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Analysis of Factors Influencing Diabetic Kidney Disease Progression Based on Multidimensional Indicators

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Abstract

Objective: This work pooled evidence gathered from observational cohort investigations alongside randomized controlled trials. We aimed to clarify how demographic traits, laboratory test indices, and anti-hyperglycemic treatments shape disease advancement among people living with diabetic kidney disease (DKD). Our goal was to deliver practical reference information for early preventive measures and standardized clinical management for patients facing progressive DKD. **Methods:** Seven major electronic databases were systematically searched to retrieve published studies regarding indicators associated with DKD progression from database inception to December 28, 2025. Validated tools were applied to evaluate the methodological quality of the included studies. Meta-analysis was performed to synthesize two distinct types of hazard ratio (HR) data with corresponding 95% confidence intervals (95% CIs): observational prognostic risk factors derived from cohort studies and therapeutic protective effects obtained from randomized controlled trials (RCTs), which jointly characterize the predictors and modifiable interventions for DKD progression. **Results:** A total of 43 eligible studies involving 290,469 diabetic patients were included in the quantitative synthesis. Sixteen independent indicators associated with DKD progression were identified and clearly categorized into two subtypes: 11 observational demographic and clinical risk markers from cohort studies, and five pharmacological protective factors validated by RCTs. The pooled HRs of adverse prognostic markers ranged from 1.11 to 3.52, whereas the pooled HRs of renoprotective medications ranged from 0.60 to 0.84. **Conclusions:** This study identified 16 independent indicators related to DKD progression. Observational demographic and laboratory markers serve as adverse prognostic factors that increase the risk of DKD deterioration. In contrast, pharmacological interventions including sodium-glucose cotransporter 2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase-4 inhibitors (DPP-4i), metformin, and finerenone exert significant protective effects against DKD progression. The clear distinction between baseline risk predictors and treatment effects provides reliable evidence for clinicians to conduct early risk screening and implement individualized therapeutic strategies for DKD prevention and management.

Keywords

Diabetes mellitus; diabetic kidney disease; delay disease progression

1. Introduction

Global diabetes prevalence keeps climbing and creates heavy public-health burdens across different regions

worldwide [1, 2]. Statistics show more than 371 million individuals suffered from diabetes mellitus (DM) back in 2012, and this figure may rise to 700 million globally by the year 2045 [3, 4].

Chronic diabetic-associated complications represent the leading cause of mortality for diabetic populations [5]. Diabetic kidney disease (DKD) counts among the most destructive long-term diabetic sequelae; its key manifestations include persistent proteinuria, gradual loss of glomerular filtration capacity, and elevated arterial blood pressure [6]. This irreversible microvascular disorder affects roughly 30 % of people with type 1 diabetes mellitus (T1DM), as well as 25-40 % of type 2 diabetes mellitus (T2DM) patients [7]. In many countries, DM acts as a leading trigger that forces patients to receive renal replacement therapy [1]. Clinicians need to spot high-risk DKD subjects at an early window so that targeted prevention can be implemented. Interventions applied in early-phase DKD/nephropathy yield better clinical returns compared with therapies given at advanced stages [8, 9]. For these reasons, it is worthwhile to sort out risk‑relevant and protective contributors to DKD progression. Such work allows clinicians to detect vulnerable patients ahead of time and build preemptive measures that slow or stop renal function decline.

Earlier research has explored factors correlated with DKD. Nevertheless, most existing analyses place emphasis only on demographic and laboratory parameters; few studies fully incorporate the effects brought by hypoglycemic medications. Such gaps limit our full picture of what drives DKD deterioration [10-12].

The present meta-analysis set out to identify prognostic and protective factors for DKD progression. DKD progression was defined as sustained ≥40 % drop in estimated glomerular filtration rate (eGFR) or the onset of end-stage kidney disease (ESKD). We combined demographic profiles, laboratory read-outs, and anti-hyperglycemic treatment information. Our results may supply reference material for risk-stratified care and individualized interventions for both T1DM and T2DM patients to slow DKD advancement.

2. Materials and Methods

2.1 Search Strategy

We carried out comprehensive literature retrieval over seven databases: CNKI, Wanfang, VIP, PubMed, Web of Science, Cochrane Library, and Embase. The retrieval time frame extended from each database's earliest available entries up to 28 December 2025. Subject-descriptors together with free-text keywords were adopted for searching. Search terms included "Diabetes Mellitus", "kidney disease", "risk factor", "DKD/nephropathy", "diabetic nephropathy", "SGLT-2i", "GLP-1RAs", "DPP-4i", "Metformin", "Finerenone". Two researchers independently screened titles plus abstracts, then performed full-text evaluation for potentially eligible articles. Whenever disagreements appeared concerning inclusion status, two additional senior investigators would join group consultation to reach final consensus.

2.2 Eligibility Criteria

We followed pre-defined inclusion standards for study enrolment. First, acceptable study types covered prospective/retrospective cohort studies as well as randomized controlled trials (RCTs). Second, papers had to report hazard ratios (HRs) paired with corresponding 95 % confidence intervals (CIs) to quantify how each variable affected DKD progression. Third, study participants needed confirmed clinical diabetes diagnoses. Fourth, non-clinical animal experiments and non-original publications were strictly ruled out: reviews, expert commentaries, editorials, conference abstracts, meeting posters, unpublished raw datasets, and letter-type communications were all excluded. Fifth, our primary endpoint was DKD progression, operationalized as sustained eGFR decline ≥40 % or transition toward ESKD. Besides these rules, only English-language articles qualified for final inclusion.

2.3 Study Registration

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024552353.

2.4 Data Extraction and Quality Evaluation

Two independent investigators finished data sorting and extraction for every eligible paper entering this synthesis. Basic bibliographic metadata for each publication was logged, such as first-author name, study region, sample-size figures, and publication year. Using standardized extraction templates, we collected study-level and participant-level baseline information: geographic distribution of subjects, age, sex, DM duration, body-mass index (BMI), smoking history, and comorbid diabetic retinopathy (DR). Biochemical markers extracted for pooled analysis covered

hypertension status, glycated hemoglobin A1c (HbA1c), triglycerides (TG), eGFR, and urinary albumin-to-creatinine ratio (UACR). Meanwhile, we collected medication-use profiles of participants, with special focus on renoprotective anti-hyperglycemic agents including SGLT-2i, GLP-1RAs, DPP-4i, metformin, and finerenone. HR values and their matching 95 % CIs for validated DKD-progression-associated factors were also abstracted to support subsequent quantitative meta-analysis.

The Newcastle-Ottawa Scale (NOS), a widely-accepted rating tool for observational-study quality appraisal, was used to judge methodological quality for cohort-type papers. Its scoring scale ranges from 0 to 9 total points. In this work, publications achieving NOS scores ≥7 were treated as high-quality studies. Two researchers completed quality scoring separately. Discrepancies in scoring outcomes were settled via group discussion together with a third senior reviewer, to guarantee fair and precise quality judgements.

For randomized controlled trials, risk-of-bias assessment was completed following guidance given within the Cochrane Handbook for Systematic Reviews of Interventions. Evaluation domains contained selection bias (random-sequence generation, allocation concealment), performance bias (blinding for participants and research personnel), detection bias (blinded outcome assessment), attrition bias (incomplete outcome datasets), reporting bias (selective outcome reporting), plus other miscellaneous bias sources such as conflicts of interest.

2.5 Statistical Analysis

HRs and their corresponding 95% CIs for each risk factor were extracted from the included studies. Pooled HRs with 95% CIs were then calculated using the fixed-effect or random-effects model. Outcomes were evaluated based on the pooled HRs together with their 95% CIs. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic. Heterogeneity was considered significant when $P \leq 0.10$ and $I^2 \geq 50\%$. In cases of significant heterogeneity, subgroup or sensitivity analyses were performed to explore potential sources of heterogeneity according to study characteristics. All statistical analyses were performed using Stata software (version 15.0, StataCorp, College Station, TX, USA). A P-value < 0.05 was considered statistically significant unless otherwise stated.

3. Results

3.1 Search Result

The literature search initially identified 1253 citations. After removing duplicates, a total of 929 records were retained. Titles and abstracts were screened, and full-text articles were subsequently assessed against the pre-specified eligibility criteria. Ultimately, 43 studies were included in this systematic review[1, 3, 6, 10, 13-51] (detailed in Figure 1).

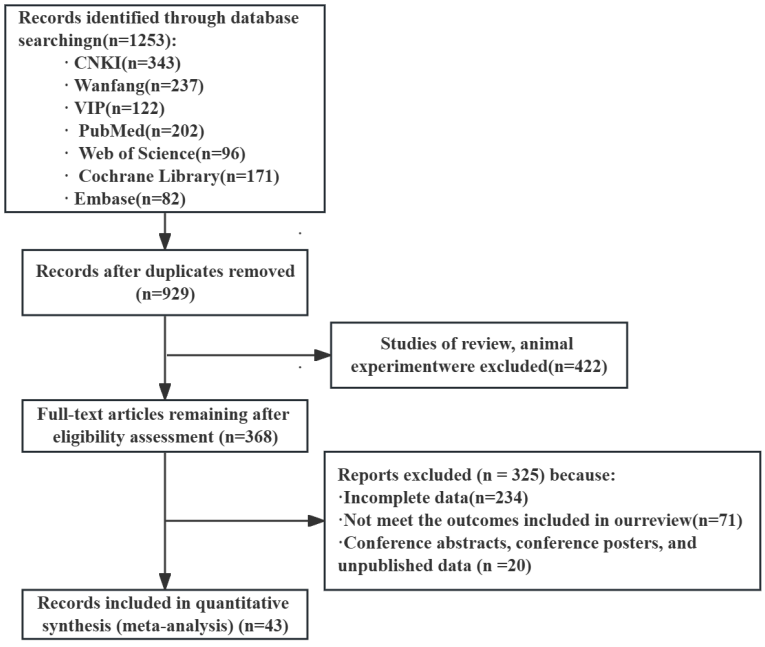

Figure 1. Flow diagram of the literature screening and selection process.

3.2 Characteristics of the Study

This study included 43 studies (24 cohort studies and 19 randomized controlled trials) involving 290,469 patients with diabetes. The pooled mean age of participants was 59.83 ± 11.05 years, with males accounting for 49.21% of the overall population. The mean duration of diabetes was 9.19 ± 7.26 years, and the median follow-up length was 7.95 years. The baseline characteristics of all included studies in this meta-analysis are summarized in Table 1.

Table 1. Baseline characteristics of the 43 included studies

Serial Number	First author	Year	Country	Study design	Sample size (male%)	Age (years)	DM duration (years)	Follow-up (years)	Risk factors
1	Dong et al. [1]	2021	China	Prospective cohort study	141516 (44.8)	65.6 ± 11.9	7.9 ± 6.5	9.8	(1), (3), (5),(7),(9),(10),(11),(12)
2	Gu et al. [3]	2016	China	Prospective cohort study	1645 (64.1)	64.2 ± 11.9	7.0-9.0	4.1	(3),(9),(11)
3	Viswanathan et al. [6]	2012	Chennai, India	Retrospective	152/(NA)	48.54 ± 9.02	6.18 ± 5.28	12	(1),(3),(6),(7),(9),(10)
4	Yang et al. [10]	2006	China	Prospective Cohort study	4438 (43.7)	64.5 ± 17.8	2-11	2.9	(3),(6),(7),(11),(12)
5	Humphrey et al. [13]	1989	America	Prospective cohort study	1832 (48.6)	NR	NR	25	(1),(2),(3),(5),(7)
6	Lee et al. [14]	1994	America	Retrospective Cohort study	1012 (37.4)	52.1 ± 11.3	7.0 ± 6.4	10.2	(1),(3),(7)
7	Keane et al. [15]	2003	28 countries	Prospective cohort study	1513 (63.2)	60.3 ± 7.3	NR	3.4	(10),(12)
8	Ahmed et al. [16]	2013	Pima Indians	Prospective cohort study	193 (29.0)	42.8 ± 10.5	12.3 ± 6.2	10.7	(1),(2),(7),(9).(11),(12)
9	Dyck et al. [17]	2014	Canada	Retrospective Cohort study	2640 (48.4)	NR	11.2 ± 5.5	10	(1),(3)
10	Chang et al. [18]	2015	China	Prospective cohort study	9997 (52.1)	56.5 ± 11.6	NR	5.7	(1),(2),(7),
11	Burdmann et al. [19]	2016	China	Prospective cohort study	604 (50)	61.7 ± 9.7	8 (3-14)	12.4	(3),(4),(5),(7),(9),(11)
12	Satirapoj et al. [20]	2019	Royal	Prospective Cohort study	257 (54.1)	66.2 ± 10.6	10 (5-7)	3	(1),(4),(10),(11),(12)
13	Hauteclocque et al. [21]	2014	France	Prospective cohort study	1146 (57.6)	65 ± 11	14.6 ± 10.4	5.7	(1),(2),(3),(7),(9),(11),(12)
14	Mann et al. [22]	2017	China	Retrospective cohort study	116455 (46.74)	61.4 ± 10.0	6.8 ± 6.1	5	(1),(3),(4),(5),(6),(7),(9),(11),(12)
15	Cannon et al. [23]	2020	NA	Randomized controlled trials	8246 (69.96)	64.4 ± 8.1	13 ± 8.35	3.5	(8)
16	Neuen et al. [24]	2018	NA	Randomized controlled trials	10142 (48.60)	63.5 ± 7.78	14.23 ± 7.82	3.9	(8)
17	Bhatt et al. [25]	2021	North America, Latin America, Western Europe, Eastern Europe, or the rest of the world	Randomized controlled trials	10584 (55.08)	69	NA	(1.3)	(8)
18	Wanner et al. [26]	2016	NA	Randomized controlled trials	7018 (71.44)	64.45 ± 8.23	NA	(3.1)	(8)

Table 1 Continued

Serial Number	First author	Year	Country	Study design	Sample size (male%)	Age (years)	DM duration (years)	Follow-up (years)	Risk factors
19	Perkovic et al. [27]	2018	667 centres in 30 countries	Randomized controlled trials	10140 (64.18)	64.9 ± 7.85	14.45±7.91	3-4	(8)
20	Wiviott et al. [28]	2019	882 sites in 33 countries	Randomized controlled trials	17160 (62.58)	63.95 ± 6.8	6-16	(4.2)	(8)
21	Wanner et al. [29]	2020	multinational trial	Randomized controlled trials	7020 (50.04)	61.7 ± 8.4	NA	(3.1)	(8)
22	Heerspink et al. [30]	2020	386 sites in 21 countries	Randomized controlled trials	4303 (66.88)	61.85 ± 12.1	NA	(2.4)	(8)
23	Gerstein et al. [31]	2019	371 sites in 24 countries	Randomized controlled trials	9901 (53.65)	64.05 ± 9.71	10.55±7.25	(5.4)	(13)
24	Lin et al. [32]	2023	China	Retrospective Cohort study	8299 (50.6)	68.4 ± 11.5	6.4±5.9	2.1	(13)
25	Perkovic et al. [33]	2024	387 sites in 28 countries	Randomized controlled trials	3533 (69.74)	66.6 ± 9.0	NA	(3.4)	(13)
26	Schechter et al. [34]	2023	Israel	Retrospective Cohort study	6848 (55.0)	59.4 ± 10.17	9.7±4.6	1.86 - 6.81	(13)
27	Gerstein et al. [35]	2021	344 sites across 28 countries	Randomized controlled trials	4076 (67.03)	64.5 ± 8.2	15.4±8.8	(1.81)	(13)
28	Chen et al. [36]	2018	China	Retrospective Cohort study	6165 (47.88)	67.34 ± 11.43	NA	3.3	(14)
29	Chao et al. [37]	2017	China	Prospective cohort study	923936 (92.13)	55.85 ± 12.8	NA	3.6	(14)
30	Rosenstock et al. [38]	2019	605 clinic sites in 27 countries	Randomized controlled trials	6991 (62.80)	65.9	14.75±9.45	2.2	(14)
31	Inagaki et al. [39]	2020	27 countries in Asia	Randomized controlled trials	555 (72.07)	65.3 ± 9.3	14.3±9.2	2.2	(14)
32	Yang et al. [40]	2022	China	Retrospective Cohort study	96643 (47.64)	67.83 ± 11.60	5.2±5.71	9.6 ± 4.1	(15)
33	Kwon et al. [41]	2020	Korea	Retrospective Cohort study	10862 (58.64)	67.0 ± 10.97	NA	7.3 ± 4.8	(15)
34	Hung M et al. [42]	2023	United States	Retrospective Cohort study	106063 (69.37)	63.9-79.5	NA	(1.5)	(15)
35	Hung et al. [43]	2015	China	Retrospective Cohort study	3252 (48.95)	67.2 ± 10.65	5.9 ±2.7	0.3-9.8	(15)
36	Kim et al. [44]	2021	Korea	Retrospective Cohort study	97713 (64.72)	66.15 ± 9.20	NA	5.3	(15)
37	Charytan et al. [45]	2019	NA	Retrospective Cohort study	4038 (42.74)	67 ± 10.5	15.61±9.55	5	(15)
38	Wan et al. [46]	2017	NA	Randomized controlled trials	9340	64	NA	(3.84)	(13)
39	Perkovic et al. [47]	2019	NA	Randomized controlled trials	4401 (66.05)	63.0 ± 9.2	15.8±8.6	(2.62)	(8)
40	Bakris et al. [48]	2015	23 countries	Randomized controlled trials	821 (78.00)	64.7 ± 9.26		90 days	(16)
41	Bakris et al. [49]	2020	48 countries	Randomized controlled trials	5674 (70.20)	65.55 ± 9.05		(2.6)	(16)
42	Pitt et al. [50]	2021	48 countries	Randomized controlled trials	7352 (69.44)	64.1 ± 9.85		(3.4)	(16)
43	Ruilope et al. [51]	2023	NA	Randomized controlled trials	7352 (67.71)	14.5 ± 8.45	14.5 ± 8.45	(3.4)	(16)

Notes: NR = Not reported. (1) Age; (2) Sex; (3) DM duration; (4) BMI; (5) Smoker; (6) DR; (7) Hypertension; (8) SGLT-2i; (9) HbA1c; (10) TG; (11) eGFR; (12) UACR; (13) GLP-1RAs; (14) DPP-4i; (15) Metformin; (16) Finerenone.

Quality assessment based on the NOS confirmed that all included cohort studies were of high quality (Table 2).

Table 2. NOS quality assessment of the 24 included cohort studies

	Selection				Comparability	Outcome			
First author/year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total scores
Dong et al. [1]/2021	1	1	1	1	2	1	1	1	9
Gu et al. [3]/2016	1	1	1	1	2	1	1	1	9
Viswanathan et al. [6]/2012	1	1	1	1	2	1	1	1	9
Yang et al. [10]/2006	1	-	1	1	2	1	1	1	8
Humphrey et al. [13]/1989	1	1	1	1	2	1	1	1	9
Lee et al. [14]/1994	1	1	1	1	2	1	1	1	9
Keane et al. [15]/2003	1	1	1	1	2	1	1	-	8
Ahmed et al. [16]/2013	1	1	-	1	2	-	1	1	7
Dyck et al. [17] /2014	1	1	-	1	2	-	1	1	7
Chang et al. [18]/2015	1	1	1	1	2	1	1	1	9
Burdmann et al. [19]/2016	1	1	1	1	2	1	1	1	9
Satirapoj et al. [20]/2019	1	1	1	1	2	1	1	1	9
Hauteclocque et al. [21]/2014	1	1	1	1	2	1	1	1	9
Mann et al. [22]/2017	1	1	1	1	2	1	1	1	9
Lin et al. [32]/2023	1	1	1	1	2	1	1	1	9
Schechter et al. [34]/2023	1	1	1	1	2	1	1	1	9
Chen et al. [36]/2018	1	1	1	1	2	1	-	1	8
Chao et al. [37]/2017	1	1	1	1	2	1	1	1	9
Yang et al. [40]/2022	1	1	1	1	2	1	1	1	9
Kwon et al. [41]/2020	1	1	1	1	2	1	1	1	9
Hung et al. [42]/2023	1	1	1	1	2	1	1	1	9
Hung et al. [43]/2015	1	1	1	1	2	1	1	1	9
Kim et al. [44]/2021	1	1	1	1	2	1	1	1	9
Charytan et al. [45]/2019	1	1	1	1	2	1	1	1	9

Risk-of-bias assessment was performed for all included RCTs. Most RCTs failed to report detailed information regarding the blinding of outcome assessment, which was therefore rated as "unclear risk" of detection bias. The study by Cannon and Wanner explicitly stated unblinded outcome assessment, corresponding to a judgement of "high risk" of detection bias. Additionally, five studies presented incomplete outcome data at the end of follow-up, compromising the assessment of primary outcomes and leading to a "high risk" of attrition bias. Thirteen studies exhibited other potential methodological flaws, resulting in an overall "high risk" of bias in relevant domains. The remaining assessment domains were predominantly rated as "low risk". Overall, the included RCTs presented a moderate level of methodological bias (Figure 2).

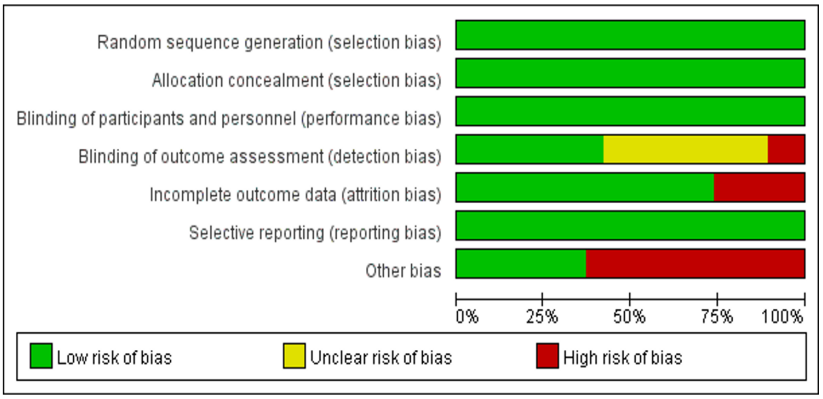

Figure 2. Risk of bias graph and summary for the included 19 randomized controlled trials.

3.3 Screening of Influencing Factors and Pharmacological Protective Effects

In this systematic review and meta-analysis, we identified 16 variables associated with DKD progression, including observational influencing factors derived from cohort studies and pharmacological protective effects obtained from randomized controlled trials (RCTs). Owing to substantial heterogeneity, we reported appropriate findings from subgroup or sensitivity analyses.

Risk factors		No.S	HR	95% CI	I^2 (%)	*P* value
Overall						
	Age	10	1.05	(1.04 to 1.06)	94.4	<0.001
	Gender	5	1.06	(0.99 to 1.14)	97.6	<0.001
	DM duration	10	1.01	(1.01 to 1.01)	86.5	<0.001
	BMI	4	1.02	(0.98 to 1.06)	83.1	0.001
	Smoking	4	1.28	(1.18 to 1.39)	26.2	0.254
	DR	4	1.76	(1.45 to 2.13)	73.2	0.011
	Hypertension	11	1.00	(1.00 to 1.01)	96.0	<0.001
	HbA1c	8	1.22	(1.15 to 1.29)	87.7	<0.001
	TG	6	1.00	(1.00 to 1.00)	79.5	<0.001
	eGFR	8	0.97	(0.97 to 0.98)	98.1	<0.001
	UACR	7	1.02	(1.01 to 1.02)	98.7	<0.001
	SGLT-2 i	9	0.60	(0.57 to 0.64)	3.6	0.411
	GLP-1RAs	6	0.77	(0.73 to 0.81)	3.1	0.418
	DDP-4 i	5	0.69	(0.66 to 0.72)	91.0	<0.001
	Metformin	7	0.73	(0.57 to 0.94)	98.0	<0.001
	Finerenone	4	0.84	(0.77 to 0.91)	0.00	0.670
Subgroup and sensitivity analysis						
Age	Increment by 1 year	5	1.06	(1.05 to 1.07)	83.2	<0.001
	Increment by 5-10 years	2	1.11	(1.01 to 1.21)	0.0	0.606
Gender	Male	3	1.69	(1.18 to 2.41)	0.0	0.531
	DM duration: Increment by 1 year old	5	1.04	(1.03 to 1.05)	7.0	0.372
	BMI Increment by 1 kg/m^2	2	1.04	(1.00 to 1.09)	41.2	0.192
	DR	3	3.03	(2.06 to 4.46)	0.0	0.568
	Hypertension	3	1.67	(1.14 to 2.46)	0.0	0.828
	HbA1c Increment by 1 % (11 mmol/mol)	5	1.25	(1.18 to 1.33)	46.3	0.097
	TG	2	1.13	(1.01 to 1.25)	0.0	0.893
	eGFR Decrement by 1 mL/min/1.73 m^{-2}	3	2.50	(1.90 to 3.30)	48.5	0.101
	UACR Increment by 1 mg/mmol	4	3.52	(3.11 to 3.99)	23.0	0.261

Figure 3. Pooled risk estimates (HRs with 95% CIs) and heterogeneity test results for factors associated with DKD progression.

Notes: BMI, body mass index; DR, diabetic retinopathy; HbA1c, glycated hemoglobin A1c; TG, triglycerides; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; DPP-4i, dipeptidyl peptidase 4 inhibitors.

The observational influencing factors from cohort studies and their corresponding pooled HRs with 95% CIs are listed as follows: age (per 5-10-year increment) (HR = 1.11, 95% CI 1.01-1.21), male sex (HR = 1.69, 95% CI 1.18-2.41), diabetes mellitus (DM) duration (per 1-year increment) (HR = 1.04, 95% CI 1.03-1.05), BMI (per 1-kg/m² increment) (HR = 1.04, 95% CI 1.00-1.09), smoking status (HR = 1.28, 95% CI 1.18-1.39), DR (HR = 3.03, 95% CI 2.06-4.46), hypertension (HR = 1.67, 95% CI 1.14-2.46), HbA1c (per 1% [11 mmol/mol] increment) (HR = 1.25, 95% CI 1.18-1.33), TG (HR = 1.13, 95% CI 1.10-1.25), eGFR (per 1-mL/min/1.73 m² decrease) (HR = 2.50, 95% CI 1.90-3.30), UACR (HR = 3.52, 95% CI 3.11-3.99).

The pharmacological protective effects against DKD progression from RCTs and their pooled HRs with 95% CIs are shown below: SGLT-2i therapy (HR = 0.60, 95% CI 0.57-0.64), GLP-1RA therapy (HR = 0.77, 95% CI 0.73-0.81), DPP-4i therapy (HR = 0.69, 95% CI 0.66-0.72), metformin therapy (HR = 0.73, 95% CI 0.57-0.94), and finerenone therapy (HR = 0.84, 95% CI 0.77-0.91). Forest plots for subgroup and sensitivity analyses are shown in Figure 3.

4. Discussion

4.1 Main Findings and Interpretations

Based on 43 eligible studies involving a total of 290,469 patients with diabetes, this meta-analysis systematically summarized two distinct types of indicators related to DKD progression. The first category comprised observational prognostic risk factors derived from cohort studies, including demographic characteristics and routine clinical indicators that significantly increase the risk of DKD progression. The second category referred to protective pharmacological effects obtained from randomized controlled trials (RCTs), which reflect the therapeutic benefits of interventions against DKD deterioration. Specifically, multiple anti-diabetic and renoprotective treatments, including SGLT-2i, GLP-1RA, DPP-4i, metformin, and finerenone, were identified to significantly reduce DKD progression risk. GLP-1RA, DPP-4i, metformin, and finerenone reduced the progression risk by 16% to 31%, while SGLT-2i exhibited the most powerful renoprotective effect with an approximately 40% risk reduction. The occurrence and progression of DKD result from the combined effects of genetic and environmental factors. Previous epidemiological studies have identified hypertension, longer diabetes duration, poor glycemic control, dyslipidemia, smoking, obesity, male sex, and the presence of diabetic retinopathy as well-established risk factors for DKD [52, 53]. Recent evidence indicates that SGLT-2i, GLP-1RA, and DPP-4i reduce the risk of DKD progression in patients with diabetes. Metformin has also demonstrated potential renoprotective effects [54-58].

Broadly speaking, DKD-associated determinants can be sorted into three major groups. Group 1 covers non-modifiable predictors: sex, age, and total diabetes duration. Group 2 represents changeable clinical risk markers, including hyperglycaemia, hypertension, dyslipidaemia, and smoking [21, 59]. Group 3 consists of medication-related factors, mainly renoprotective hypoglycemic agents such as SGLT-2i, GLP-1RA, DPP-4i and metformin. Appropriate management targeting these factors may hold back DKD onset and improve long-term patient survival outcomes.

Published clinical work yields the following observations:

(1) Male individuals face higher chances for DKD progression. This phenomenon may stem from intrinsic sex-related differences in renal anatomical structures, divergent glomerular haemodynamic behaviour, plus direct regulatory influences exerted by oestrogen and androgen over kidney tissues [60, 61].

(2) Alongside biological ageing, kidney volume gradually shrinks and renal functional capacity keeps declining. Age-related renal functional shifts include reduced glomerular filtration rates, elevated glomerular capillary pressure, lower erythropoietin synthesis, as well as impaired urinary sodium excretion. Surveillance datasets from the United States Centers for Disease Control and Prevention (CDC) support that advancing age independently correlates with higher DKD incidence [62, 63].

(3) Diabetes duration shows tight linkage with DKD onset and advancement. T2DM patients living with diabetes for over ten years carry substantial risks of developing macroalbuminuria [64].

(4) People who are overweight or obese have markedly elevated odds of DKD onset compared with subjects maintaining normal BMI ranges [65].

(5) Cigarette smoking amplifies whole-body oxidative stress, speeds lipid and advanced glycation end-product (AGE) accumulation, and finally triggers glomerular basement-membrane thickening, mesangial-matrix expansion, and accelerated glomerulosclerosis [66].

(6) As classic microvascular complications caused by diabetes, DR and DKD share comparable pathogenetic pathways and onset patterns; these two disorders frequently occur simultaneously in diabetic populations [67].

(7) Higher systolic blood pressure (SBP) raises urinary albumin loss and accelerates nephron loss [68]. One prior study reported that DKD patients presented distinctly higher systolic-pressure values compared with participants without DKD [65]. Mechanistically, elevated blood pressure increases renal perfusion volume, injures microvascular endothelial cells, speeds renal microangiopathy advancement, and aggravates renal damage, thereby substantially increasing DKD risk for T2DM subjects.

(8) Large-scale prospective randomized controlled trials have demonstrated intensive glycaemic control can cut incidence and slow DKD /nephropathy advancement for both T1DM and T2DM groups [12]. Keeping HbA1c under 6.5 % effectively prevents microvascular-complication onset, including DKD [60].

(10) The UK Prospective Diabetes Study (UKPDS) showed higher TG concentrations represent an independent risk marker for both microalbuminuria and macroalbuminuria [69].

(11) Renal function maintains a close correlation with UACR measurements. One large-sized Japanese prospective cohort demonstrated that T2DM subjects whose UACR exceeded 10 mg/g (female participants) or 5 mg/g (male participants) had obviously faster eGFR decline versus participants with UACR < 5 mg/g [70, 71].

(12) Accumulating clinical evidence suggests early-phase diabetic hyperfiltration acts as a strong predictive marker for DKD onset and worsening; it constitutes one core pathophysiological mechanism driving DKD development [72].

Pooled outputs from our meta-analysis indicated advanced age, male sex, extended diabetes duration, overweight-obesity status, concurrent diabetic retinopathy, smoking, raised HbA1c, hypertension, elevated triglyceride concentration, higher urinary albumin-to-creatinine ratio, and reduced estimated glomerular filtration rate are meaningful prognostic risk markers for DKD progression among diabetic patients. In contrast, receiving SGLT-2i, GLP-1RA, DPP-4i, or metformin treatment correlates with lowered DKD-progression risk, which aligns with results reported in previous published investigations.

4.2 Strength and Limitations

This meta-analysis comprehensively sorted out and summarised core prognostic markers behind DKD deterioration. The variables under analysis covered conventional clinical baseline indicators as well as modern anti-diabetic-drug-related markers, delivering an integrated overview of predictors linked to DKD worsening. Even so, several unavoidable weaknesses remain. Although subgroup and sensitivity analyses were applied to reduce cross-study statistical heterogeneity, the exact origins of residual heterogeneity for several variables could not be fully clarified. Unresolved heterogeneity may come from inter-study differences in participant baseline features, inconsistent diagnostic standards, or variable follow-up durations; these factors may inevitably exert influences over pooled-result reliability.

5. Conclusion

By synthesizing lifestyle-related indicators alongside clinical datasets, this meta-analysis performed a multi-dimensional assessment of variables associated with DKD advancement. It covers demographic traits, routine laboratory biomarkers plus clinical anti-hyperglycemic intervention strategies. Our pooled findings can help clinicians screen diabetic individuals prone to DKD worsening in routine clinical work and community-based health-management practice. Early-phase risk identification and accurate targeted interventions help cut progression risks among vulnerable diabetic subgroups. It is worth noting that pooled estimates confirm multiple renoprotective anti-diabetic medicines, including SGLT-2i, GLP-1RA, DPP-4is, metformin, and finerenone, produce prominent protective effects against DKD progression. For patients diagnosed with early-stage DKD, timely and standardised use of the above-mentioned medications can effectively hold back disease deterioration, preserve optimal therapeutic windows, and improve long-term prognostic outcomes for affected patients.

Declarations

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Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

MLS and QRT performed the research, analyzed the data, and drafted the manuscript. YPY and JYW participated in data collection. HH and YPY contributed to the study conception and design, quality assessment of included studies, and manuscript revision. All authors have read and approved the final submitted version of the manuscript.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

Not applicable.

Patient Consent for Publication

Not applicable.

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