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Systematic review and meta-analysis to identify the risk factors of diabetic kidney disease initiation

The systematic review followed the recommendations by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement(1) as well as the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement(2). Two investigators (H-WJ and Y-JW) independently conducted literature screening, quality assessment, information extraction and statistical analysis. Disagreements between the two authors were resolved by discussion. If the disagreement persisted, two other senior investigators (C-BC and H-JY) were consulted to attain consensus.

Objective

To identify the risk factors for diabetic kidney disease (DKD) initiation.

Inclusion Criteria

Study Type

- (1) We will include studies examining the risk factors for initiation of DKD and reporting the risk ratios (RRs) and corresponding 95% confidence limits (CIs) of these risk factors.
- (2) Studies of cohort design, including both prospective and retrospective cohort studies.

Participants

Type 2 diabetic patients with eGFR ≥ 60 ml/min per 1.73m² and urinary albumin-to-creatinine ratio (UACR) < 30 mg/g (or urinary albumin excretion rate (UAER) < 30 mg) at the baseline will be eligible.

Outcome

Initiation of DKD.

When duplicate reports from the same study were identified, only the most recent publication, or the one with the longest follow-up period, was included. There was no restriction on language of publication.

Search strategy

Studies were identified by searching electronic databases of MEDLINE, EMBASE and the Cochrane Library from the time of their inception to October 2017. To verify potentially relevant studies, the references from retrieved articles and reviews were manually scrutinized. The search strategy comprised a combination of text and Medical Subject Headings (MeSH). Two investigators (H-WJ and Y-JW) independently performed the search. Disagreements between the two authors were resolved by discussion. If the disagreement persisted, two other senior investigators (C-BC and H-JY) were consulted to attain consensus.*Detailed search strategy in MEDLINE*

#1 "diabetes mellitus, type 2"[MeSH Terms]

#2 "Kidney Diseases"[MeSH Terms] OR "albuminuria"[MeSH Terms] OR "proteinuria"[MeSH Terms] OR "glomerular filtration rate"[MeSH Terms] OR "urinary albumin excretion rate" OR "albumin excretion rate" OR "albumin creatinine ratio" OR "albumin to creatinine ratio" OR "microalbuminuria" OR "macroalbuminuria" OR "creatinine clearance rate" OR "serum creatinine"

#3 "risk factors"[MeSH Terms] OR "hypertension"[MeSH Terms] OR "blood pressure"[MeSH Terms] OR "hyperglycemia"[MeSH Terms] OR "hyperuricemia"

[MeSH Terms] OR "uric acid"[MeSH Terms] OR "lipids"[MeSH Terms] OR "triglycerides"[MeSH Terms] OR "cholesterol"[MeSH Terms] OR "hyperlipidemias"

[MeSH Terms] OR "obesity"[MeSH Terms] OR "waist hip ratio"[MeSH Terms] OR "waist circumference"[MeSH Terms] OR "waist-height ratio"[MeSH Terms] OR "gender identity"[MeSH Terms] OR "sex"[MeSH Terms] OR "life style"[MeSH Terms] OR "smoking"[MeSH

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Terms] OR "drinking"[MeSH Terms] OR "Diabetic retinopathy"[MeSH Terms] OR "body mass index"[MeSH Terms] OR "region" OR "race" OR "glycaemic control" OR "family history" OR "age" OR "duration" OR "plasma CRP" OR "low physical activity" OR "HbA1c" OR "glycosylated hemoglobin A1c"

#4 "cohort studies"[MeSH Terms]

#5 #1 AND #2 AND #3 AND #4

Detailed search strategy in EMBASE

'non-insulin dependent diabetes mellitus'/exp AND ('kidney disease'/exp OR 'albuminuria'/exp OR 'proteinuria'/exp OR ('albumin excretion rate'/exp OR 'albumin excretion rate') OR ('urinary albumin excretion rate'/exp OR 'urinary albumin excretion rate') OR ('albumin creatinine ratio'/exp OR 'albumin creatinine ratio') OR ('albumin to creatinine ratio'/exp OR 'albumin to creatinine ratio') OR 'glomerulus filtration rate'/exp OR 'creatinine clearance rate' OR 'creatinine blood level'/exp) AND ('risk factor'/exp OR 'hypertension'/exp OR 'blood pressure'/exp OR 'hyperglycemia'/exp OR 'hyperuricemia'/exp OR 'uric acid'/exp OR 'hyperlipidemia'/exp OR 'obesity'/exp OR 'waist circumference'/exp OR 'waist to height ratio'/exp OR 'gender and sex'/exp OR 'lifestyle'/exp OR 'smoking'/exp OR 'lipid'/exp OR 'hyperlipidemia'/exp OR 'waist hip ratio'/exp OR 'drinking'/exp OR 'diabetic retinopathy'/exp OR 'body mass'/exp OR 'race'/exp OR 'region' OR 'glycaemic control' OR 'family history'/exp OR ('age'/exp OR 'age') OR ('duration'/exp OR 'duration') OR 'plasma crp' OR 'low physical activity' OR 'hemoglobin a1c') AND ('cohort analysis'/exp OR 'prospective study'/exp OR 'longitudinal study'/exp)

Detailed search strategy in Cochrane Library

#1 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees

#2 MeSH descriptor: [Kidney Diseases] or [Albuminuria] or [Proteinuria] or [Glomerular Filtration Rate] explode all trees

#3 "urinary albumin excretion rate" or "albumin excretion rate" or "albumin creatinine ratio" or "albumin to creatinine ratio" or "microalbuminuria" or "macroalbuminuria" or "creatinine clearance rate" or "serum creatinine" (Word variations have been searched)

#4 #2 or #3

#5 MeSH descriptor: [Risk Factors] or [Hypertension] or [Blood Pressure] or [Hyperglycemia] or [Hyperuricemia] or [Uric Acid] or [Lipids] or [Triglycerides] or [Cholesterol] or [Hyperlipidemias] or [Obesity] or [Waist-Hip Ratio] or [Waist Circumference] or [Waist-Height Ratio] or [Gender Identity] or [Sex] or [Life Style] or [Smoke] or [Drinking] or [Diabetic Retinopathy] or [Body Mass Index] or [Glomerular Filtration Rate] explode all trees

#6 "region" or "race" or "glycaemic control" or "family history" or "age" or "plasma CRP" or "low physical activity" or "HbA1c" or "glycosylated hemoglobin A1c" (Word variations have been searched)

#7 #5 or #6

#8 MeSH descriptor: [Cohort Studies] explode all trees

#9 #1 and #4 and #7 and #8

Definition

Type 2 diabetes was defined as fasting plasma glucose (FPG) of ≥ 7.0 mmol/L, 2-h plasma glucose (2-h PG) value of ≥ 11.1 mmol/L during a 75-g oral glucose tolerance test (OGTT), glycated hemoglobin A1c (HbA1c) of $\geq 6.5\%$ (48mmol/mol), use of glucose-lowering drugs, self-reported diabetes, or using administrative data coding algorithms(3; 4).

DKD was diagnosed according to K/DOQI Clinical Practice Guidelines, DKD was defined as eGFR < 60 mL/min per 1.73 m² and/or UACR ≥ 30 mg/g for ≥ 3 months caused by diabetes(5) or using ICD codes.

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Ethics Statement

The Institutional Review Board of Tianjin Medical University Metabolic Diseases Hospital & Tianjin Institute of Endocrinology has approved this study and waived the requirement for informed consent, because this study was designed to retrospectively collect available data from articles published in peer-reviewed journals.

Data Extraction and Quality Assessment

The following information was extracted and entered into a database: details of the study design, location and published year of study, patient demographic characteristics (age and sex), numbers of patients enrolled and onset numbers, the UACR and eGFR at baseline, duration of the follow-up, study outcomes, identified risk factors and their RRs with corresponding 95% CIs. We assessed the quality of cohorts using the Newcastle–Ottawa scales(6). Articles with a score of 8 or higher were considered of high quality.

Data Synthesis and Analysis

All data from each eligible study were extracted and entered into a computer database using a spreadsheet software (Microsoft Excel 2016; Microsoft Corp, Redmond, WA). Hazard ratio (HR) and risk ratio (RR) were assumed to approximate the same relative risk and were collectively described as the RR in this meta-analysis. Considering the reliability of the results, only the risk factors involving more than two cohort studies were included in the meta-analysis. We extracted the RRs with their 95% CIs for each specific initiating risk factor of DKD and generated the pooled estimates of RR and 95% CI across studies using random-effect model or fixed-effect model. We used the inverse of the variance of the RR to weight studies on the basis of an estimate of statistical size(7). Heterogeneity across studies were assessed using the Cochrane Q-test, and measured by I^2 . I^2 value > 50% or P -value in Cochran Q test less than 0.10 indicated statistically significant heterogeneity and then a random-effect model was applied; otherwise, a fixed-effect model was selected(8). Subgroup analyses were conducted by the stratification of each risk factor, including age (1-year increments vs. 5–10 year increments), body mass index (BMI) (1 kg/m² increments vs. 5 kg/m² increments), and systolic blood pressure (SBP) (1 mmHg increments vs. 5 mmHg increments vs. 10–20 mmHg increments). Sensitivity analyses were conducted by omitting a single study in each turn to test the robustness of our results(9). To assess the publication bias, we visually inspected funnel plots; however, because of the limitations of this method, we also added the Egger regression test P value for funnel symmetry. All tests were two-sided and statistical significance was defined as $P < 0.05$, with the exception of the heterogeneity assessment, which was considered statistically significant at $P < 0.10$. All analyses were performed using STATA software, version 14.0 (StataCorp, College Station, TX).

Results

Search results

We found 2,132 articles from MEDLINE, 2,298 from EMBASE and 338 from the Cochrane Library. After these articles were combined and duplicates were removed, the total number of articles was 3,857. Of these, 2,631 and 884 articles were excluded on the basis of their titles and abstracts, respectively. Of the 342 articles that underwent full-text evaluation and 35 additional articles from hand searching, 20 cohort studies met our inclusion criteria.

Characteristics and quality of included studies

Of the 20 included studies, 14 were prospective cohorts and 6 were retrospective cohorts. There were 41,271 patients with type 2 diabetes and 11,991 incident DKD cases were observed during follow-up, and the estimated incidence of DKD in type 2 diabetic patients was 29%. The duration of follow-up ranged from 1 year to 20 years. Cohorts were from Europe (including Italy, Denmark, Sweden and Finland), Asia (including China, China Taiwan, Japan, India and Singapore) as well as Americas (including the United States and Brazil). The age of the

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study participants was between 39 to 75 years and the diabetes durations ranged from 0 to 19 years. 80% of the participants were from Europe and Americas while the additional 20% were from Asia. The characteristics of all these 20 cohorts were shown in Supplementary Table 1. According to the Newcastle–Ottawa scales, all of the included studies had a quality score over 8, which indicated high quality (Shown in Supplementary Table 2).

Risk factors of DKD in type 2 diabetic patients

There were 19 risk factors available from the included cohorts, including age, sex, diabetes duration, smoking, BMI, diabetic retinopathy (DR), HbA1c, FPG, hypertension, SBP, pulse pressure (PP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), UACR, serum creatinine and eGFR. Detailed information of these risk factors was shown in Supplementary Table 3.

Of the 19 risk factors for meta-analysis, there were 10 risk factors associated with the incipient of DKD, including age, BMI, DR, smoking, HbA1c, SBP, HDL-C, TG, UACR and eGFR with pooled RRs of 1.09, 1.07, 1.72, 1.49, 1.17, 1.03, 0.75, 1.15, 1.25 and 2.20, respectively. Considering the feasibility of clinical practice, we chose the results from subgroup analysis or sensitivity analysis which were more reasonable. Age increment by 5-10 years old (RR 1.38, 95% CI 1.20-1.59; $P < 0.001$), BMI increment by 5 kg/m² (RR 1.16, 95% CI 1.09-1.23; $P < 0.001$), DR (RR 1.31, 95% CI 1.00-1.73; $P = 0.05$), smoking (RR 1.49, 95% CI 1.30-1.71; $P < 0.001$), HbA1c (RR 1.17, 95% CI 1.09-1.26; $P < 0.001$), SBP increment by 10-20 mmHg (RR 1.21, 95% CI 1.15-1.27; $P < 0.001$), HDL-C increment by 1 mmol/L (RR 0.78, 95% CI 0.61-0.99; $P = 0.04$), TG increment by 1 mmol/L (RR 1.42, 95% CI 1.16-1.74; $P < 0.001$) and UACR increment by 1 mg/g (RR 1.13, 95% CI 1.10-1.17; $P < 0.001$). The details of these risk factors in the involving studies are shown in Supplementary Figure 1-10.

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Supplementary Table 1. Baseline characteristics of the 20 cohorts included in the systematic review and meta-analysis.

First Author/Year/ Country or region (continent)	Source of cohort	Study design and period	Sample size (% female)	Age (years)	Follow- up (years)	DM duration (years)	Risk factors for DKD development
Cardoso(10)/2017 /Brazil (South America)	Rio de Janeiro Type 2 Diabetes Cohort Study	Prospective cohort 2004-2008	432 (62.3)	60 ± 9.6	4	8 (3-15)	Increased aortic stiffness, SBP
Hui(11)/2014/Chi na (Asia)	Hong Kong West Diabetes Registry	Prospective cohort 2008-2013	462 (42.6)	54 ± 9	4	NA	Sex, Age, WC, DM duration, HbA1c, SBP, eGFR
Afghahi(12)/2010 /Sweden (Europe)	Swedish National Diabetes Register (NDR)	Prospective cohort 2002-2007	3,667 (61)	60.3 ± 8.2	5	7.5 ± 6.2	Age, Sex, SBP, HbA1c, Smoker, BMI, TG, HDL- C, SCr
Low(13)/2016/ Singapore (Asia)	Diabetic Nephropathy (DN) Cohort Study	Prospective cohort 2002-2014	553 (38.4)	53.2 ± 11.1	5.8	9.2 ± 7.4	Age, BMI, HbA1c variability, Ln ACR, eGFR, TG

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Supplementary Table 1. Continued.

Takagi(14)/2015/ Japan (Asia)	Japanese Type 2 Diabetes	Prospective cohort Cohort Study	1,802 (59) 2003-2013	58 ± 12 8.0	6.9 -	13 ± 9	Age, Sex, SBP, DR, HbA1c, HDL-C, eGFR, Non-HDL, Log UACR, UA
Hu(15)/2016/China (Asia)	Chinese Type 2 Diabetes	retrospective cohort Population	344 (37.5) 2010-2013	62 ± 13 3.0-14	0.5-5	Age, Sex, Smoker, PP, FPG, eGFR	
De Cosmo (16)/2015 /Italy (Europe)	AMD	Prospective cohort 2004-2008	13,964 (44)	64 ± 10 4	4	10 ± 8	Hypertension (BP ≥ 140/85 mmHg), Smoker
De Cosmo (17)/2016 /Italy (Europe)	AMD	Prospective cohort 2004-2008	27,029 (43.6)	64 ± 10 4 ± 0.5	4 ± 0.5	10 ± 8	Age, Sex, DM duration, BMI, eGFR, HbA1c, TG, HDL-C, LDL-C, SBP, DR
Takao(18)/2014/ Japan (Asia)	Japanese Type 2 Diabetes	retrospective cohort Population	352 (81.8) 1995-2012	55.7 ± 9.5 17)	≥ 1 (1- 12)	6.0 ± 7.0	SBP
Viswanathan(19)/ 2010/India (Asia)	Indian Type 2 Diabetes	Prospective cohort	152 (39.5)	48 ± 9 6 ± 5	12	6 ± 5	Age, DM duration, HbA1c

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Population 1996-2008

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Supplementary Table 1. Continued.

Chen(20)/2013/ China Taiwan (Asia)	Taiwan Type 2 Diabetes Population	Retrospective cohort	461 (49.7)	55.77 ± 9.74	6.82 ± 0.79	8.15 ± 6.28	Age, Sex, DM duration, BMI, Hypertension, DR, HbA1c, TC, UACR
Sheen(21)/2014/ China Taiwan (Asia)	Taiwan Type 2 Diabetes Population	Retrospective cohort	132 (45.6)	61 ± 11	1	NA	Age, Sex, BMI, Smoker, HbA1c, LDL-C, SBP, PP, UACR
Yamada(22)/ 2005/Japan (Asia)	Japanese Type 2 Diabetes Population	Prospective cohort	179 (42)	58 ± 10	8	NA	log UAE, SBP, DBP
Okada(23)/2013 /Japan (Asia) (Asia)	Japanese Type 2 Diabetes Population	Retrospective cohort	256	66	4.6 ± 1.7	15.1	Age, Sex, DM duration, BMI, SBP, HbA1c, TC, Log TG, UA, UAE, Smoker
Sugawara(24)/ 2012/Japan (Asia)	Tsukuba Kawai DM Registry	Prospective cohort	812 (31.3)	55 ± 10	4.3 ± 2.7	NA	Age, Sex, DM duration, SBP, BMI, TC, HDL-C, Smoker, HbA1c

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Supplementary Table 1. Continued.

Forsblom(25)/ 1998/Finland (Europe)	Finnish Type 2 Diabetes Population	Prospective cohort 1983-1995	108	58	9	9	Age, Sex, Smoker, HbA1c, DPN
Gall(26)/1997/ Denmark (Europe)	Danish Type 2 Diabetes Population	Prospective cohort 1987-1993	191	55	5.8	5.5	Age, Sex, DR, Log UAER, TC, HbA1c
Campagna(27)/ 1998/USA (North America)	the strong heart study	Prospective cohort 1989-1992	671 (68.6)	56 ± 7	3.9	10 ± 7	TC, VLDL, LDL-C, HDL, TG
Xu(28)/2008/ USA (North America)	the strong heart study	Prospective cohort 1989-1999	1,318 (67)	58 ± 7	8	0-12	UACR, SBP, Smoker, FPG, SCr
Miao(29)/2017/ China (Asia)	CRPCD	Retrospective cohort (unavailable)	5,705 (59.35)	55 ± 10	NA	NA	Age, BMI, SCr, HDL-C, Region, Hypertension or dyslipidemia, DR, Diet control or exercise

Note: WC, waist circumference; SCr, serum creatinine; UA, uric acid; PP, pulse pressure; DPN, diabetic peripheral neuropathy; VLDL, Very-low-density lipoprotein.

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Supplementary Table 2. Newcastle-Ottawa Quality Assessment Scale of the 20 cohort studies.

Study (First author/year)	Selection				Comparability	Outcome			Total scores
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Cardoso/2017	★	★	★	★	★★	★	★	★	9
Hui/2014	★	★	★	★	★★	★	★	★	9
Afghahi/2010	★	★	★	★	★★	★	★	★	9
Low/2016	★	★	★	★	★★	★	★		8
Takagi/2015	★	★	★	★	★★	★	★	★	9
Hu/2016	★	★	★	★	★★	★	★	★	9
De Cosmo/2015	★	★	★	★	★★	★	★	★	9
De Cosmo/2016	★	★	★	★	★★	★	★	★	9
Takao/2014	★	★	★	★	★★	★	★	★	9
Viswanathan/2010	★	★	★	★	★★	★	★	★	9
Chen/2014	★	★	★	★	★★	★	★	★	9
Sheen/2014	★	★	★	★	★★	★		★	8
Yamada/2005	★	★	★	★	★★	★	★	★	9
Okada/2013	★	★	★	★	★★	★	★	★	9
Sugawara/2012	★	★	★	★	★★	★	★	★	9
Forsblom/1998	★	★	★	★	★★	★	★	★	9
Gall/1997	★	★	★	★	★★	★	★	★	9
Campagna/ 1998	★	★	★	★	★★	★	★		8
Xu/2009	★	★	★	★	★★	★	★		8
Miao/2017	★	★	★	★	★★	★	★	★	9

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Supplementary Table 3. 19 risk factors included in the systematic review and meta-analysis.

Risk factors	First author/ Year	Sample size	No. of DKD initiation	Definition of risk factor	RR	95% CI	P value
Age	Okada/2013	256	30	Increment by 1 year	1.005	0.950-1.070	0.8652
Age	Sugawara/2012	812	193	Increment by 1 year	1.02	1.00-1.04	0.013
Age	Forsblom/1998	108	31	Increment by 1 year	1.126	0.990-1.280	0.066
Age	Gall /1997	191	41	Increment by 1 year	1.07	1.02-1.12	< 0.01
Age	Hui/2014	462	94	Increment by 1 year	1.01	0.98-1.04	0.595
Age	Afghahi/2010	3,667	729	Increment by 8 years	1.27	1.16-1.40	< 0.001
Age	Afghahi/2010	3,667	407	Increment by 6.5 years	2.00	1.75-2.28	< 0.001
Age	Low/2016	553	64	Increment by 10 years	1.62	1.12-2.33	0.01
Age	Takagi/2015	1,777	316	Increment by 1 year	1.04	1.02-1.05	< 0.001
Age	Hu/2016	344	53	Increment by 1 year	1.089	1.050-1.130	< 0.05
Age	De Cosmo/2016	27,029	2,788	Increment by 5 years	1.373	1.330-1.420	< 0.001
Age	De Cosmo/2016	27,029	4,978	Increment by 5 years	1.075	1.030-1.120	< 0.001
Age	De Cosmo/2016	27,029	1,207	Increment by 5 years	1.38	1.31-1.46	< 0.001
Age	Viswanathan/2010	152	67	Increment by 1 year	1.05	1.02-1.08	0.001
Age	Chen/2014	461	68	Increment by 1 year	0.99	0.96-1.03	0.733

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Age	Sheen/2014	132	20	Increment by 1 year	1.01	0.95-1.08	0.776
DM duration	Okada/2013	256	30	Increment by 1 year	1.035	0.990-1.080	0.0972

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Supplementary Table 3. Continued.

DM duration	Sugawara/2012	812	193	Increment by 1 year	1.03	1.01-1.05	0.005
DM duration	Hui/2014	462	94	Increment by 1 year	0.99	0.96-1.03	0.702
DM duration	De Cosmo/2016	27,029	2,788	Increment by 5 years	1.02	0.98-1.06	0.3
DM duration	De Cosmo/2016	27,029	4,978	Increment by 5 years	0.981	0.950-1.020	0.3
DM duration	De Cosmo/2016	27,029	1,207	Increment by 5 years	1.001	0.950-1.060	0.96
DM duration	Chen/2014	461	68	DM duration	1.01	0.96-1.08	0.639
Sex	Okada/2013	256	30	Male	0.609	0.200-1.740	0.3586
Sex	Sugawara/2012	812	193	Male	0.70	0.47-1.06	0.089
Sex	Forsblom/1998	108	31	Male	3.808	0.98-14.81	0.054
Sex	Gall /1997	191	41	Male	2.6	1.2-5.4	< 0.02
Sex	Hui/2014	462	94	Male	0.72	0.47-1.10	0.129
Sex	Afghahi/2010	3,667	729	Female	0.65	0.55-0.79	< 0.001
Sex	Afghahi/2010	3,667	407	Female	4.03	2.97-5.48	< 0.001
Sex	Takagi/2015	1,655	181	Male	1.69	1.21-2.35	0.002
Sex	Hu/2016	344	53	Male	0.572	0.300-1.080	0.082
Sex	De Cosmo/2016	27,029	2,788	Male	0.767	0.680-0.860	< 0.001
Sex	De Cosmo/2016	27,029	4,978	Male	1.355	1.220-1.500	< 0.001

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Sex	De Cosmo/2016	27,029	1,207	Male	1.09	0.93-1.24	< 0.001
Sex	Chen/2014	461	68	Male	1.62	0.80-3.27	0.178
Sex	Sheen/2014	132	20	Male	0.96	0.29-3.15	0.946

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Supplementary Table 3. Continued.

BMI	Okada/2013	256	30	Increment by 1 kg/m ²	1.085	0.960-1.200	0.167
BMI	Sugawara/2012	812	193	Increment by 1 kg/m ²	1.05	1.01-1.10	0.016
BMI	Afghahi/2010	3,667	729	Increment by 5 kg/m ²	1.13	1.04-1.24	0.0064
BMI	Afghahi/2010	3,667	407	Increment by 5 kg/m ²	1.19	1.06-1.33	0.0026
BMI	Low/2016	553	251	Increment by 5 kg/m ²	1.27	1.01-1.58	0.039
BMI	De Cosmo/2016	27,029	2,788	Increment by 1 kg/m ²	1.033	1.020-1.050	< 0.001
BMI	De Cosmo/2016	27,029	4,978	Increment by 1 kg/m ²	1.019	1.010-1.030	< 0.001
BMI	De Cosmo/2016	27,029	1,207	Increment by 1 kg/m ²	1.036	1.020-1.050	< 0.001
BMI	Chen/2014	461	68	Increment by 1 kg/m ²	1.06	0.95-1.18	0.294
BMI	Sheen/2014	132	20	Increment by 1 kg/m ²	1.00	0.84-1.19	0.996
Smoker	Okada/2013	256	30	Smoker	1.21	0.44-2.90	0.6867
Smoker	Sugawara/2012	812	193	Smoker	1.68	1.13-2.49	0.01
Smoker	Forsblom/1998	108	31	Smoker	5.77	1.51-22.14	0.011
Smoker	Xu/2007	1,318	378	Current smoker	1.49	1.12-1.99	< 0.01
Smoker	Afghahi/2010	3,667	729	Smoker	1.50	1.21-1.86	< 0.001
Smoker	Hu/2016	344	53	Smoker	2.886	1.370-6.080	< 0.05
Smoker	De Cosmo/2015	20,142	1,109	Smoker	0.85	0.65-1.11	0.246

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Smoker	De Cosmo/2015	20,142	1,968	Smoker	1.23	1.02-1.48	0.028
Smoker	De Cosmo/2015	20,142	286	Smoker	1.61	1.00-2.59	0.05
Smoker	Sheen/2014	132	20	Smoker	0.51	0.07-3.69	0.505

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Supplementary Table 3. Continued.

DR	Gall/1997	191	41	Diabetic retinopathy	2.4	1.3-4.7	< 0.01
DR	Miao/2017	5,705	NA	Diabetic retinopathy	4.76	3.67-6.17	< 0.05
DR	Takagi/2015	1,630	415	Diabetic retinopathy	1.57	1.17-2.12	0.003
DR	Takagi/2015	1,655	181	Diabetic retinopathy	1.36	1.08-1.71	0.008
DR	De Cosmo/2016	27,029	2,788	Diabetic retinopathy	1.181	0.990-1.410	0.06
DR	De Cosmo/2016	27,029	4,978	Diabetic retinopathy	1.112	0.930-1.330	0.2
DR	De Cosmo/2016	27,029	1,207	Diabetic retinopathy	1.135	0.870-1.470	0.34
DR	Chen/2014	461	68	Diabetic retinopathy	0.60	0.24-1.45	0.254
HbA1c	Okada/2013	256	30	Increment by 1% (11mmol/mol)	0.68	0.40-1.07	0.1026
HbA1c	Sugawara/2012	812	193	Increment by 1% (11mmol/mol)	1.22	1.06-1.40	0.004
HbA1c	Forsblom/1998	108	31	Increment by 1% (11mmol/mol)	2.05	1.36-3.07	0.0005
HbA1c	Gall/1997	191	41	Increment by 1% (11mmol/mol)	1.2	1.0-1.4	< 0.05
HbA1c	Hui/2014	462	94	Increment by 1% (11mmol/mol)	1.10	0.95-1.27	0.193
HbA1c	Afghahi/2010	3,667	729	Increment by 1 SD (1.1-1.2%) (12.1-13.2mmol/mol)	1.23	1.13-1.33	< 0.001
HbA1c	Takagi/2015	1,630	415	Increment by 1 mmol/mol (0.1%)	1.02	1.01-1.03	< 0.001

SUPPLEMENTARY DATA

HbA1c	De Cosmo/2016	27,029	2,788	Increment by 1% (11mmol/mol)	1.049	0.989-1.112	0.1
HbA1c	De Cosmo/2016	27,029	4,978	Increment by 1% (11mmol/mol)	1.069	1.001-1.141	0.04
HbA1c	De Cosmo/2016	27,029	1,207	Increment by 1% (11mmol/mol)	1.100	1.019-1.188	0.01
HbA1c	Viswanathan/2010	152	67	Increment by 1% (11mmol/mol)	1.7	1.3-2.2	< 0.001
HbA1c	Chen/2014	461	68	Increment by 1% (11mmol/mol)	1.38	1.04-1.81	0.024

SUPPLEMENTARY DATA

Supplementary Table 3. Continued.

HbA1c	Sheen/2014	132	20	Increment by 1% (11mmol/mol)	1.144	0.790-1.670	0.483
SBP	Yamada/2005	179	27	Increment by 1 mmHg	1.004	0.960-1.050	0.87
SBP	Okada/2013	256	30	Increment by 1 mmHg	1.033	1.010-1.060	0.016
SBP	Sugawara/2012	812	193	Increment by 1 mmHg	1.01	1.00-1.03	0.090
SBP	Xu/2007	1,318	378	Increment by 5 mmHg	1.02	1.01-1.04	0.01
SBP	Cardoso/2017	463	100	Increment by 1 mmHg	1.49	1.04-2.12	0.029
SBP	Hui/2014	462	94	Increment by 1 mmHg	1.02	1.01-1.03	0.003
SBP	Afghahi/2010	3,667	729	Increment by 16-17 mmHg	1.25	1.15-1.37	< 0.001
SBP	Afghahi/2010	3,667	407	Increment by 16-17 mmHg	1.18	1.06-1.31	0.003
SBP	Takagi/2015	1777	316	Increment by 1 mmHg	1.01	1.00-1.01	0.031
SBP	De Cosmo/2016	27,029	2,788	Increment by 5 mmHg	1.013	0.996-1.030	0.1
SBP	De Cosmo/2016	27,029	4,978	Increment by 5 mmHg	1.000	0.985-1.016	0.9
SBP	De Cosmo/2016	27,029	1,207	Increment by 5 mmHg	1.022	0.998-1.047	0.07
SBP	Takao/2014	352	90	Increment by 10 mmHg	1.164	1.035-1.309	0.0114
SBP	Sheen/2014	132	20	Increment by 1 mmHg	1.04	1.002-1.081	0.041
TC	Okada/2013	256	30	Increment by 1 mmol/L	0.99	0.98-1.01	0.4229
TC	Sugawara/2012	812	193	Increment by 1 mmol/L	0.87	0.73-1.03	0.097

SUPPLEMENTARY DATA

TC	Gall/1997	191	41	Increment by 1 mmol/L	1.4	1.1-1.7	< 0.01
TC	Campagna/1998	211	67	Increment by 1 mmol/L (male)	1.0	0.4-2.5	NA
TC	Campagna/1998	460	144	Increment by 1 mmol/L (female)	1.20	0.66-2.10	NA

SUPPLEMENTARY DATA

Supplementary Table 3. Continued.

TC	Chen/2014	461	68	Increment by 1 mmol/L	0.99	0.98-1.00	0.073
HDL-C	Sugawara/2012	812	193	Increment by 1 mmol/L	0.90	0.59-1.40	0.65
HDL-C	Campagna/1998	211	67	Increment by 1 mmol/L (male)	1.50	0.66-3.40	NA
HDL-C	Campagna/1998	460	144	Increment by 1 mmol/L (female)	0.56	0.32-0.98	< 0.05
HDL-C	Miao/2017	5,705	NA	Increment by 1 mmol/L (female)	0.27	0.15-0.46	< 0.05
HDL-C	Miao/2017	5,705	NA	Increment by 1 mmol/L (male)	0.28	0.17-0.47	< 0.05
HDL-C	Afghahi/2010	3,667	729	Increment by 0.4 mmol/L	0.90	0.82-0.99	0.045
HDL-C	Takagi/2015	1,777	316	Increment by 1 mmol/L	0.71	0.52-0.98	0.035
HDL-C	De Cosmo/2016	27,029	2,788	Increment by 5 mg/dL	0.981	0.958-1.004	0.1
HDL-C	De Cosmo/2016	27,029	4,978	Increment by 5 mg/dL	0.973	0.954-0.993	0.008
HDL-C	De Cosmo/2016	27,029	1,207	Increment by 5 mg/dL	0.936	0.905-0.969	< 0.001
TG	Okada/2013	256	30	Log TG	1.80	0.20-16.37	0.5969
TG	Campagna/1998	211	67	Increment by 1 mmol/L (male)	0.67	0.27-1.70	NA
TG	Campagna/1998	460	144	Increment by 1 mmol/L (female)	1.70	0.98-2.90	NA
TG	Afghahi/2010	3,667	729	Increment by 0.7 mmol/L	1.12	1.02-1.22	0.016
TG	Afghahi/2010	3,667	407	Increment by 0.7 mmol/L	1.20	1.07-1.34	0.0013
TG	Low/2016	553	251	Increment by 1 mmol/L	1.44	1.15-1.81	0.002

SUPPLEMENTARY DATA

TG	De Cosmo/2016	27,029	2,788	Increment by 10 mg/dL	1.018	1.009-1.026	< 0.001
TG	De Cosmo/2016	27,029	4,978	Increment by 10 mg/dL	1.008	1.001-1.015	0.02
TG	De Cosmo/2016	27,029	1,207	Increment by 10 mg/dL	1.031	1.022-1.041	< 0.001

SUPPLEMENTARY DATA

Supplementary Table 3. Continued.

LDL-C	Campagna/1998	211	67	Increment by 1 mmol/L (male)	1.10	0.43-2.9	NA
LDL-C	Campagna/1998	460	144	Increment by 1 mmol/L (female)	1.20	0.67-2.00	NA
LDL-C	De Cosmo/2016	27,029	2,788	Increment by 10 mg/dL	0.974	0.957-0.992	0.004
LDL-C	De Cosmo/2016	27,029	4,978	Increment by 10 mg/dL	0.980	0.967-0.993	0.003
LDL-C	De Cosmo/2016	27,029	1,207	Increment by 10 mg/dL	0.957	0.933-0.981	< 0.001
LDL-C	Sheen/2014	132	20	Increment by 1 mg/dL	0.990	0.972-1.008	0.276
UA	Okada/2013	256	30	Increment by 1 μ mol/L	0.91	0.64-1.29	0.5753
UA	De Cosmo/2015	20,142	1,109	3.7-4.3 mg/dL (female) or 4.3-4.8mg/dL (male)	1.46	1.14-1.88	0.003
UA	De Cosmo/2015	20,142	1,109	4.4-4.9 mg/dL (female) or 4.9-5.5 mg/dL (male)	1.44	1.11-1.87	0.006
UA	De Cosmo/2015	20,142	1,109	5.0-5.7 mg/dL (female) or 5.6-6.3 mg/dL (male)	1.95	1.48-2.58	< 0.001
UA	De Cosmo/2015	20,142	1,109	UA \geq 5.8 mg/dL (female) or \geq 6.4 mg/dL (male)	2.61	1.98-3.42	< 0.001
UA	Takagi/2015	1,655	181	Increment by 1 μ mol/L	1.00	1.00-1.01	< 0.001
UACR	Yamada/2005	179	27	Increment by 1 mg/g	1.069	0.995-1.148	0.07

SUPPLEMENTARY DATA

UACR	Okada/2013	256	30	Increment by 1 mg/g	1.13	1.06-1.21	0.0001
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SUPPLEMENTARY DATA

Supplementary Table 3. Continued.

UACR	Gall/1997	191	41	Log UAER (Increment by 10 folds)	11.1	3.4-35.9	< 0.001
UACR	Xu/2007	1,318	378	UACR 5-10 mg/g	1.17	0.79-1.71	0.4
UACR	Xu/2007	1,318	378	UACR ≥ 10 mg/g	2.71	1.89-3.90	< 0.001
UACR	Low/2016	553	251	Ln [ACR (μ g/mg)]	1.74	1.32-2.28	< 0.001
UACR	Takagi/2015	1,630	415	Log [UACR (mg/g)] (albuminuria cohort)	219.45	95.75-502.93	< 0.001
UACR	Takagi/2015	1,655	181	Log [UACR (mg/g)] (eGFR cohort)	2.74	1.64-4.57	< 0.001
UACR	Chen/2014	461	68	Increment by 1 mg/g	1.19	1.12-1.26	< 0.001
UACR	Sheen/2014	132	20	Increment by 1 mg/g	1.120	1.048-1.196	0.001
eGFR	Hui/2014	462	94	Log eGFR	0.37	1.00-1.37	0.318
eGFR	Low/2016	553	64	Each 5 mL/min/1.73 m ² drop	1.96	1.56-2.5	< 0.001
eGFR	Takagi/2015	1,655	181	eGFR	0.89	0.87-0.90	< 0.001
eGFR	Hu/2016	344	53	60 ≤ eGFR < 90 mL/min/1.73 m ²	4.667	2.390-9.110	< 0.05
eGFR	Hu/2016	344	53	eGFR ≥ 120 mL/min/1.73 m ²	5.677	1.540-20.870	< 0.05
eGFR	De Cosmo/2016	27,029	2,788	eGFR < 90 mL/min/1.73 m ² ,	2.614	2.430-2.810	< 0.001

SUPPLEMENTARY DATA

Each 10 mL/min/1.73 m² drop

SUPPLEMENTARY DATA

Supplementary Table 3. Continued.

eGFR	De Cosmo/2016	27,029	4,978	eGFR < 90 mL/min/1.73 m ² , each 10 mL/min/1.73 m ² drop	1.00	0.94-1.07	0.9
eGFR	De Cosmo/2016	27,029	1,207	eGFR < 90 mL/min/1.73 m ² , each 10 mL/min/1.73 m ² drop	2.837	2.590-3.110	< 0.001
Hypertension	De Cosmo/2015	20,142	1,109	BP ≥ 140/85 mmHg	1.16	0.98-1.36	0.081
Hypertension	De Cosmo/2015	20,142	1,968	BP ≥ 140/85 mmHg	1.05	0.91-1.20	0.533
Hypertension	De Cosmo/2015	20,142	286	BP ≥ 140/85 mmHg	1.08	0.82-1.43	0.58
Hypertension	Chen/2014	461	68	Current use of antihypertension drug or BP ≥ 140/90 mmHg	1.63	0.43-6.13	0.473
FPG	Xu/2007	1,318	378	Increment by 10 mg/dL	1.01	1.00-1.02	0.02
FPG	Hu/2016	344	53	Increment by 1 mmol/L (126 mg/dL)	1.104	1.020-1.190	< 0.05
PP	Hu/2016	344	53	Increment by 1 mmHg	1.022	1.004-1.040	< 0.05
PP	Sheen/2014	132	20	Increment by 1 mmHg	1.045	0.995-1.098	0.079
SCr	Xu/2007	1,318	378	Increment by 1 mg/dL (88.4 μmol/L)	2.92	1.27-6.69	0.01

SUPPLEMENTARY DATA

SCr	Afghahi/2010	3,667	407	Increment by 1 SD (20 µmol/L)	2.11	1.80-2.46	< 0.001
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Note: NA, not available; BMI, body mass index; DR, diabetic retinopathy; HbA1c, Hemoglobin A1c; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; UACR, urinary albumin creatinine ratio; UAER, urinary albumin excretion rate; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; PP, pulse pressure; SCr, serum creatinine.

SUPPLEMENTARY DATA

Supplementary Table 4. Baseline characteristics of patients in validation cohort

Variables	Total	Development of DKD		<i>P</i> value
		No	Yes	
N	380	282	98	
Follow-up (months)	34.8 (24.0, 46.8)	36.0 (24.0, 46.8)	34.8 (21.6, 45.6)	0.12
Age (years)	55 ± 9	54 ± 8	59 ± 9	< 0.001
Female (%)	170 (44.7)	140 (49.6)	30 (30.6)	< 0.001
Smokers [n (%)]	157 (41.3)	104 (36.9)	53 (54.1)	< 0.001
Diabetes duration (years)	7 (3, 12)	6 (3, 12)	8 (3, 13)	0.19
BMI (kg/m ²)	26.57 ± 3.36	26.67 ± 3.38	26.31 ± 3.30	0.12
SBP (mmHg)	130 (120, 140)	130 (120, 135)	140 (140, 150)	< 0.001
DR [n (%)]	94 (24.7)	52 (18.4)	42 (42.9)	< 0.001
HbA1c (%) [mmol/mol]	8.5 (7.3, 9.8) [69 (56, 84)]	8.3 (7.2, 9.7) [67 (55, 83)]	8.9 (7.5, 10.2) [74 (58, 88)]	< 0.001
TG (mmol/L)	1.74 (1.18, 2.70)	1.60 (1.10, 2.52)	2.25 (1.47, 3.06)	< 0.001
HDL (mmol/L)	1.20 (1.10, 1.40)	1.20 (1.10, 1.43)	1.23 (1.10, 1.40)	< 0.001
Baseline UACR (mg/g)	14.7 (11.9, 18.5)	14.0 (11.4, 17.4)	18.5 (13.7, 26.0)	< 0.001
Baseline eGFR (ml/min/1.73 m ²)	99.4 ± 17.9	101.6 ± 17.3	92.9 ± 18.2	0.06
Oral diabetic medications [n (%)]	375 (98.7)	279 (98.9)	96 (98)	0.23
Insulin [n (%)]	205 (53.9)	147 (52.1)	58 (59.2)	0.18
ACEI/ARB [n (%)]	105 (27.6)	75 (26.6)	30 (30.6)	0.11
Statins [n (%)]	95 (25.0)	69 (24.5)	26 (26.5)	0.20

Data are median (IQR), mean ± SD, or n (%).

SUPPLEMENTARY DATA

Supplementary Table 5. No. of revolving studies, sample size, pooled RRs (95% CIs), β -coefficients, and risk scores of risk factors included in the DKD risk prediction model

Risk factors for DKD	No. of studies	Sample size	Pooled RR	95% CI	β -coefficient	Scores
Age (by 5-10 years)	3	31,249	1.38	1.20-1.59	0.32	3.0
BMI (by 5 kg/m ²)	2	4,220	1.16	1.09-1.23	0.15	1.5
Smoking (yes/no)	8	26,779	1.49	1.30-1.71	0.40	4.0
Diabetic retinopathy (yes/no)	4	29,311	1.31	1.00-1.73	0.27	3.0
HbA1c (by 1% [11mmol/mol])	11	34,900	1.17	1.09-1.26	0.15	1.5
SBP (by 10-20 mmHg)	2	4,019	1.21	1.15-1.27	0.19	2.0
HDL-C (by 1 mmol/L)	3	2,800	0.78	0.61-0.99	-0.25	-2.5
TG (by 1 mmol/L)	3	1,480	1.42	1.16-1.74	0.37	4.0
UACR (by 1 mg/g)	4	1,028	1.13	1.10-1.17	0.12	1.0

SUPPLEMENTARY DATA

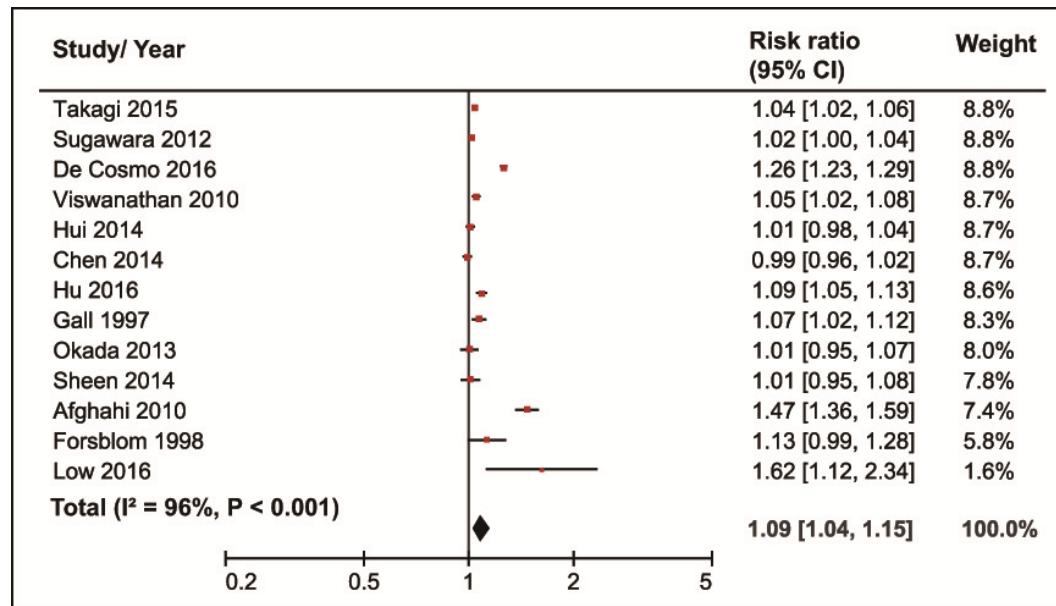
Supplementary Table 6. Performance of DKD risk prediction model at different cut-off value

Cut-off value	Sensitivity	Specificity
0	1	0
7	0.98	0.064
8	0.969	0.085
9	0.959	0.117
10	0.959	0.177
11	0.959	0.223
12	0.949	0.333
13	0.939	0.39
14	0.908	0.482
14.5	0.898	0.557
15	0.888	0.592
15.5	0.857	0.642
16	0.847	0.677
16.5	0.796	0.713
17	0.776	0.745
17.5	0.755	0.77
18	0.714	0.798
18.5	0.673	0.812
19	0.622	0.826
20	0.561	0.858
21	0.51	0.894
22	0.398	0.918
23	0.337	0.926
24	0.276	0.961
25	0.184	0.975
26	0.153	0.986
27	0.122	0.996
28	0.102	0.996
29	0.071	0.996
30	0.02	1
37	0	1

SUPPLEMENTARY DATA

Supplementary Figure 1. Age

a



SUPPLEMENTARY DATA

b

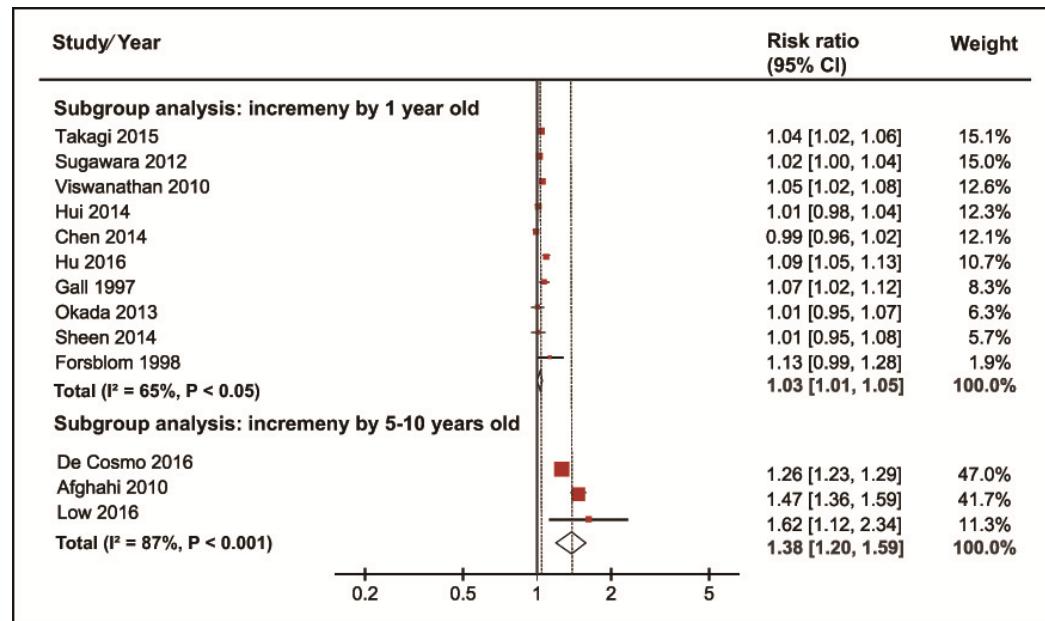
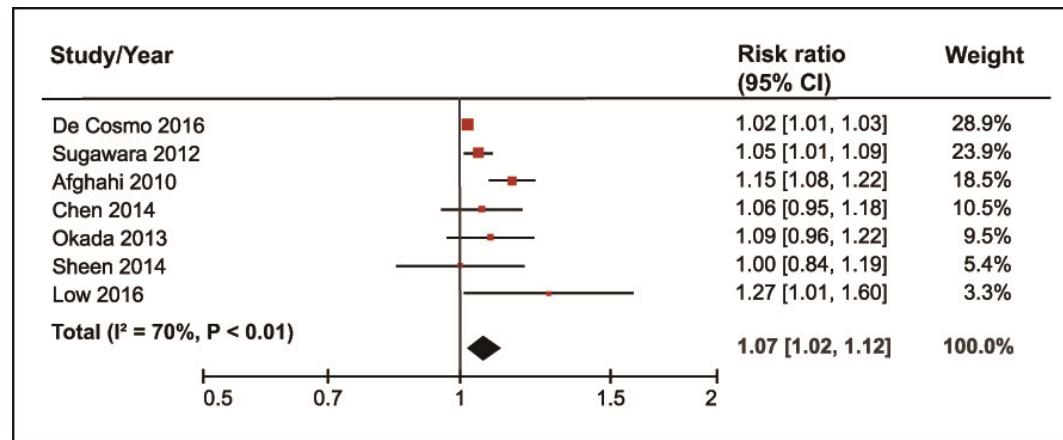


Figure 1- a. Association of age with diabetic kidney disease; b. Subgroup analysis of association of age with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 2. BMI

a



SUPPLEMENTARY DATA

b

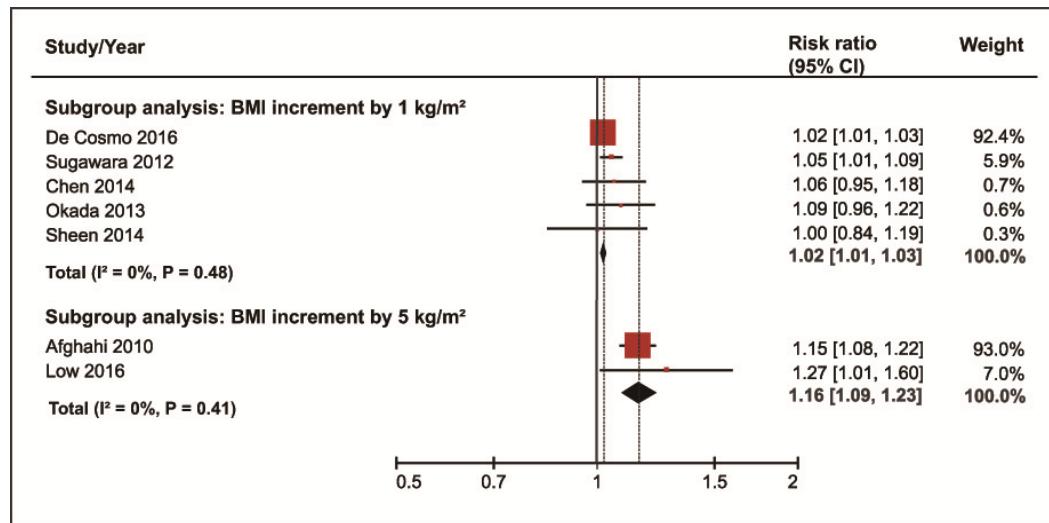


Figure 2- a. Association of BMI with diabetic kidney disease; b. Subgroup analysis of association of BMI with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 3. Smoker

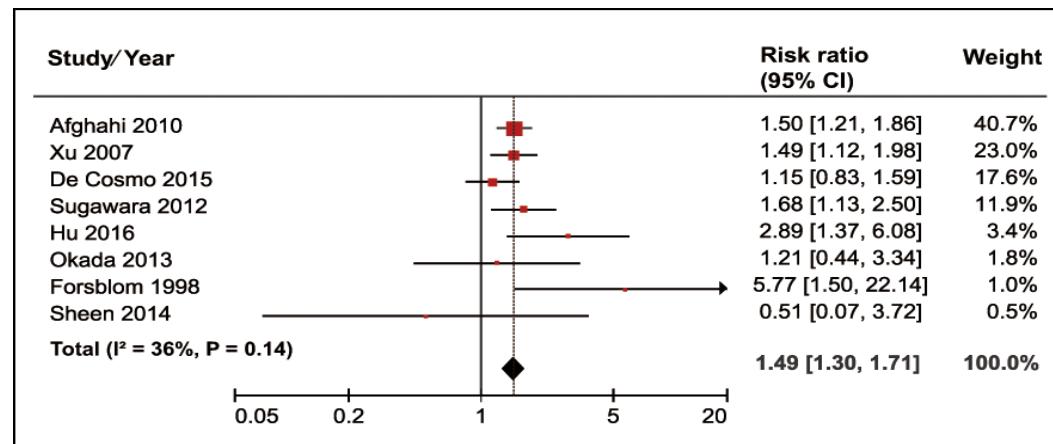


Figure 3. Association of smoker with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 4. Diabetic retinopathy

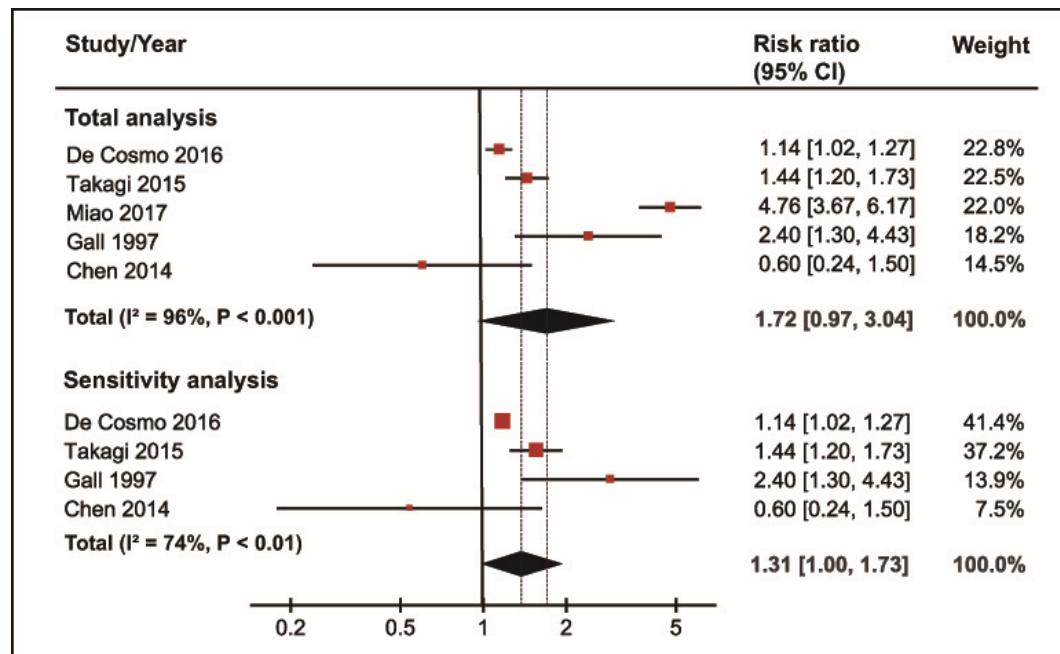


Figure 4. Association of diabetic retinopathy with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 5. HbA1c

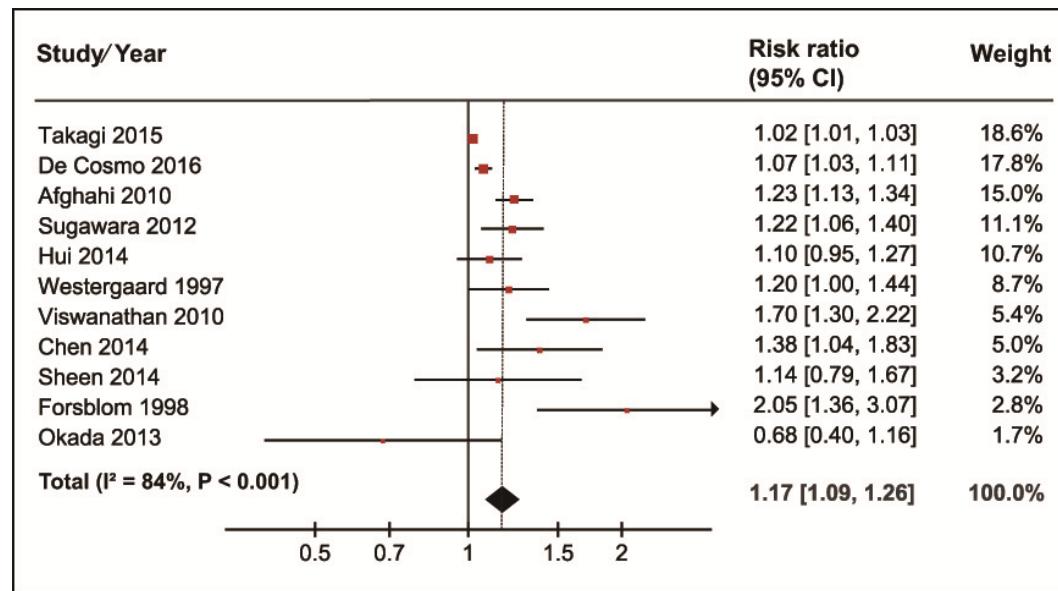
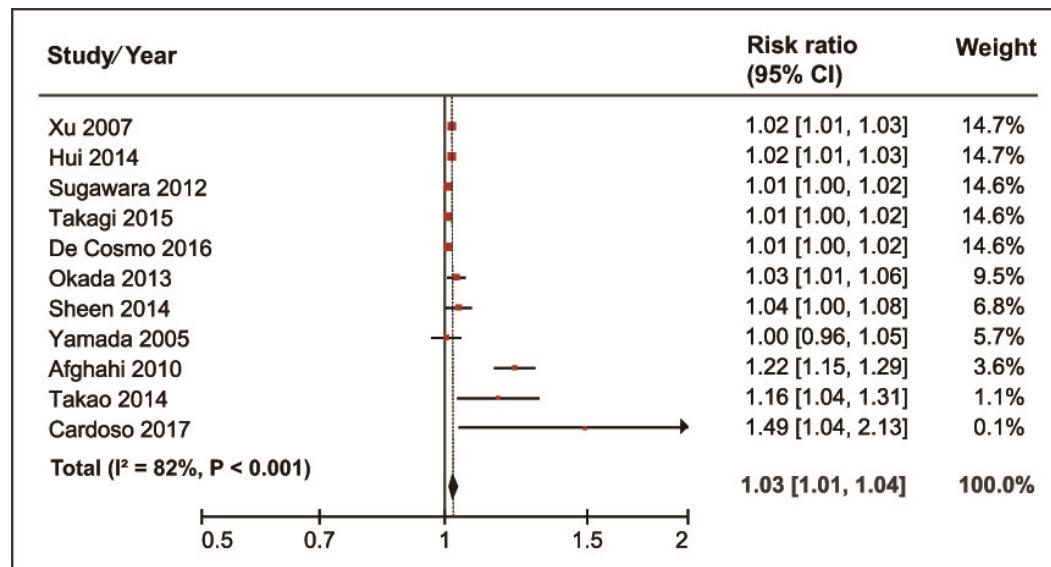


Figure 5. Association of HbA1c with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 6. SBP

a



SUPPLEMENTARY DATA

b

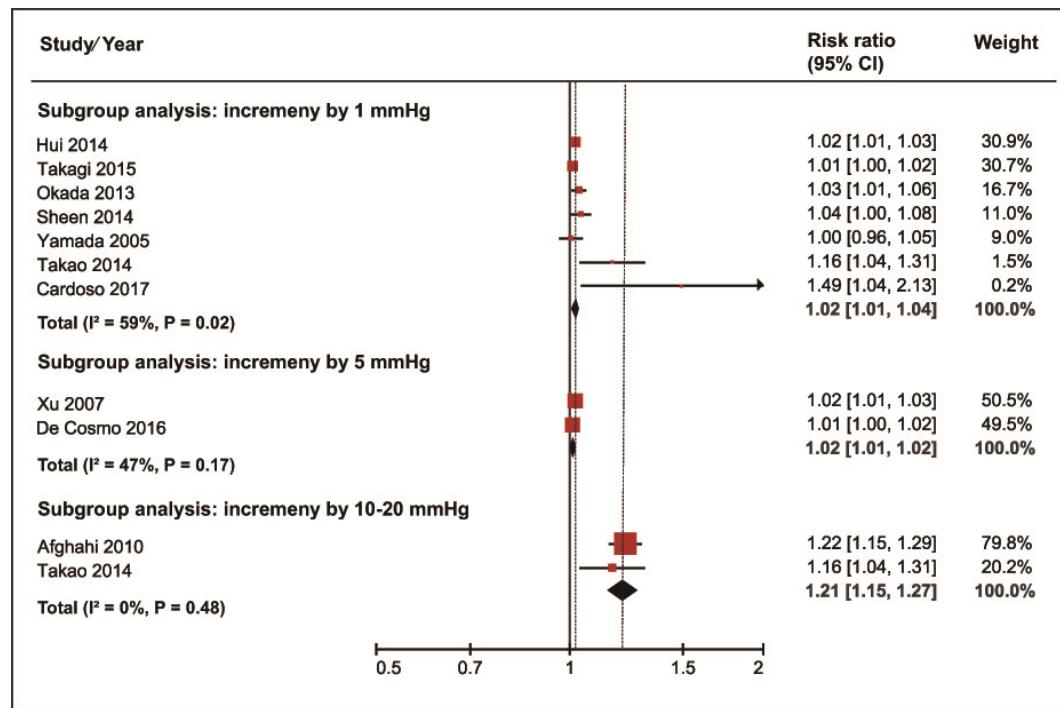
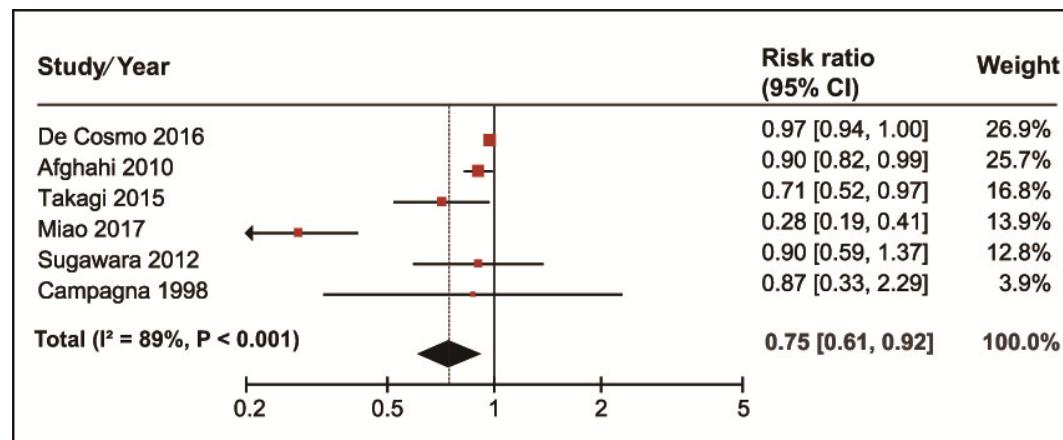


Figure 6-a. Association of SBP with diabetic kidney disease. b. Subgroup analysis of association of SBP with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 7. HDL-C

a



SUPPLEMENTARY DATA

b

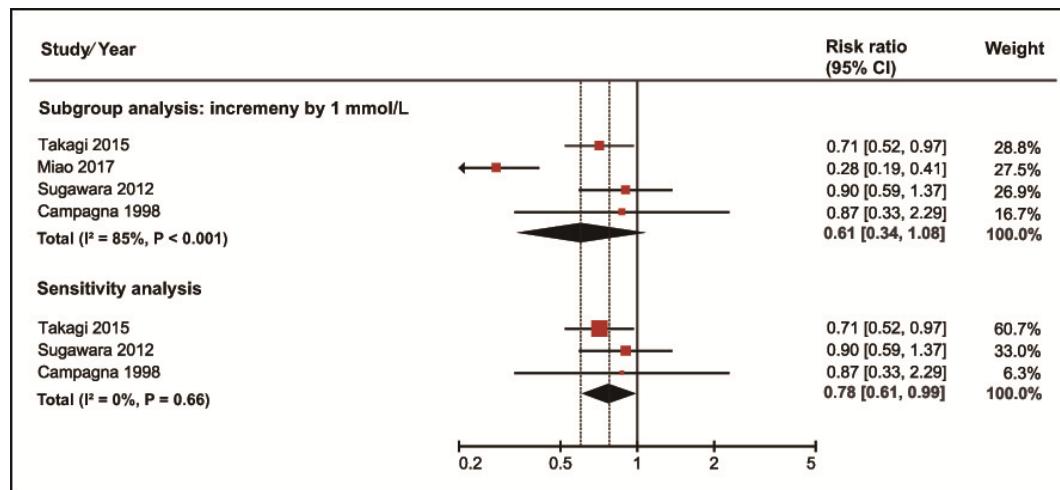
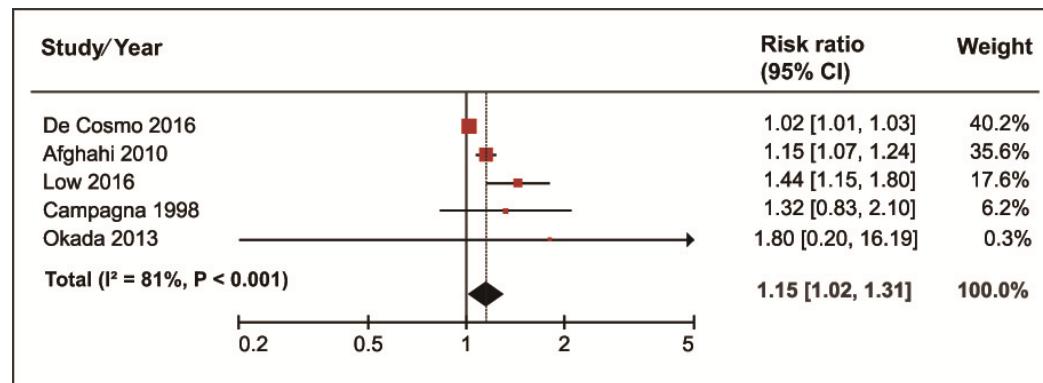


Figure 7-a. Association of HDL-C with diabetic kidney disease. b. Subgroup and sensitivity analysis of association of HDL-C with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 8. TG

a



b

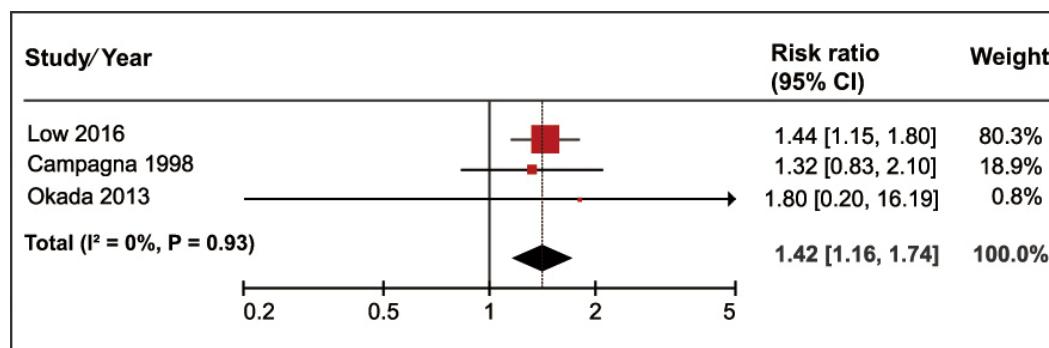
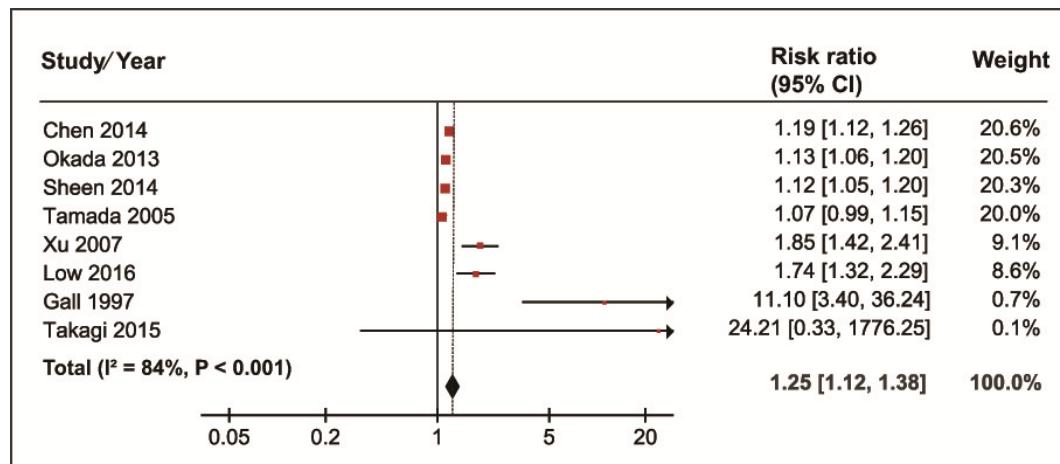


Figure 8-a. Association of TG with diabetic kidney disease. b. Sensitivity analysis of association of TG with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 9. UACR

a



b

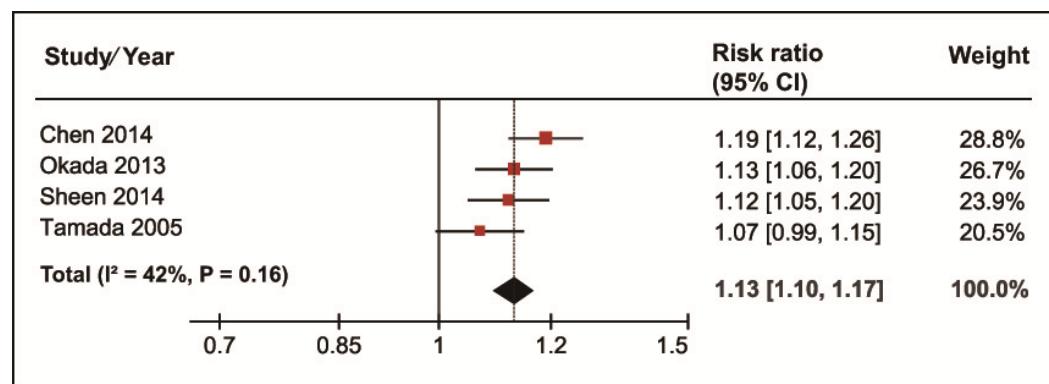


Figure 9-a. Association of UACR with diabetic kidney disease. b. Sensitivity analysis of association of UACR with diabetic kidney disease.

SUPPLEMENTARY DATA

Supplementary Figure 10. eGFR

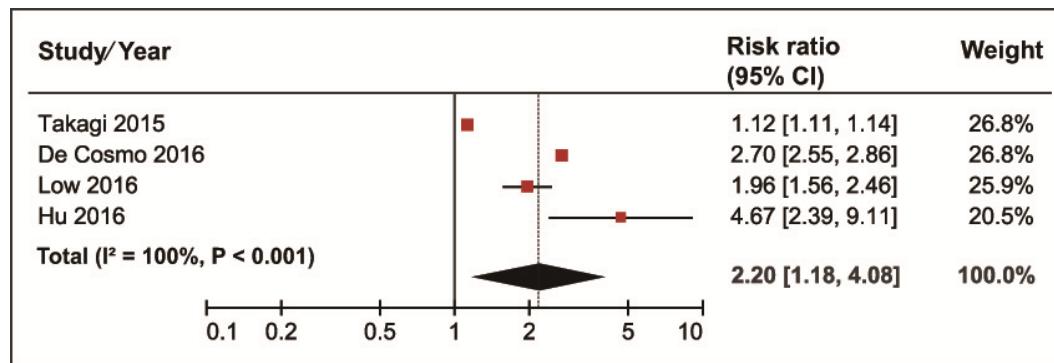


Figure 10. Association of eGFR with diabetic kidney disease.

SUPPLEMENTARY DATA

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