 mm Hg or diastolic >85 mm Hg or treatment. (5) fasting serum glucose >5.6 mmol/L or treatment	Fasting serum glucose >5.6 mmol/L or treatment	Questionnaire re: symptoms of renal colic and ultrasonography	49:51	63.8±15.8
	West *et al*[35]	Cross-sectional	USA	NHANES III participants (1988–1994) - those with metabolic syndrome/impaired glucose tolerance	two or fewer MetS traits/no MetS traits	American Heart Association; National Heart, Lung, and Blood Institute as per Rendina *et al*	Fasting serum glucose >5.6 mmol/L or treatment	Self report of physician diagnosis	48:52	58.8±17.1
	Jeong *et al*[37]	Cross-sectional	South Korea	Single centre - health promotion patients - those with IGT or MetS	Unclear - ?those without MetS or IGT	NCEP ATP III; American Heart Association; National Heart, Lung, and Blood Institute - three or more of: Systolic >130 mm Hg, diastolic >85 mm Hg, random blood glucose >110 mg/dL, random serum triglycerides >150 mg/dL, random serum HDL <40 mg/dL in men or <50 mg/dL in women, obese range waist circumference	Fasting blood glucose >110 mg/dL	Radiological records (ultrasound and CT)	60:40	50.0±10.4

Continued

Table 1 Continued

DM	Study	Study type	Country	Sample	Controls	Metabolic syndrome definition	Diabetes mellitus ascertainment	KSD ascertainment	M:F (%)	Mean age
	Jung *et al*[36]	Cross-sectional	South Korea	Single Centre - patients recruited to health promotion centre to undergo metabolic + KSD screen - study group - those with impaired glucose tolerance and those with metabolic syndrome	Unclear - ?patients without impaired glucose tolerance or metabolic syndrome	NCEP ATP III - three or more of: Systolic >130 mm Hg, diastolic >85 mm Hg, random blood glucose >110 mg/dL, random serum triglycerides >150 mg/dL, random serum HDL <40 mg/dL in men o r<50 mg/dL in women, obese range waist circumference	Fasting blood glucose >110 mg/dL	Ultrasonography	55:45	44.9±11.5
	Kim *et al*[38]	Cross-sectional	South Korea	Single centre - health promotion patients - those with IGT or MetS	Unclear - ?those without MetS or IGT	NCEP ATP III; American Heart Association; National Heart, Lung, and Blood Institute - three or more of: Systolic >130 mm Hg, diastolic >85 mm Hg, random blood glucose >110 mg/dL, random serum triglycerides >150 mg/dL, random serum HDL <40 mg/dL in men or <50 mg/dL in women	Fasting blood glucose >110 mg/dL	Ultrasonography	58:42	42.3±8.4
	Lee *et al*[39]	Cross-sectional	Taiwan	Single centre - men undergoing free health screening - those with MetS/DM	Unclear - ?those without MetS or DM	Three of the five following criteria: patients were defined as having MetS by the presence of at least three of five of the following criteria: waist circumference (WC) 90 cm, high-density lipoprotein (HDL) cholesterol 540 mg/dL, triglyceride (TG) 150 mg/ dL, blood pressure (BP) 130/85 mm Hg or diagnosed hypertension on therapy and fasting blood glucose (FBG) 4100 mg/dL or have a diagnosis of T2DM.	T2DM - fasting BGL >126 mg/dL	(a) Characteristic clinical findings diagnosed by a physician with available medical records; (b) evidence of kidney stones from ultrasonography judged by an investigator (urologist); (c) operative history of stones removal from kidney.	100:0	55.6±4.6

CaCo = Case Control; XS = Cross-Sectional; OGTT = Oral Glucose Tolerance Test; FPG = Fasting Plasma Glucose; AXR = Abdominal X-Ray; IVU = Intravenous Urogram; NCEP ATP III = National Cholesterol Education Programme Adult Treatment Programme 3rd Iteration.
BGL, blood glucose level; DM, diabetes mellitus; f/u, follow-up; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IGT, impaired glucose tolerance; KSD, kidney stone disease; MetS, metabolic syndrome; N/A, not available; NHANES, National Health and Nutrition Examination Survey; NHS, National Health Service; T1, type 1 diabetes mellitus; T2, type 2 diabetes mellitus.

3. Studies with less than 100 patients – likely to be underpowered.

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24] The search strategy was conducted to find relevant studies from Ovid MEDLINE without revisions (1996 to June 2018), Cochrane Library (2018), CINAHL (1990 to June 2018), ClinicalTrials.gov, Google Scholar and individual journals including the Journal of Urology, European Urology and Kidney International. The review was registered prospectively with PROSPERO.

Terms used included: 'Diabetes', 'Diabetes mellitus', 'metabolic syndrome', 'urolithiasis', 'nephrolithiasis', 'kidney', 'uret*', 'ston*', 'calcul*'. Boolean operators (AND, OR) were used to refine the search.

The search was limited to English language articles between January 2001 and June 2018. Only published data were used.

Two reviewers (RG and AA) identified all studies. All studies that appeared to fit the inclusion criteria were included for full review. Each reviewer independently selected studies for inclusion in the review (see figure 1). If there was disagreement, PR and BS made final decision on inclusion.

Data extraction and assessment of quality

The following variables were extracted from each study: first author, year of publication, type of study, sample size, age, country, male:female ratio, ascertainment of DM/IGT/MetS/KSD, type of DM, number of patient reporting/presenting with stone disease for diabetes mellitus, metabolic syndrome and specifically IGT in the context of MetS (given the common mechanism – hyperglycaemia and insulin resistance).

Risk of KSD in RR, HR, OR or PR with 95% CIs was also extracted. HR and RR, and OR and PR, were considered the same and are presented as RR and OR, respectively. Unadjusted and adjusted risk values were extracted from the studies. Adjustment factors were recorded. If adjusted values were missing then the study was removed from the adjusted meta-analysis.

Cross-sectional and case-control studies were pooled as there were no case-control studies for MetS, and two case-control studies for DM, only one of which gave adjusted values.

Data were collated using Microsoft Excel (V.12.2.4). Level of evidence was assessed and study bias was analysed using the Newcastle-Ottawa bias assessment tool.[25]

Data sharing

Data has been uploaded to PROSPERO or can be obtained, on reasonable request, by emailing the corresponding author.

Statistical methods

Risk is presented with a 95% CI as RR for cohort studies and OR for case-control (CaCo) and cross-sectional (XS) studies. Statistical heterogeneity was tested for using I^2, Tau^2 and Cochran's Q. P values <0.05 were considered statistically significant, I^2 values were interpreted according to chapter 9.5.2 of the Cochrane Handbook. Heterogeneity was also tested with 'leave-one-out' analyses. Publication bias was assessed with Egger's test and 'trim and fill' analysis. Meta-regression analysis was performed, adjusting for age and gender. Student's t-statistic is used for df.

Statistical analyses and figures were generated in R (R foundation for statistical computing, Vienna, Austria) with the metafor package.[26]

Evidence synthesis

Fifteen studies were included in the systematic review from an initial search total of 2340 (see figure 1). Articles excluded on the basis of title were 2301, 15 on the basis of abstract and 15 on reading the full text. This left 13 studies, 7 examining DM and 6 examining IGT in the context of MetS. Inter-rater reliability as assessed by Cohen's kappa was 0.95.

DEMOGRAPHICS OF INCLUDED STUDIES

Diabetes mellitus

Seven studies were included examining DM.[27–33] Three were cohort,[27–29] three were case-control[30–32] and three were cross-sectional.[27 29 33] Taylor *et al*[27] and Akoudad *et al*[29] performed both cross-sectional and prospective cohort studies with their cohorts. The studies were conducted in Turkey, Taiwan and USA. They sampled varying populations, from hospital inpatients to national patient data. Patients with type 1 DM were included in all but one of the studies[32] (see table 1).

The male to female ratio and mean age for each study is detailed in table 1. DM and KSD ascertainment ranged from the patient reporting the diagnosis to International Classification of Diseases (ICD) codes in medical records.

Overall there were 618 120 patients, of which 28 329 (4.6%) had DM. These figures include 17 577 patients with DM in cohort studies with 348 036 controls (see table 2) and 10 752 patients with DM in case-control or cross-sectional studies with 241 755 controls (see table 3). In the cohort studies, 1312 (7.5%) of patients with DM developed KSD compared with 11 516 (3.3%) of controls. In the case-control and cross-sectional studies, 1097 (10.2%) of diabetics had KSD compared with 11 985 (5.0%) of controls. Study reported risk is detailed in tables 2 and 3.

Metabolic syndrome

There were six studies[34–39] examining metabolic syndrome, of which five provided data on chronic hyperglycaemia (IGT/DM).[34–37 39] All of these studies were cross-sectional. These took place in Italy, South Korea, Taiwan and USA. The samples ranged from hospital inpatients to representative population-based studies, which were representative of target populations (see table 1).

Table 2 DM cohort studies

Cohort	Study	Baseline DM, n	Controls, n	With DM, person-years	Without DM, person-years	DM with KSD, n (% of DM)	Control with KSD, n (% of no DM)	Study reported unadjusted risk (95% CI)	Study reported adjusted risk (95% CI)	Adjusted for
DM	Taylor *et al*[27] *2005: NHS I (younger female)*	1409	93 758	65 566	1 371 080	109 (7.7%)	1578 (1.7%)	RR 1.45 (1.20 to 1.77)	RR 1.29 (1.05 to 1.58)	Age, BMI, thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor *et al*[27] *2005: NHS II (older female)*	891	101 877	12 291	824 076	40 (4.5%)	1491 (1.5%)	RR 1.86 (1.36 to 2.56)	RR 1.60 (1.16 to 2.21)	Age, BMI, thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor *et al*[27] *2005: HPFS (male)*	1391	46 062	21 676	450 984	44 (3.2%)	1426 (3.1%)	RR 0.76 (1.56 to 1.03)	RR 0.81 (0.59 to 1.09)	Age, BMI, thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Chen *et al*[28]	12 257	96 781	75 975	607 842	1096 (8.9%)	6950 (7.2%)	HR 1.22 (1.15 to 1.30)	HR 1.18 (1.10 to 1.27)	Age, sex, occupation, urbanisation, income and UTIs
	Akoudad *et al*[29]	1629	9558	N/A	N/A	N/A	N/A	N/A	HR 1.98 (1.20 to 3.28)	Age, sex, race, waist circumference, hypertension, triglyceride level, uric acid, gallstones
	Total	17 577	348 036	253 365	3 253 982	**1289 (8.1%)**	**11 445 (3.4%)**			

HPFS = Healthcare Professionals Follow-up Study (all male)
BMI, body mass index; DM, diabetes mellitus; KSD, kidney stone disease; N/A, not available; NHS, National Health Service; RR, risk ratio; UTIs, urinary tract infections.

Table 3 DM and IGT case-control and cross-sectional studies

DM	Study	Study population (DM), n	Controls, n	DM with KSD, n (% of DM)	Control with KSD, n (% of No DM)	Study reported unadjusted risk (95% CI)	Study reported adjusted risk (95% CI)	Adjusted for
CaCo	Lieske *et al*[31]	3561	3561	335 (9.4%)	268 (7.5%)	OR 1.29 (1.09 to 1.53)	OR 1.22 (1.03 to 1.46)	Age, sex, year of diagnosis, DM, hypertension and obesity
	Davarci *et al*[32]	23	177	14 (17.5%)	66 (37.3%)	RR 1.63 (1.12 to 2.39)	N/A	N/A
XS	Meydan *et al*[30]	321	115	84 (26.2%)	14 (12.2%)	*OR 2.5 (1.39 to 4.71) (calculated)*	N/A	N/A
	Taylor *et al*[27] *2005: NHS I (younger female)*	1473	74266	64 (4.3%)	2029 (2.7%)	RR 1.55 (1.20 to 1.99)	RR 1.38 (1.06 to 1.79)	Age, BMI, thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor *et al*[27] *2005: NHS II (older female)*	949	94485	58 (6.1%)	3093 (3.3%)	RR 1.84 (1.41 to 2.41)	RR 1.67 (1.28 to 2.20)	Age, BMI, thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor *et al*[27] *2005: HFPS (male)*	1568	47737	177 (11.3%)	4002 (8.4%)	RR 1.21 (1.03 to 1.42)	RR 1.31 (1.11 to 1.54)	Age, BMI, thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Akoudad *et al*[29]	1812	10349	183 (18.8%)	1629 (14.6%)	N/A	PR 1.27 (1.08 to 1.49)	Age, sex, race, region, waist circumference, triglycerides, hypertension, uric acid, gallstones
	Weinberg *et al*[33]	*1045 (estimated)*	*11065 (estimated)*	*182 (17.1%) (estimated)*	*884 (8.0%) (estimated)*	OR 2.44 (1.84 to 3.25)	OR 1.76 (1.33 to 2.32)	Age, sex, race, smoking history, BMI
	Sub Total	10752	241755	**1097 (10.2%)**	**11985 (5.0%)**			
IGT in context of MetS		***Impaired glucose tolerance (IGT) only n (% of total)***		***IGT with KSD, n (% of IGT)***				
XS	Rendina *et al*[34]	317 (14.9%)	*1815 (calculated estimate)*	43 (13.6%)	*177 (8.7%) (calculated estimate)*	N/A	Male: OR 1.1 (0.5 to 2.4) Female: OR 1.1 (0.3 to 1.8)	Age, waist circumference, high serum triglycerides, low serum HDL, hypertension
	West *et al*[35]	1260 (8.5%)	*7268 (calculated estimate)*	17 (1.3%)	71 (1.0%)	*OR 1.39 (0.81 to 2.36) (calculated)*	OR 1.27 (0.77 to 2.10) (One metabolic syndrome component)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use

Continued

Table 3 Continued

DM	Study	Study population (DM), n	Controls, n	DM with KSD, n (% of DM)	Control with KSD, n (% of No DM)	Study reported unadjusted risk (95% CI)	Study reported adjusted risk (95% CI)	Adjusted for
	Jeong *et al*[37]	6929 (19.9%) (Quintile 5 -≥104 mg/dL)	13 700 (Quintile 1 -≤85 mg/dL)	211 (3.0%)	240 (1.8%)	OR 1.57 (1.26 to 1.95)	OR 1.09 (0.87 to 1.37)	Age, sex, metabolic syndrome components, MetS status
	Jung *et al*[36]	4192 (10.3%)	*28 692 (calculated estimate)*	102 (2.4%)	*450 (1.6%) (calculated estimate)*	1.26 (1.12 to 1.42)	OR 1.30 (1.03 to 1.64)	Age, GFR, serum urate, phosphorous and calcium
	Kim *et al*[38]	N/A	N/A	N/A	N/A	Male: OR 1.18 (1.10 to 1.26) Female: OR 1.26 (1.12 to 1.42)	Male: OR 1.03 (0.97 to 1.11) Female: OR 1.02 (0.90 to 1.16)	Age, serum creatinine, serum urate, past medical history of KSD
	Lee *et al*[39]	72 (11.3%) (DM)	622	14 (19.4%)	71 (11.7%)	*OR 1.87 (0.99 to 3.53) (calculated)*	N/A	N/A
	Sub Total	**12 770 (6.1%)**	**52 097**	**387 (3.2%)**	**1009 (1.9%)**			
	Total	23 522	293 852	**1484 (6.3%)**	**12 994 (4.4%)**			

BMI, body mass index; DM, diabetes mellitus; GFR, glomerular filtration rate; HDL, high-density lipoprotein; KSD, kidney stone disease; MetS, metabolic syndrome; N/A, not available; NHS, National Health Service; PR, prevalence ratio; RR, risk ratio.

The male to female ratio and mean age for each study is detailed in table 1. MetS and KSD ascertainment ranged from the patient-reported diagnosis to ICD codes in medical records.

Overall there were 209 817 patients, of whom 31 767 (17.8%) had MetS, 12 770 (6.1%) had IGT only (see table 4); 2258 (7.1%) of those with MetS had KSD, compared with 7593 (4.3%) of controls and 387 (3.2%) of those with IGT had KSD, compared with 1009 (1.9%) of controls (see table 3). Unfortunately control population had to be calculated from the OR for some of the studies,[34–36] therefore the figures for IGT are estimates. Study reported risk is detailed in tables 3 and 4.

Meta-analysis

Tests for overall unadjusted effect in those with DM demonstrated significantly higher risk of KSD (RR=1.66 (95% CI: 1.27 to 2.18, p<0.001). Subgroup analyses by study type demonstrated significantly higher risk of KSD in patients with DM in cohort studies in both unadjusted (1.36, 95% CI: 1.11 to 1.60, p<0.001) (see figure 1) and adjusted risk (RR=1.23, 95% CI: 0.94 to 1.51, p<0.001) (see figure 2). Significantly increased risk was also demonstrated in cross-sectional/case-control studies in both unadjusted (OR=1.49, 95% CI: 1.09 to 1.89, p<0.0001) and adjusted risk (OR=1.32, 95% CI: 1.21 to 1.43, p<0.001) (see figure 3). IGT in the context of MetS demonstrated significantly increased risk in both unadjusted (OR=1.25, 95% CI: 1.16 to 1.54, p<0.0001) and adjusted risk (OR=1.26, 95% CI: 0.94 to 1.58) [see figure 3]. Combining DM case-control and cross-sectional studies with IGT demonstrated significantly increased risk in both unadjusted (OR=1.38, 95% CI: 1.18 to 1.59, p<0.0001) and adjusted risk (OR=1.32, 95% CI: 1.17 to 1.49, p<0.0001).

Cross-sectional studies examining MetS also demonstrated significantly increased risk of KSD in both unadjusted (OR=1.74, 95% CI: 1.45 to 2.04, p<0.0001) and adjusted (OR=1.35, 95% CI: 1.16 to 1.54, p<0.0001) (see figure 4) values.

Heterogeneity and sensitivity analysis

There was borderline significant statistical heterogeneity between DM cohort studies in unadjusted risk (Tau^2=0.042, Cochran's Q=9.50, p=0.05, I^2=62.3%), however there was significant heterogeneity when risk was adjusted (Tau^2=0.070, Cochran's Q=13.70, p=0.008, I^2=80.2%).

There was significant statistical heterogeneity between DM case-control/cross-sectional studies in unadjusted risk (Tau^2=0.258, Cochran's Q=104.67, p<0.0001, I^2=93.2%), however this was non-significant for adjusted risk (Tau^2=0.00, Cochran's Q=6.46, p=0.26, I^2=0.0%).

There was non-significant statistical heterogeneity between IGT cross-sectional studies for unadjusted risk (Tau^2=0.003, Cochran's Q=7.18, p=0.30, I^2=21.6%), however this was significant for adjusted risk (Tau^2=0.086, Cochran's Q=62.21, p<0.0001, I^2=92.7%).

Table 4 MetS cross-sectional studies

MetS	Study	Total participants, n	Metabolic syndrome, n (% of total)	Controls, n	Metabolic syndrome with KSD, n (% of MetS)	Control with KSD, n (%)	Study reported unadjusted risk (95% CI)	Study reported adjusted risk (95% CI)	Adjusted for
XS	Rendina *et al*[34]	2132	725 (34.0%)	1407	112 (15.4%)	108 (7.7%)	OR 2.2 (1.7 to 2.9)	OR 2.0 (1.3 to 3.0)	Age, sex, history of KSD
	West *et al*[35]	14 870	4952 (33.3%)	9921	628 (12.7%)	363 (3.7%)	OR 2.13 (1.74 to 2.62)	OR 1.52 (1.22 to 1.89)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jeong *et al*[37]	34 895	4602* (13.2%)	30 293	177 (3.8%)	662 (2.2%)	OR 1.71 (1.45 to 2.03)	1.25 (1.03 to 1.50)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jung *et al*[36]	40 687	7803 (19.2%)	32 884	166 (2.1%)	443 (1.3%)	N/A	OR 1.36 (1.13 to 1.64)	Age, GFR, serum urate, phosphorous and calcium
	Kim *et al*[38]	116 536	13 416 (11.5%)	103 120	1129 (8.4%)	5978 (5.8%)	OR 1.33 (1.24 to 1.44)	OR 1.11 (1.03 to 1.20)	Age, serum creatinine, serum urate, past medical history of KSD
	Lee *et al*[39]	694	269 (42.1%)	425	46 (17.1%)	39 (9.2%)	N/A	OR 1.83 (1.14 to 2.93)	Age
	Total	209 814	**31 767 (15.1%)**	178 050	**2258 (7.1%)**	**7593 (4.3%)**			

*Discrepancy between text and table.
DM, diabetes mellitus; GFR, glomerular filtration rate; KSD, kidney stone disease; MetS, metabolic syndrome; N/A, not available.

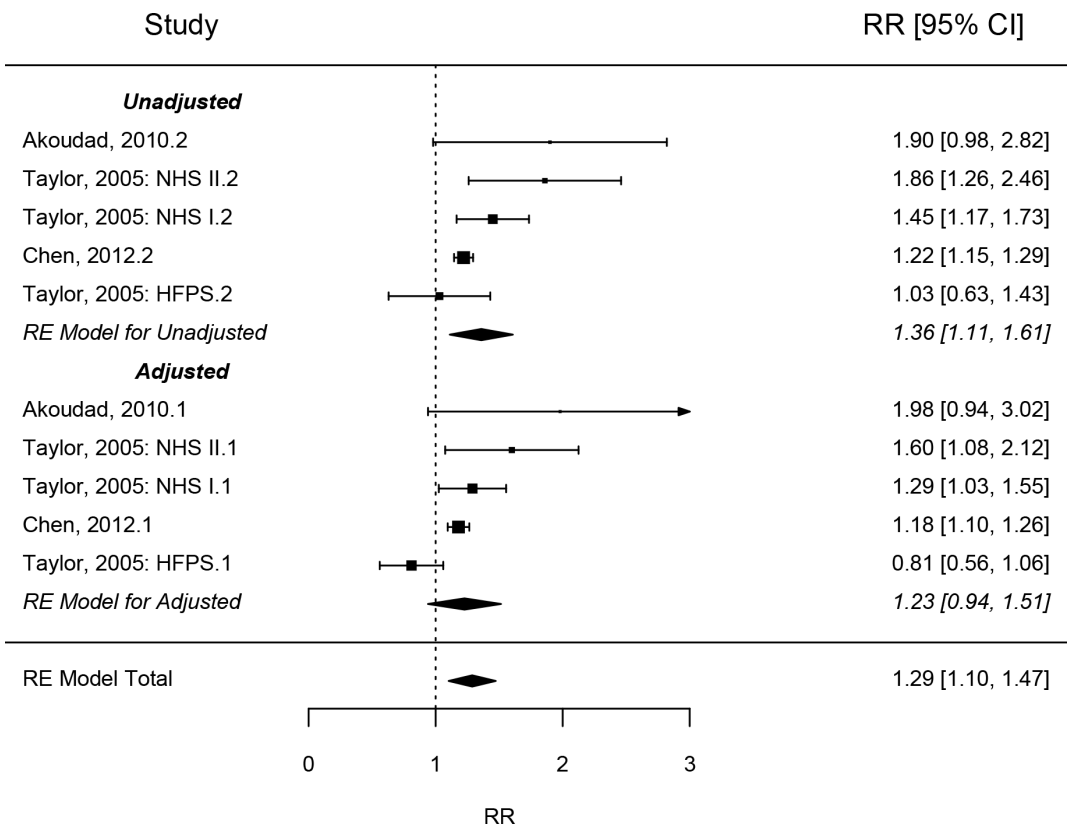

Figure 2 Forest plot analysis – diabetes mellitus cohort. NHS, NationalHealth Service; RR, risk ratio.

Combination of cross-sectional IGT studies with cross-sectional/case-control DM studies demonstrated significant heterogeneity for both unadjusted (Tau^2=0.11, Cochran's Q=160.10, p<0.0001, I^2=91.2%) and adjusted risk (Tau^2=0.044, Cochran's Q=75.4, p<0.001, I^2=81.2%). However, there was no statistical difference between subgroups for either unadjusted (I^2=0%, p=0.54) or adjusted risk (I^2=0%, p=0.60).

There was significant statistical heterogeneity between MetS cross-sectional studies for both unadjusted risk (Tau^2=0.092, Cochran's Q=26.08, p<0.0001, I^2=79.5%), and adjusted risk (Tau^2=0.034, Cochran's Q=22.71, p<0.001, I^2=72.7%).

Publication bias and quality of evidence

Leave-one-out analysis did not identify any studies that significantly changed the RR or OR for DM with and without IGT inclusion, nor for MetS.

Trim and fill analysis did no demonstrate any missing studies for DM without IGT (SE=2.21). Inclusion of IGT with DM demonstrated six missing studies (SE=2.75) (see figure 5). The analysis demonstrated lack of negative studies. Trim and fill analysis of MetS demonstrated two missing studies (SE=1.78) (see figure 6), both negative.

Egger's regression demonstrated no significant results for: DM without IGT (z=0.81, p=0.42), DM with IGT (z=0.85, p=0.40) or MetS (z=0.15, p=0.88).

Overall there was a moderate risk of bias. All but two studies[27 28] had scores greater than 7 on examination with the Newcastle-Ottawa quality assessment scale (see tables 5–7). Broadly taking in all studies there were no sample size calculations or demonstrable levels of response. None of the cohort studies provided Consolidated Standards of Reporting Trials diagrams nor did they provide loss to follow-up data in the text.

DISCUSSION

In this review and meta-analysis DM carried a significantly increased risk of developing KSD in cohort studies with a low risk of bias. Cross-sectional and case-control studies also demonstrate significantly increased likelihood of having KSD in those who have DM with a moderate risk of bias. IGT in the context of MetS carries a similar likelihood to DM in cross-sectional studies.

MetS carries a similar likelihood to DM and IGT in the context of MetS, with little difference between each in terms of adjusted ORs, again with a moderate risk of bias.

This is the first systematic review and meta-analysis to examine DM and MetS together. The results are highly significant although are limited by heterogeneity, despite meta-regression analysis. The results for DM are likely to be reflective of the true situation given that there were no missing studies identified on 'trim and fill' analysis. The situation for IGT and MetS may not be reflective given some negative studies were identified, and therefore there is a risk of publication bias.

The main strength in this study is the cohort studies examining DM, which have long follow-up periods and

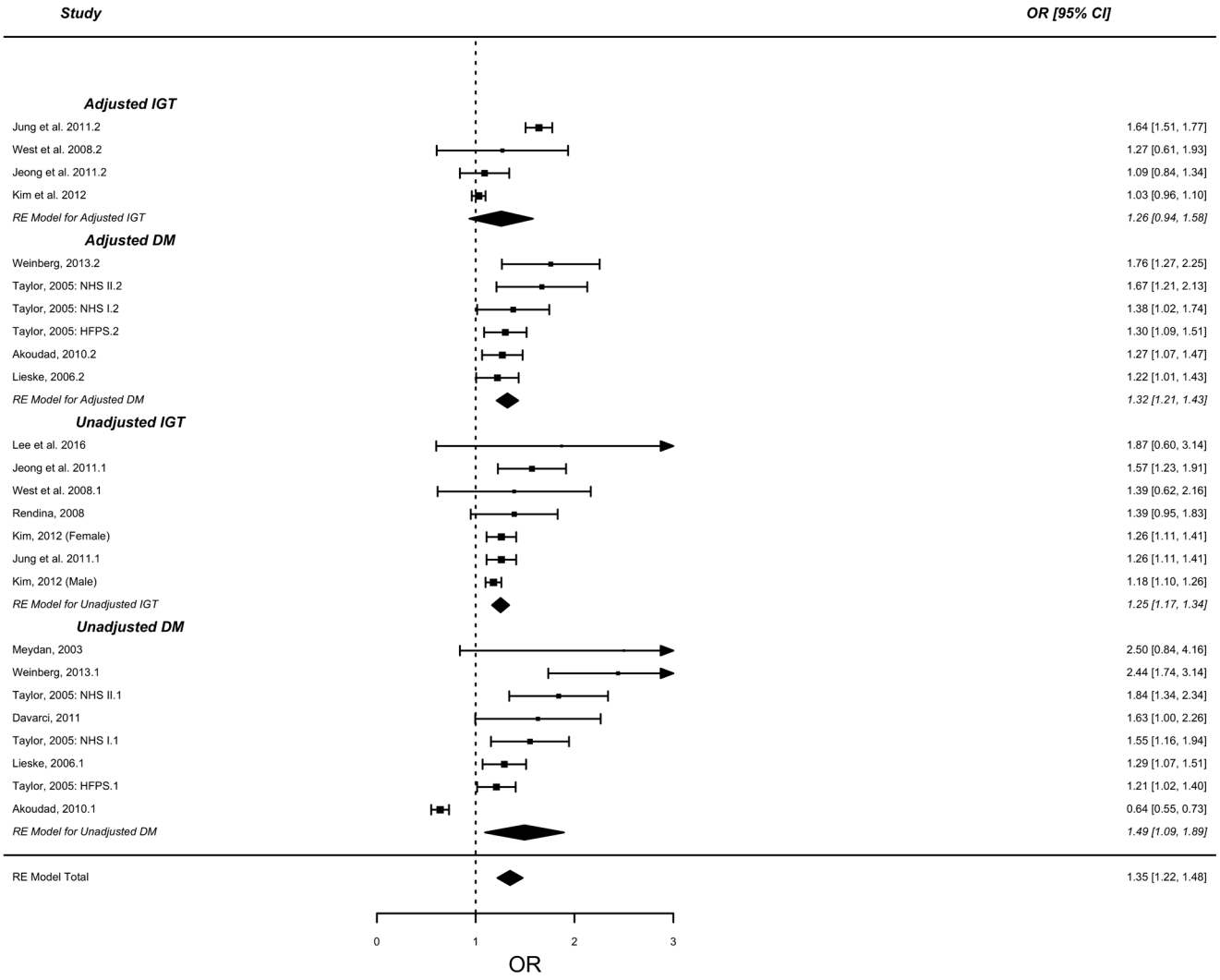

Figure 3 Forest plot analysis – diabetes mellitus + impaired glucose tolerance cross-sectional and case-control studies. NHS, National Health Service.

demonstrate highly significant results with a low risk of bias, despite suffering from significant statistical heterogeneity. This may be the result of differing adjustments between studies.

The case-control and cross-sectional studies examining DM were of variable quality but demonstrated highly significant results, similar to the cohort studies. Direct comparison between cohorts and these studies is difficult due to the differing outcome measure

There was no differentiation between type 1 and type 2 DM in most studies. It is unclear if type 1 confers the same risk as type 2.

It was unclear from the studies whether IGT was considered in isolation or in combination with other MetS components, nor was it clear whether the comparator groups contained those with MetS components, without reaching the required three components needed for diagnosis. This risks falsely lowering the risk associated with IGT due to the comparisons with other potential KSD risk factors.

Statistical heterogeneity demonstrated in most of the analyses may be due to ascertainment of KSD, variability in study populations and design and publication bias. There were significant variations in KSD ascertainment from patient-reported to medical notes to radiologically proven. Some studies may therefore under-report the true number of stones.

Variability in study populations and design (cohort, cross-sectional and case-control) ranged from hospital attendees in a single centre to large regional or national cohort studies. The effect of this variability is somewhat negated by dividing the studies by study design and analysing each separately.

DM cohort study adjusted values although the overall figure was significant the CI includes 1, therefore this could represent type 1 error.

Publication bias was low in this study with trim and fill analyses demonstrating few missing studies (mostly for MetS) and leave-one-out analysis not demonstrating any significantly heterogeneous studies.

The most common stone composition in all KSD formers is calcium oxalate, followed closely by calcium phosphate, together comprising around 85% of all stones. Uric acid stones are third, accounting for 12% in men,

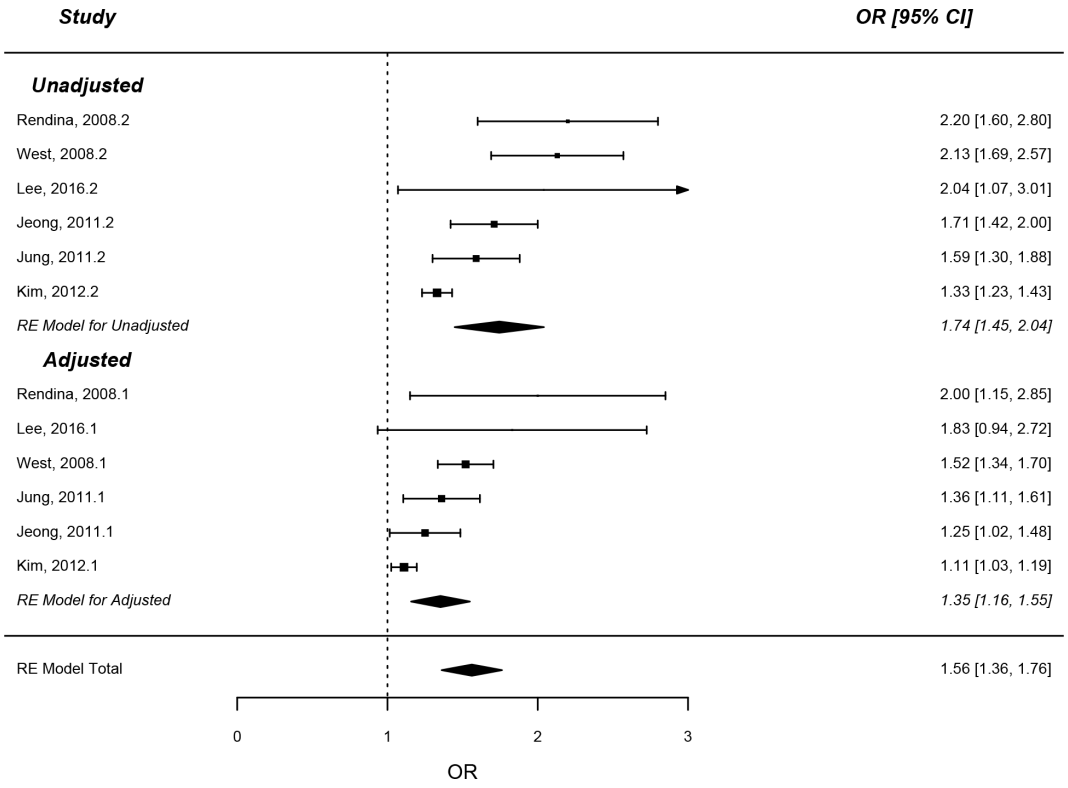

Figure 4 Forest plot analysis – metabolic syndrome (cross-sectional).

7% in women, while the far rare cystine stones account for less than 1% in either gender.[40] Both DM and MetS have been linked to increased uric acid stone formation, while calcium stone formation remains static, seemingly un-influenced by either DM or MetS.[41]

The increased risk of KSD in DM is thought to be secondary to two factors, glycaemic control (common to both types 1 and 2 and impaired glucose tolerance) and insulin resistance (as seen in type 2DM and MetS). Hyperglycaemia has been demonstrated to increase urinary calcium,[42 43] phosphorous,[42 43] uric acid[44 45] and oxalate[46] secretion. Whereas increased insulin resistance increases renal ammonium secretion[47] and decreased urinary pH,[46] which in turn increases urinary calcium and uric acid secretion[48] while decreases urinary citrate[49] (an alkalizing agent), compounding urinary acidification. Together these mechanisms lead to increased risk of precipitation and subsequent formation of uric acid stones.

Notably, Chung *et al*[50] and Weikert[51] in prospective cohort studies demonstrated patients who suffered from KSD were more likely to develop DM over a 5-year period than those who did not form stones. This muddies the water, giving a 'chicken and egg' scenario. It could be that

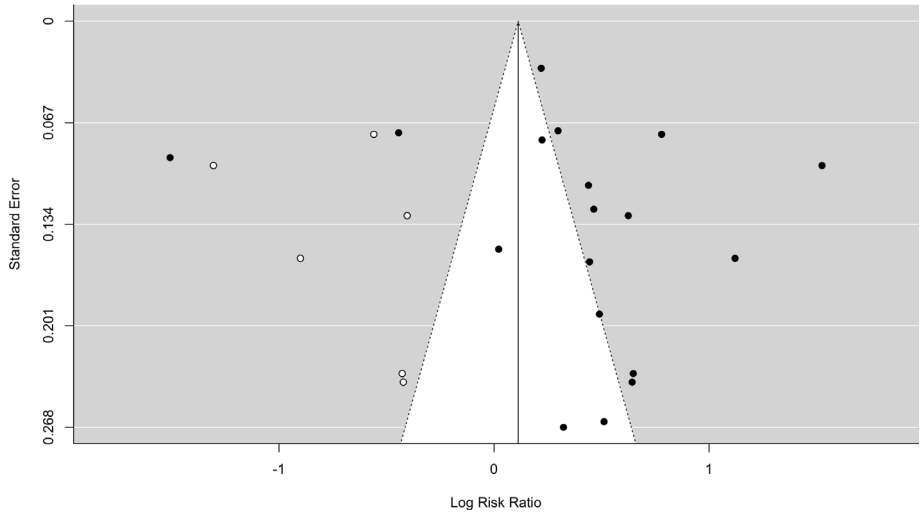

Figure 5 Funnel plot - diabetes mellitus with impairedglucose tolerance. Black dots=included studies, white dots=missing studies identified on 'trim and fill analysis'.

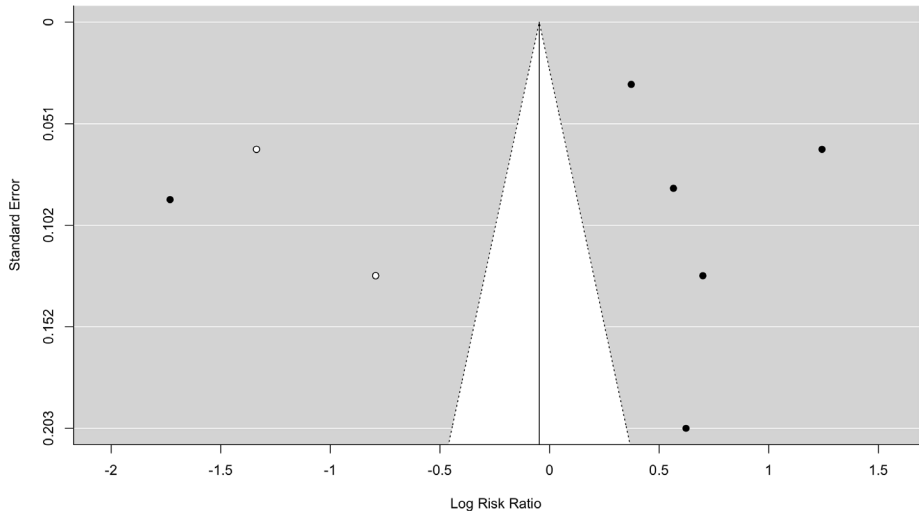

Figure 6 Funnel plot - metabolic syndrome. Black dots=included studies, white dots=missing studies identified on 'trim and fill analysis'.

KSD is a symptom of an underlying systemic metabolic disorder, or something intrinsic to KSD formers increases the risk of metabolic derangement. The former is more likely given the evidence for biochemical disruption in urinary excretions prior to stone formation.

Metabolic syndrome has been defined multiple times,[52] however all definitions are in agreement that it comprises a combination of insulin resistance, hypertension and dyslipidaemia. Insulin resistance in metabolic syndrome is the same mechanism resulting in type 2 diabetes and thus the findings of urinary acidification,[48 53] increased risk of uric acid secretion[53] and uric acid stone formation[48] via the pathophysiology described above are the same.

In this review a small, although non-significant increase in risk suffering from heterogeneity, was associated with MetS versus IGT/DM. This may be attributable to the other components of MetS.

There is conflicting evidence about hypertension and a possible link to increased risk of KSD[35] and vice versa.[54] A prospective cohort study by Cappuccio *et al*[55] demonstrated a significantly increased crude risk of hypertensives developing KSD than non-hypertensives. However, when observing the difference between stone formers and non-stone formers, the stone formers had no significant difference in blood pressure. It was noted that the hypertensives were significantly heavier, older and had higher BMI's. Madore *et al* in consecutive studies on both genders,[54 56] demonstrated there was no increased risk compared with non-hypertensive individuals when age, BMI and electrolyte intake were adjusted for. Akoudad *et al*[27] in their prospective cohort study demonstrated an increased risk of KSD with hypertension. However on multivariate analysis the effect was rendered non-significant. Perhaps the risk found by Cappuccio was confounded by the presence of metabolic syndrome, which at the time of publication was not defined.[20] Hypertension is more likely indicative of underlying metabolic disturbance than having a truly lithogenic effect.

Dyslipidaemia, defined as hypercholesterolaemia, low serum high-density lipoprotein and high serum triglycerides[20] has also been associated with increased risk of KSD.[57] However, when adjusted in multivariate analysis the association is lost.[57] Moreover, the only demonstrable biochemical abnormality after multivariate analysis is high urinary uric acid. Therefore the risk associated with dyslipidaemia is due to insulin resistance instead.

Renal lipotoxicity, defined as lipid accumulation in non-adipose tissues, has been linked to decreased ammonium secretion and therefore lower pH in rat models.[58] However, this observation has yet to be reflected in humans. Renal lipotoxicity may represent the endpoint of chronic dyslipidaemia.

Table 5 Bias analysis of cohort studies

	Cohort	Newcastle-Ottawa quality assessment scale			
DM/MetS	Study	Selection (four stars total)	Comparability (two stars total)	Outcome (three stars total)	Total (out of 9)
DM	*Taylor et al*[27]	***	**	**	7
	Akoudad *et al*[29]	****	**	***	9
	Chen *et al*[28]	***	**	***	8

DM, diabetes mellitus; MetS, metabolic syndrome.

Table 6 Bias analysis of cross-sectional studies

DM/MetS	Cross-sectional Study	Newcastle-Ottawa quality assessment scale Selection (five stars total)	Comparability (two stars total)	Outcome (three stars total)	Total (out of 10)
DM	Meydan *et al*[30]	0	0	**	2
	Taylor *et al*[27]	**	**	**	6
	Akoudad *et al*[29]	***	**	**	7
	Weinberg *et al*[33]	***	**	**	7
MetS	Rendina *et al*[34]	***	*	***	7
	West *et al*[35]	****	**	**	8
	Jeong *et al*[37]	***	**	***	8
	Kim *et al*[38]	***	**	***	8
	Lee *et al*[39]	**	*	***	6

DM, diabetes mellitus; MetS, metabolic syndrome.

The addition of renal lipotoxicity to insulin resistance may explain the seemingly increased risk of KSD observed in patients with MetS versus IGT. Further studies are required to accurately demonstrate the underlying mechanism.

The rise in prevalence of DM and MetS is well documented and is now perceived as a global pandemic.[9 18] KSD prevalence has risen in parallel.[3 5 6] The Global Burden of Disease study[9 10] demonstrated morbidity and absolute mortality associated with KSD has increased, perhaps due to the pandemic of DM/MetS,[19] although age standardised mortality rates have decreased globally,. The effect is marked in higher income countries, but is attenuated in lower-middle income countries.[8 10] This may be attributable to lack of availability of prompt intervention in developing countries, leading to later presentation and invasive treatments including nephrectomy.[59–61] Following surgical treatment, management to prevent recurrence is recommended,[13] again this may not be available in developing countries.

In this review, those with impaired glucose tolerance (pre-diabetes) had an increased likelihood of KSD, which was similar to those with DM in cross-sectional/case-control studies, although this may be suffering from publication bias and the real situation may be that the likelihood of KSD in IGT is lower than DM. Indeed, The NationalHealth and Nutrition Examination Survey III cross-sectional study[33] demonstrated with increasingly poor glycaemic control led to increasing likelihood of KSD as determined by fasting plasma glucose and glycosylated haemoglobin. Given the evidence suggesting those with DM or MetS are at increased risk of developing KSD measures to improve glycaemic control should be examined for their efficacy in KSD prevention in this 'at-risk' population. It should be noted that the stone type in those with DM or MetS is most commonly calcium oxalate, however although still small, the proportion of urate stones increases in these related populations.[22 62]

Clarity is required on the risk in type 1 diabetics and future studies should differentiate these patients from type 2. Further prospective examination of DM and MetS should be undertaken to accurately portray whether additional risk is posed by MetS over DM and quantify this. Tight glycaemic control and weight loss should be explored in primary prevention studies for both MetS and DM, given the common pathophysiological mechanism. Further investigation is required to demonstrate if these patient are at increased risk of recurrence.

The risk of developing kidney stones is significantly increased in populations with chronic hyperglycaemia. This has global implications with rising morbidity and absolute mortality attributable to stones and is likely to increase the health and economic burden on patients and healthcare providers. Tight glycaemic control and weight loss are low-cost and non-invasive measures, which should be investigated for their primary preventative

Table 7 Bias analysis of case-control studies

DM/MetS	Case-control Study	Newcastle-Ottawa quality assessment scale Selection (four stars total)	Comparability (two stars total)	Exposure (three stars total)	Total (out of 9)
DM	Lieske *et al*[31]	****	**	**	8
	Davarci et al[32]	*	*	***	5

DM, diabetes mellitus; MetS, metabolic syndrome.

effect on KSD in these populations and included as part of the long-term management of kidney stone disease.

Twitter Robert Geraghty @RobertGeraght16 and Bhaskar Somani @endouro

Contributors RG performed the search, statistical analysis and wrote the manuscript. AA performed the search and reviewed the manuscript. PC, BS and PR edited the manuscript and critiqued the statistical analysis. BS and PR decided whether or not to include studies as the senior authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request.

ORCID iD

Robert Geraghty http://orcid.org/0000-0002-9128-5173

REFERENCES

1 Lotan Y. Economics and cost of care of stone disease. *Adv Chronic Kidney Dis* 2009;16:5–10.
2 Sakhaee K. Recent advances in the pathophysiology of nephrolithiasis. *Kidney Int* 2009;75:585–95.
3 Pearle MS, Calhoun EA, Curhan GC, *et al*. Urologic diseases in America project: urolithiasis. *J Urol* 2005;173:848–57.
4 Yasui T, Okada A, Hamamoto S, *et al*. Pathophysiology-based treatment of urolithiasis. *Int J Urol* 2017;24:32–8.
5 Edvardsson VO, Indridason OS, Haraldsson G, *et al*. Temporal trends in the incidence of kidney stone disease. *Kidney Int* 2013;83:146–52.
6 Yasui T, Iguchi M, Suzuki S, *et al*. Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. *Urology* 2008;71:209–13.
7 Geraghty RM, Jones P, Somani BK. Worldwide trends of urinary stone disease treatment over the last two decades: a systematic review. *J Endourol* 2017;31:547–56.
8 Bayne D, Chi T, Harris C, *et al*. PD47-02 global trends in urolithiasis morbidity and mortality from 1990-2010. *Journal of Urology* 2016;195:e1170–1.
9 Murray CJL, Vos T, Lozano R, *et al*. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2197–223.
10 Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2095–128.
11 Uribarri J, Oh MS, Carroll HJ. The first kidney stone. *Ann Intern Med* 1989;111:1006–9.
12 Bensalah K, Tuncel A, Gupta A, *et al*. Determinants of quality of life for patients with kidney stones. *J Urol* 2008;179:2238–43. discussion 2243.
13 Pearle MS, Goldfarb DS, Assimos DG, *et al*. Medical management of kidney stones: AUA guideline. *J Urol* 2014;192:316–24.
14 Türk C, Petřík A, Sarica K, *et al*. EAU guidelines on interventional treatment for urolithiasis. *Eur Urol* 2016;69:475–82.
15 Saucier NA, Sinha MK, Liang KV, *et al*. Risk factors for CKD in persons with kidney stones: a case-control study in Olmsted County, Minnesota. *Am J Kidney Dis* 2010;55:61–8.
16 Liu LH, Kang R, He J, *et al*. Diabetes mellitus and the risk of urolithiasis: a meta-analysis of observational studies. *Urolithiasis* 2015;43:293–301.
17 Wong Y, Cook P, Roderick P, *et al*. Metabolic syndrome and kidney stone disease: a systematic review of literature. *J Endourol* 2016;30:246–53.
18 Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 2008;28:629–36.
19 Vos T, Allen C, Arora M, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the global burden of disease study 2015. *Lancet* 2016;388:1545–602.
20 Grundy SM, Brewer HB, Cleeman JI, *et al*. Definition of metabolic syndrome: report of the National heart, lung, and blood Institute/ American heart association conference on scientific issues related to definition. *Circulation* 2004;109:433–8.
21 Daudon M, Traxer O, Conort P, *et al*. Type 2 diabetes increases the risk for uric acid stones. *J Am Soc Nephrol* 2006;17:2026–33.
22 Daudon M, Lacour B, Jungers P. Influence of body size on urinary stone composition in men and women. *Urol Res* 2006;34:193–9.
23 Besiroglu H, Otunctemur A, Ozbek E. The metabolic syndrome and urolithiasis: a systematic review and meta-analysis. *Ren Fail* 2015;37:1–6.
24 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
25 Luchini C, Stubbs B, Solmi M, *et al*. Assessing the quality of studies in meta-analyses: advantages and limitations of the Newcastle Ottawa scale. *World J Metaanal* 2017;5:80.
26 Viechtbauer W. Conducting Meta-Analyses in *R* with the metafor Package. *J Stat Softw* 2010;36:1–48.
27 Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 2005;68:1230–5.
28 Chen H-S, Su L-T, Lin S-Z, *et al*. Increased risk of urinary tract calculi among patients with diabetes mellitus--a population-based cohort study. *Urology* 2012;79:86–92.
29 Akoudad S, Szklo M, McAdams MA, *et al*. Correlates of kidney stone disease differ by race in a multi-ethnic middle-aged population: the ARIC study. *Prev Med* 2010;51:416–20.
30 Meydan N, Barutca S, Caliskan S, *et al*. Urinary stone disease in diabetes mellitus. *Scand J Urol Nephrol* 2003;37:64–70.
31 Lieske JC, de la Vega LSP, Gettman MT, *et al*. Diabetes mellitus and the risk of urinary tract stones: a population-based case-control study. *Am J Kidney Dis* 2006;48:897–904.
32 Davarci M, Helvaci MR, Aydin M. What is the relationship between type 2 diabetes mellitus and urolithiasis? *Bratisl Lek Listy* 2011;112:711–4.
33 Weinberg AE, Patel CJ, Chertow GM, *et al*. Diabetic severity and risk of kidney stone disease. *Eur Urol* 2014;65:242–7.
34 Rendina D, Mossetti G, De Filippo G, *et al*. Association between metabolic syndrome and nephrolithiasis in an inpatient population in southern Italy: role of gender, hypertension and abdominal obesity. *Nephrol Dial Transplant* 2009;24:900–6.
35 West B, Luke A, Durazo-Arvizu RA, *et al*. Metabolic syndrome and self-reported history of kidney stones: the National health and nutrition examination survey (NHANES III) 1988-1994. *Am J Kidney Dis* 2008;51:741–7.
36 Jung HS, Chang IH, Kim KD, *et al*. Possible relationship between metabolic syndrome traits and nephrolithiasis: incidence for 15 years according to gender. *Korean J Urol* 2011;52:548–6.
37 Jeong IG, Kang T, Bang JK, *et al*. Association between metabolic syndrome and the presence of kidney stones in a screened population. *Am J Kidney Dis* 2011;58:383–8.
38 Kim Y-J, Kim C-H, Sung E-J, *et al*. Association of nephrolithiasis with metabolic syndrome and its components. *Metabolism* 2013;62:808–13.
39 Lee Y-C, Huang S-P, Juan Y-S, *et al*. Impact of metabolic syndrome and its components on kidney stone in aging Taiwanese males. *Aging Male* 2016;19:197–201.
40 Knoll T. Epidemiology, pathogenesis, and pathophysiology of urolithiasis. *Eur Urol Suppl* 2010;9:802–6.
41 Kadlec AO, Greco K, Fridirici ZC, *et al*. Metabolic syndrome and urinary stone composition: what factors matter most? *Urology* 2012;80:805–10.
42 Nagasaka S, Murakami T, Uchikawa T, *et al*. Effect of glycemic control on calcium and phosphorus handling and parathyroid hormone level in patients with non-insulin-dependent diabetes mellitus. *Endocr J* 1995;42:377–83.
43 Thalassinos NC, Hadjiyanni P, Tzanela M, *et al*. Calcium metabolism in diabetes mellitus: effect of improved blood glucose control. *Diabet Med* 1993;10:341–4.
44 Cook DG, Shaper AG, Thelle DS, *et al*. Serum uric acid, serum glucose and diabetes: relationships in a population study. *Postgrad Med J* 1986;62:1001–6.
45 Gotfredsen A, McNair P, Christiansen C, *et al*. Renal hypouricaemia in insulin treated diabetes mellitus. *Clinica Chimica Acta* 1982;120:355–61.

46 Eisner BH, Porten SP, Bechis SK, *et al*. Diabetic kidney stone formers excrete more oxalate and have lower urine pH than nondiabetic stone formers. *J Urol* 2010;183:2244–8.
47 Maalouf NM, Cameron MA, Moe OW, *et al*. Metabolic basis for low urine pH in type 2 diabetes. *Clin J Am Soc Nephrol* 2010;5:1277–81.
48 Abate N, Chandalia M, Cabo-Chan AV, *et al*. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int* 2004;65:386–92.
49 Cupisti A, Meola M, D'Alessandro C, *et al*. Insulin resistance and low urinary citrate excretion in calcium stone formers. *Biomed Pharmacother* 2007;61:86–90.
50 Chung S-D, Chen Y-K, Lin H-C. Increased risk of diabetes in patients with urinary calculi: a 5-year followup study. *J Urol* 2011;186:1888–93.
51 Weikert C, Weikert S, Schulze MB, *et al*. Presence of gallstones or kidney stones and risk of type 2 diabetes. *Am J Epidemiol* 2010;171:447–54.
52 Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415–28.
53 Okamoto M, Kohjimoto Y, Iba A, *et al*. Calcium oxalate crystal deposition in metabolic syndrome model rat kidneys. *Int J Urol* 2010;17:996–1003.
54 Madore F, Stampfer MJ, Willett WC, *et al*. Nephrolithiasis and risk of hypertension in women. *Am J Kidney Dis* 1998;32:802–7.
55 Cappuccio FP, Siani A, Barba G, *et al*. A prospective study of hypertension and the incidence of kidney stones in men. *J Hypertens* 1999;17:1017–22.
56 Madore F, Stampfer MJ, Rimm EB, *et al*. Nephrolithiasis and risk of hypertension. *Am J Hypertens* 1998;11:46–53.
57 Torricelli FCM, SK D, Gebreselassie S, *et al*. Urolithiasis/Endourology dyslipidemia and kidney stone risk. *J Urol* 2014;191:667–72.
58 Bobulescu IA, Dubree M, Zhang J, *et al*. Effect of renal lipid accumulation on proximal tubule Na^+/H^+ exchange and ammonium secretion. *Am J Physiol Renal Physiol* 2008;294:F1315–22.
59 Rimtebaye K, Sillong FD, Tashkand AZA, *et al*. Urolithiasis: Diagnostic and Therapeutic Aspects in Urology Department of N'Djamena in Chad. *OJU* 2015;05:199–206.
60 Hounnasso PP, Avakoudjo JDG, Paré AK, *et al*. Symptomatic urinary lithiasis: epidemiology and management at urology department of university hospital of Cotonou. *OJU* 2015;05:7–12.
61 Marchini GS, Mello MF, Levy R, *et al*. Contemporary trends of inpatient surgical management of stone disease: national analysis in an economic growth scenario. *J Endourol* 2015;29:956–62.
62 Cho ST, Jung SI, Myung SC, *et al*. Correlation of metabolic syndrome with urinary stone composition. *Int J Urol* 2013;20:208–13.