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Chronic Hyperglycaemia Increases the Risk of Kidney Stone disease, Results from a Systematic Review and Meta-Analysis

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1   <u>Chronic Hyperglycaemia Increases the Risk of Kidney Stone disease, Results from a</u>
2   <u>Systematic Review and Meta-Analysis</u>
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36 <u>Abstract</u>

37 **Design:** Systematic review and meta-analysis of observational studies

38 was performed using PRISMA guidelines for studies reporting on Diabetes

39 Mellitus (DM) or Metabolic syndrome (MetS) and kidney stone disease (KSD).

40 **Objective:** To examine the association between chronic

41 hyperglycaemia, in the form of DM and IGT in the context of MetS, and KSD.

42 **Setting:** Population based observational studies.

43 **Participants:** Patients with and without chronic hyperglycaemic states

44 (DM and MetS).

45 **Main Outcome Measures:** English language articles from January

46 2001-June 2018 reporting on observational studies. Exclusions: no

47 comparator group or fewer than 100 patients. Both unadjusted and adjusted

48 (where reported) values were identified and used for meta-analysis. Bias was

49 assessed using Newcastle-Ottawa scale.

50 **Results:** 2340 articles were screened with 13 studies included for

51 meta-analysis, 7 DM (3 cohort) and 6 MetS. 5 of the MetS studies provided

52 data on IGT alone. These included: DM, n=28,329; MetS, n=31,767; IGT,

53 n=12,770. Controls: DM, n=589,791; MetS, n=178,050; IGT, n=293,852

54 patients.

55 Adjusted risk for DM cohort studies, RR=1.23 (0.94-1.51) (p<0.001).

56 Adjusted Odds ratios for: DM cross-sectional/case-control studies, OR=1.32

57 (1.21-1.43) (p<0.001); IGT, OR=1.26 (0.92-1.58) (p<0.0001) and MetS,

58 OR=1.35 (1.16-1.54) (p<0.0001).

59   There was no significant difference between IGT and DM (XS/CaCo),

60   nor IGT and MetS. There was a moderate risk of publication bias. Statistical

61   heterogeneity was significant in adjusted DM cohort values and adjusted IGT

62   XS/CaCo, but non-signficant for DM XS/CaCo.

63   **Conclusion:** Chronic hyperglycaemia increases the risk of developing

64   kidney stone disease. In the context of the diabetes pandemic, this will

65   increase the burden of stone related morbidity and mortality.

66   **Trial registration:** PROSPERO registration number CRD42018093382.

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Strengths and Limitations of This Study

71   • Largest systematic review and meta-analysis examining the risk of

72   chronic hyperglycaemic states and kidney stone disease (KSD), with

73   bias analysis.

74   • Only observational studies available

75   • Meta-analysis of Cohort studies examining Diabetes Mellitus

76   demonstrates an increased risk of KSD of of 1.23 (0.94-1.51) (p<0.001)

77   over the general population.

78   • There was a moderate risk of publication bias.

79   • Statistical heterogeneity was significant in adjusted DM cohort values

80   and adjusted IGT

81

Introduction

Kidney stone disease (KSD) is a painful and costly condition[1] where precipitates of normal urinary solutes aggregrate 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]. 5-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 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 BMI in both diabetic and non-diabetic patients, the incidence of uric acid stones rises, whilst calcium oxalate stones fall[21,22].

105   Previous systematic reviews have examined either DM[23] or

106   MetS[24,25] in isolation. These studies performed either no meta-

107   analysis[25], or else their heterogeneity/ sensitivity analyses were

108   limited[23,24]. Given the overlap between the two conditions we aimed to

109   perform a systematic review and meta-analysis of the existing literature on

110   both DM and MetS with complete sensitivity, bias and heterogeneity

111   analyses.

112

113

114   <u>Evidence Acquisition</u>

115   <u>*Search strategy and study selection*</u>

116   Population – Chronic hyperglycaemics (diabetes mellitus, impaired glucose

117   tolerance in context of metabolic syndrome) and those with metabolic

118   syndrome

119   Comparator – Those without hyperglycaemia (DM/IGT) or metabolic

120   syndrome, respectively

121   Outcome – Kidney stone disease (KSD) – all compositions

122   Study design – Systematic review and meta-analysis of published

123   observational studies (cohort, case control and cross-sectional)

124

125   Inclusion criteria:

126   1) All articles written in the English language

127   2) Adults (>18 years)

128   3) All articles reporting on risk of developing kidney stone disease in

129   diabetes mellitus (type 1 and type 2) in comparison to general

130   population

131   4) All articles reporting on risk of developing kidney stone disease in

132   patients with metabolic syndrome in comparison to general

133   population.

134   5) Risk in risk ratio (RR), hazard ratio (HR), odds ratio (OR) or prevalence

135   ratio (PR) with 95% confidence intervals.

136

137   Exclusion criteria:

138   1) Older studies using the same data as a more recent study – longest

139   follow-up used.

140   2) Studies exclusively using patients with kidney stone disease – unable

141   to calculate risk

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

143

144   The systematic review was performed according to the PRISMA

145   guidelines[26]. The search strategy was conducted to find relevant studies

146   from Ovid Medline without revisions (1996-June 2018), Cochrane Library

147   (2018), CINAHL (1990-June 2018), Clinicaltrials.gov, Google Scholar and

148   individual urologic, renal, metabolic and epidemiologic journals. The review

149   was registered prospectively with PROSPERO, ID number: CRD42018093382.

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151   Terms used included: "Diabetes", "Diabetes mellitus", "metabolic syndrome",

152   "urolithiasis", "nephrolithiasis", "kidney", "uret*", "ston*", "calcul*". Boolean

153   operators (AND, OR) were used to refine the search.

154   The search was limited to English language articles between January 2001 and

155   June 2018. Only published data were used.

156   Two reviewers (RG and AM) identified all studies. All studies that appeared to

157   fit the inclusion criteria were included for full review. Each reviewer

158   independently selected studies for inclusion in the review [see fig. 1]. If there

159   was disagreement, PR and BKS made final decision on inclusion.

160   _Data extraction and Assessment of Quality_

161   The following variables were extracted from each study: first author, year of

162   publication, type of study, sample size, age, country, male:female ratio,

163   ascertainment of DM/IGT/MetS/KSD, type of DM, number of patient

164   reporting/presenting with stone disease for diabetes mellitus, metabolic

165   syndrome and specifically IGT in the context of MetS (given the common

166   mechanism – hyperglycaemia and insulin resistance).

167   Risk of KSD in RR, HR, OR or PR with 95% confidence intervals was also

168   extracted. HR and RR, and OR and PR, were considered the same and are

169   presented as RR and OR respectively. Unadjusted and adjusted risk values were

170   extracted from the studies. Adjustment factors were recorded. If adjusted

171 values were missing then the study was removed from the adjusted meta-

172 analysis.

173 Cross-sectional and case-control studies were pooled as there were no case-

174 control studies for MetS, and 2 case-control studies for DM, only one of which

175 gave adjusted values.

176 Data were collated using Microsoft Excel (version 12.2.4). Level of evidence

177 was assessed and study bias was analysed using the Newcastle-Ottawa bias

178 assessment tool[27].

179 Data can be obtained by emailing the corresponding author.

180 *Statistical Methods*

181 Risk is presented with a 95% confidence interval as risk ratio (RR) for cohort

182 studies and odds ratio (OR) for case control and cross-sectional studies.

183 Statistical heterogeneity was tested for using I^2, Tau^2 and Cochran's Q. P values

184 <0.05 were considered statistically significant, I^2 values were interpreted

185 according to chapter 9.5.2 of the Cochrane handbook. Heterogeneity was also

186 tested with 'leave one out' analyses. Publication bias was assessed with Egger's

187 test and 'trim and fill' analysis.

188 Statistical analyses and figures were generated in R (R foundation for statistical

189 computing, Vienna, Austria) with the metafor package[28].

190 *Role of the funding source*

191 Health Education England had no role in study design, data collection, data

192 analysis, data interpretation or writing of the report. The corresponding author

193 had full access to all the data in the study and had final responsibility for the

194 decision to submit for publication.

195

196 *Figure 1. PRISMA flow diagram for article selection*

197 Contributorship

198   PR and RG came up with the initial idea. RG and AA performed the search, with PR

199 and BS resolving inclusion disputes. RG extracted the data, performed the analyses and

200 wrote the manuscript, with PR, BS and PC helping edit.

201 Patient and Public Involvement

202   Patients/the public were not involved in this review article.

203

204 Evidence Synthesis

205   Fifteen studies were included in the systematic review from an initial

206 search total of 2340 [see figure 1]. 2301 articles were excluded on the basis of

207 title, 15 on the basis of abstract and 15 on reading the full text. This left 13

208 studies, 7 examining diabetes mellitus (DM) and 6 examining impaired

209 glucose tolerance (IGT) in the context of metabolic syndrome (MetS).

210

211 *Demographics of included studies*

212   *Diabetes Mellitus*

213   Seven studies were included examining DM[29-35]. Three were

214   cohort[29-31], three were case-control[32-34] and three were cross-

215   sectional[29,31,35]. Taylor et al.[29] and Akoudad et al.[31] performed both

216   cross-sectional and prospective cohort studies with their cohorts. The studies

217   were conducted in Turkey, Taiwan and USA. They sampled varying

218   populations, from hospital inpatients to national patient data. Patients with

219   Type 1 DM were included in all but one of the studies[34] [see table 1].

220   The male to female ratio and mean age for each study is detailed in

221   table 1. DM and KSD ascertainment ranged from the patient reporting the

222   diagnosis to ICD codes in medical records.

223   Overall there were 618,120 patients, of which 28,329 (4.6%) had DM.

224   These figures include 17,577 patients with DM in cohort studies with 348,036

225   controls [see table 2] and 10,752 patients with DM in case-control or cross-

226   sectional studies with 241,755 control [see table 3]. In the cohort studies,

227   1312 (7.5%) of patients with DM developed KSD compared to 11,516 (3.3%)

228   of controls. In the case-control and cross-sectional studies, 1097 (10.2%) of

229   diabetics had KSD compared to 11,985 (5.0%) of controls. Study reported risk

230   is detailed in tables 2 and 3.

231

232

DM	Study	Study type	Country	Sample	Controls	Metabolic syndrome definition	Diabetes Mellitus ascertainment	KSD ascertainment	M:F (%)	Mean age
Cohort	Taylor et al. 2005	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) (male health professionals) – '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; HFPS: 60.9
	Chen et al. 2012	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 3 outpatient visits for DM from 2000-2002 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. 2010	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>110mg/dL, FPG>126mg/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. 2006	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 calender year of stone	N/A	Electronic medical records using codes: ICD9 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: ICD9-CM 592, 594, 275.11 with case review	62: 38	45.0±18
	Davarci et al. 2011	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>110mg/dL, FPG>126mg/dL. T1 excluded	USS, AXR, patient reported	47.5:52.5	49.0±10
XS	Meydan et al. 2003	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. 2005	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
	Akoudad et al. 2010	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>110mg/dL, FPG>126mg/dL, patient reported physician diagnosis	Patient reported physician diagnosis	44:56 (calculated)	60.0 ± 5.7 (calculated)
	Weinberg et al. 2013	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. 2008	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: 3 or more of: 1) Waist circumference >102cm in men, >88cm in women. 2) fasting serum triglycerides >1.7mmol/L or treatment. 3) fasting serum HDL <1.03mmol/L in men, <1.30mmol/L in women or treatment. 4) Systolic >130mmHg or Diastolic >85mmHg or treatment. 5) fasting serum glucose >5.6mmol/L or treatment	Fasting serum glucose >5.6mmol/L or treatment	Questionnaire re: symptoms of renal colic and Ultrasonography	49:51	63.8 ± 15.8
	West et al. 2008	Cross-sectional	USA	NHANES III participants (1988-1994) - those with metabolic syndrome/impaired glucose tolerance	2 or fewer MetS traits/no MetS traits	American Heart Association; National Heart, Lung, and Blood Institute as per Rendina et al.	Fasting serum glucose >5.6mmol/L or treatment	Self report of physician diagnosis	48:52	58.8 ± 17.1
	Jeong et al. 2011	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 - 3 or more of: Systolic >130mmHg, Diastolic >85mmHg, random blood glucose >110mg/dL, random serum triglycerides >150mg/dL, random serum HDL <40mg/dL in men or <50mg/dL in women, obese range waist circumference	Fasting blood glucose >110mg/dL	Radiological records (ultrasound and CT)	60:40	50.0 ± 10.4
	Jung et al. 2011	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 - 3 or more of: Systolic >130mmHg, Diastolic >85mmHg, random blood glucose >110mg/dL, random serum triglycerides >150mg/dL, random serum HDL <40mg/dL in men or <50mg/dL in women, obese range waist circumference	Fasting blood glucose >110mg/dL	Ultrasonography	55:45	44.9 ± 11.5
	Kim et al. 2012	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 - 3 or more of: Systolic >130mmHg, Diastolic >85mmHg, random blood glucose >110mg/dL, random serum triglycerides >150mg/dL, random serum HDL <40mg/dL in men or <50mg/dL in	Fasting blood glucose >110mg/dL	Ultrasonography	58:42	42.3 ± 8.4
	Lee et al. 2016	Cross-sectional	Taiwan	Single centre - men undergoing free health screening - those with MetS/DM	Unclear - ?Those without MetS or DM	3 of the 5 following criteria: patients were defined as having MtS by the presence of at least three of five of the following criteria: waist circumference (WC) 90cm, high-density lipoprotein (HDL) cholesterol540 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 >126mg/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

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234   *Table 1. Study demographics. F/U=follow up, T1= Type 1 diabetes mellitus, T2=Type 2 diabetes mellitus*

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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. 2005: NHS I (younger female)	1,409	93,758	65,566	1,371,080	109 (7.7%)	1578 (1.7%)	RR 1.45 (1.20-1.77)	RR 1.29 (1.05-1.58)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: NHS II (older female)	891	101,877	12,291	824,076	40 (4.5%)	1491 (1.5%)	RR 1.86 (1.36-2.56)	RR 1.60 (1.16-2.21)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: HFPS (male)	1391	46,062	21,676	450,984	44 (3.2%)	1426 (3.1%)	RR 0.76 (1.56-1.03)	RR 0.81 (0.59-1.09)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Chen et al. 2012	12,257	96,781	75,975	607,842	1,096 (8.9%)	6950 (7.2%)	HR 1.22 (1.15-1.30)	HR 1.18 (1.10-1.27)	Age, Sex, Occupation, urbanisation, income and UTIs
	Akoudad et al. 2010	1,629	9,558	N/A	N/A	N/A	N/A	N/A	HR 1.98 (1.20-3.28)	Age, Sex, Race, waist circumference, hypertension, triglyceride level, uric acid, gallstones
	Total	17,577	348,036	253,365	3,253,982	1289 (8.1%)	11445 (3.4%)			

239   *Table 2. DM Cohort studies.*

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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. 2006	3,561	3561	335 (9.4%)	268 (7.5%)	OR 1.29 (1.09-1.53)	OR 1.22 (1.03-1.46)	Age, Sex, year of diagnosis, DM, hypertension and obesity
	Davarci et al. 2011	23	177	14 (17.5%)	66 (37.3%)	RR 1.63 (1.12-2.39)	N/A	N/A
XS	Meydan et al. 2003	321	115	84 (26.2%)	14 (12.2%)	OR 2.5 (1.39-4.71) (calculated)	N/A	N/A
	Taylor et al. 2005: NHS I (younger female)	1,473	74,266	64 (4.3%)	2029 (2.7%)	RR 1.55 (1.20-1.99)	RR 1.38 (1.06-1.79)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: NHS II (older female)	949	94,485	58 (6.1%)	3093 (3.3%)	RR 1.84 (1.41-2.41)	RR 1.67 (1.28-2.20)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: HFPS (male)	1,568	47,737	177 (11.3%)	4002 (8.4%)	RR 1.21 (1.03-1.42)	RR 1.31 (1.11-1.54)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Akoudad et al. 2010	1,812	10,349	183 (18.8%)	1629 (14.6%)	N/A	PR 1.27 (1.08-1.49)	Age, Sex, Race, Region, waist circumference, triglycerides, hypertension, uric acid, gallstones
	Weinberg et al. 2013	1,045 (estimated)	11,065 (estimated)	182 (17.1%) (estimated)	884 (8.0%) (estimated)	OR 2.44 (1.84-3.25)	OR 1.76 (1.33-2.32)	Age, Sex, Race, Smoking history, BMI
	Sub Total	**10,752**	**241,755**	**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. 2008	317 (14.9%)	1815 (calculated estimate)	43 (13.6%)	177 (8.7%) (calculated estimate)	N/A	Male: OR 1.1 (0.5-2.4) Female: OR 1.1 (0.3-1.8)	Age, waist circumference, high serum triglycerides, low serum HDL, hypertension
	West et al. 2008	1260 (8.5%)	7268 (calculated estimate)	17 (1.3%)	71 (1.0%)	OR 1.39 (0.81-2.36) (calculated)	OR 1.27 (0.77-2.10) (One metabolic syndrome component)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jeong et al. 2011	6929 (19.9%) (Quintile 5 - ≥104mg/dL)	13,700 (Quintile 1 - ≤85mg/dL)	211 (3.0%)	240 (1.8%)	OR 1.57 (1.26-1.95)	OR 1.09 (0.87-1.37)	Age, sex, metabolic syndrome components, MetS status
	Jung et al. 2011	4192 (10.3%)	28,692 (calculated estimate)	102 (2.4%)	450 (1.6%) (calculated estimate)	1.26 (1.12-1.42)	OR 1.30 (1.03-1.64)	Age, GFR, serum urate, phosphorous and calcium
	Kim et al. 2012	N/A	N/A	N/A	N/A	Male: OR 1.18 (1.10-1.26) Female: OR 1.26 (1.12-1.42)	Male: OR 1.03 (0.97-1.11) Female: OR 1.02 (0.90-1.16)	Age, serum creatinine, serum urate, past medical history of KSD
	Lee et al. 2016	72 (11.3%) (DM)	622	14 (19.4%)	71 (11.7%)	OR 1.87 (0.99-3.53) (calculated)	N/A	N/A
	Sub Total	**12770 (6.1%)**	**52,097**	**387 (3.2%)**	**1009 (1.9%)**			
	Total	**23,522**	**293,852**	**1484 (6.3%)**	**12,994 (4.4%)**			

249 *Table 3. DM and IGT case-control and cross-sectional studies.*

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251

252

MetS	Study	Total participants, n	Metabolic Syndome, 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. 2008	2132	725 (34.0%)	1407	112 (15.4%)	108 (7.7%)	OR 2.2 (1.7-2.9)	OR 2.0 (1.3-3.0)	Age, sex, history of KSD
	West et al. 2008	14,870	4952 (33.3%)	9,921	628 (12.7%)	363 (3.7%)	OR 2.13 (1.74-2.62)	OR 1.52 (1.22-1.89)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jeong et al. 2011	34,895	4602* (13.2%)	30,293	177 (3.8%)	662 (2.2%)	OR 1.71 (1.45-2.03)	1.25 (1.03-1.50)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jung et al. 2011	40,687	7803 (19.2%)	32,884	166 (2.1%)	443 (1.3%)	N/A	OR 1.36 (1.13-1.64)	Age, GFR, serum urate, phosphorous and calcium
	Kim et al. 2012	116,536	13416 (11.5%)	103,120	1129 (8.4%)	5978 (5.8%)	OR 1.33 (1.24-1.44)	OR 1.11 (1.03-1.20)	Age, serum creatinine, serum urate, past medical history of KSD
	Lee et al. 2016	694	269 (42.1%)	425	46 (17.1%)	39 (9.2%)	N/A	OR 1.83 (1.14-2.93)	Age
	Total	**209,814**	**31,767 (15.1%)**	**178,050**	**2258 (7.1%)**	**7593 (4.3%)**			

253   *Table 4. MetS cross-sectional studies. *=discrepancy between text and table.*

1
2
3   254
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5   255
6
7   256   *Metabolic syndrome*
8
9   257   There were six studies[36-41] examining metabolic syndrome, of
10
11   258   which five provided data on chronic hyperglycaemia (IGT/DM)[36-39,41]. All
12
13   259   the studies were cross-sectional. These took place in Italy, South Korea,
14
15   260   Taiwan and USA. The samples ranged from hospital inpatients to
16
17
18   261   representative population based studies, which were representative of target
19
20   262   populations [see table 1].
21
22
23   263   The male to female ratio and mean age for each study is detailed in
24
25   264   table 1. MetS and KSD ascertainment ranged from the patient reported
26
27
28   265   diagnosis to ICD codes in medical records.
29
30   266   Overall there were 209,817 patients, of whom 31,767 (17.8%) had
31
32   267   MetS, 12,770 (6.1%) had IGT only [see table 4]. 2258 (7.1%) of those with
33
34
35   268   MetS had KSD, compared to 7593 (4.3%) of controls. 387 (3.2%) of those with
36
37   269   IGT had KSD compared to 1009 (1.9%) of controls [see table 3]. Unfortunately
38
39   270   control population had to be calculated from the OR for some of the
40
41
42   271   studies[36-38], therefore the figures for IGT are estimates. Study reported
43
44   272   risk is detailed in table 3 and 4.
45
46
47   273   *Meta-Analysis*
48
49   274   Tests for overall unadjusted effect in those with DM demonstrated
50
51   275   significantly higher risk of KSD (RR=1.66 (95% CI: 1.27-2.18, $p<0.001$).
52
53
54   276   Subgroup analyses by study type demonstrated significantly higher risk of
55
56   277   KSD in patients with DM in cohort studies in both unadjusted (1.36, 95% CI:
57
58
59   278   1.11-1.60, $p<0.001$) [see fig. 1] and adjusted risk (RR=1.23, 95% CI: 0.94-1.51,
60

279 p<0.001) [see fig. 2]. Significantly increased risk was also demonstrated in

280 cross-sectional/case-control studies in both unadjusted (OR=1.49, 95% CI:

281 1.09-1.89, p<0.0001) and adjusted risk (OR=1.32, 95% CI: 1.21-1.43, p<0.001)

282 [see fig. 3]. IGT in the context of MetS demonstrated significantly increased

283 risk in both unadjusted (OR=1.25, 95% CI: 1.16-1.54, p<0.0001) and adjusted

284 risk (OR=1.26, 95% CI: 0.94-1.58) [see fig. 3]. Combining DM case-control and

285 cross-sectional studies with IGT demonstrated significantly increased risk in

286 both unadjusted (OR=1.38, 95% CI: 1.18-1.59, p<0.0001) and adjusted risk

287 (OR=1.32, 95% CI: 1.17-1.49, p<0.0001).

288 Cross-sectional studies examining MetS also demonstrated

289 significantly increased risk of KSD in both unadjusted (OR=1.74, 95% CI: 1.45-

290 2.04, p<0.0001) and adjusted (OR=1.35, 95% CI: 1.16-1.54, p<0.0001) [see fig.

291 4] values.

292

293 *Figure 2. Forest Plot analysis – DM Cohort.*

294 *Figure 3. Forest Plot analysis – DM + IGT Cross-sectional and Case Control*

295 *studies.*

296 *Figure 4. Forest Plot analysis – Metabolic syndrome (cross-sectional)*

297

298 *Heterogeneity and Sensitivity Analysis*

299

300 There was borderline significant statistical heterogeneity between DM

301 cohort studies in unadjusted risk (Tau^2=0.042, Cochran's Q=9.50, p=0.05,

302   I^2=62.3%), however there was significant heterogeneity when risk was

303   adjusted (Tau^2=0.070, Cochran's Q=13.70, p=0.008, I^2=80.2%).

304   There was significant statistical heterogeneity between DM case-

305   control/cross-sectional studies in unadjusted risk (Tau^2=0.258, Cochran's

306   Q=104.67, p<0.0001, I^2=93.2%), however there this was non-significant for

307   adjusted risk (Tau^2=0.00, Cochran's Q=6.46, p=0.26, I^2=0.0%).

308   There was non-significant statistical heterogeneity between IGT cross-

309   sectional studies for unadjusted risk (Tau^2=0.003, Cochran's Q=7.18, p=0.30,

310   I^2=21.6%), however this was significant for adjusted risk (Tau^2=0.086,

311   Cochran's Q=62.21, p<0.0001, I^2=92.7%).

312   Combination of cross-sectional IGT studies with cross-sectional/case-

313   control DM studies demonstrated significant heterogeneity for both

314   unadjusted (Tau^2=0.11, Cochran's Q=160.10, p<0.0001, I^2=91.2%) and

315   adjusted risk (Tau^2=0.044, Cochran's Q=75.4, p<0.001, I^2=81.2%). However,

316   there was no statistical difference between subgroups for either unadjusted

317   (I^2=0%, p=0.54) or adjusted risk (I^2=0%, p=0.60).

318   There was significant statistical heterogeneity between MetS cross-

319   sectional studies for both unadjusted risk (Tau^2=0.092, Cochran's Q=26.08,

320   p<0.0001, I^2=79.5%), and adjusted risk (Tau^2=0.034, Cochran's Q=22.71,

321   p<0.001, I^2=72.7%).

322

323

324   *Publication Bias and Quality of Evidence*

325

326   Leave one out analysis did not identify any studies that significantly

327 changed the RR or OR for DM with and without IGT inclusion, nor for MetS.

328   Trim and fill analysis did no demonstrate any missing studies for DM

329 without IGT (SE=2.21). Inclusion of IGT with DM demonstrated 6 missing

330 studies (SE=2.75) (see fig. 5). The analysis demonstrated lack of negative

331 studies. Trim and fill analysis of MetS demonstrated 2 missing studies

332 (SE=1.78) [see fig. 6], both negative.

333   Egger's regression demonstrated no significant results for: DM

334 without IGT (z=0.81, p=0.42), DM with IGT (z=0.85, p=0.40) or MetS (z=0.15,

335 p=0.88).

336

337 *Figure 5. Funnel plot - DM with IGT. Black dots = included studies, white dots =*

338 *missing studies identified on 'trim and fill analysis'.*

339 *Figure 6. Funnel plot - Metabolic syndrome. Black dots = included studies,*

340 *white dots = missing studies identified on 'trim and fill analysis'.*

341

342   Overall there was a moderate risk of bias. All but two studies[29,30]

343 had scores greater than 7 on examination with the Newcastle –Ottawa

344 quality assessment scale [see tables 5-7]. Broadly taking in all studies there

345 were no sample size calculations or demonstrable levels of response. None of

346 the cohort studies provided CONSORT diagrams nor did they provide loss to

347 follow-up data in the text.

348

DM/MetS	Cohort	Newcastle-Ottawa Quality Assessment Scale			
	Study	Selection (4 stars total)	Comparability (2 stars total)	Outcome (3 stars total)	Total (out of 9)
DM	Taylor et al. 2005	***	**	**	7
	Akoudad et al. 2010	****	**	***	9
	Chen et al. 2012	***	**	***	8

Table 5. Bias analysis of Cohort studies

DM/MetS	Cross-sectional	Newcastle-Ottawa Quality Assessment Scale			
	Study	Selection (5 stars total)	Comparability (2 stars total)	Outcome (3 stars total)	Total (out of 10)
DM	Meydan et al. 2003	0	0	**	2
	Taylor et al. 2005	**	**	**	6
	Akoudad et al. 2010	***	**	**	7
	Weinberg et al. 2013	***	**	**	7
MetS	Rendina et al. 2008	***	*	***	7
	West et al. 2008	****	**	**	8
	Jeong et al. 2011	***	**	***	8
	Kim et al. 2012	***	**	***	8
	Lee et al. 2016	**	*	***	6

Table 6. Bias analyis of cross-sectional studies

DM/MetS	Case-control	Newcastle-Ottawa Quality Assessment Scale			
	Study	Selection (4 stars total)	Comparability (2 stars total)	Exposure (3 stars total)	Total (out of 9)
DM	Lieske et al. 2006	****	**	**	8
	Davarci et al. 2011	*	*	***	5

Table 7. Bias analysis of case-control studies.

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3   359
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6   360   <u>Conclusions</u>
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11   362   In this review and meta-analysis diabetes mellitus (DM) carried a
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13   363   significantly increased risk of developing kidney stone disease (KSD) in cohort
14
15
16   364   studies with a low risk of bias. Cross-sectional and case-control studies also
17
18   365   demonstrate significantly increased likelihood of having KSD in those who
19
20
21   366   have DM with a moderate risk of bias. Impaired glucose tolerance (IGT) in the
22
23   367   context of metabolic syndrome (MetS) carries a similar likelihood to DM in
24
25   368   cross-sectional studies.
26
27
28   369   MetS carries a similar likelihood to DM and IGT in the context of MetS,
29
30   370   with little difference between each in terms of adjusted odds ratios, again
31
32   371   with a moderate risk of bias.
33
34
35   372   This is the first systematic review and meta-analysis to examine DM
36
37   373   and MetS together. The results are highly significant although are limited by
38
39   374   heterogeneity. The results for DM are likely to be reflective of the true
40
41   375   situation given that there were no missing studies identified on 'trim and fill'
42
43   376   analysis. The situation for IGT and MetS may not be reflective given some
44
45   377   negative studies were identified, and therefore there is a risk of publication
46
47
48   378   bias.
49
50   379   The main strength in this study is the cohort studies examining DM,
51
52   380   which have long follow-up periods and demonstrate highly significant results
53
54
55   381   with a low risk of bias, despite suffering from significant statistical
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382 heterogeneity. This may be the result of differing adjustments between

383 studies.

384 The case-control and cross-sectional studies examining DM were of

385 variable quality but demonstrated highly significant results, similar to the

386 cohort studies. Direct comparison between cohorts and these studies is

387 difficult due to the differing outcome measure

388 There was no differentiation between Type 1 and Type 2 DM in most

389 studies. It is unclear if type 1 confers the same risk as type 2.

390 It was unclear from the studies whether IGT was considered in

391 isolation or in combination with other MetS components, nor was it clear

392 whether the comparator groups contained those with MetS components,

393 without reaching the required three components needed for diagnosis. This

394 risks falsely lowering the risk associated with IGT due to the comparisons with

395 other potential KSD risk factors.

396 Statistical heterogeneity demonstrated in most of the analyses may

397 be due to ascertainment of KSD, variability in study populations and design

398 and publication bias.

399 There were significant variations in KSD ascertainment from patient reported

400 to medical notes to radiologically proven. Some studies may therefore under-

401 report the true number of stones.

402 Variability in study populations and design (cohort, cross-sectional

403 and case-control) ranged from hospital attendees in a single centre to large

404 regional or national cohort studies. The effect of this variability is somewhat

405   negated by dividing the studies by study design and analyzing each

406   separately.

407   DM cohort study adjusted values although the overall figure was

408   significant the confidence interval includes one, therefore this could

409   represent type 1 error.

410   Publication bias was low in this study with trim and fill analyses

411   demonstrating few missing studies (mostly for MetS) and leave-one-out

412   analysis not demonstrating any significantly heterogenous studies.

413   The pathophysiology for KSD in both DM and MetS is similar, both

414   have been linked to increased uric acid stone formation, whilst calcium stone

415   formation remains static, seemingly un-influenced by either DM or MetS[42].

416   The increased risk of KSD in DM is thought to be secondary to two factors,

417   glycaemic control[43-47] (common to both types 1 & 2 and impaired glucose

418   tolerance) and insulin resistance[47-49] (as seen in type 2 DM and MetS). The

419   adjusted odds ratios in this study for DM (OR=1.32, 95% CI: 1.21-1.43), IGT

420   (OR=1.26, 95% CI: 0.94-1.58) and MetS (OR=1.35, 95% CI: 1.16-1.54) were all

421   similar, potentially reflecting the common pathophysiology.

422   The rise in prevalence of DM and MetS is well documented and is now

423   perceived as a global pandemic[9,18]. KSD prevalence has risen in

424   parallel[3,5,6]. The Global Burden of Disease study[9,10] demonstrated

425   morbidity and absolute mortality associated with KSD has increased, perhaps

426   due to the pandemic of DM/MetS[19], although age standardized mortality

427   rates have decreased globally,. The effect is marked in higher income

428   countries (HIC), but is attenuated in lower-middle income countries

429 (LMIC)[8,10]. This may be attributable to lack of availability of prompt

430 intervention in developing countries, leading to later presentation and

431 invasive treatments including nephrectomy[50]. Following surgical treatment,

432 management to prevent recurrence is recommended[13], again this may not

433 be available in developing countries.

434　In this review, those with impaired glucose tolerance (pre-diabetes)

435 had an increased likelihood of KSD, which was similar to those with DM in

436 cross-sectional/case-control studies, although this may be suffering from

437 publication bias and the real situation may be that the likelihood of KSD in

438 IGT is lower than DM. Indeed, The NHANES III cross-sectional study[35]

439 demonstrated with increasingly poor glycaemic control led to increasing

440 likelihood of KSD as determined by fasting plasma glucose and glycosylated

441 haemoglobin. Given the evidence suggesting those with DM or MetS are at

442 increased risk of developing KSD measures to improve glycaemic control

443 should be examined for their efficacy in KSD prevention in this 'at-risk'

444 population. It should be noted that the stone type in those with DM or MetS

445 is most commonly calcium oxalate, however although still small, the

446 proportion of urate stones increases in these related populations[22] .

447　Clarity is required on the risk in type 1 diabetics and future studies

448 should differentiate these patients from type 2. Further prospective

449 examination of DM and MetS should be undertaken to accurately portray

450 whether additional risk is posed by MetS over DM and quantify this. Tight

451 glycaemic control and weight loss should be explored in primary prevention

452 studies for both MetS and DM, given the common pathophysiologic

453   mechanism. Further investigation is required to demonstrate if these patient

454   are at increased risk of recurrence.

455   The risk of developing kidney stones is significantly increased in

456   populations with chronic hyperglycaemia. This has global implications with

457   rising morbidity and absolute mortality attributable to stones and is likely to

458   increase the health and economic burden on patients and healthcare

459   providers. Tight glycaemic control and weight loss are low-cost and non-

460   invasive measures, which should be investigated for their primary

461   preventative effect on KSD in these populations and included as part of the

462   long-term management of kidney stone disease.

463

464

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Identification

Articles identified through database searching
(n = 2340)

Articles excluded on basis of title
(n = 2301)

Screening

Articles included on basis of title (n = 39)

Articles excluded on basis of abstract (n = 15):

Eligibility

Full-text articles assessed for eligibility
(n = 24)

Full-text articles rejected (n = 15):
*No non-KSD comparators (n = 9)
Incomplete data (n = 4)
Examining risk of DM with KSD (n = 2)*

Included

Articles included for Meta-Analysis

Diabetes Mellitus
(n = 7)

Metabolic syndrome
(n = 6)

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Study		RR [95% CI]
Unadjusted		
Akoudad, 2010.2		1.90 [0.98, 2.82]
Taylor, 2005: NHS II.2		1.86 [1.26, 2.46]
Taylor, 2005: NHS I.2		1.45 [1.17, 1.73]
Chen, 2012.2		1.22 [1.15, 1.29]
Taylor, 2005: HFPS.2		1.03 [0.63, 1.43]
RE Model for Unadjusted		*1.36 [1.11, 1.61]*
Adjusted		
Akoudad, 2010.1		1.98 [0.94, 3.02]
Taylor, 2005: NHS II.1		1.60 [1.08, 2.12]
Taylor, 2005: NHS I.1		1.29 [1.03, 1.55]
Chen, 2012.1		1.18 [1.10, 1.26]
Taylor, 2005: HFPS.1		0.81 [0.56, 1.06]
RE Model for Adjusted		*1.23 [0.94, 1.51]*
RE Model Total		1.29 [1.10, 1.47]

RR

Study	OR [95% CI]
Adjusted IGT	
Jung et al. 2011.2	1.64 [1.51, 1.77]
West et al. 2008.2	1.27 [0.61, 1.93]
Jeong et al. 2011.2	1.09 [0.84, 1.34]
Kim et al. 2012	1.03 [0.96, 1.10]
RE Model for Adjusted IGT	1.26 [0.94, 1.58]
Adjusted DM	
Weinberg, 2013.2	1.76 [1.27, 2.25]
Taylor, 2005: NHS II.2	1.67 [1.21, 2.13]
Taylor, 2005: NHS I.2	1.38 [1.02, 1.74]
Taylor, 2005: HFPS.2	1.30 [1.09, 1.51]
Akoudad, 2010.2	1.27 [1.07, 1.47]
Lieske, 2006.2	1.22 [1.01, 1.43]
RE Model for Adjusted DM	1.32 [1.21, 1.43]
Unadjusted IGT	
Lee et al. 2016	1.87 [0.60, 3.14]
Jeong et al. 2011.1	1.57 [1.23, 1.91]
West et al. 2008.1	1.39 [0.62, 2.16]
Rendina, 2008	1.39 [0.95, 1.83]
Kim, 2012 (Female)	1.26 [1.11, 1.41]
Jung et al. 2011.1	1.26 [1.11, 1.41]
Kim, 2012 (Male)	1.18 [1.10, 1.26]
RE Model for Unadjusted IGT	1.25 [1.17, 1.34]
Unadjusted DM	
Zeydan, 2003	2.50 [0.84, 4.16]
Weinberg, 2013.1	2.44 [1.74, 3.14]
Taylor, 2005: NHS II.1	1.84 [1.34, 2.34]
Davarci, 2011	1.63 [1.00, 2.26]
Taylor, 2005: NHS I.1	1.55 [1.16, 1.94]
Lieske, 2006.1	1.29 [1.07, 1.51]
Taylor, 2005: HFPS.1	1.21 [1.02, 1.40]
Akoudad, 2010.1	0.64 [0.55, 0.73]
RE Model for Unadjusted DM	1.49 [1.09, 1.89]
RE Model Total	1.35 [1.22, 1.48]

OR

Study	OR [95% CI]
Unadjusted	
Rendina, 2008.2	2.20 [1.60, 2.80]
West, 2008.2	2.13 [1.69, 2.57]
Lee, 2016.2	2.04 [1.07, 3.01]
Jeong, 2011.2	1.71 [1.42, 2.00]
Jung, 2011.2	1.59 [1.30, 1.88]
Kim, 2012.2	1.33 [1.23, 1.43]
RE Model for Unadjusted	*1.74 [1.45, 2.04]*
Adjusted	
Rendina, 2008.1	2.00 [1.15, 2.85]
Lee, 2016.1	1.83 [0.94, 2.72]
West, 2008.1	1.52 [1.34, 1.70]
Jung, 2011.1	1.36 [1.11, 1.61]
Jeong, 2011.1	1.25 [1.02, 1.48]
Kim, 2012.1	1.11 [1.03, 1.19]
RE Model for Adjusted	*1.35 [1.16, 1.55]*
RE Model Total	1.56 [1.36, 1.76]

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5,6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7

PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8,9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8 + figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8,9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9,10 + fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

For more information, visit: **www.prisma-statement.org**.

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Does Chronic Hyperglycaemia Increase the Risk of Kidney Stone disease? Results from a Systematic Review and Meta-Analysis

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4   2   <u>Systematic Review and Meta-Analysis</u>
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39   30   Abstract word count: 289
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41   32   Text word count: 3587
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44   34   Keywords: Diabetes Mellitus; Impaired Glucose Tolerance; Metabolic Syndrome: Kidney
45   35   Stone Disease
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37   Abstract

38   **Design:** Systematic review and meta-analysis of observational studies

39   was performed using PRISMA guidelines for studies reporting on Diabetes

40   Mellitus (DM) or Metabolic syndrome (MetS) and kidney stone disease (KSD).

41   **Objective:** To examine the association between chronic

42   hyperglycaemia, in the form of DM and Impaired Glucose Tolerate (IGT) in the

43   context of MetS, and KSD.

44   **Setting:** Population based observational studies. Databases searched:

45   Ovid Medline without revisions (1996-June 2018), Cochrane Library (2018),

46   CINAHL (1990-June 2018), Clinicaltrials.gov, Google Scholar and individual

47   journals including the Journal of Urology, European Urology and Kidney

48   International.

49   **Participants:** Patients with and without chronic hyperglycaemic states

50   (DM and MetS).

51   **Main Outcome Measures:** English language articles from January

52   2001-June 2018 reporting on observational studies. Exclusions: no

53   comparator group or fewer than 100 patients. Unadjusted values were used

54   for meta-analysis, with further meta-regression presented as adjusted values.

55   Bias was assessed using Newcastle-Ottawa scale.

56   **Results:** 2340 articles were screened with 13 studies included for

57   meta-analysis, 7 DM (3 cohort) and 6 MetS. 5 of the MetS studies provided

58   data on IGT alone. These included: DM, n=28,329; MetS, n=31,767; IGT,

59   n=12,770. Controls: DM, n=589,791; MetS, n=178,050; IGT, n=293,852

60   patients.

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3   61   Adjusted risk for DM cohort studies, RR=1.23 (0.94-1.51) (p<0.001).
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6   62   Adjusted Odds ratios for: DM cross-sectional/case-control studies, OR=1.32
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8   63   (1.21-1.43) (p<0.001); IGT, OR=1.26 (0.92-1.58) (p<0.0001) and MetS,
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11   64   OR=1.35 (1.16-1.54) (p<0.0001).
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13   65   There was no significant difference between IGT and DM (cross-
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15   66   sectional/case-control), nor IGT and MetS. There was a moderate risk of
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18   67   publication bias. Statistical heterogeneity remained significant in adjusted
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20   68   DM cohort values and adjusted IGT (cross-sectional/case-control), but non-
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23   69   signficant for adjusted DM (cross-sectional/case-control).
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25   70   **Conclusion:** Chronic hyperglycaemia increases the risk of developing
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28   71   kidney stone disease. In the context of the diabetes pandemic, this will
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30   72   increase the burden of stone related morbidity and mortality.
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33   73   **Trial registration:** PROSPERO registration number CRD42018093382.
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35   74   **Strengths and Limitations of This Study**
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38   75   • Largest systematic review and meta-analysis examining the risk of
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40   76   chronic hyperglycaemic states and kidney stone disease (KSD), with
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43   77   bias analysis.
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45   78   • Meta-analysis of Cohort studies examining Diabetes Mellitus
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48   79   demonstrates an increased risk of KSD of of 1.23 (0.94-1.51) (p<0.001)
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50   80   over the general population.
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52   81   • There was a moderate risk of publication bias.
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55   82   • Statistical heterogeneity remained significant in adjusted DM cohort
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57   83   values and adjusted IGT
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60   84   • No data on stone type

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85 Introduction

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87   Kidney stone disease (KSD) is a painful and costly condition[1] where

88 precipitates of normal urinary solutes aggregrate to form stones of varying

89 sizes and compositions[2]. Incidence of acute urolithiasis is rising

90 worldwide[3-6], with corresponding rises in surgical treatment rates[7] and

91 morbidity[8,9] although mortality has declined[8,10]. 5-year recurrence rates

92 have been reported as high as 50%[11]. Long term problems associated with

93 recurrent KSD are decreased quality of life, missed work days[12], disabling

94 pain, need for repeated operations, complications including infection and

95 acute kidney injury[13,14], as well as long term increased risk of developing

96 chronic kidney disease[15].

97   Patients with Diabetes mellitus (DM)[16] and metabolic syndrome

98 (MetS)[17] have been identified as carrying a higher risk of developing KSD.

99 The global prevalence of both conditions has risen to pandemic levels[9,18]

100 seemingly in parallel with KSD[19]. There is overlap between the two

101 conditions, with impaired glucose tolerance (IGT), or pre-diabetes being one

102 of the five components of the 'metabolic syndrome'[20]. Although the

103 pathophysiology with respect to KSD is yet to be definitively described,

104 patients with either MetS or DM have been shown to have increased urinary

105 acidification and produce more uric acid stones than controls. Notably, with

106 rising BMI in both diabetic and non-diabetic patients, the incidence of uric

107 acid stones rises, whilst calcium oxalate stones fall[21,22].

108   Previous systematic reviews have examined either DM[23] or

109   MetS[24,25] in isolation. These studies performed either no meta-

110   analysis[25], or else their heterogeneity/ sensitivity analyses were

111   limited[23,24]. Given the overlap between the two conditions we aimed to

112   perform a systematic review and meta-analysis of the existing literature on

113   both DM and MetS with complete sensitivity, bias and heterogeneity

114   analyses.

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117   <u>Evidence Acquisition</u>

118   *<u>Search strategy and study selection</u>*

119   Population – Chronic hyperglycaemics (diabetes mellitus, impaired glucose

120   tolerance in context of metabolic syndrome) and those with metabolic

121   syndrome

122   Comparator – Those without hyperglycaemia (DM/IGT) or metabolic

123   syndrome, respectively

124   Outcome – Kidney stone disease (KSD) – all compositions

125   Study design – Systematic review and meta-analysis of published

126   observational studies (cohort, case control and cross-sectional)

127

128   Inclusion criteria:

129   1) All articles written in the English language

130   2) Adults (>18 years)

131　　3) All articles reporting on risk of developing kidney stone disease in

132　　　　diabetes mellitus (type 1 and type 2) in comparison to general

133　　　　population

134　　4) All articles reporting on risk of developing kidney stone disease in

135　　　　patients with metabolic syndrome in comparison to general

136　　　　population.

137　　5) Risk in risk ratio (RR), hazard ratio (HR), odds ratio (OR) or prevalence

138　　　　ratio (PR) with 95% confidence intervals.

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140　Exclusion criteria:

141　　1) Older studies using the same data as a more recent study – longest

142　　　　follow-up used.

143　　2) Studies exclusively using patients with kidney stone disease – unable

144　　　　to calculate risk

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

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147　The systematic review was performed according to the PRISMA

148　guidelines[26]. The search strategy was conducted to find relevant studies

149　from Ovid Medline without revisions (1996-June 2018), Cochrane Library

150　(2018), CINAHL (1990-June 2018), Clinicaltrials.gov, Google Scholar and

151　individual journals including the Journal of Urology, European Urology and

152　Kidney International. The review was registered prospectively with

153　PROSPERO, ID number: CRD42018093382.

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154   Terms used included: "Diabetes", "Diabetes mellitus", "metabolic syndrome",

155   "urolithiasis", "nephrolithiasis", "kidney", "uret*", "ston*", "calcul*". Boolean

156   operators (AND, OR) were used to refine the search.

157   The search was limited to English language articles between January 2001 and

158   June 2018. Only published data were used.

159   Two reviewers (RG and AM) identified all studies. All studies that appeared to

160   fit the inclusion criteria were included for full review. Each reviewer

161   independently selected studies for inclusion in the review [see fig. 1]. If there

162   was disagreement, PR and BKS made final decision on inclusion.

163   *Data extraction and Assessment of Quality*

164   The following variables were extracted from each study: first author, year of

165   publication, type of study, sample size, age, country, male:female ratio,

166   ascertainment of DM/IGT/MetS/KSD, type of DM, number of patient

167   reporting/presenting with stone disease for diabetes mellitus, metabolic

168   syndrome and specifically IGT in the context of MetS (given the common

169   mechanism – hyperglycaemia and insulin resistance).

170   Risk of KSD in RR, HR, OR or PR with 95% confidence intervals was also

171   extracted. HR and RR, and OR and PR, were considered the same and are

172   presented as RR and OR respectively. Unadjusted and adjusted risk values were

173   extracted from the studies. Adjustment factors were recorded. If adjusted

174   values were missing then the study was removed from the adjusted meta-

175   analysis.

176   Cross-sectional and case-control studies were pooled as there were no case-

177   control studies for MetS, and 2 case-control studies for DM, only one of which

178   gave adjusted values.

179   Data were collated using Microsoft Excel (version 12.2.4). Level of evidence

180   was assessed and study bias was analysed using the Newcastle-Ottawa bias

181   assessment tool[27].

182   *Data Sharing*

183   Data has been uploaded to PROSPERO or can be obtained, upon reasonable

184   request, by emailing the corresponding author.

185   *Statistical Methods*

186   Risk is presented with a 95% confidence interval as risk ratio (RR) for cohort

187   studies and odds ratio (OR) for case control and cross-sectional studies.

188   Statistical heterogeneity was tested for using I^2, Tau^2 and Cochran's Q. P values

189   <0.05 were considered statistically significant, I^2 values were interpreted

190   according to chapter 9.5.2 of the Cochrane handbook. Heterogeneity was also

191   tested with 'leave one out' analyses. Publication bias was assessed with Egger's

192   test and 'trim and fill' analysis.   Meta-regression analysis was performed,

193   adjusting for age and gender. Student T Statistic is utilized for degrees of

194   freedom.

195 Statistical analyses and figures were generated in R (R foundation for statistical

196 computing, Vienna, Austria) with the metafor package[28].

197 *Role of the funding source/Competing interests*

198 There is no funding to report. None of the authors have any competing

199 interests to declare.

200

201 *Figure 1. PRISMA flow diagram for article selection*

202 Contributorship

203 RG performed the search, statistical analysis and wrote the manuscript. AA

204 performed the search and reviewed the manuscript. PC, BS and PR edited the manuscript

205 and critiqued the statistical analysis. BS and PR decided whether or not to include studies as

206 the senior authors

207 Patient and Public Involvement

208 Patients/the public were not involved in this review article.

209

210 Evidence Synthesis

211 Fifteen studies were included in the systematic review from an initial

212 search total of 2340 [see figure 1]. 2301 articles were excluded on the basis of

213 title, 15 on the basis of abstract and 15 on reading the full text. This left 13

214 studies, 7 examining diabetes mellitus (DM) and 6 examining impaired

215 glucose tolerance (IGT) in the context of metabolic syndrome (MetS). Inter-

216 rater reliability as assessed by Cohen's kappa was 0.95.

Demographics of included studies

Diabetes Mellitus

Seven studies were included examining DM[29-35]. Three were

cohort[29-31], three were case-control[32-34] and three were cross-

sectional[29,31,35]. Taylor et al.[29] and Akoudad et al.[31] 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[34] [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 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 control [see table 3]. In the cohort studies,

1312 (7.5%) of patients with DM developed KSD compared to 11,516 (3.3%)

of controls. In the case-control and cross-sectional studies, 1097 (10.2%) of

diabetics had KSD compared to 11,985 (5.0%) of controls. Study reported risk

is detailed in tables 2 and 3.

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DM	Study	Study type	Country	Sample	Controls	Metabolic syndrome definition	Diabetes Mellitus ascertainment	KSD ascertainment	M:F (%)	Mean age
Cohort	Taylor et al. 2005	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) (male health professionals) – '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 ($\geq$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; HFPS: 60.9
	Chen et al. 2012	Retrospective Cohort	Taiwan	National Health Insurance system database - prospectively maintained - patients with DM (T1 + T2) (2000-2007: 7	Without DM and excluding patients who developed DM in Follow-	N/A	At least 3 outpatient visits for DM from 2000-2002 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

	Study	Design	Country	Population	Controls		Diabetes definition	KSD definition	M:F	Age
				years f/u). Known KSD excluded at start.	up period					
	Akoudad et al. 2010	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>110mg/dL, FPG>126mg/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)
Ca Co	*Lieske et al. 2006*	Case control	USA	Rochester, Olmsted County, Minnesota residents with electronically documented KSD - random sample of results of electronic medical record search of Mayo	Patients without electronic documentation of KSD, matched for age, sex and calender year of stone	N/A	Electronic medical records using codes: ICD9 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: ICD9-CM 592, 594, 275.11 with case review	62: 38	45.0±18

				clinic and Olmsted clinic databases (Original search n>7000)						
	Davarci et al. 2011	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>110mg/dL, FPG>126mg/dL. T1 excluded	USS, AXR, patient reported	47.5:52.5	49.0±10
XS	Meydan et al. 2003	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. 2005	Cross-sectional	USA	Baseline characteristics: NHS I (1980) + II (1991) (female nurses), HFPS participants	Baseline characteristics: NHS I + II, HFPS participa	N/A	Biennial health questionnaire with supplementary questionnaire on symptoms, diagnostic tests and treatment -	Biennial health questionnaire and medical record review for corroboration -	22:78	NHS I: 48.6; NHS II: 37.6; HFPS: 60.9

						DM Diagnosis / IGT/DM ascertainment			
			(1986) (male health professionals) - diabetics	nts - non-diabetics		DM Diagnosis corroborated by medical record review	kidney stone history		
Akouda d et al. 2010	Cross-sectio nal	USA	ARIC study participants: Visit 3 (1993-1995), patient reported physician diagnosis of KSD	Without KSD	N/A	Receiving diabetic medication, OGTT with FPG>110mg/dL, FPG>126mg/dL, patient reported physician diagnosis	Patient reported physician diagnosis	44:56 (calcul ated)	60.0 ± 5.7 (calcula ted)
Weinbe rg et al. 2013	Cross-sectio nal	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
Me tS						**IGT/DM ascertainment**			
Rendin a et al. 2008 XS	Cross-sectio nal	Italy	Single centre inpatients between 2004-2005 - those with MetS or IGT. Exclusions: acute/chronic renal failure, abnormal renal	Those without MetS or IGT	American Heart Association; National Heart, Lung, and Blood Institute: 3 or more of: 1) Waist circumference >102cm in men, >88cm in women. 2) fasting serum triglycerides >1.7mmol/L or treatment. 3) fasting serum HDL <1.03mmol/L in men, <1.30mmol/L in women or	Fasting serum glucose >5.6mmol/L or treatment	Questionnaire re: symptoms of renal colic and Ultrasonography	49:51	63.8 ± 15.8

			anatomy, hyperthyroidism, hyperparathyroidism, treatment for osteoporosis, metabolic bone disorders, neoplasia		treatment. 4) Systolic >130mmHg or Diastolic >85mmHg or treatment. 5) fasting serum glucose >5.6mmol/L or treatment		
West et al. 2008	Cross-sectional	USA	NHANES III participants (1988-1994) - those with metabolic syndrome/impaired glucose tolerance	2 or fewer MetS traits/no MetS traits	American Heart Association; National Heart, Lung, and Blood Institute as per Rendina et al.	Fasting serum glucose >5.6mmol/L or treatment	Self report of physician diagnosis
Jeong et al. 2011	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 - 3 or more of: Systolic >130mmHg, Diastolic >85mmHg, random blood glucose >110mg/dL, random serum triglycerides >150mg/dL, random serum HDL <40mg/dL in men or <50mg/dL in women, obese range waist circumference	Fasting blood glucose >110mg/dL	Radiological records (ultrasound and CT)

West et al. 2008: 48:52 | 58.8 ± 17.1

Jeong et al. 2011: 60:40 | 50.0 ± 10.4

Jung et al. 2011	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 - 3 or more of: Systolic >130mmHg, Diastolic >85mmHg, random blood glucose >110mg/dL, random serum triglycerides >150mg/dL, random serum HDL <40mg/dL in men or <50mg/dL in women, obese range waist circumference	Fasting blood glucose >110mg/dL	Ultrasonography	55:45	44.9 ± 11.5
Kim et al. 2012	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 - 3 or more of: Systolic >130mmHg, Diastolic >85mmHg, random blood glucose >110mg/dL, random serum triglycerides >150mg/dL, random serum HDL <40mg/dL in men or <50mg/dL in	Fasting blood glucose >110mg/dL	Ultrasonography	58:42	42.3 ± 8.4
Lee et al. 2016	Cross-sectional	Taiwan	Single centre - men undergoing free health screening -	Unclear - ?Those without	3 of the 5 following criteria: patients were defined as having MtS by the presence of at least three of five of the following	T2DM - fasting BGL >126mg/dL	(a) characteristic clinical findings diagnosed by a physician with	100:0	55.6 ± 4.6

			those with MetS/DM	MetS or DM	criteria: waist circumference (WC) 90cm, high-density lipoprotein (HDL) cholesterol540 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.		available medical records; (b) evidence of kidney stones from ultrasonography judged by an investigator (urologist); (c) operative history of stones removal from kidney.		

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240   *Table 1. Study demographics. F/U=follow up, T1= Type 1 diabetes mellitus, T2=Type 2 diabetes mellitus*

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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. 2005: NHS I (younger female)*	1,409	93,758	65,566	1,371,080	109 (7.7%)	1578 (1.7%)	RR 1.45 (1.20-1.77)	RR 1.29 (1.05-1.58)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: NHS II (older female)	891	101,877	12,291	824,076	40 (4.5%)	1491 (1.5%)	RR 1.86 (1.36-2.56)	RR 1.60 (1.16-2.21)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: HFPS (male)	1391	46,062	21,676	450,984	44 (3.2%)	1426 (3.1%)	RR 0.76 (1.56-1.03)	RR 0.81 (0.59-1.09)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Chen et al. 2012	12,257	96,781	75,975	607,842	1,096 (8.9%)	6950 (7.2%)	HR 1.22 (1.15-1.30)	HR 1.18 (1.10-1.27)	Age, Sex, Occupation, urbanisation, income and UTIs
	Akoudad et al. 2010	1,629	9,558	N/A	N/A	N/A	N/A	N/A	HR 1.98 (1.20-3.28)	Age, Sex, Race, waist circumference, hypertension, triglyceride level, uric acid, gallstones
	Total	**17,577**	**348,036**	**253,365**	**3,253,982**	**1289 (8.1%)**	**11445 (3.4%)**			

245   *Table 2. DM Cohort studies.*

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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. 2006*	3,561	3561	335 (9.4%)	268 (7.5%)	OR 1.29 (1.09-1.53)	OR 1.22 (1.03-1.46)	Age, Sex, year of diagnosis, DM, hypertension and obesity
	Davarci et al. 2011	23	177	14 (17.5%)	66 (37.3%)	RR 1.63 (1.12-2.39)	N/A	N/A
XS	*Meydan et al. 2003*	321	115	84 (26.2%)	14 (12.2%)	*OR 2.5 (1.39-4.71) (calculated)*	N/A	N/A
	Taylor et al. 2005: NHS I (younger female)	1,473	74,266	64 (4.3%)	2029 (2.7%)	RR 1.55 (1.20-1.99)	RR 1.38 (1.06-1.79)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: NHS II (older female)	949	94,485	58 (6.1%)	3093 (3.3%)	RR 1.84 (1.41-2.41)	RR 1.67 (1.28-2.20)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Taylor et al. 2005: HFPS (male)	1,568	47,737	177 (11.3%)	4002 (8.4%)	RR 1.21 (1.03-1.42)	RR 1.31 (1.11-1.54)	Age, BMI, Thiazide use, fluid intake, alcohol use, calcium supplementation and diet
	Akoudad et al. 2010	1,812	10,349	183 (18.8%)	1629 (14.6%)	N/A	PR 1.27 (1.08-1.49)	Age, Sex, Race, Region, waist circumference, triglycerides, hypertension, uric acid, gallstones

	Study					OR	OR	Adjustments
	Weinberg et al. 2013	*1,045 (estimated)*	*11,065 (estimated)*	*182 (17.1%) (estimated)*	*884 (8.0%) (estimated)*	OR 2.44 (1.84-3.25)	OR 1.76 (1.33-2.32)	Age, Sex, Race, Smoking history, BMI
	Sub Total	**10,752**	**241,755**	**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. 2008*	317 (14.9%)	*1815 (calculated estimate)*	43 (13.6%)	*177 (8.7%) (calculated estimate)*	N/A	Male: OR 1.1 (0.5-2.4) Female: OR 1.1 (0.3-1.8)	Age, waist circumference, high serum triglycerides, low serum HDL, hypertension
	West et al. 2008	1260 (8.5%)	*7268 (calculated estimate)*	17 (1.3%)	71 (1.0%)	*OR 1.39 (0.81-2.36) (calculated)*	OR 1.27 (0.77-2.10) (One metabolic syndrome component)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jeong et al. 2011	6929 (19.9%) (Quintile 5 - ≥104mg/dL)	13,700 (Quintile 1 - ≤85mg/dL)	211 (3.0%)	240 (1.8%)	OR 1.57 (1.26-1.95)	OR 1.09 (0.87-1.37)	Age, sex, metabolic syndrome components, MetS status

	Study	Total participants		Case Control				Study Reported Unadjusted	Study Reported Adjusted	Adjusted For
	Jung et al. 2011	4192 (10.3%)	*28,692 (calculated estimate)*	102 (2.4%)	*450 (1.6%) (calculated estimate)*	1.26 (1.12-1.42)	OR 1.30 (1.03-1.64)			Age, GFR, serum urate, phosphorous and calcium
	Kim et al. 2012	N/A	N/A	N/A	N/A	Male: OR 1.18 (1.10-1.26) Female: OR 1.26 (1.12-1.42)	Male: OR 1.03 (0.97-1.11) Female: OR 1.02 (0.90-1.16)			Age, serum creatinine, serum urate, past medical history of KSD
	Lee et al. 2016	72 (11.3%) (DM)	622	14 (19.4%)	71 (11.7%)	*OR 1.87 (0.99-3.53) (calculated)*	N/A			N/A
	Sub Total	**12770 (6.1%)**	**52,097**	**387 (3.2%)**	**1009 (1.9%)**					
	Total	**23,522**	**293,852**	**1484 (6.3%)**	**12,994 (4.4%)**					

255 *Table 3. DM and IGT case-control and cross-sectional studies.*

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MetS	Study	Total participants, n	Metabolic Syndrom	Controls, n	Metabolic Syndrom	Control with	Study Reported Unadjuste	Study Reported Adjusted	Adjusted For

			e, n (% of total)		e with KSD, n (% of MetS)	KSD, n (%)	d Risk (95% CI)	Risk (95% CI)	
XS	*Rendina et al. 2008*	2132	725 (34.0%)	1407	112 (15.4%)	108 (7.7%)	OR 2.2 (1.7-2.9)	OR 2.0 (1.3-3.0)	Age, sex, history of KSD
	West et al. 2008	14,870	4952 (33.3%)	9,921	628 (12.7%)	363 (3.7%)	OR 2.13 (1.74-2.62)	OR 1.52 (1.22-1.89)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jeong et al. 2011	34,895	4602* (13.2%)	30,293	177 (3.8%)	662 (2.2%)	OR 1.71 (1.45-2.03)	1.25 (1.03-1.50)	Sex, race, socioeconomic status, gout, thiazide use, allopurinol use
	Jung et al. 2011	40,687	7803 (19.2%)	32,884	166 (2.1%)	443 (1.3%)	N/A	OR 1.36 (1.13-1.64)	Age, GFR, serum urate, phosphorous and calcium
	Kim et al. 2012	116,536	13416 (11.5%)	103,120	1129 (8.4%)	5978 (5.8%)	OR 1.33 (1.24-1.44)	OR 1.11 (1.03-1.20)	Age, serum creatinine, serum urate, past medical history of KSD
	Lee et al. 2016	694	269 (42.1%)	425	46 (17.1%)	39 (9.2%)	N/A	OR 1.83 (1.14-2.93)	Age
	Total	**209,814**	**31,767 (15.1%)**	**178,050**	**2258 (7.1%)**	**7593 (4.3%)**			

259 *Table 4. MetS cross-sectional studies. *=discrepancy between text and table.*

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262   *Metabolic syndrome*

263   There were six studies[36-41] examining metabolic syndrome, of

264   which five provided data on chronic hyperglycaemia (IGT/DM)[36-39,41]. All

265   the studies were cross-sectional. These took place in Italy, South Korea,

266   Taiwan and USA. The samples ranged from hospital inpatients to

267   representative population based studies, which were representative of target

268   populations [see table 1].

269   The male to female ratio and mean age for each study is detailed in

270   table 1. MetS and KSD ascertainment ranged from the patient reported

271   diagnosis to ICD codes in medical records.

272   Overall there were 209,817 patients, of whom 31,767 (17.8%) had

273   MetS, 12,770 (6.1%) had IGT only [see table 4]. 2258 (7.1%) of those with

274   MetS had KSD, compared to 7593 (4.3%) of controls. 387 (3.2%) of those with

275   IGT had KSD compared to 1009 (1.9%) of controls [see table 3]. Unfortunately

276   control population had to be calculated from the OR for some of the

277   studies[36-38], therefore the figures for IGT are estimates. Study reported

278   risk is detailed in table 3 and 4.

279   *Meta-Analysis*

280   Tests for overall unadjusted effect in those with DM demonstrated

281   significantly higher risk of KSD (RR=1.66 (95% CI: 1.27-2.18, p<0.001).

282   Subgroup analyses by study type demonstrated significantly higher risk of

283   KSD in patients with DM in cohort studies in both unadjusted (1.36, 95% CI:

284   1.11-1.60, p<0.001) [see fig. 1] and adjusted risk (RR=1.23, 95% CI: 0.94-1.51,

285   p<0.001) [see fig. 2]. Significantly increased risk was also demonstrated in

286   cross-sectional/case-control studies in both unadjusted (OR=1.49, 95% CI:

287   1.09-1.89, p<0.0001) and adjusted risk (OR=1.32, 95% CI: 1.21-1.43, p<0.001)

288   [see fig. 3]. IGT in the context of MetS demonstrated significantly increased

289   risk in both unadjusted (OR=1.25, 95% CI: 1.16-1.54, p<0.0001) and adjusted

290   risk (OR=1.26, 95% CI: 0.94-1.58) [see fig. 3]. Combining DM case-control and

291   cross-sectional studies with IGT demonstrated significantly increased risk in

292   both unadjusted (OR=1.38, 95% CI: 1.18-1.59, p<0.0001) and adjusted risk

293   (OR=1.32, 95% CI: 1.17-1.49, p<0.0001).

294   Cross-sectional studies examining MetS also demonstrated

295   significantly increased risk of KSD in both unadjusted (OR=1.74, 95% CI: 1.45-

296   2.04, p<0.0001) and adjusted (OR=1.35, 95% CI: 1.16-1.54, p<0.0001) [see fig.

297   4] values.

298

299   *Figure 2. Forest Plot analysis – DM Cohort.*

300   *Figure 3. Forest Plot analysis – DM + IGT Cross-sectional and Case Control*

301   *studies.*

302   *Figure 4. Forest Plot analysis – Metabolic syndrome (cross-sectional)*

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304   *Heterogeneity and Sensitivity Analysis*

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306   There was borderline significant statistical heterogeneity between DM

307   cohort studies in unadjusted risk (Tau^2=0.042, Cochran's Q=9.50, p=0.05,

308   I^2=62.3%), however there was significant heterogeneity when risk was

309   adjusted (Tau^2=0.070, Cochran's Q=13.70, p=0.008, I^2=80.2%).

310   There was significant statistical heterogeneity between DM case-

311   control/cross-sectional studies in unadjusted risk (Tau^2=0.258, Cochran's

312   Q=104.67, p<0.0001, I^2=93.2%), however there this was non-significant for

313   adjusted risk (Tau^2=0.00, Cochran's Q=6.46, p=0.26, I^2=0.0%).

314   There was non-significant statistical heterogeneity between IGT cross-

315   sectional studies for unadjusted risk (Tau^2=0.003, Cochran's Q=7.18, p=0.30,

316   I^2=21.6%), however this was significant for adjusted risk (Tau^2=0.086,

317   Cochran's Q=62.21, p<0.0001, I^2=92.7%).

318   Combination of cross-sectional IGT studies with cross-sectional/case-

319   control DM studies demonstrated significant heterogeneity for both

320   unadjusted (Tau^2=0.11, Cochran's Q=160.10, p<0.0001, I^2=91.2%) and

321   adjusted risk (Tau^2=0.044, Cochran's Q=75.4, p<0.001, I^2=81.2%). However,

322   there was no statistical difference between subgroups for either unadjusted

323   (I^2=0%, p=0.54) or adjusted risk (I^2=0%, p=0.60).

324   There was significant statistical heterogeneity between MetS cross-

325   sectional studies for both unadjusted risk (Tau^2=0.092, Cochran's Q=26.08,

326   p<0.0001, I^2=79.5%), and adjusted risk (Tau^2=0.034, Cochran's Q=22.71,

327   p<0.001, I^2=72.7%).

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329

330   _Publication Bias and Quality of Evidence_

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332   Leave one out analysis did not identify any studies that significantly

333   changed the RR or OR for DM with and without IGT inclusion, nor for MetS.

334   Trim and fill analysis did no demonstrate any missing studies for DM

335   without IGT (SE=2.21). Inclusion of IGT with DM demonstrated 6 missing

336   studies (SE=2.75) (see fig. 5). The analysis demonstrated lack of negative

337   studies. Trim and fill analysis of MetS demonstrated 2 missing studies

338   (SE=1.78) [see fig. 6], both negative.

339   Egger's regression demonstrated no significant results for: DM

340   without IGT (z=0.81, p=0.42), DM with IGT (z=0.85, p=0.40) or MetS (z=0.15,

341   p=0.88).

342

343   _Figure 5. Funnel plot - DM with IGT. Black dots = included studies, white dots =_

344   _missing studies identified on 'trim and fill analysis'._

345   _Figure 6. Funnel plot - Metabolic syndrome. Black dots = included studies,_

346   _white dots = missing studies identified on 'trim and fill analysis'._

347

348   Overall there was a moderate risk of bias. All but two studies[29,30]

349   had scores greater than 7 on examination with the Newcastle –Ottawa

350   quality assessment scale [see tables 5-7]. Broadly taking in all studies there

351   were no sample size calculations or demonstrable levels of response. None of

352   the cohort studies provided CONSORT diagrams nor did they provide loss to

353   follow-up data in the text.

354

DM/MetS	Cohort	Newcastle-Ottawa Quality Assessment Scale			
	Study	Selection (4 stars total)	Comparability (2 stars total)	Outcome (3 stars total)	Total (out of 9)
DM	Taylor et al. 2005	***	**	**	7
	Akoudad et al. 2010	****	**	***	9
	Chen et al. 2012	***	**	***	8

355   *Table 5. Bias analysis of Cohort studies*

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DM/MetS	Cross-sectional	Newcastle-Ottawa Quality Assessment Scale			
	Study	Selection (5 stars total)	Comparability (2 stars total)	Outcome (3 stars total)	Total (out of 10)
DM	Meydan et al. 2003	0	0	**	2
	Taylor et al. 2005	**	**	**	6
	Akoudad et al. 2010	***	**	**	7
	Weinberg et al. 2013	***	**	**	7
MetS	Rendina et al. 2008	***	*	***	7
	West et al. 2008	****	**	**	8
	Jeong et al. 2011	***	**	***	8
	Kim et al. 2012	***	**	***	8
	Lee et al. 2016	**	*	***	6

362   *Table 6. Bias analyis of cross-sectional studies*

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DM/MetS	Case-control	Newcastle-Ottawa Quality Assessment Scale

	Study	Selection (4 stars total)	Comparability (2 stars total)	Exposure (3 stars total)	Total (out of 9)
DM	*Lieske et al. 2006*	****	**	**	8
	Davarci et al. 2011	*	*	***	5

364 *Table 7. Bias analysis of case-control studies.*

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366 <u>Discussion</u>

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368 In this review and meta-analysis diabetes mellitus (DM) carried a

369 significantly increased risk of developing kidney stone disease (KSD) in cohort

370 studies with a low risk of bias. Cross-sectional and case-control studies also

371 demonstrate significantly increased likelihood of having KSD in those who

372 have DM with a moderate risk of bias. Impaired glucose tolerance (IGT) in the

373 context of metabolic syndrome (MetS) carries a similar likelihood to DM in

374 cross-sectional studies.

375 MetS carries a similar likelihood to DM and IGT in the context of MetS,

376 with little difference between each in terms of adjusted odds ratios, again

377 with a moderate risk of bias.

378 This is the first systematic review and meta-analysis to examine DM

379 and MetS together. The results are highly significant although are limited by

380 heterogeneity, despite meta-regression analysis. The results for DM are likely

381 to be reflective of the true situation given that there were no missing studies

382 identified on 'trim and fill' analysis. The situation for IGT and MetS may not

383 be reflective given some negative studies were identified, and therefore

384 there is a risk of publication bias.

385 The main strength in this study is the cohort studies examining DM,

386 which have long follow-up periods and demonstrate highly significant results

387 with a low risk of bias, despite suffering from significant statistical

388 heterogeneity. This may be the result of differing adjustments between

389 studies.

390 The case-control and cross-sectional studies examining DM were of

391 variable quality but demonstrated highly significant results, similar to the

392 cohort studies. Direct comparison between cohorts and these studies is

393 difficult due to the differing outcome measure

394 There was no differentiation between Type 1 and Type 2 DM in most

395 studies. It is unclear if type 1 confers the same risk as type 2.

396 It was unclear from the studies whether IGT was considered in

397 isolation or in combination with other MetS components, nor was it clear

398 whether the comparator groups contained those with MetS components,

399 without reaching the required three components needed for diagnosis. This

400 risks falsely lowering the risk associated with IGT due to the comparisons with

401 other potential KSD risk factors.

402 Statistical heterogeneity demonstrated in most of the analyses may

403 be due to ascertainment of KSD, variability in study populations and design

404 and publication bias. There were significant variations in KSD ascertainment

405 from patient reported to medical notes to radiologically proven. Some studies

406 may therefore under-report the true number of stones.

407   Variability in study populations and design (cohort, cross-sectional

408   and case-control) ranged from hospital attendees in a single centre to large

409   regional or national cohort studies. The effect of this variability is somewhat

410   negated by dividing the studies by study design and analyzing each

411   separately.

412   DM cohort study adjusted values although the overall figure was

413   significant the confidence interval includes one, therefore this could

414   represent type 1 error.

415   Publication bias was low in this study with trim and fill analyses

416   demonstrating few missing studies (mostly for MetS) and leave-one-out

417   analysis not demonstrating any significantly heterogenous studies.

418   The most common stone composition in all KSD formers is calcium oxalate, followed

419   closely by calcium phosphate, together comprising around 85% of all stones. Uric acid

420   stones are third, accounting for 12% in men, 7% in women, whilst the far rare cystine stones

421   account for less than 1% in either gender[42]. Both DM and MetS have been linked to

422   increased uric acid stone formation, whilst calcium stone formation remains static,

423   seemingly un-influenced by either DM or MetS[43].

424   The increased risk of KSD in DM is thought to be secondary to two factors, glycaemic

425   control (common to both types 1 & 2 and impaired glucose tolerance) and insulin resistance

426   (as seen in type 2 DM and MetS). Hyperglycaemia has been demonstrated to increase

427   urinary calcium[44,45], phosphorous[44,45], uric acid[46,47] and oxalate[48] secretion.

428   Whereas increased insulin resistance increases renal ammonium secretion[49] and

429   decreased urinary pH[48], which in turn increases urinary calcium and uric acid

430   secretion[50] whilst decreases urinary citrate[51] (an alkalizing agent), compounding urinary

431   acidification. Together these mechanisms lead to increased risk of precipitation and

432   subsequent formation of uric acid stones.

433   Notably, Chung et al.[52] and Weikert[53] in prospective cohort studies

434   demonstrated patients who suffered from KSD were more likely to develop DM over a five

435   year period than those who did not form stones. This muddies the water, giving a 'chicken

436   and egg' scenario. It could be that KSD is a symptom of an underlying systemic metabolic

437   disorder, or something intrinsic to KSD formers increases the risk of metabolic

438   derangement. The former is more likely given the evidence for biochemical disruption in

439   urinary excretions prior to stone formation.

440   Metabolic syndrome has been defined multiple times[54], however all definitions

441   are in agreement that it comprises a combination of insulin resistance, hypertension and

442   dyslipidaemia. Insulin resistance in metabolic syndrome is the same mechanism resulting in

443   type 2 diabetes and thus the findings of urinary acidification[55,56], increased risk of uric

444   acid secretion[55] and uric acid stone formation[56] via the pathophysiology described

445   above are the same.

446   In this review a small, albeit non-significant increase in risk suffering from

447   heterogeneity, was associated with MetS versus IGT/DM. This may be attributable to the

448   other components of MetS.

449   There is conflicting evidence about hypertension and a possible link to increased risk

450   of KSD[37] and vice versa[57]. A prospective cohort study by Cappuccio et al.[58]

451   demonstrated a significantly increased crude risk of hypertensives developing KSD than non-

452   hypertensives. However, when observing the difference between stone formers and non-

453   stone formers, the stone formers had no significant difference in blood pressure. It was

454   noted that the hypertensives were significantly heavier, older and had higher BMI's. Madore

455   et al. in consecutive studies on both genders[57,59], demonstrated there was no increased

456   risk compared to non-hypertensive individuals when age, BMI and electrolyte intake were

457   adjusted for. Akoudad et al.[29] in their prospective cohort study demonstrated an increased

458   risk of KSD with hypertension. However on multivariate analysis the effect was rendered

459   non-significant. Perhaps the risk found by Cappuccio was confounded by the presence of

460   metabolic syndrome, which at the time of publication was not defined[20]. Hypertension is

461   more likely indicative of underlying metabolic disturbance than having a truly lithogenic

462   effect.

463   Dyslipidaemia, defined as hypercholesterolaemia, low serum high-density

464   lipoprotein and high serum triglycerides[20] has also been associated with increased risk of

465   KSD[60]. However, when adjusted in multivariate analysis the association is lost[60].

466   Moreover, the only demonstrable biochemical abnormality after multivariate analysis is

467   high urinary uric acid. Therefore the risk associated with dyslipidaemia is due to insulin

468   resistance instead.

469   Renal lipotoxicity, defined as lipid accumulation in non-adipose tissues, has been

470   linked to decreased ammonium secretion and therefore lower pH in rat models[61].

471   However, this observation has yet to be reflected in humans. Renal lipotoxicity may

472   represent the end-point of chronic dyslipidaemia.

473   The addition of renal lipotoxicity to insulin resistance may explain the seemingly

474   increased risk of KSD observed in patients with MetS versus IGT. Further studies are

475   required to accurately demonstrate the underlying mechanism.

476   The rise in prevalence of DM and MetS is well documented and is now

477   perceived as a global pandemic[9,18]. KSD prevalence has risen in

478   parallel[3,5,6]. The Global Burden of Disease study[9,10] demonstrated

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479 morbidity and absolute mortality associated with KSD has increased, perhaps

480 due to the pandemic of DM/MetS[19], although age standardized mortality

481 rates have decreased globally,. The effect is marked in higher income

482 countries (HIC), but is attenuated in lower-middle income countries

483 (LMIC)[8,10]. This may be attributable to lack of availability of prompt

484 intervention in developing countries, leading to later presentation and

485 invasive treatments including nephrectomy[62-64]. Following surgical

486 treatment, management to prevent recurrence is recommended[13], again

487 this may not be available in developing countries.

488   In this review, those with impaired glucose tolerance (pre-diabetes)

489 had an increased likelihood of KSD, which was similar to those with DM in

490 cross-sectional/case-control studies, although this may be suffering from

491 publication bias and the real situation may be that the likelihood of KSD in

492 IGT is lower than DM. Indeed, The NHANES III cross-sectional study[35]

493 demonstrated with increasingly poor glycaemic control led to increasing

494 likelihood of KSD as determined by fasting plasma glucose and glycosylated

495 haemoglobin. Given the evidence suggesting those with DM or MetS are at

496 increased risk of developing KSD measures to improve glycaemic control

497 should be examined for their efficacy in KSD prevention in this 'at-risk'

498 population. It should be noted that the stone type in those with DM or MetS

499 is most commonly calcium oxalate, however although still small, the

500 proportion of urate stones increases in these related populations[22,65] .

501   Clarity is required on the risk in type 1 diabetics and future studies

502 should differentiate these patients from type 2. Further prospective

503   examination of DM and MetS should be undertaken to accurately portray

504   whether additional risk is posed by MetS over DM and quantify this. Tight

505   glycaemic control and weight loss should be explored in primary prevention

506   studies for both MetS and DM, given the common pathophysiologic

507   mechanism. Further investigation is required to demonstrate if these patient

508   are at increased risk of recurrence.

509   The risk of developing kidney stones is significantly increased in

510   populations with chronic hyperglycaemia. This has global implications with

511   rising morbidity and absolute mortality attributable to stones and is likely to

512   increase the health and economic burden on patients and healthcare

513   providers. Tight glycaemic control and weight loss are low-cost and non-

514   invasive measures, which should be investigated for their primary

515   preventative effect on KSD in these populations and included as part of the

516   long-term management of kidney stone disease.

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Study		RR [95% CI]
Unadjusted		
Akoudad, 2010.2		1.90 [0.98, 2.82]
Taylor, 2005: NHS II.2		1.86 [1.26, 2.46]
Taylor, 2005: NHS I.2		1.45 [1.17, 1.73]
Chen, 2012.2		1.22 [1.15, 1.29]
Taylor, 2005: HFPS.2		1.03 [0.63, 1.43]
RE Model for Unadjusted		*1.36 [1.11, 1.61]*
Adjusted		
Akoudad, 2010.1		1.98 [0.94, 3.02]
Taylor, 2005: NHS II.1		1.60 [1.08, 2.12]
Taylor, 2005: NHS I.1		1.29 [1.03, 1.55]
Chen, 2012.1		1.18 [1.10, 1.26]
Taylor, 2005: HFPS.1		0.81 [0.56, 1.06]
RE Model for Adjusted		*1.23 [0.94, 1.51]*
RE Model Total		1.29 [1.10, 1.47]

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Study		OR [95% CI]
Adjusted IGT		
Jung et al. 2011.2		1.64 [1.51, 1.77]
West et al. 2008.2		1.27 [0.61, 1.93]
Jeong et al. 2011.2		1.09 [0.84, 1.34]
Kim et al. 2012		1.03 [0.96, 1.10]
RE Model for Adjusted IGT		*1.26 [0.94, 1.58]*
Adjusted DM		
Weinberg, 2013.2		1.76 [1.27, 2.25]
Taylor, 2005: NHS II.2		1.67 [1.21, 2.13]
Taylor, 2005: NHS I.2		1.38 [1.02, 1.74]
Taylor, 2005: HFPS.2		1.30 [1.09, 1.51]
Akoudad, 2010.2		1.27 [1.07, 1.47]
Liaske, 2006.2		1.22 [1.01, 1.43]
RE Model for Adjusted DM		*1.32 [1.21, 1.43]*
Unadjusted IGT		
Lee et al. 2016		1.87 [0.60, 3.14]
Jeong et al. 2011.1		1.57 [1.23, 1.91]
West et al. 2008.1		1.39 [0.62, 2.16]
Rendina, 2008		1.39 [0.95, 1.83]
Kim, 2012 (Female)		1.26 [1.11, 1.41]
Jung et al. 2011.1		1.26 [1.11, 1.41]
Kim, 2012 (Male)		1.18 [1.10, 1.26]
RE Model for Unadjusted IGT		*1.25 [1.17, 1.34]*
Unadjusted DM		
Aydan, 2003		2.50 [0.84, 4.16]
Weinberg, 2013.1		2.44 [1.74, 3.14]
Taylor, 2005: NHS II.1		1.84 [1.34, 2.34]
Davarci, 2011		1.63 [1.00, 2.26]
Taylor, 2005: NHS I.1		1.55 [1.16, 1.94]
Liaske, 2006.1		1.29 [1.07, 1.51]
Taylor, 2005: HFPS.1		1.21 [1.02, 1.40]
Akoudad, 2010.1		0.64 [0.55, 0.73]
RE Model for Unadjusted DM		*1.49 [1.09, 1.89]*
RE Model Total		1.35 [1.22, 1.48]

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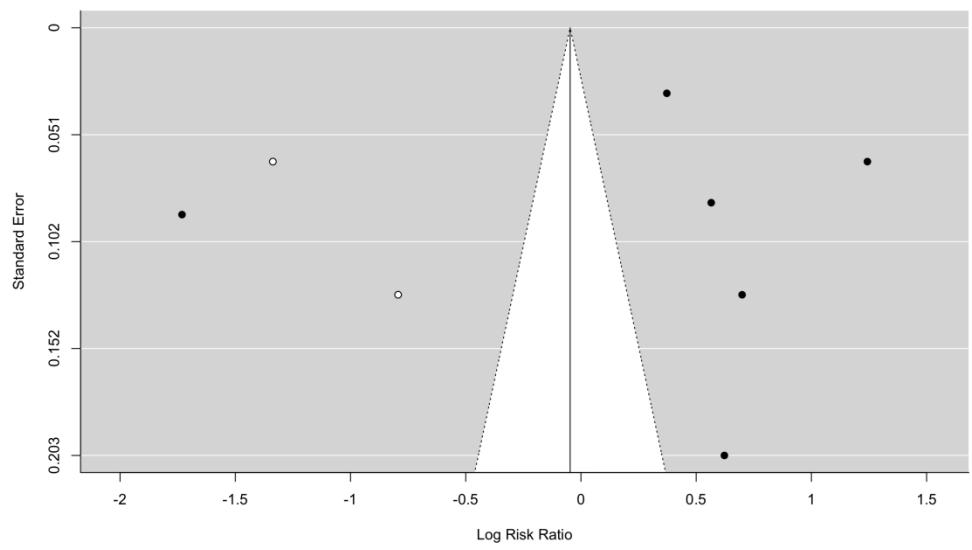| Study	OR [95% CI]
Unadjusted	
Rendina, 2008.2	2.20 [1.60, 2.80]
West, 2008.2	2.13 [1.69, 2.57]
Lee, 2016.2	2.04 [1.07, 3.01]
Jeong, 2011.2	1.71 [1.42, 2.00]
Jung, 2011.2	1.59 [1.30, 1.88]
Kim, 2012.2	1.33 [1.23, 1.43]
RE Model for Unadjusted	*1.74 [1.45, 2.04]*
Adjusted	
Rendina, 2008.1	2.00 [1.15, 2.85]
Lee, 2016.1	1.83 [0.94, 2.72]
West, 2008.1	1.52 [1.34, 1.70]
Jung, 2011.1	1.36 [1.11, 1.61]
Jeong, 2011.1	1.25 [1.02, 1.48]
Kim, 2012.1	1.11 [1.03, 1.19]
RE Model for Adjusted	*1.35 [1.16, 1.55]*
RE Model Total	1.56 [1.36, 1.76]

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5,6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7

PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8,9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8 + figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8,9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9,10 + fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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