Dose-response association of diabetic kidney disease with routine clinical parameters in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

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Summary

Background Diabetic kidney disease (DKD) is a leading cause of end-stage kidney disease and is associated with high mortality rates. The influence of routine clinical parameters on DKD onset in patients with type 2 diabetes mellitus (T2DM) remains uncertain.

Methods In this systematic review and meta-analysis, we searched multiple databases, including PubMed, Embase, Scopus, Web of Science, and Cochrane Library, for studies published from each database inception until January 11, 2024. We included cohort studies examining the association between DKD onset and various clinical parameters, including body mass index (BMI), hemoglobin A1c (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and serum uric acid (UA). Random-effect dose–response meta-analyses utilizing one-stage and/or cubic spline models, were used to estimate correlation strength. This study is registered in PROSPERO (CRD42022326148).

Findings This analysis of 46 studies involving 317,502 patients found that in patients with T2DM, the risk of DKD onset increased by 3% per 1 kg/m^2 increase in BMI (relative risk (RR) = 1.03, confidence interval (CI) [1.01–1.04], I^2 = 70.07%; GRADE, moderate); a 12% increased risk of DKD onset for every 1% increase in HbA1c (RR = 1.12, CI [1.07–1.17], I^2 = 94.94%; GRADE, moderate); a 6% increased risk of DKD onset for every 5 mmHg increase in SBP (RR = 1.06. CI [1.03–1.09], I^2 = 85.41%; GRADE, moderate); a 2% increased risk of DKD onset per 10 mg/dL increase in TG (RR = 1.02, CI [1.01–1.03], I^2 = 78.45%; GRADE, low); an 6% decreased risk of DKD onset per 10 mg/dL increase in HDL (RR = 0.94, CI [0.92–0.96], I^2 = 0.33%; GRADE, high), and a 11% increased risk for each 1 mg/dL increase in UA (RR = 1.11, CI [1.05–1.17], I^2 = 79.46%; GRADE, moderate). Subgroup analysis revealed a likely higher risk association of clinical parameters (BMI, HbA1c, LDL, and UA) in patients with T2DM for less than 10 years.

Interpretation BMI, HbA1c, SBP, TG, HDL and UA are potential predictors of DKD onset in patients with T2DM. Given high heterogeneity between included studies, our findings should be interpreted with caution, but they suggest monitoring of these clinical parameters to identify individuals who may be at risk of developing DKD.

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Keywords: Dose-response meta-analysis; Type 2 diabetes mellitus; Diabetic nephropathy; Clinical parameters

Research in context

Evidence before this study

In a preliminary search of PubMed, Embase, Scopus, Web of Science, and Cochrane library databases, spanning from each database's inception to January 2024, we reviewed the existing evidence on the impact of routine clinical parameters (body mass index, hemoglobin A1c, blood pressure, cholesterol levels, and serum uric acid) on the risk of diabetic kidney disease in patients with type 2 diabetes, without language restrictions. We employed specific search terms included "type 2 diabetes OR diabetes" AND "chronic kidney disease OR diabetic kidney disease OR diabetic nephropathy" AND "cohort", identifying some cohort studies explored these routine clinical parameters on the risk. A systematic review and meta-analysis published in 2022 examined the impact of serum uric acid on the development of diabetic kidney disease in patients with type 2 diabetes, pooling analysis from 8 cohort studies, which lacking evidence grading and exploration of other routine clinical parameters.

Added value of this study

This study included cohort studies involving patients with type 2 diabetes mellitus and found that routine clinical parameters, including body mass index, hemoglobin A1c, systolic blood pressure, triglycerides, high-density lipoprotein, low-density lipoprotein, and serum uric acid, were significant factors for the risk of developing diabetic kidney disease. The effect of systolic blood pressure was more pronounced on the increase in albuminuria than on the decrease in glomerular filtration rate, whereas high-density lipoprotein and triglycerides levels had a more significant impact on the decrease in glomerular filtration rate. We found that in European patients with type 2 diabetes, the levels of triglycerides, high-density lipoprotein, and serum uric acid were more likely to influence the onset of diabetic kidney disease than in their Asian counterparts.

Implications of all the available evidence

Our findings suggest that routine clinical parameters in patients with type 2 diabetes mellitus require further attention to prevent the onset of diabetic kidney disease, with a particular focus on body mass index, hemoglobin A1c, systolic blood pressure, triglyceride, high-density lipoprotein, and serum uric acid levels. The effects of these parameters on the increase in albuminuria, decrease in glomerular filtration rate, and type 2 diabetes mellitus in different regions should receive more attention.

Introduction

Diabetes mellitus (DM) presents a growing global public health concern, comprising type 1 DM characterized by insufficient insulin production in islet beta cells and T2DM characterized by insulin resistance.[1,2] The World Health Organization projects that approximately 642 million individuals will be affected by DM worldwide by the year 2040.[3] DM is associated with peripheral neuropathy, kidney diseases, and cardiovascular complications, including myocardial infarction, unstable angina, and stroke, significantly affecting patients' quality of life and elevating mortality rates. Diabetic kidney disease (DKD) is clinically diagnosed through albuminuria (Alb), decreased glomerular filtration rate, or both.[4,5] Approximately 40% of patients with DM develop DKD, with 30%–50% of cases arising from T2DM.[6,7] DKD is the leading cause of end-stage kidney disease, posing a significant economic burden.[8–11]

Routine clinical parameters, especially in patients with T2DM, such as body mass index (BMI),[12] blood glucose,[13] blood pressure,[13,14] blood lipids,[15–17] and uric acid (UA),[18] have been utilized to identify individuals at DKD risk. While previous studies have examined associations between the baseline levels of these exposure factors and the onset of DKD, research on dose-response relationships is lacking. Furthermore, studies exploring the effects of routine clinical parameters on the occurrence of Alb or a decrease of estimated glomerular filtration rate (eGFR) in patients with T2DM are limited. Therefore, focusing on these parameters is essential, which is currently subject to controversy. This study aims to explore the predictive effects of routine clinical parameters on the risk of developing DKD in T2DM, using linear and non-linear dose–response models to provide valuable insights for nephropathy prevention in diabetic patients.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted in compliance with the Cochrane Handbook for Systematic Reviews guidelines and registered on the PROSPERO platform (CRD42022326148). This was also reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. PubMed, Embase, Scopus, Web of Science, and Cochrane library electronic databases were independently searched by two researchers (JBG and TLF) for English-language studies, from each database inception up to 11 January 2024. eTable 1 in the supplement presents the detailed search strategies for the PubMed database.

The retrieved studies were screened by two researchers (JBG and TLF). Among the duplicates, only those with complete reports were retained. The remaining studies were assessed by two researchers (JBG and NCL) who independently read the titles, abstracts, and full texts. Any discrepancies were resolved by a third researcher (HYC).

The criteria for inclusion were as follows: study type including prospective and retrospective cohort studies; study participants with T2DM; BMI, hemoglobin A1c (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or UA as the exposure factor(s); onset of DKD, occurrence of Alb or decrease of eGFR as the outcome indicator (urinary albumin to creatinine ratio ≥30 mg/g or eGFR decline (<60 ml/min/1.73 m^2)); reported the number of patients with diabetes, the duration of follow-up, and the number of patients with DKD onset; reported the effect size (odds ratio (OR), relative risk (RR), or hazard ratio (HR)) of a specific unit increase or segmented dose range of the exposure factor on the risk of DKD onset.

Exclusion criteria were as follows: the initial participants were not diabetic patients; no relevant exposure or outcome indicators; animal-related study; study protocol, review, comment, cross-sectional study, case report, case–control study, clinical trial, guideline, or consensus; and presence patients who already had DKD (eGFR <60 or presenting with elevated Alb) at the time of initial participation and could not be differentiated for analysis according to each study's report; no data available for analysis even if the original authors were contacted.

The data from the included cohort studies were independently extracted by three researchers (JBG, BYS and YFW), including the name of the first author, type of cohort study, year of publication, country or region of study, number of participants, age, diabetes duration, follow-up duration, number of DKD-onset patients, number of patients presenting with the occurrence of Alb or decrease in eGFR, special unit increases or segmental doses of the exposure factor, and the corresponding effect sizes and confidence intervals. Disagreements were resolved through consensus among the research teams. For studies lacking data for analysis, the research team sent data requests to the corresponding authors via e-mail. Pooled meta-analyses were performed for studies that did not have segmented doses after enquiring and descriptive analyses were added for studies that did not have available data.

The Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E) tool[19] was used to evaluate the quality of cohort studies. Based on four criteria of "low", "some concerns", "high" and "very high" risk of bias, the items were independently evaluated by two researchers (JBG and CL), including confounding, measurement of the exposure, selection of participants into the study (or into the analysis), post-exposure interventions, missing data, measurement of the outcome, selection of the reported result, and overall risk of bias. Disagreements arising from the evaluation were resolved through joint consultation with a third researcher (HYC).

Data analysis

The random effects model was conducted with RR and 95% CI as the reported effect sizes.[20] The cohort in which the effect size was initially reported as HR was deemed to be equivalent to RR.[21] OR was transformed to RR according to the following formulas: $OR = (P_1/(1-P_1))/(P_0/(1-P_0))$, $RR = P_1/P_0$, $RR = OR/((1-P_0)+(P_0 * OR))$, where P_0 and P_1 indicate the incidence of the outcome of interest in the non-exposed and exposed groups, respectively.[21,22] Besides, the effect-value estimation was performed for the results presented in graphically.[23] For the risk of the DKD onset, the selection data consistent with the diagnosis of DKD,[24] including directly reported the risk of DKD onset, Alb presence (urinary albumin to creatinine ratio ≥30 mg/g), or eGFR decline (<60 ml/min/1.73 m^2).

Both linear and non-linear dose–response models were employed in this study. In a linear dose–response analysis, we standardised exposure levels separately per a 1-kg/m^2 rise in BMI, per 1-percent rise in HbA1c, per 5-mmHg elevation in SBP, per 5-mmHg elevation in DBP, per 10-mg/dL increase in TC, per 10-mg/dL increase in TG, per 10-mg/dL increase in HDL, per 10-mg/dL increase in LDL, and per 1-mg/dL rise in UA, per 5-year increase in age, gender, and per 5-year duration of diabetes (eTable 5). For each clinical parameter, a subgroup analysis was performed by a cut-off 10-year of DM duration in patients. For outcomes in which the onset of DKD, occurrence of Alb, and decrease in eGFR occurred with increased exposure factors at the levels already reported above, linear dose-response relationships were derived by pooled analysis. The median dose for each segment was calculated as the dose element of the analysis for cohort studies that reported different segmental dose ranges for exposure factors. The width of the lowest-dose segment in the open interval was considered equal to the width of the higher adjacent segment. In the highest dose segment of the open interval, a low boundary value (1.5×) was selected as the dose element (eTable 4).[25] A one-stage approach[26] was used to allow the analysis of fewer dose segments.

For the pooled analysis of more than three studies, a restricted cubic spline model with three fixed nodes (10%, 50%, and 90%) was used to determine whether there was a trend toward a non-linear dose response relationship.[27] In the non-linear dose–response analysis, the baseline dose of exposure factors used to diagnose

the disease or health abnormality was applied as a reference to avoid subjective selection bias. In addition, in combination with the one-stage approach,[26] trends of non-linear dose response were simulated. For the pooled analysis with fewer than two studies, the best-fit second-order fractional polynomial was applied to replace the restricted cubic spline model, and the deviation of the data from linearity was assessed using the Wald test.

I^2 and Q statistics were used to report heterogeneity in the pooled analysis, with high heterogeneity of results indicated when I^2 was greater than 50% or the P-value of the Q statistic was less than 0.05. For analyses combining ≥10 studies, publication bias was assessed using Egger's test and funnel plots of the trim-and-fill analysis. Sensitivity analyses were performed to ensure the robustness of the findings for studies that included the OR as the effect size. Statistical analyses were performed using Stata software version 17.0, and a $P < 0.05$ was considered statistically significant. The Akaike information criterion (AIC) and log likelihood were used to evaluate the degree of fit of the linear and non-linear models. A smaller AIC value and larger log likelihood, in combination with significant P-values, indicated a better fit of the model.

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE),[28] a transparent, and structured quality evaluation method, was used to assess the evidence level of the results. The results were independently assessed by the researchers (BYS and YFW) and included four grades: high, moderate, low, or very low. Among the GRADE tools appropriate for use in observational studies, starting with a high level of evidence rating, criteria were used to downgrade the evidence rating, including limitations in the use of risk of bias tools for assessment, high heterogeneity due to combined analysis of different studies,[29] lack of generalisability of studies,[30] imprecision of results due to lack of statistically significant,[31] and publication bias.[32]

Role of the funding source

The funder(s) of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. HYC had access to dataset and had final responsibility for the decision to submit for publication.

Results

Eligible studies and characteristics

A total of 144,227 studies were retrieved through the initial search, and after removing duplicates, 94,442 studies were identified. After screening the titles and abstracts, 190 studies remained. Forty-six studies met the inclusion criteria. The Fig. 1 shows specific screening process, and eTable 2 shows the reasons for study exclusion during full-text screening.

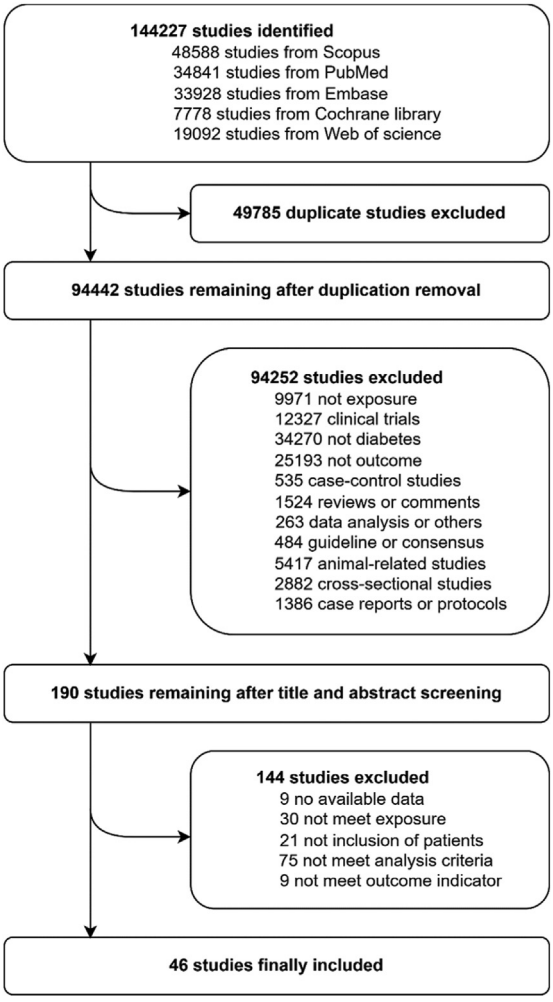

Fig. 1: **Flow chart of literature screening.**

The included studies were published between 1997 and 2022 over 20 countries or regions and involving 317,502 patients with T2DM. The cohort studies enrolled 191 to 105,552 (median, 1327) patients with the follow-up duration of 1.8–15 years (median, 5 years). The Table 1 presents the characteristics of the included studies. The eTable 3 presents the risk of bias assessment of the included studies. The eTable 4 lists the original segmented dose data. The eTable 5 lists each parameter level and the study selection for analysis. The eTable 6 details fit statistics for the linear and non-linear models.

Body mass index

The dose–response analysis of fifteen studies with 78,828 patients with T2DM indicated that each 1-kg/m^2 increase in BMI was associated with a 3% increased risk of DKD onset in patients with T2DM (RR = 1.03, CI [1.01–1.04], I^2 = 70.07%, $P_Q < 0.0001$) (Fig. 2). The BMI level had a higher risk association of DKD onset patients

Study ID	Country/Region	Age, year	Sample size	Duration of diabetes, year	Follow up, year	Exposure	Adjustment
Ahmed 2022	Ethiopia	30.0	415	NR	5.0	Gender, age, TC, LDL	NR
Hukportie 2021	America, Canada	62.0 (57.7–67.1)	8887	9.0 (5.0–15.0)	5.8	BMI	Age, gender, BP, lipid, duration of diabetes, SBP, HbA1c, eGFR, UACR, CVD history, HDL, LDL
Wu 2022	China	53.4 ± 14.7	8948	NR	4.8	VAI, CVAI	Age, gender, BMI group, education level, smoking status, drinking status, physical activity, hypertension, dyslipidaemia, fasting glucose and use of antidiabetic medication
Low 2017	Singapore	50.0 to 65.0	1628	10.0 to 15.0	5.5 (4.2–7.0)	HbA1c	Age at entry, gender, duration of diabetes mellitus (DM), ethnicity, systolic blood pressure (SBP) ≥140 mmHg, ln-transformed baseline eGFR, albumin to creatinine ratio (ACR) group, low-density lipoprotein cholesterol (LDL-C) ≥2.6 mmol/L, ln-transformed number of HbA1c measurements, and the use of renin–angiotensin system (RAS) inhibitor
Petter 2021	America	14.0	677	NR	10.2 ± 4.5	Gender, age, BMI, HbA1c, SBP, TG	Gender, age, race-ethnicity, SBP, BMI, reported use of antihypertensive medication, HbA1c
Wan 2021	Hong Kong	63.7 ± 9.5	105,552	8.0 ± 6.4	5.5	LDL, TC to HDL, TG	Gender, age, duration of diabetic mellitus, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, haemoglobin A1c, estimated glomerular fltration rate, urine albumin to creatinine ratio, the usages of anti-diabetic drugs, anti-hypertensive drugs, statins and fbrates, Charlson's index and usual LDL-C, TC to HDL-C ratio or triglyceride (as appropriate)
Tamru 2020	Ethiopia	56.7 ± 10.5	346	5.6 ± 3.0	10.0	Gender, BP, HbA1c, HDL	NR
Yang 2020	Hong Kong	62.4 ± 10.4	26,197	7.8 ± 6.3	1.8	Gender, age, BMI, SBP, DBP, HbA1c, TC, LDL, HDL, TG	Gender, age, BMI, HbA1c
Ravid 1998	America	47.7 ± 4.5	574	1.9 ± 1.2	7.8 ± 0.9	Gender, BMI, BP, HbA1c, TC, LDL, HDL, TG	NR
Cosmo 2016a	Italy	64.0 ± 10.0	27,029	10.0 ± 8.0	4.0 ± 0.5	Gender, age, BMI, TG, HDL, LDL	NR
Hu 2016	China	63.0 ± 14.0	451	10.0 (3.0–15.0)	3.3	Age, BP	NR
Cosmo 2015	Italy	64.0 ± 10.0	13,964	10.0 ± 8.0	4.0	Gender, age, diabetes duration, HbA1c, BMI, BP, TG, HDL, LDL, UA	Gender, age, duration of diabetes, BMI, HbA1c, SUA, lipid profile, BP, eGFR, albuminuria, retinopathy, smoking habits, treatment
Ceriello 2017	Italy	67.4 (60.3–73.4); 65.0 (58.5–71.3)	4231; 7560	8.0 (4.0–15.0); 7.0 (3.0–14.0)	3.4 (1.7–4.2); 2.6 (1.1–4.1)	Gender, age, diabetes duration, HbA1c, SBP, DBP, TC, TG, HDL, LDL, UA	Gender, age, smoking, diabetes duration, hypertension, HbA1c, SBP, DBP, UA, TC, HDL, LDL, TG, eGFR, drug treatment for diabetes, cardiovascular risk factors
Morton 2012	Twenty countries	63.0 ± 11.0	11,140	NR	5.0	HDL	Gender, age, regression dilution, ethnicity, treatment groups, history of microvascular disease, smoking status, current drinking, HbA1c, BMI, SBP, diabetes duration, statin use, baseline creatinine, TC, TG
Russo 2016	Italy	64.0 ± 9.0	15,362	10.0 ± 8.0	4.0	HDL, TG	Gender, age, baseline glomerular filtration rate
Cosmo 2016b	Italy	64.3 ± 8.8	12,995	10.2 ± 8.2	4.0 ± 0.5	Gender, age, HbA1c, BP, SBP, DBP, UA	Baseline glomerular filtration rate
Kitagawa 2021	Japan	64.0 (59.0–70.0)	424	9.0 (4.8–15.0)	5.0	SBP, DBP	Gender, age, diabetes duration, BMI, HbA1c, TC, creatinine, use of antihypertensive medications, use of renin angiotensin system inhibitors instead of the use of antihypertensive medications
Nakanishi 2019	Japan	61.0 ± 12.2	2306	NR	6.0 ± 6.9	HbA1c, BMI	Gender, age, diabetes duration, medication for hypertension or dyslipidemia
Tanaka 2016	Japan	58.5 ± 6.9	1532	15.8 ± 10.2	8.0	BMI	Gender, age at baseline, HbA1c, years after diagnosis
Hayashino 2016	Japan	64.6 ± 11.9	1385	NR	1.9	UA	Gender, age, BMI, smoking, SBP, DBP, Hs-CRP, HDL, LDL, TG, serum creatinine level, EGFR, angiotensin-converting enzyme inhibitor use, antihyperuricemic drug use, angiotensin II receptor blocker use, HbA1c level, past history of cardiovascular disease, diabetic retinopathy
Gall 1997	Denmark	66.0	191	NR	5.8 (1.5–6.0)	Gender, age, TC, HbA1c	NR
Lai 2021	Taiwan	64.7 ± 11.3	247	NR	3.3 ± 1.2	UA, HbA1c, TC, TG, HDL	NR
Mohammedi 2018	Asia, Established market economies, Eastern Europe	66.0 ± 6.0	10,537	8.0 ± 6.0	5.0 (4.5–5.0)	BMI	Gender, age, region of origin, prior cardiovascular disease, eGFR, urinary albumin to creatinine ratio, history of ever smoking, and study allocations, duration of diabetes, HbA1c, systolic blood pressure, total-cholesterol and HDL-cholesterol, and triglycerides
Barbieri 2015	Italy	50.0 ± 6.0	377	NR	6.5	BP	Gender, age, BMI, SBP, glycated hemoglobin, duration of diabetes, total cholesterol, triglycerides, fasting plasma glucose

(Table 1 continues on next page)

Study ID	Country/Region	Age, year	Sample size	Duration of diabetes, year	Follow up, year	Exposure	Adjustment
(Continued from previous page)							
Sugawara 2012	Japan	54.9 ± 10.4	812	5.8 ± 6.2; 7.8 ± 8.1	4.3 ± 2.7	Gender, age, diabetes duration, SBP, BMI, TC, HDL	All models were adjusted by various known predictors of nephropathy in addition to those related to HbA1c
Dorajoo 2017	Singapore	56.1 ± 12.9	1170	NR	4.0 ± 0.5	BP, HbA1c	AUC
Zoppini 2009	Italy	65.0 ± 10.0; 72.0 ± 8.0	1897	14.0 ± 9.0; 17.0 ± 9.0	4.9 ± 1.2	Gender, age, HDL, diabetes duration, BMI, HbA1c, LDL, TG, BP	Gender, age, BMI, HDL, LDL, triglycerides, HbA1c, diabetes duration, smoking history, hypertension, baseline micro- or macroalbuminuria, baseline GFR, use of hypoglycemic, antihypertensive, anti-platelet or lipid-lowering agents, presence of diabetic retinopathy
Kim 2014	Korea	56.0 ± 11.3	512	9.2 ± 6.8; 8.1 ± 6.6; 9.2 ± 5.9; 8.2 ± 6.3	3.0 (1.0–4.8)	Gender, age, BMI, diabetes duration, SBP, HbA1c, LDL, HDL, TG, UA	Gender
Geletu 2018	Ethiopia	NR	435	NR	5.9 (3.4–7.4)	Gender, age, SBP, DBP, LDL, HDL, TC, TG, BMI	NR
Kebede 2021	Ethiopia	53.2 ± 10.1	462	8.2 ± 3.8	15.0	Gender, age, FBS, diabetes duration, SBP, DBP	NR
Tan 2018	Singapore	54.0 ± 11.0	1016	NR	5.0	Gender, age, BMI, SBP, DBP, HbA1c, LDL, HDL, TG, TC	NR
Viazzi 2019	Italy	65.0 ± 9.0	30,851	11.0 ± 8.0	4.0	Gender, age, diabetes duration, BMI, HbA1c, TG, HDL, LDL, SBP	eGFR, ACE-Is, angiotensin converting enzyme-inhibitors; ARBs, angiotensin II receptor antagonists, BP, eGFR, HbA1c, HDL cholesterol, LDL
Lim 2015	Korea	55.0 ± 10.0	861	8.0 ± 6.6	10.1	TC, TG, HDL, LDL	Gender, age, diabetic duration, mean HbA1c, albuminuria, treatment of insulin, ACE inhibitor/angiotensin receptor blocker, lipid lowering agents
Chung 2017	Taiwan	56.3 ± 8.4; 56.7 ± 8.5; 54.1 ± 8.7	1187	6.5 ± 6.2; 5.0 ± 5.3; 4.0 ± 5.4	7.0	Gender, age, BMI, diabetes duration, SBP, DBP, HbA1c, TG, TC	Gender, diabetes duration, education (≤6 y, >6 y), smoking (never, past, current smoker), drinking habit (yes, no)
Takao 2017	Japan	54.5 ± 9.9	1912	5.5 ± 6.6	11.3 (5.7–15.0); 8.2 (3.5–14.2)	HbA1c	Gender, age, the number of visits (ln-transformed), diabetes duration, BMI, TC/HDL, baseline smoking status, baseline alcohol intake, baseline use of insulin, and baseline use of ACE inhibitors
Retnakaran 2006	UK	52.6 ± 8.7	4031	NR	15.0	Gender, age, SBP, DBP, HbA1c, TC, LDL, HDL, TG	NR
Afghahi 2011	Sweden	60.3 ± 8.2	3667	7.5 ± 6.2	5.0	Gender, age, diabetes duration, HbA1c, SBP, BMI, TG, HDL	Gender, age, SBP, HbA1c, smoker, BMI, TG, HDL, Creatinine, Pulse pressure
Zoppini 2012a	Italy	66.0 ± 10.0; 67.0 ± 9.0	1449	16.0 ± 9.0; 14.0 ± 8.0	5.0	UA	Age, gender, BMI, smoking status, duration of diabetes, insulin therapy, HbA1c, eGFR, albuminuria
Le 2021	Vietnam	61.2 ± 7.8	405	8.8 ± 4.6	5.0	UA	Age, gender, cholesterol, triglyceride, diuretic use
Amini 2007	Iran	57.4 ± 9.5	505	10.2 ± 4.7	5.0	Gender, age, diabetes duration, BMI, HbA1c, BP	Duration of diabetes, HbA1c, SBP, retinopathy
Zoppini 2012b	Italy	68.0 ± 9.0; 66.0 ± 10.0; 64.0 ± 9.0	979	15.0 ± 9.0; 14.0 ± 9.0; 12.0 ± 8.0	4.9 ± 1.0	TG/HDL	Gender, age, BMI, diabetes duration, HbA1c, hypertension, smoking history, LDL, albuminuria, medication use
Noshad 2014	Iran	51.7 ± 12.3	194	6.8 ± 5.2	2.6 (2.0–4.0)	BP	Gender, age, duration of diabetes, number of visits
Tkao 2014	Japan	55.6 ± 9.4; 55.7 ± 9.2	644	6.0 ± 7.0; 5.6 ± 6.7	11.5 (4.4–16.0)	SBP	Gender, age, duration of diabetes, insulin therapy, use of ACE inhibitors, use of statins and current smoker at baseline, and for the mean SBP, mean HbA1c, mean TC
Wang 2018	China	64.1 ± 7.0	3123	NR	5.0	UA	Gender, age
Gu 2017	China	61.8 ± 11.5	1339	3.7 (0.2–9.9)	4.0 (2.3–5.2)	UA	Gender, age, BMI, SBP, HbA1c, LDL, eGFR, use of statins, use of ACEI or ARB
Liu 2020	China	53.7 ± 8.0	1327	NR	10.2 ± 0.4	UA	Gender, age

Note: NR, no reported; BMI, body mass index; HbA1c, Hemoglobin A1c; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid.

Table 1: **Characteristics of included studies.**

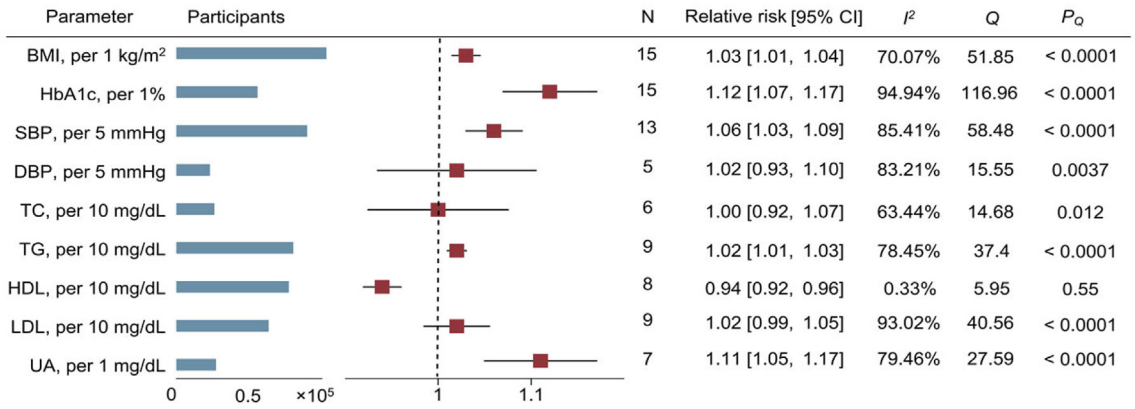

Fig. 2: **Routine clinical parameters and risk of DKD in patients with T2DM**. DKD, diabetic kidney disease; T2DM, type 2 diabetes mellitus; N, number; CI, confidence interval; BMI, body mass index; HbA1c, Hemoglobin A1c; SBP: systolic blood pressure; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid; I^2 and Q statistics represent the size of heterogeneity, and PQ represents the significance of heterogeneity.

with less than 10-year DM compared to those with over 10-year DM (1.04 [1.01–1.06], 1.02 [1.01–1.03]), and had a higher risk in Asia compared to that in Europe or the Americas (America: 1.01 (0.99–1.02), Europe: 1.02 (1.01–1.03), Asia: 1.03 (1.01–1.05)). Table 2 shows the subgroup analysis of DKD onset based on the presence of Alb or eGFR decline in patients with T2DM. Each 1 kg/m^2 increase in BMI has a 2% increased risk of Alb presence (RR = 1.02, CI [1.01–1.03], I^2 = 0.01%, P_Q = 0.25) (33,775 patients with T2DM; 7 studies) or a 3% increased risk of eGFR decline in patients with T2DM (RR = 1.03, CI [1.01–1.04], I^2 = 42.59%, P_Q = 0.024) (62,664 patients with T2DM; 5 studies) (Table 2 and eFig. 1). Based on the extracted BMI segmented dose data, we found a significant non-linear dose-response relationship between BMI and risk of developing DKD in patients with T2DM ($P_{non\text{-}linearity}$ = 0.0010, AIC = 16.00, Log likelihood = –3.00; $P_{linearity}$ < 0.0001, AIC = 21.49, Log likelihood = –8.74) in the included cohort studies. The non-linear trend showed an increasing risk of DKD at a BMI >23 kg/m^2 (Fig. 3A). Subgroup analysis of BMI showed linear and non-linear relationships for Alb presence ($P_{linearity}$ < 0.0001) and eGFR decline ($P_{non\text{-}linearity}$ < 0.0001), respectively (eFig. 1). The Egger test found a significant bias (P = 0.053), and the funnel plot asymmetry of the trim-and-fill analysis also indicated a publication bias. Sensitivity analysis showed that the effect of BMI remained significant even after excluding studies that reported OR as the effect size (eTable 8 and eFig. 1). The GRADE rating showed a moderate recommendation for BMI prediction (eTable 7).

Hemoglobin A1c

Of the 15 studies in which HbA1c levels were associated with DKD development, 56,180 patients with T2DM were included (Fig. 2 and Table 2). The dose–response analysis showed that each 1% increase in HbA1c is associated with a 12% increased risk of DKD in patients (RR = 1.12, CI [1.07–1.17], I^2 = 94.94%, P_Q < 0.0001) (Fig. 3B). The HbA1c level had a higher risk association of DKD onset patients with less than 10-year DM compared to those with over 10-year DM (1.18 [1.10–1.25], 1.05 [1.01–1.08]), and had a higher risk in Asia compared to that in Europe (Europe: 1.06 (1.02–1.10), Asia: 1.20 (1.13–1.27)). The subgroup analysis indicated that each 1% increase in HbA1c leads to a 14% risk of Alb presence (RR = 1.14, CI [1.07–1.21], I^2 = 89.17%, P_Q < 0.0001) (42,799 patients; 11 studies) or a 10% risk of eGFR decline (RR = 1.10, CI [1.03–1.17], I^2 = 61.37%, P_Q = 0.065) (34,519 patients; 3 studies). Based on the extracted HbA1c segmental dose data, our analysis revealed a significant linear dose-response relationship between HbA1c in patients with T2DM and the risk of DKD onset ($P_{linearity}$ < 0.0002, AIC = 6.34, log likelihood = –1.17; $P_{non\text{-}linearity}$ = 0.23, AIC = 14.43, Log likelihood = –2.21). Subgroup analysis of HbA1c showed a linear relationship with Alb levels ($P_{linearity}$ = 0.0065) and eGFR decline ($P_{linearity}$ = 0.0099) (eFig. 2). The Egger test revealed a significant bias (P < 0.0001), and the funnel plot asymmetry of the trim-and-fill analysis indicated a publication bias. Sensitivity analysis showed that the effect of the HbA1c level remained significant after excluding studies reporting OR values as effect sizes (eTable 8 and eFig. 2). The GRADE rating showed a moderate recommendation for HbA1c prediction (eTable 7).

Blood pressure

Of the 13 studies in which SBP was associated with DKD onset, 90,654 patients with T2DM were included (Fig. 2 and Table 2). Each 5-mmHg increase in SBP is

Exposure	N (Participants)	Relative risk (95% CI)	I^2	Q	P_Q
BMI, per 1 kg/m^2					
Diagnostic level					
Alb	7 (33,775)	1.02 (1.01–1.03)[a]	0.01%	7.90	0.25
eGFR	5 (62,664)	1.03 (1.01–1.04)[a]	42.59%	11.22	0.024
T2DM duration					
<10 years	8 (32,271)	1.04 (1.01–1.06)[a]	87.33%	36.72	<0.0001
≥10 years	7 (71,692)	1.02 (1.01–1.03)[a]	60.10%	14.93	0.025
Geographical region					
America	2 (9564)	1.01 (0.99–1.02)	0.15%	0.95	0.33
Europe	7 (74,682)	1.02 (1.01–1.03)[a]	63.99%	15.73	0.015
Asia	5 (19,282)	1.03 (1.01–1.05)[a]	35.79%	5.66	0.23
HbA1c, per 1%					
Diagnostic level					
Alb	11 (42,799)	1.14 (1.07–1.21)[a]	89.17%	98.03	<0.0001
eGFR	3 (34,519)	1.10 (1.03–1.17)[a]	61.37%	5.48	0.065
T2DM duration					
<10 years	9 (15,511)	1.18 (1.10–1.25)[a]	84.02%	104.50	<0.0001
≥10 years	6 (40,669)	1.05 (1.01–1.08)[a]	53.46%	10.51	0.014
Geographical region					
Europe	8 (51,567)	1.06 (1.02–1.10)[a]	91.48%	26.50	<0.0001
Asia	6 (3936)	1.20 (1.13–1.27)[a]	0	6.55	0.26
SBP, per 5 mmHg					
Diagnostic level					
Alb	10 (43,745)	1.04 (1.02–1.06)[a]	81.75%	40.81	<0.0001
eGFR	5 (69,037)	1.03 (0.99–1.08)	92.36%	22.35	<0.0001
T2DM duration					
<10 years	8 (53,082)	1.06 (1.02–1.09)[a]	77.17%	17.87	0.013
≥10 years	5 (37,572)	1.06 (1.02–1.10)[a]	90.02%	37.47	<0.0001
Geographical region					
Europe	6 (38,588)	1.05 (1.01–1.08)[a]	88.97%	32.68	<0.0001
Asia	5 (23,448)	1.07 (1.01–1.12)[a]	65.84%	13.25	0.010
DBP, per 5 mmHg					
Diagnostic level					
Alb	4 (22,734)	0.97 (0.93–1.01)	25.14%	4.61	0.20
eGFR	2 (21,524)	0.96 (0.88–1.04)	85.26%	6.78	0.010
T2DM duration					
<10 years	3 (8770)	1.00 (0.96–1.03)	0.03%	2.60	0.27
≥10 years	2 (14,399)	1.04 (0.85–1.24)	92.17%	12.78	<0.0001
Geographical region					
Europe	2 (21,524)	0.98 (0.93–1.03)	62.25%	2.65	0.10
Asia	2 (1210)	1.05 (0.74–1.37)	54.84%	2.21	0.14
TC, per 10 mg/Dl					
Diagnostic level					
Alb	4 (10,568)	0.94 (0.90–1.00)	29.44%	4.77	0.19
T2DM duration					
<10 years	6 (26,367)	1.00 (0.92–1.07)	63.44%	14.68	0.012
Geographical region					
Europe	2 (7736)	1.05 (0.94–1.15)	74.13%	3.87	0.049
Asia	4 (18,631)	0.97 (0.93–1.00)	0	4.98	0.17
TG, per 10 mg/dL					
Diagnostic level					
Alb	8 (79,108)	1.00 (0.99–1.01)	49.99%	23.17	0.010
eGFR	6 (77,845)	1.01 (1.00–1.02)[a]	33.15%	7.95	0.16
T2DM duration					

(Table 2 continues on next page)

Exposure	N (Participants)	Relative risk (95% CI)	I^2	Q	P_Q
(Continued from previous page)					
<10 years	4 (12,490)	1.02 (0.99–1.06)	95.39%	15.73	<0.0001
≥10 years	5 (68,605)	1.02 (1.00–1.03)[a]	79.90%	19.47	0.0010
Geographical region					
Europe	7 (79,832)	1.02 (1.01–1.02)[a]	71.12%	20.82	0.0030
Asia	2 (1263)	1.05 (0.95–1.14)	91.87%	12.29	<0.0001
HDL, per 10 mg/dL					
Diagnostic level					
Alb	8 (76,285)	0.98 (0.93–1.03)	81.57%	40.03	<0.0001
eGFR	5 (74,178)	0.97 (0.93–0.99)[a]	53.32%	8.52	0.074
T2DM duration					
<10 years	3 (9388)	0.97 (0.90–1.04)	0	0.15	0.93
≥10 years	5 (68,605)	0.94 (0.92–0.96)[a]	0	5.07	0.28
Geographical region					
Europe	6 (76,165)	0.94 (0.92–0.96)[a]	0.77%	5.79	0.33
Asia	2 (1828)	0.96 (0.70–1.22)	0	0.14	0.71
LDL, per 10 mg/dL					
Diagnostic level					
Alb	6 (60,111)	1.02 (0.98–1.07)	94.55%	35.46	<0.0001
eGFR	4 (58,816)	0.97 (0.94–1.00)	68.00%	7.89	0.018
T2DM duration					
<10 years	5 (19,979)	1.08 (1.01–1.15)[a]	67.67%	12.94	0.012
≥10 years	4 (43,935)	0.99 (0.98–1.01)	60.88%	7.23	0.014
Geographical region					
Europe	6 (61,758)	1.01 (0.98–1.04)	92.29%	43.30	<0.0001
Asia	3 (2156)	1.15 (1.04–1.27)	0	1.90	0.39
UA, per 1 mg/dL					
Diagnostic level					
Alb	4 (22,448)	1.11 (1.01–1.21)[a]	59.83%	10.98	0.012
eGFR	4 (25,052)	1.11 (1.03–1.18)[a]	80.61%	17.44	0.0009
T2DM duration					
<10 years	5 (12,012)	1.14 (1.05–1.23)[a]	81.95%	25.89	<0.0001
≥10 years	2 (15,413)	1.05 (1.02–1.08)[a]	0.01%	0	1.00
Geographical region					
Europe	3 (22,973)	1.09 (1.04–1.15)[a]	63.79%	5.94	0.046
Asia	3 (3775)	1.17 (0.93–1.40)	89.37%	15.23	<0.0001

Note: N, number; CI, confidence interval; DKD, diabetic kidney disease; T2DM, type 2 diabetes mellitus; Alb, albuminuria; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, Hemoglobin A1c; SBP: systolic blood pressure; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid; I^2 and Q statistics represent the size of heterogeneity, and P_Q represents the significance of heterogeneity. [a]Statistically significance.

Table 2: **Subgroup analysis of routine clinical parameters and risk of DKD in patients with T2DM.**

associated with a 6% increased risk of DKD onset in patients (RR = 1.06, CI [1.03–1.09], I^2 = 85.41%, P_Q < 0.0001) (Fig. 3C). The SBP level had a similar risk association of DKD onset patients with less than 10-year DM compared to those with over 10-year DM (1.06 [1.02–1.09], 1.06 [1.02–1.10]), and had a higher risk in Asia compared to that in Europe (Europe: 1.05 (1.01–1.08), Asia: 1.07 (1.01–1.12)). The subgroup analysis showed that each 5-mmHg increase in SBP has a 4% increase in the risk of developing Alb (RR = 1.04, CI [1.02–1.06], I^2 = 81.75%, P_Q < 0.0001) (43,745 patients; 10 studies) but not in the risk of eGFR decline (RR = 1.03, CI [0.99–1.08], I^2 = 92.36%, P_Q < 0.0001) (69,037 patients; 5 studies) in patients with T2DM. Based on the extracted SBP segmental dose data, our analysis revealed a significant linear dose-response relationship between SBP and the risk of DKD onset ($P_{linearity}$ = 0.043, AIC = 14.10, Log likelihood = –5.05; $P_{non\text{-}linearity}$ = 0.14, AIC = 25.19, Log likelihood = –7.60). Sensitivity analysis showed that the effect of SBP remained significant after excluding studies that reported OR as the effect size (eFig. 3). The Egger test revealed a significant bias (P = 0.0004), and the funnel plot asymmetry of the trim-and-fill analysis also indicated publication bias. The GRADE rating provided a moderate recommendation for the SBP prediction

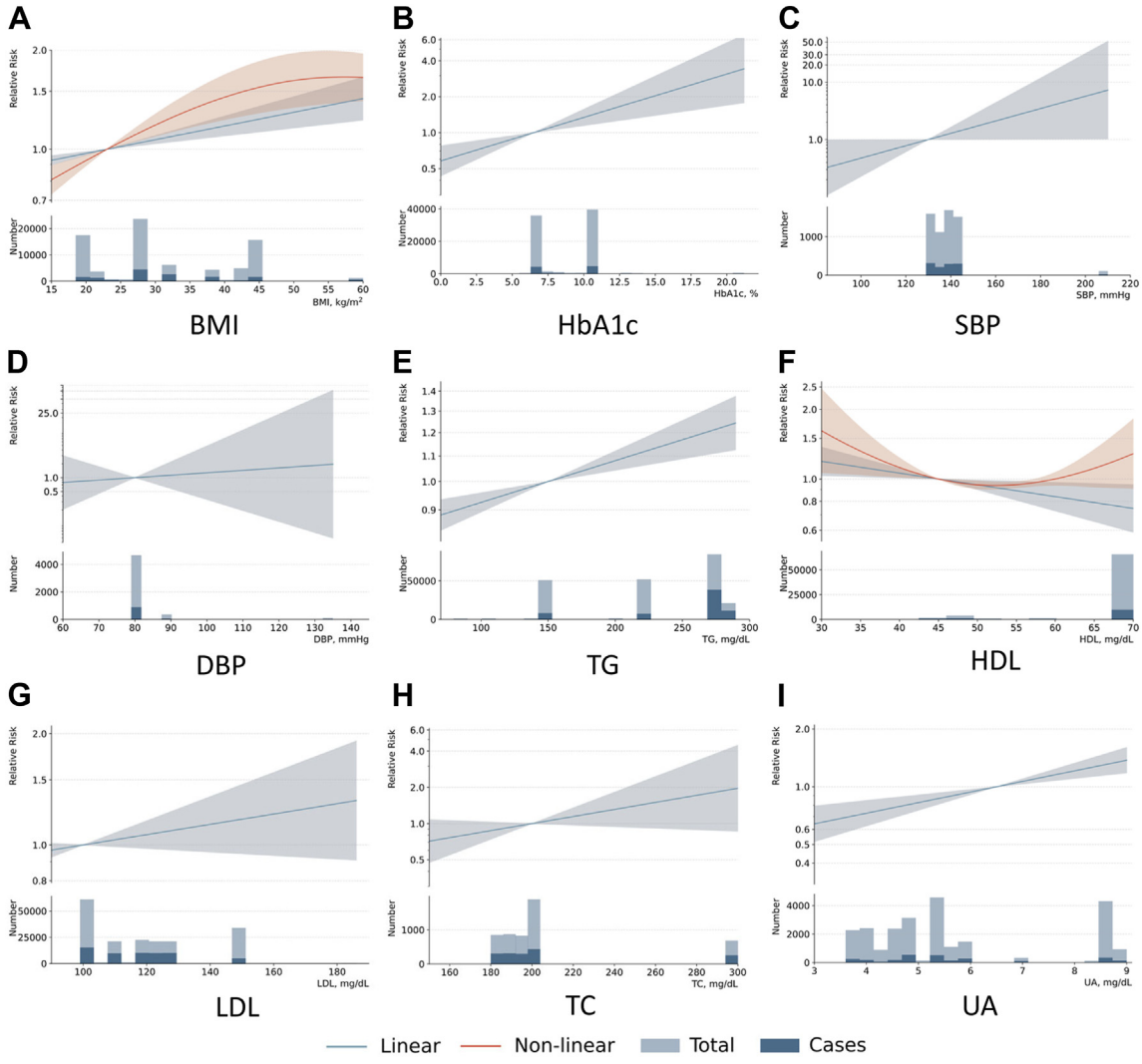

***Fig. 3*: Dose-response association between routine clinical parameters and risk of DKD in patients with T2DM**. (A) Linear and non-linear dose-response plots of BMI (N = 12, $P_{linearity}$ < 0.0001, AIC = 21.49, Log likelihood = −8.74; $P_{non\text{-}linearity}$ = 0.001, AIC = 16.00, Log likelihood = −3.00), (B) Linear dose-response plot of HbA1c (N = 9, $P_{linearity}$ = 0.0002), (C) Linear dose-response plot of SBP (N = 4, $P_{linearity}$ = 0.043), (D) Linear dose-response plot of DBP (N = 2, $P_{linearity}$ = 0.72), (E) Linear dose-response plot of TG (N = 8, $P_{linearity}$ < 0.0001), (F) Linear and non-linear dose-response plots of HDL (N = 9, $P_{linearity}$ = 0.013, AIC = 16.31, Log likelihood = −6.16; $P_{linearity}$ = 0.046, AIC = 25.96, Log likelihood = −7.98), (G) Linear dose-response plot of LDL (N = 9, $P_{linearity}$ = 0.14), (H) Linear dose-response plot of TC (N = 5, $P_{linearity}$ = 0.10), (I) Linear dose-response plot of UA (N = 6, $P_{linearity}$ < 0.0001). Note: DKD, diabetic kidney disease; T2DM, type 2 diabetes mellitus; Solid line represents the dose–response and colored area represents the 95% confidence interval.

(eTable 7). DBP has no significant association with the risk of DKD onset (RR = 1.02, CI [0.93–1.10], I^2 = 83.21%, P_Q = 0.0037) (23,169 patients; 5 studies) (Figs. 2 and 3D), Alb presence, eGFR decline, geographical region, and T2DM duration (Table 2, eTable 8, and eFig. 3).

Blood lipids

As shown in Fig. 2 and Table 2, nine studies with 81,095 patients with T2DM were included to determine the predictive effect of TG. Dose–response analysis showed that each 10 mg/dL increase in TG level was associated with a 2% increase in the risk of DKD onset (RR = 1.02, CI [1.01–1.03], I^2 = 78.45%, P_Q < 0.0001) (Fig. 3E). In patient with DM duration over 10 years, the TG level showed a significant risk association with the onset of DKD (1.02 [1.00–1.03]), while no significant association was observed in those with less than 10 years of DM (1.02 [0.99–1.06]). Furthermore, a significant risk association was found in Europe (1.02

[1.01–1.02]), but not in Asia (1.05 [0.95–1.14]). The subgroup analysis indicated that each 10-mg/dL increase in TG had a 1% increased risk of eGFR (RR = 1.01, CI [1.00–1.02], I^2 = 33.15%, P_Q = 0.16) (77,845 patients; 6 studies) but not of Alb presence (RR = 1.00, CI [0.99–1.01], I^2 = 49.99%, P_Q < 0.010) (79,108 patients; 8 studies) in patients (Table 2). Our analysis revealed a significant linear dose-response relationship between TG and onset of DKD ($P_{linearity}$ < 0.0001, AIC = –18.98, Log likelihood = 11.49; $P_{non\text{-}linearity}$ = 0.043, AIC = –4.86, Log likelihood = 7.43). Sensitivity analysis showed that the effect of TG level remained significant after excluding studies that reported OR values as effect sizes (eTable 8 and eFig. 4). The GRADE rating indicated a low level of recommendation for TG prediction (eTable 7).

Eight studies involving 77,993 patients were included to determine the predictive value of HDL. Each 10-mg/dL increase in HDL is associated with an 6% decreased risk of DKD onset in patients with T2DM (RR = 0.94, CI [0.92–0.96], I^2 = 0.33%, P_Q = 0.55) (Figs. 2 and 3F). Each 10-mg/dL increase in HDL has a 3% reduction in the risk of the eGFR decline (RR = 0.97, CI [0.93–0.99], I^2 = 53.52%, P_Q = 0.074) (74,178 patients; 5 studies), but had no significant association with the Alb presence (RR = 0.98, CI [0.93–1.03], I^2 = 81.57%, P_Q < 0.0001) (76,285 patients; 8 studies) (Table 2 and eFig. 4). In patients with DM duration over 10 years, the HDL level showed a significant risk association with the DKD onset (0.94 [0.92–0.96]), compared to those with less than 10 years of DM (0.97 [0.90–1.04]). Furthermore, a significant risk association was found in Europe (0.94 [0.92–0.96]), but not in Asia (0.96 [0.70–1.22]). Based on the extracted HDL segmental dose data, a significant non-linear dose-response relationship between HDL and the risk of DKD onset in patients with T2DM was found ($P_{non\text{-}linearity}$ = 0.046, AIC = 25.96, log likelihood = –7.98; $P_{linearity}$ = 0.013, AIC = 16.31, log likelihood = –6.16). The non-linear trend is shown (Fig. 3F). Sensitivity analyses showed that the effect of HDL remained significant after excluding studies that reported OR as an effect size and had no statistically significant effect on the decrease in eGFR (eTable 8 and eFig. 4). The GRADE rating showed a high level of recommendation for HDL prediction (eTable 7).

The analysis revealed that LDL (63,914 patients; 9 studies) and TC (26,367 patients; 6 studies) were not associated with DKD onset (RR = 1.02, CI [0.99–1.05], I^2 = 93.02%, P_Q < 0.0001; RR = 1.00, CI [0.92–1.07], I^2 = 63.44%, P_Q = 0.012, respectively) The LDL level had a significant risk association of DKD onset patients with less than 10-year DM, but not in those over 10-year with DM (1.08 [1.01–1.15], 0.99 [0.98–1.01]) (Figs. 2, 3G & H, eTable 8, and eFig. 4). The GRADE rating had a low level of recommendation level for the HDL prediction (eTable 7).

Serum uric acid

Seven studies involving 27,425 patients were included to determine the predictive value of serum UA level. The dose–response analysis indicted that each 1-mg/dL increase in UA is associated with a 11% increase in the risk of DKD onset (RR = 1.11, CI [1.05–1.17], I^2 = 79.46%, P_Q < 0.0001) (Fig. 2). The UA level had a higher risk association of DKD onset patients with less than 10-year DM compared than in those with over 10-year DM (1.14 [1.05–1.23], 1.05 [1.02–1.08]). Subgroup analysis showed that each 1-mg/dL increase in UA had an 11% increased risk in developing Alb (RR = 1.11, CI [1.01–1.21], I^2 = 59.83%, P_Q = 0.012) (22,480 patients; 4 studies) and eGFR decline in patients with T2DM (RR = 1.11, CI [1.03–1.18], I^2 = 80.61%, P_Q = 0.0009) (25,052 patients; 4 studies) (eFig. 5). Our analysis revealed a significant linear dose-response relationship between UA and DKD onset ($P_{linearity}$ < 0.0001, AIC = 12.53, log likelihood = –4.26; $P_{non\text{-}linearity}$ = 0.060, AIC = 14.27, log likelihood = –2.14). The subgroup analysis showed that UA had a linear relationship with the presence of Alb ($P_{linearity}$ = 0.052) and eGFR decline ($P_{linearity}$ < 0.0001) (eFig. 5). Sensitivity analyses showed that the effect of UA remained significant after excluding studies that reported OR values as effect sizes. However, the effect on the emergence of Alb was not statistically significant (eTable 8 and eFig. 5). The GRADE rating provided a moderate recommendation for the UA prediction (eTable 7).

Age

As shown in eTable 9, and eFig. 6 in the supplement, when age was included as an exposure factor, a 20% increased risk of DKD onset in patients with T2DM for every 5-year increase in age (RR = 1.24, CI [1.14–1.35], I^2 = 93.23%, P_Q < 0.0001) (100,443 patients; 11 studies). The subgroup analysis showed that each 5-year increase in age is associated with a 26% increase in the risk of eGFR decline (RR = 1.26, CI [1.12–1.39], I^2 = 95.25%, P_Q < 0.0001) (96,066 patients; 6 studies) but not in the risk of Alb presence (RR = 1.08, CI [0.95–1.21], I^2 = 59.60%, P_Q = 0.083) (6478 patients; 3 studies). Sensitivity analysis showed that the effect of age remained significant after excluding studies that reported OR as an effect size. The GRADE rating showed a moderate recommendation for age prediction (eTable 7).

Gender

The analysis of gender indicated that male gender is significantly associated with the development of Alb in patients with T2DM (Alb: RR = 1.22, CI [1.06–1.38], I^2 = 77.24%, P_Q = 0.0024; eGFR: RR = 0.78, CI [0.52–1.05], I^2 = 53.91%, P_Q = 0.14; DKD: RR = 1.09, CI [0.89–1.28], I^2 = 89.75%, P_Q < 0.0001) (eTable 9 and eFig. 7). Egger's test and funnel plots showed no significant publication bias (P = 0.07). Sensitivity analyses

confirmed this relationship after excluding studies that reported the OR as the effect size. The gender analysis showed that female gender is not significantly associated with the onset of DKD, the occurrence of Alb, and the decrease of eGFR in patients with T2DM (DKD: RR = 1.06, CI [0.82–1.30], I^2 = 62.65%, P_Q = 0.019; Alb: RR = 0.96, CI [0.82–1.11], I^2 = 0, P_Q = 0.64; eGFR: RR = 1.35, CI [0.63–2.08], I^2 = 47.69%, P_Q = 0.17) (eTable 9 and eFig. 7). The GRADE rating indicated a moderate level of recommendation level for male prediction (eTable 7).

Duration of T2DM

The analysis of disease duration showed each 5-year duration of T2DM has a 9% increase in the risk of DKD (RR = 1.09, CI [1.00–1.18], I^2 = 92.77%, P_Q < 0.0001), and the duration of T2DM was significantly associated with the Alb presence, and eGFR decline (Alb: RR = 1.16, CI [1.07–1.25], I^2 = 0, P_Q = 0.65; eGFR: RR = 1.05, CI [1.01–1.09], I^2 = 0, P_Q = 0.35) (eTable 9 and eFig. 8). The GRADE rating provided a moderate recommendation for the duration prediction (eTable 7).

Discussion

In this study, we assessed the association between routine clinical parameters (BMI, HbA1c, SBP, DBP, TC, TG, HDL, LDL, and UA levels) and the onset of DKD in patients with T2DM. Our findings indicate that BMI, HbA1c, SBP, TG, HDL, and UA can predict the onset of DKD in patients with T2DM. HbA1c, SBP, TG, and UA levels exhibited linear relationships with DKD onset, whereas BMI and HDL displayed non-linear relationships. Subgroup analysis using kidney function indices (Alb or eGFR) were indicated significant relationships between BMI, HbA1c, SBP, TG, and UA and the presence of Alb or a decline in eGFR in patients with T2DM. HDL levels were significantly associated with Alb occurrence but not with eGFR decline. In assessment of model, the non-linear model for BMI outperformed the linear model based on the fit judgment criteria. While in the case of HDL and TG levels, none of the non-linear models demonstrated a better fit than the linear model. Notably, the AIC and log likelihood values were more variable for TG and less variable for HDL. In an attempt to interpret the results with clinical references, we included the non-linear trend for HDL in the analysis.

We systematically evaluated the predictive effects of routine clinical parameters on DKD onset in patients with T2DM. Previous studies have indicated a positive correlation between HbA1c, a marker of long-term glucose control, and a decline in kidney function among diabetic patients with HbA1c levels ≥7.0%.[33,34] Our meta-analysis revealed that a 1% increase in HbA1c was predictive of a 12% increased risk of developing DKD in patients with T2DM.

BMI has been identified as a predictive factor for the onset of DKD in patients with T2DM. Previous studies have reported associations between BMI and DKD, with some indicating an increased risk in women but not in men,[35] while others revealing an increased risk of kidney function decline in men but not in women.[36–39] Interestingly, several studies demonstrate that the low BMI is associated with risk of chronic kidney disease in patients with T2DM.[12,40] The Cohort studies highlight BMI ≥25 kg/m^2 as a protective factor for kidney function deterioration in diabetic patients with stage 3 or 4 chronic kidney disease,[12] while a low BMI is associated with in an elevated risk of newly onset DKD in the Chinese population.[40] These findings underscore the variability of BMI's predictive effect based on ethnicity and remaining kidney function in patients with T2DM. Additionally, the previous observational study suggests that waist circumference may offer more comprehensive insights into various outcome indicators compared to BMI[41] warranting increased attention in future research.

Higher levels of HDL have been linked to a lower incidence of DKD in patients with T2DM.[42] However, our findings revealed a U-shaped relationship between HDL and DKD onset in patients with T2DM. This suggests that higher HDL levels above 55 mg/dL are associated with an increased risk of DKD onset. The relationship between HDL and T2DM is similar to that of cardiovascular events, in that an HDL level above 60 mg/dL is associated with an increased risk.[43,44]

Serum UA also has been found to be associated with the risk of Alb or decreased kidney function in both type 1 and type 2 diabetic patients.[18,45] Nevertheless, some studies have not adequately considered potential confounders, resulting in a relatively low quality of evidence, and variations in the reported effect sizes across these studies.[46–49]

Hypertension is an independent risk factor for kidney disease,[14] and our findings demonstrated a significant association between SBP and DKD onset, whereas DBP did not exhibit a significant association. This finding aligns with previous studies.[50] Notably, blood pressure control has been included as a routine management approach in the DKD treatment guidelines.[51]

As a complementary analysis, we examined age, gender, and duration of diabetes as risk factors for DKD onset. Our results indicate that age significantly contributes to the risk factors for DKD in patients with T2DM, following a linear relationship. Moreover, males exhibited a higher likelihood of developing Alb in patients with T2DM, consistent with previous studies.[52] However, another cohort study reported that females have a lower risk of developing, progressing, and succumbing to kidney diseases compared to males with chronic kidney diseases.[53] This diversity in findings may be attributed to the influence of sex hormones, specifically 17β-oestradiol and testosterone, on the

progression of nephropathy.[54–56] The duration of diabetes was associated with a 12% increased risk of DKD onsets. Importantly, our subgroup analysis revealed that the risk of DKD onset predicted by clinical parameters was likely higher in patients with DM duration less than 10 years than in those with DM duration over 10 years. This suggests the importance of early identification of DKD onset using clinical parameters.

Effective management of these routine clinical parameters may reduce the risk of DKD in patients with T2DM. Recent clinical practice guidelines recommend utilizing sodium glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, non-steroidal mineralocorticoid receptor antagonists, finerenone, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for patients with T2DM and related symptoms (e.g. albuminuria, hypertension, and obesity) to slow the progression of DKD.[57,58]

This meta-analysis based on published cohort studies, aimed to investigate potential changes in routine clinical parameters and their association with the risk of DKD over time in patients with T2DM, using a dose–response approach. This methodology allowed us to derive precise estimates than the analysis solely at the baseline level of exposure factors. The dose–response analysis not only examined DKD as an outcome indicator but also explored the occurrence of Alb and decline in eGFR as separate subgroups. The association between the clinical parameters and DKD was further validated through a subgroup analysis investigating the occurrence of Alb or eGFR decline in patients with T2DM. Moreover, sensitivity analysis was conducted to assess the robustness of our findings by excluding studies utilizing OR as the effect size.

This study has certain limitations. Firstly, the use of routine clinical parameters as search terms may not be universally applicable in analysing the relationship between certain exposure factors (such as age, gender, and duration of diabetes) and the risk of developing DKD. Therefore, caution should be exercised when interpreting these results. Secondly, we included studies that directly reported the onset of chronic kidney disease in patients with T2DM. Although the diagnostic criteria for DKD were met based on the occurrence of Alb or a decrease in eGFR, it is essential to note that chronic kidney disease is not fully equivalent to DKD in clinical settings. This distinction might contribute to the high heterogeneity in the results of some pooled analyses. Furthermore, variations in DM management (e.g. blood glucose, hypertension, and lipid controls) among patients with T2DM, as significant confounding factors, may contribute to the high heterogeneity observed across these studies. However, due to the lack of detailed information for further analysis, we were unable to account for these variations in our study. Consequently, we downgraded the recommendations for evidence using GRADE downgrading. This emphasizes the need for future studies to improve our understanding of the effects of DM management on the risk of DKD development.

In patients with T2DM, HbA1c, SBP, TG, and UA exhibited a significant positive linear dose-response relationship with DKD onset, while BMI and HDL showed a significant non-linear dose–response. Additional evidence is required to determine the potential impact of age, gender, and diabetes duration on the risk of DKD.

Contributors

All authors take responsibility for the integrity of the data and the accuracy of the data analysis. HYC designed the study. HYC and QYH revised the manuscript. JBG and CL performed the data analysis. JBG wrote the manuscript. JBG, CL, BYS, YFW, TLF, NCL, HDL, JNW, LCL, XWC, HZ, XYL, AQW, FL and XMM retrieved studies and extracted data. All authors revised and approved the final manuscript. JBG, CL, and HYC have access to and verify the underlying study data.

Data sharing statement

The full dataset included in this study has been submitted as an attachment (eTable 4) and are not subject to embargo or restrictions.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102482.

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