A systematic review of the effects of impaired glucose tolerance (IGT) on the incidence of chronic kidney disease (CKD) in young adults

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Abstract

Objective: **The risk of chronic kidney disease (CKD) is elevated in patients with diabetes mellitus but the effect of impaired glucose tolerance (IGT) is not known. This systematic review investigates the risk of CKD associated with IGT in young adults aged 18–40 years.**

Methods: **CINAHL, EMBASE, MEDLINE, PubMed, Cochrane libraries and grey literature were searched from inception to January 2015 without language restriction for case-control and cohort studies comparing the frequency of CKD in cases aged 18–40 years with IGT/IFG (impaired fasting glucose) with controls without glycaemic abnormality or with type 2 diabetes (T2DM). CKD outcomes were determined by: estimated glomerular filtration rate, albumin creatinine ratio, proteinuria ≥1, serum creatinine, protein creatinine ratio and creatinine clearance levels.**

Results: **Initial searches identified 90 citations potentially meeting the inclusion criteria. After full text review, 19 cohort studies and no case-control studies met the inclusion criteria, but only one cohort study reported separate data for persons aged 18–40 years. This study only compared the incidence of CKD in individuals with IGT with those with T2DM. The annual incidence of CKD was 0.13% per person-year compared with 2.4% in patients with T2DM.**

Conclusion: **The results of this systematic review demonstrate that the risk of CKD in young adults with IGT/IFG is lacking. Further research is needed to estimate the incidence of CKD in this cohort of individuals. To bridge this gap in evidence, large epidemiological databases may be examined to quantify the risk of CKD in young adults aged 18–40 years with IGT/IFG compared with those with normoglycaemia. Data from these databases may potentially inform a prognostic study which may be useful in understanding the course and factors associated with CKD development. Finally, the results may emphasise the importance of identifying individuals with IGT/IFG earlier and implementing interventions to prevent or delay the development of CKD.**

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Key words: impaired glucose tolerance, chronic kidney disease, estimated glomerular filtration rate, albumin creatinine ratio, type 2 diabetes

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Introduction

Chronic kidney disease (CKD) is a long-term condition characterised by the presence of kidney damage and/or a gradual loss of kidney function.[1] Diabetes is a leading cause of CKD due to either diabetic nephropathy or vascular damage. A prospective cohort study conducted in England and Wales found the hazard of developing CKD in patients aged 35–74 years was five times higher in women and six times higher in men with diabetes than in those with normal glucose tolerance.[2]

Pre-diabetes indicates both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), collectively known as impaired glucose regulation (IGR). Individuals with IGR have a blood glucose raised beyond the normal level but not high enough for a diabetes diagnosis.[3] Furthermore, the risk of young adults aged 18–40 years with IGT developing CKD is not well characterised. Despite the heavy burden of cardiovascular disease (CVD) including CKD, very few studies have evaluated the CVD risk profile in young adults using a prediction algorithm such as the Framingham risk score or QRISK. There is some evidence that the incidence of CKD is elevated in individuals with IGT; however, this is often confined to a specific population.[4] It is not clear whether the risk of CKD is elevated in patients with IGT or whether any increased risk only occurs after patients develop diabetes. Cross-sectional studies show that albuminuria – an early marker of CKD – was approximately three times more common in patients with IGT than in those with normoglycaemia.[5] These data are subject to some limitations, as it is unclear whether CKD precedes impaired glucose metabolism or vice versa. The purpose of this systematic review is to find out whether the presence of

IGT in young adults aged 18–40 years is associated with an increased risk of CKD by comparing the risk of CKD in individuals with IGT and those without IGT, and also to evaluate whether any increased risk occurs only after they develop type 2 diabetes (T2DM).

Methods

Established guidelines for reviews were used to inform the search strategy, selection of studies, assessment of risks of bias and reporting of results.[6,7] The comparison groups were either participants with normoglycaemia or those with confirmed diabetes. The review protocol has been published elsewhere.[8]

Eligibility criteria

Types of participants and comparison group

This review includes studies where some participants are aged 18–40 years and results reported separately in this age group without a diagnosis of type 1 and type 2 diabetes but with IGT, 'pre-diabetes' or 'pre-diabetic state'. IGT/IFG can be referred to as pre-diabetes,[9] or metabolic syndrome where IGT is part of the metabolic syndrome. The comparison group was either participants with normoglycaemia or patients with diabetes. For the purpose of this review, IGT was classified as a fasting plasma glucose (FPG) <7 mmol/L (<126 mg/dL) or an oral glucose tolerance test (OGTT) ≥7.8 mmol/L and <11.1 mmol/L (140–200 mg/dL) or glycated haemoglobin (HbA_{1c}) of 5.7–6.4% (42–47 mmol/mol), and IFG was defined as FPG 5.6–6.9 mmol/L (100–125 mg/dL) and HbA_{1c} 5.7–6.4%.[10]

Participants and outcomes – cohort studies

This review includes any cohort studies where some participants are aged 18–40 years and results are reported separately in this age group with (1) IGT/IFG (exposed group) compared with participants without glycaemic abnormality (comparator); or (2) IGT/IFG but without a diagnosis of type 1 diabetes compared with participants with T2DM. Participants were free from CKD at baseline. A broad range of measures was used to ascertain CKD (outcome). This included estimated glomerular filtration rate (eGFR) stages 3A, 3B, 4 and 5; albuminuria; albumin creatinine ratio (ACR; ≥2.5 mg/mmol or ≥30 mg/g); protein creatinine ratio (PCR ≥45 mg/mmol or ≥300 mg/g); serum creatinine (SCr; 1.0 mg/dL or ≥50 μmol/L), proteinuria (≥1+) and creatinine clearance (CrCl; ≥60 ml/min). Studies reporting mean changes in continuous variables (e.g. eGFR) were also included. Studies reporting a single measure instead of two measures of eGFR or only by any of the above measures were included. Measures of association (HR, OR, IRR and RR) were extracted and reported or sufficient information to calculate these figures.

Participants and outcomes – case-control studies

This review also includes any case-control studies in which some cases were aged 18–40 years with an incident diagnosis of CKD (the outcome of interest) by any of the above definitions and controls without a diagnosis of CKD. The frequency of previous IGT/IFG (exposure to IGT/IFG) was compared with either the frequency of normoglycaemia (unexposed) or the frequency of diabetes (an alternative exposure). There was no restriction on the length of participant follow-up.

Search strategy and data extraction

The following electronic databases were systematically searched without language restriction from inception to January 2015: MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, PubMed, Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), Trip Database and Google Scholar. Ongoing studies, scientific literature and abstract proceedings were identified by searching the following databases: ClinicalTrials.gov, Cochrane Renal Group specialised register, Renal Registry Database, British Renal Society, Renal Association, American Society of Nephrology, World Congress of Nephrology, Diabetes UK Conference, Primary Care Diabetes Society Conference and Zetoc. A comprehensive search of the Conference Proceedings Citation Index (CPCI) was also carried out. Search of these databases spanned from January 2011 to January 2014 as it is likely that studies would have been completed and published. Grey literature databases such as Grey Literature Report, OpenGrey, PubliCat and ScienceDaily.com were examined. Open access theses and dissertations were retrieved from the ProQuest Dissertation Thesis Database and thesis.com. The Science Citation Index (SCI) was used to scan and track study titles. The search strategy is shown in Appendix 1 (available online at bjd-abcd.com).

Two reviewers independently reviewed all titles and abstracts in two phases. First the retrieved titles and abstracts were reviewed to identify relevant studies. The full texts of retrieved studies were then read to determine eligibility. Any discrepancies or differences in opinion were resolved by consensus. An inclusion criteria checklist (Appendix 2 available online at bjd-abcd.com) was developed based on study eligibility criteria piloted on five papers.

Quality assessment

Study quality was assessed according to a modified tool based on the Ottawa-Newcastle scale (NOS).[11] Risk of bias was assessed on the following domains: (1) sampling; (2) outcome measurement; (3) attrition; (4) analytical method; and (5) confounders (Appendix 3 available online at bjd-abcd.com). A composite score was not provided; instead, a risk of bias of 'yes' indicating adequate data were provided, 'no' if data were provided but did not meet the criteria for that domain and 'unclear' potentially at high risk of bias.[12]

Publication bias

If sufficient studies are identified for future updates, the Begg's[13] and Egger's[14] regression test will be carried out to detect publication bias. At least 10 studies will be needed to sufficiently detect publication bias.[15] Studies will be grouped according to effects measures and reporting risk of CKD determined by any of the measures listed above.

Results

Search results

Initial database searches identified 5,568 studies. After scanning

Table 1 Quality assessment of included studies: IGT/IFG compared with normoglycaemia

Study	Selection of participants	Adequate description of study population	Validated method to ascertain exposure	Validated method to confirm outcome	Adequate follow-up	Completeness of follow-up (attrition)	Analysis control for confounding	Sample size calculation	Analytical methods appropriate	Adjustment for confounders
Nelson *et al* (1996)[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	YES	None
Fox *et al* (2005)[4]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	Age, sex, baseline GFR, SBP, hypertension treatment, smoking, BMI, total and HDL cholesterol, MI, congestive heart failure
Meigs *et al* (2002)[18]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	Age, SBP, BMI, smoking, ACE inhibitor, total cholesterol, HDL, triglyceride, hypertensive drugs.
Nelson *et al* (1999)[19]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	None
Nelson *et al* (1989)[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Age, sex, BP
Yokoyama *et al* (2009)[21]	Yes	Yes	Yes	Yes	No	Unclear	Yes	No	Yes	None
Tozawa *et al* (2007)[22]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Age, sex, current cigarette smoking, alcohol drinking habit
Nelson *et al* (1993)[23]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	None
Rashidi *et al* (2007)[24]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	None
Kitiyakara *et al* (2007)[25]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Age, sex and smoking status
Sun *et al* (2010)[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Age, sex, check-up centers and current smoking
Yang *et al* (2012)[27]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Age, sex, BMI, serum level, total cholesterol, BP, triglyceride, HDL, waist circumference
Kovács *et al* (2013)[28]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	No adjustments
Watanabe *et al* (2010)[29]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Sex and age
Ryu *et al* (2009)[30]	Yes	Yes	Yes	Yes	Unclear	No	Yes	No	Yes	Age, baseline GFR, glutamyl-transpeptide, uric acid, triglyceride, HDL cholesterol, BP, obesity
Tohidi *et al* (2012)[32]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	BMI, total cholesterol, SBP
Jee *et al* (2005)[31]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	None

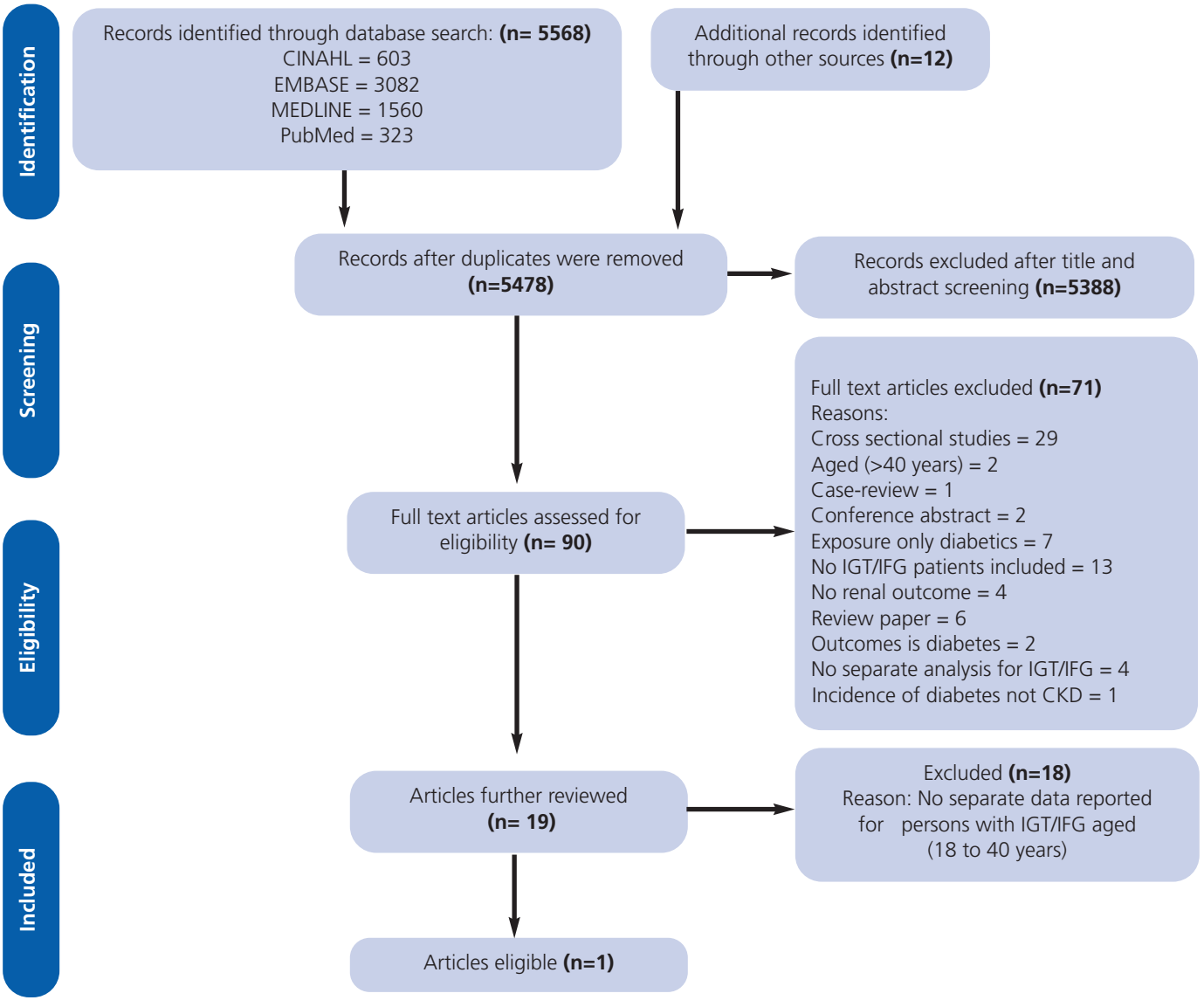
BP, blood pressure; BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HDL, high density lipoprotein; MI, myocardial infarction; SBP, systolic blood pressure.

Table 2 Quality assessment of included studies: IGT/IFG compared with T2DM

Study	Selection of participants	Adequate description of study population	Validated method to ascertain exposure	Validated method to confirm outcome	Adequate follow-up	Completeness of follow-up (attrition)	Analysis control for confounding	Sample size calculation	Analytical methods appropriate	Adjustment for confounders
Kim *et al* (2010)[16]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	Age and sex
Iseki *et al* (2004)[33]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	Age, sex, baseline GFR, SBP, DBP, BMI, total cholesterol, triglyceride, serum creatinine, haematuria and proteinuria

BP, blood pressure; BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MI, myocardial infarction; SBP, systolic blood pressure.

Figure 1. Study selection and reasons for exclusion



the titles, 90 citations potentially met the inclusion criteria. These were reviewed in detail (full text) and 19 cohort studies were selected for further review (no case-control studies were selected). A summary of the overall quality of the 19 studies is provided in Table 1 and 2. Only one of the 19 cohort studies reported separate data for persons aged 18–40 years. This study compared the incidence of CKD in patients with IGT and those with T2DM. A PRISMA study flow diagram of included and excluded studies is provided along with reasons for exclusion in Figure 1. Data from this study were reported narratively.

Study characteristics

The characteristics of the 19 cohort studies are summarised in Appendix 4 and 5 (available online at bjd-abcd.com). Briefly, no case-control studies meeting the inclusion criteria were identified. Nineteen cohort studies were identified. One reported separate data in persons aged 18–40 years with IGT compared with T2DM.

Incidence of CKD in persons aged 18–40 years with IGT compared with T2DM

Kim *et al* reported the risk of CKD in young adults aged 18–40 years with IGT compared with T2DM.[16] This cohort study followed 2,666 Pima Indian young adults aged ≤20 years with IGT and T2DM during a follow-up period of 25.2 years for the development of macroalbuminuria, defined as an ACR of ≥300 mg/g. The incidence of macroalbuminuria was 1.3 new cases of macroalbuminuria per 1,000 person-years, with a total of 28 cases in 21,830 person-years of follow-up in subjects with IGT, or 0.13% developing macroalbuminuria each year compared with 2.4% in patients with T2DM.

Discussion

This systematic review showed that existing evidence does not allow quantification of CKD risk in young adults aged 18–40 years with IGT/IFG compared with normoglycaemia or T2DM. Pooled estimates of CKD and a meta-analysis were not possible because most studies did not report separate results in this age group. Only one study reported the risk of CKD in young adults aged 18–40 years. The annual incidence of CKD was 0.13% per person-year compared with 2.4% in those with T2DM.

Strengths of the study

This review was not limited to the English language or geographical area and a broad range of markers was used to ascertain CKD. Furthermore, to the best of our knowledge, no systematic review has evaluated the risk of CKD in young adults aged 18–40 years with IGT/IFG compared with normoglycaemia or T2DM.

Limitations of the study

Only one study provided risk estimates of CKD in persons aged 18–40 years with IGT compared with those with T2DM. Sufficient studies were not available to conduct a meta-analysis, therefore a more generalisable and precise estimate of CKD could not be presented. Furthermore, the results of this one study should be interpreted with caution because of the small sample size and study population (Pima Indians).

Key messages

- Existing evidence does not allow quantification of CKD risk in young adults aged 18 to 40 years with IGT/IFG
- The review shows a paucity of studies exploring incidence of CKD in young adults with IGT/IFG
- The exact magnitude of CKD associated with IGT/IFG in young adults remains to be clarified

Conclusion

The results of this systematic review demonstrate that the risk of CKD in young adults aged 18–40 years with IGT/IFG is lacking. Further research is needed to estimate the incidence of CKD in this cohort of individuals. To bridge this gap in evidence, large epidemiological databases may be examined to quantify the risk of CKD in young adults aged 18–40 years with IGT/IFG compared with those with normoglycaemia.

Conflict of interest None.

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Authors' contributions FJ was responsible for developing the search strategy and conducting the literature search. TM and PG were involved in the design of the review. FJ performed data extraction and interpretation of the data. TM and PG provided important intellectual input and revised the manuscript critically. TM and PG read and approved the final manuscript. FJ was first reviewer, TM and PG acted as second reviewers for this systematic review. All authors read and approved the final manuscript.

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Appendix 1: Electronic search for Medline for CKD outcomes

Count	Searches	Results
1	exp Renal Insufficiency Chronic/	84840
2	chronic kidney disease.mp.	18247
3	chronic kidney disease$.mp.	18745
4	exp Kidney Failure, Chronic/	78448
5	chronic kidney failure.mp.	975
6	chronic kidney failure$.mp.	976
7	chronic renal failure.mp.	20307
8	chronic renal failure$.mp.	20319
9	end stage kidney disease.mp.	997
10	end stage kidney disease$.mp.	1005
11	esrd.mp.	9767
12	esrd$.mp.	9769
13	chronic kidney insufficiency.mp.	195
14	chronic kidney insufficiency$.mp.	195
15	end stage renal disease.mp.	19454
16	end stage renal disease$.mp.	19625
17	end stage renal failure.mp.	4888
18	end stage renal failure$.mp.	4891
19	kidney failure.mp.	81179
20	kidney failure$.mp.	81828
21	renal insufficiency/	10919
22	renal failure.mp.	71184
23	renal failure$.mp.	71271
24	kidney insufficiency.mp.	577
25	kidney insufficiency$.mp.	577
26	exp renal dialysis/	93204
27	renal dialysis.mp.	74276
28	renal dialysis$.mp.	74276
29	extracorporeal dialysis.mp.	161
30	extracorporeal dialysis$.mp.	162
31	hemodialysis.mp.	47033
32	hemodialysis$.mp.	47039
33	haemodialysis.mp.	11565
34	haemodialysis$.mp.	11576
35	exp peritoneal dialysis/	22761
36	peritoneal dialysis.mp.	26208
37	peritoneal dialysis$.mp.	26210
38	renal disease.mp.	39428
39	renal disease$.mp.	43692
40	exp kidney diseases/	414228
41	kidney disease.mp.	30990
42	kidney disease$.mp.	103750
43	nephropathy.mp.	37719
44	nephropathy$.mp.	37721
45	exp diabetic nephropathies/	19707
46	diabetic nephropathy.mp.	11909
47	diabetic nephropathy$.mp.	11909
48	exp kidney transplantation/	79900
49	kidney transplantation.mp.	81478
50	kidney transplantation$.mp.	81539
51	renal transplant.mp.	18888
52	renal transplant$.mp.	36596
53	exp dialysis/	22124
54	dialysis.mp.	132315
55	dialysis$.mp.	132329
56	exp renal insufficiency/	127094
57	renal insufficiency.mp.	33560
58	renal insufficiency$.mp.	33571
59	EGFR.mp.	27296
60	EGFR$.mp.	27669
61	exp glomerular filtration rate/	33096
62	glomerular filtration rate.mp.	42765
63	glomerular filtration rate$.mp.	43111
64	exp creatinine/	46991
65	creatinine.mp.	95418
66	creatinine$.mp.	95673
67	serum creatinine.mp.	26670
68	serum creatinine$.mp.	26781
69	serum creatinine clearance.mp.	53
70	serum creatinine clearance$.mp.	58
71	exp albuminuria/	12045
72	albuminuria$.mp.	14614
73	exp proteinuria/	32445
74	proteinuria.mp.	36905
75	proteinuria$.mp.	36921
76	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75	683333
77	exp diabetes mellitus, type 2/	87630
78	diabetes mellitus type 2.mp.	87782
79	type 2 diabetes.mp.	60366
80	type 2 diabetes$.mp.	60434
81	niddm.mp.	6673
82	niddm$.mp.	6704
83	exp diabetes insipidus/	7011
84	diabetes insipidus.mp.	8589
85	diabetes insipidus$.mp.	8589

Appendix 1: Electronic search for Medline for CKD outcomes (continued)

Count	Searches	Results
86	77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85	113193
87	exp glucose intolerance/	6360
88	impaired glucose tolerance.mp.	8065
89	impaired glucose tolerance$.mp.	8066
90	glucose intolerance.mp.	11300
91	glucose intolerance$.mp.	11302
92	exp prediabetic state/	3852
93	prediabetes.mp.	1633
94	prediabetic state.mp.	4004
95	prediabetic state$.mp.	4053
96	exp blood glucose/	130285
97	blood glucose.mp.	147811
98	blood glucose$.mp.	147841
99	glucose metabolism.mp.	23463
100	glucose metabolism$.mp.	23713
101	exp glucose tolerance test/	29397
102	glucose tolerance test.mp.	33799
103	glucose tolerance test$.mp.	34976
104	OGTT.mp.	5382
105	OGTT$.mp.	5481
106	exp Hyperglycemia/	26636
107	hyperglycemia.mp.	37642
108	hyperglycemia$.mp.	37682
109	hyperglycaemia.mp.	6827
110	hyperglycaemia$.mp.	6840
111	impaired fasting glucose.mp.	2336
112	impaired fasting glucose$.mp.	2336
113	postprandial hyperglycemia.mp.	911
114	postprandial hyperglycaemia.mp.	283
115	exp hemoglobin a, glycosylated/	23254
116	hemoglobin a, glycosylated.mp.	23255
117	hemoglobin a, glycosylated$.mp.	23255
118	Haemoglobin a, glycosylated.mp.	1
119	HbA1c.mp.	13678
120	HbA1c$.mp.	13741
121	glycemic abnormality.mp.	7
122	Glycaemic abnormality.mp.	0
123	Fasting plasma glucose.mp.	7250
124	Fasting plasma glucose$.mp.	7259
125	87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124	223393
126	76 and 86 and 125	4367
127	exp cohort studies/	1387399
128	cohort$.tw.	263907
Count	**Searches**	**Results**
129	controlled clinical trial.pt.	88411
130	epidemiologic methods/	29569
131	exp case-control studies/	688110
132	(case$ and control$).tw.	311313
133	127 or 128 or 129 or 130 or 131 or 132	1909067
134	cohort studies/	170386
135	longitudinal studies/	87299
136	follow-up studies/	504746
137	prospective studies/	376036
138	retrospective studies/	512412
139	cohort.ti,ab.	239106
140	longitudinal.ti,ab.	132074
141	prospective.ti,ab.	339467
142	retrospective.ti,ab.	264289
143	Case-Control Studies/	188791
144	Control Groups/	1435
145	Matched-Pair Analysis/	4154
146	retrospective studies/	512412
147	((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.	374925
148	127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147	2266708
149	126 and 148	1563
150	Remove duplicates from 149	1560

Appendix 2: Review eligibility criteria checklist

Study design	Cohort studies
	Case-control studies
Study characteristics	Full articles
	Conference proceedings
	Grey literature
	Theses/dissertations
	Other (please specify)
Participants	Studies where some participants are aged 18–40 years
	With impaired glucose tolerance (IGT)
	With pre-diabetes (can refer to either IGT or impaired fasting glucose (IFG).
	With metabolic syndrome (where IGT is part of metabolic syndrome)
	Free from chronic kidney disease at baseline
Comparator	Participant with normoglycaemia
	Participants with diabetes
Outcome	Chronic kidney disease (eGFR stages: 3A, 3B, 4 and 5)
	Albuminuria
	Proteinuria ≥1
	Albumin creatinine ratio ≥30 mg/mmol
	Protein creatinine ratio ≥50 mg/mmol
	Serum creatinine data
	Creatinine clearance data

Appendix 3: Quality assessment form adapted from Ottawa-Newcastle scale (NOS) for assessing non-randomised studies

<table>
<tr><th></th><th></th><th>Yes/No/Unclear</th></tr>
<tr><td>Selection of participants</td><td>[1] Was inclusion/exclusion clearly described (for example, age, diagnosis status, IGT/IFG)?
[2] Was inclusion/exclusion assessed using valid and reliable measures (for example, if there are important inclusion/exclusion criteria that are not directly related to exposure and outcome and for which the accuracy of measurement may need scrutiny, e.g. age, diagnosis)?
[3] Was the recruitment strategy clearly described?
[4] Did the investigators ensure that the exposed/unexposed group were comparable (for example, did they use stratification, matching or propensity score)?</td><td></td></tr>
<tr><td>Adequate description of study population</td><td>[1] Was the study population well characterised?
• Age
• Sex
• Ethnicity
• Suitable definition of IGT/IFG</td><td></td></tr>
<tr><td>Validated method for ascertaining exposure</td><td>[1] Was the method used to ascertain exposure clearly defined?
[2] Was a valid and reliable measure used to ascertain exposure (for example, what diagnostic test was used to confirm IGT/IFG)?
<table><tr><td>Fasting plasma glucose</td><td>6.1–6.9 mmol/L</td></tr><tr><td>Oral glucose tolerance test (2h value)</td><td>7.8–11.0 mmol/L</td></tr><tr><td>HbA1c</td><td>42–47 mmol/mol / 5.4-6.7%</td></tr></table></td><td></td></tr>
<tr><td>Validated method to confirm outcome</td><td>[1] Were valid and reliable measures used to ascertain outcome? For example,
<table><tr><td>Stage</td><td>eGFR (ml/min/1.73m^2)</td></tr><tr><td>1</td><td>≥90</td></tr><tr><td>2</td><td>60-89</td></tr><tr><td>3A</td><td>45-59</td></tr><tr><td>3B</td><td>30-44</td></tr><tr><td>4</td><td>15-29</td></tr><tr><td>5</td><td><15</td></tr></table>ACR >30mg/mmol
PCR >45 mg/mmol
SCr measures
CrCl measures</td><td></td></tr>
<tr><td>Adequate follow-up period</td><td>[1] Was follow-up long enough for the outcome to occur?
[2] Was the follow-up period the same across all groups?
[3] Were differences in follow-up adjusted for using statistical techniques (e.g. survival analysis)?</td><td></td></tr>
<tr><td>Completeness of follow-up (attrition)</td><td>[1] Were drop-out rates and reasons for drop-out similar across exposed and unexposed?
[2] Were numbers of drop-outs/withdrawals documented at each time point?</td><td></td></tr>
<tr><td>Analysis controls for confounding</td><td>[1] Does the study identify and control for important confounding variables and effect modifiers?</td><td></td></tr>
<tr><td>Sample size calculated</td><td>[1] Is the sample size adequate?
[2] Did the study describe how the sample size was calculated?
• Did the investigators conduct a power analysis to determine the adequacy of study group sizes for the outcome of interest?
• Was the sample size large enough to detect differences in event or a significant OR/RR between groups? Mean (±SE) change in GFR</td><td></td></tr>
<tr><td>Analytical methods appropriate</td><td>[1] Was the kind of analysis done appropriate for the kind of outcome data? For example,
• Dichotomous – logistic regression, survival analysis
• Categorical – mixed model for categorical outcomes
• Continuous – mixed model, ANCOVA
• Mean change (±SE)
[2] Was loss to follow-up accounted for in the analysis (for example, through sensitivity analysis)?</td><td></td></tr>
</table>

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (including reasons for exclusion):