Acta Pharm. **75** (2025) 1–22
https://doi.org/10.2478/acph-2025-0002

Meta-analysis review

The impact of blood lipids and statins on renal function and mortality in patients with diabetic nephropathy: A meta-analysis

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Accepted November 12, 2024
Published online November 18, 2024

ABSTRACT

The aim of this study is to explore the impact of blood lipids and statins on renal function and all-cause mortality in patients with diabetic nephropathy (DN). PubMed, Embase, Web of Science, and Cochrane Library were systematically searched until April 9, 2024, for relevant studies of blood lipids and statins on renal function and all-cause mortality in patients with DN. After the selection, total cholesterol levels (TC), total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), estimated glomerular filtration rate (eGFR), urinary albumin excretion (UAE), serum creatinine (SCR), end-stage renal disease (ESRD), and all-cause mortality indexes were extracted for finally meta-analysis. In total, 25 papers containing 21,411 patients with DN were finally included in this study. Levels of TC and LDL-C, which are continuous variables, were higher in DN patients who developed ESRD [TC/weighted mean difference (WMD) = 0.517, 95 % confidence interval (CI): (0.223, 0.812), $p = 0.001$; LDL-C/WMD = 0.449, 95%CI: (0.200, 0.698), $p < 0.001$]. In addition, this study also observed that statins may reduce UAE levels [WMD = –46.814, 95% CI: (–71.767, –21.861), $p < 0.001$]. Finally, the survey indicated that statins may be associated with an ESRD reduction [HR = 0.884, 95% CI: (0.784, 0.998), $p = 0.045$]. Blood lipids, particularly TC and LDL-C, may slow the progression of DN to ESRD. Besides, statins may protect the kidneys by lowering the excretion of UAE levels and reducing the risk of ESRD. Based on the above outcomes, the findings of this study provided robust evidence-based medical support for the future prevention, surveillance, and management of DN.

Keywords: statins, blood lipids, all-cause mortality, end-stage renal disease, diabetic nephropathy, meta-analysis

INTRODUCTION

Diabetic nephropathy (DN) is categorized as one of the most severe sequelae of diabetes, clinically recognized by the enduring presence of albuminuria for over three months and/or a simultaneous persistent decrease in the estimated glomerular filtration rate (eGFR) (1, 2). In recent years, as the prevalence of diabetes has accelerated, the prevalence of DN has also increased tremendously, resulting in a serious disease burden and economic loss worldwide (3–5). The development of DN is a gradual and multifaceted process, often initially manifesting through a spectrum of abnormal indicators that signal short-term renal function

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impairment – eGFR, urinary albumin excretion (UAE), serum creatinine (SCr), *etc.* (6). As DN advances, the renal impairment intensifies, leading to culminate in severe end-stage renal disease (ESRD) or even death (7). Thus the development of DN affects not only the patient's quality of life but also presents substantial medical, financial, and emotional challenges (8, 9). Therefore, it is imperative that future research directions do not merely focus on the short-term renal impairment in patients with DN but also on the long-term renal outcomes or even death.

The pathogenesis of DN is multifaceted involving a variety of biological processes and factors, of which blood lipids are one of the prominent influencing variables (10, 11). Dyslipidemia may lead to abnormal cytokine expression and induction of apoptosis by exacerbating inflammatory responses, oxidative stress, and other pathways, resulting in localized tissue damage in the kidney (12, 13). There was research evidence of a strong association between dyslipidemia and the development and progress of DN (14, 15). In addition, existing research indicated that lipid-lowering therapies played a significant role in the management of DN by potentially decelerating its progression (16). This evidence supported the necessity for a focused examination of lipid-lowering agents as a key element of therapeutic interventions in this context (16). Whereas statins, a class of blood lipid-lowering agents, had emerged as the cornerstone of dyslipidemia management, offering a potent mechanism to regulate blood lipid levels, especially reducing low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels (TC) (17, 18). With more research over the years, toxicological studies have found that statins could be renoprotective by reducing kidney-related metabolic abnormalities in diabetic rats (19). Similarly, a growing number of surveys have identified statins not only as lipid-lowering drugs but also as possessing a protective role on the kidneys and thus an enormous potential for prognosis in DN (20, 21). For example, a randomized controlled trial (RCT) reported by de Zeeuw *et al.* demonstrated that statins could reduce blood lipid concentrations and were nephroprotective in diabetes mellitus patients with associated progressive kidney disease (22). Qin *et al.* also established that statins had a positive effect on the prognosis of patients with DN (23). What's more, Zhou *et al.* found that statins had a protective effect on kidney injury while Hanai *et al.*'s study reached the opposite conclusion (19, 24), which reflected the existence of contradictory conclusions in the current relevant studies to a certain extent. Although related reviews or meta-analyses have been conducted to address this issue, most of the articles were limited to concentrating on the effects of statins or blood lipids on short-term renal function impairment indexes in patients with DN, ignoring the focus on the long-term progression of DN that could lead to ESRD or even death (20, 21, 23).

The investigation will first examine the association between blood lipid levels and ESRD, all-cause mortality in patients with DN. Furthermore, the present study will focus on the effect of statins on early biomarkers of kidney damage, exploring the impact of statins on ESRD and all-cause mortality. The elements of the study mentioned above have critical implications for the effect of statins on the prognosis of DN and the impact of changes in blood lipid levels on the development of health in patients with DN.

EXPERIMENTAL

This study was designed and implemented according to the Preferred Reporting Items for Meta-Analyses (PRISMA)(25).

Search strategy

Relevant articles until 9 April 2024 were screened as extensively as possible through PubMed, Embase, Cochrane Library, and Web of Science electronic databases. The specific keywords searched and a search strategy for the PubMed database both were shown in Supplementary Table 1. In particular, in order to avoid neglecting other relevant investigations, the research was also conducted for relevant information from other sources.

Study selection

Literature screening for this article was conducted independently by the authors according to the following inclusion-exclusion criteria. The inclusion criteria based on PICO principles were used to identify suitable articles for this study: subjects – patients with DN; influencing factors – blood lipids, including total cholesterol, triglycerides (TG), LDL-C and high-density lipoprotein cholesterol (HDL-C), statins; endpoints – short-term outcome: change in eGFR, UAE and SCr; long-term outcomes – ESRD, all-cause mortality; study type – RCT, cohort study, and case-control study. Exclusion criteria: literature with overlapping populations – only the most recent or most complete data were extracted; data not to be mentioned – results that were only pictures or only mean values without standard deviation are reported; type of articles – meta, review, analysis, abstract, case report, letter, retracted publication.

Data extraction

In data extraction, after downloading all articles that met the criteria, authors read the full text to extract and collect relevant data indicators carefully and independently. The data collected for each article were listed below: Publication year, authors, title, country, type of study, sample size of study population, number of men and women, mean age, duration of diabetes, statins use, eGFR, TC/TG/HDL-C/LDL-C, and study outcomes.

Methodology literature quality assessment

Due to the existence of articles with different types of studies, this study used a corresponding methodology for the articles when conducting the literature quality assessment. In the quality assessment of RCT, a modified Jadad rating scale was employed (26). This scale evaluates four key aspects: generation of random sequences, concealment of random allocation, implementation of blinding, and accounting for missed visits. The scale awards a total score of 7, with scores categorized as follows: 1–3 indicates low quality, and 4–7 signifies high quality.

For the evaluation of case-control and cohort studies, the Newcastle-Ottawa Scale (NOS) was utilized, which assigned a total score of 9 (27). The quality is classified into three tiers: poor (0–3), fair (4–6), and good (7–9). In the case of case-control studies, the assessment focused on three principal components: the selection of the study population, the comparability of groups, and the ascertainment of exposure. Cohort studies were appraised based on three similar components: the selection of the study population, the comparability of groups, and the measurement of outcomes.

Statistical analysis

All endpoints covered in this paper were baseline-endpoint changes. In this study, the weighted mean difference (WMD) was utilized as the statistical measure for continuous outcomes, while the relative risk (RR) or hazard ratio (HR) was employed for dichotomous outcomes. The magnitude of effects was presented with 95 % confidence intervals (CIs).

Heterogeneity was assessed for each outcome, and the presence of substantial heterogeneity, defined by $I^2 \geq 50$ %, dictated the use of a random-effects model; otherwise, a fixed-effects model was applied. For outcomes exhibiting significant heterogeneity, this article conducted subgroup analyses to explore potential sources of variability. These analyses were stratified by ethnicity (Asian, Caucasian), type of intervention, and length of follow-up, categorized as greater than or equal to 12 months or less than 12 months. To evaluate the robustness of our findings, sensitivity analyses were conducted using a one-by-one exclusion approach. Statistical analyses were performed in all studies using Stata 15.1, while statistical significance was defined as $p < 0.05$ ($\alpha = 0.05$).

RESULTS AND DISCUSSIONS

Results of literature screening and quality analysis

A total of 7151 potentially relevant papers were searched in the appropriate databases according to the search strategy, of which 1462 were from PubMed, 1132 from Embase, 3048

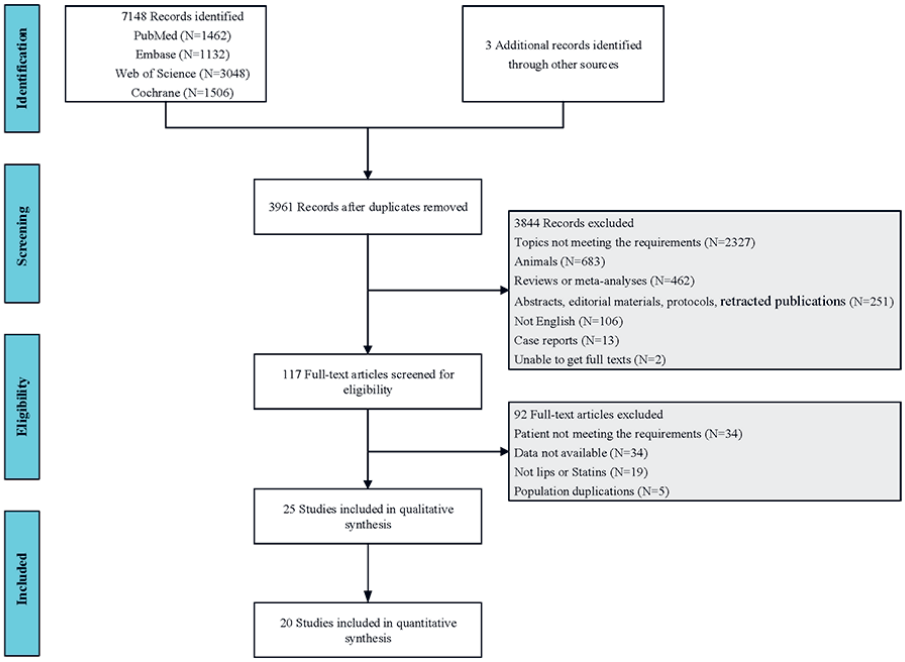

Fig. 1. The search and selection flowchart.

from Web of Science, 1506 from Cochrane Library, and 3 from other sources. The retrieved literature was processed by EndNote X19 software and 3961 articles remained after deleting duplicates. The literature was screened according to the established inclusion-exclusion criteria and 25 papers were finally included in this study (28–52). The specific search process, as well as the results, is shown in Fig. 1. In the final selection of 25 articles (20 were included for quantitative analysis), after scoring according to the corresponding criteria, all nine RCT studies were of high quality. Among the 14 cohort studies, there were five high-quality articles and nine of medium quality. In addition, there were two case-control studies, both of which were of medium quality. The specific scores for each article are detailed in Table I. Overall, the literature tended to be of higher quality.

Study characteristics

In sum, 21,411 patients with DN were included in the study. The basic characteristics and relevant indicators of the selected studies are presented in Table I. Nine countries were involved in the included studies, with one of the studies involving multiple countries. The age and sex distribution of the study population were reported for all studies. Nineteen surveys recorded the duration of diabetes in subjects of study. Eighteen studies reported on the use of statins. Levels of eGFR were counted in all but 11 studies. In addition, for the extraction of data on blood lipid indicators, 19, 14, 15, and 17 articles gave values for TC, TG, HDL-C, and LDL-C respectively. Finally, almost all studies provided specific years of follow-up (except one).

Table I. Characteristics of the included studies

Ref.	Year	Country	Study design	Sample size	Sex (M/F)	Age (year)	Diabetes duration (year)	Statin	eGFR (mL/min/1.73 m^2)	TC (mmol L^{-1})	TG (mmol L^{-1})	HDL-C (mmol L^{-1})	LDL-C (mmol L^{-1})	FU (month)	QA	Influencing factors	Outcomes
43	2023	China	Retrospective cohort	529	289/240	60.0 (51.0, 67.0)	4.0 (1.0, 9.0)	275	38.8 (36.4, 41.6)	5.4 (4.4, 6.2)	1.9 (1.2, 2.7)	–	–	63.5 (37.7, 67.1)	6	TC, TG, statins	ESRD
52	2022	China	Case-control	390	273/117	51 ± 9.6	8.1 ± 5.6	–	66.63 ± 34.07	5.16 ± 1.61	2.19 ± 1.71	1.37 ± 0.61	2.98 ± 1.28	36	6	TC, TG, HDL-C, LDL-C	ESRD
48	2021	China	Retrospective cohort	336	239/97	51.7 ± 8.95	8 (3, 11.75)	193	59 (43, 93)	5.24 ± 1.63	2.20 ± 1.76	1.34 ± 0.54	3.08 ± 1.27	20 (14, 35)	7	TC, TG, HDL-C, LDL-C	ESRD
51	2021	China	Retrospective cohort[a]	322	222/100	51 ± 10	7 (3, 11)	191	60 (43, 93)	5.0 (4.3, 6.0)	1.7 (1.2, 2.4)	1.3 (1.0, 1.6)	2.9 (2.3, 3.7)	24	7	Statins	ESRD
35	2020	Thailand	Retrospective cohort	8464	2571/5893	69.3 ± 9.5	9.9 ± 5.7	6195	44.6 ± 10.7	–	–	–	–	29.1 ± 5.5	7	Statins	ESRD
42	2018	Japan	Prospective cohort[a]	100	54/46	62.7 ± 9.9	11.8 ± 9.2	–	77.1 ± 19.2	–	–	1.38 ± 0.34	3.03 ± 0.64	87	6	HDL-C, LDL-C	All-cause mortality
28	2017	Iran	RCT	42	F	45–68	5–15	Atorvastatin 21	72.13 ± 35.32	5.39 ± 1.62	2.15 ± 0.77	1.00 ± 0.44	3.18 ± 1.04	3	4	Statins	SCr, eGFR
37	2016	Multi countries	Prospective cohort	4038	1726/2312	67.3 ± 10.7	–	2364	20–60	–	–	–	2.36 ± 1.03	26.4	6	LDL–C, statins	ESRD

Ref.	Year	Country	Study design	Sample size	Sex (M/F)	Age (year)	Diabetes duration (year)	Statin	eGFR (mL/min/1.73 m^2)	TC (mmol L^{-1})	TG (mmol L^{-1})	HDL-C (mmol L^{-1})	LDL-C (mmol L^{-1})	FU (month)	QA	Influencing factors	Outcomes
45	2016	Spain	Prospective cohort	201	81/120	53.5 ± 9.1	8 (4, 14)	–	123.5 ± 33.4	5.80 ± 1.35	1.93 ± 1.74	1.30 ± 0.50	3.71 ± 1.12	206.4 ± 78.0	7	TC, TG, HDL–C, LDL-C	ESRD
46	2016	Den-mark	Prospective cohort	200	151/49	58.5 ± 9.0	12.4 ± 7.2	189	–	3.9 ± 0.9	–	–	–	73.2	5	TC, statins	All-cause mortality
47	2016	Den-mark	Prospective cohort[a]	200	151/49	58.5 ± 9.0	12.4 ± 7.2	189	89.8 ± 18.2	–	–	–	1.8 ± 0.8	73.2 (70.8, 79.2)	5	LDL-C	All-cause mortality
41	2014	France	Prospective cohort	522	299/223	70.4 ± 9.4	18.3 ± 10.6	238	48.9 ± 22.7	4.93 ± 1.29	–	–	–	48	6	TC, statins	All-cause mortality
29	2011	Japan	RCT	104	59/45	64.7 ± 9.4	-	Rosuva-statin 52	69.9 ± 10.7	5.83 ± 0.62	1.81 ± 0.95	1.27 ± 0.28	3.54 ± 0.48	6	4	Statins	SCr, eGFR
36	2011	Ger-many	RCT[a]	1255	677/578	65.7 ± 8.3	18.1 ± 8.8	Atorva-statin 619	–	–	2.98 ± 1.87	0.93 ± 0.36	3.26 ± 0.78	48	7	LDL-C, statins	All-cause mortality
31	2009	UK	RCT	970	465/505	65.0 ± 6.7	–	Atorva-statin 482	53.8 ± 5.4	5.46 ± 0.81	–	1.45 ± 0.35	3.10 ± 0.69	4o6.8	5	Statins	All-cause mortality, eGFR
33	2005	Ger-many	Prospective cohort	445	244/201	64.9 ± 8.7	17.9 ± 10.5	122	–	–	–	–	2.70 ± 1.21	52	6	Statins	All-cause mortality
38	2005	Japan	RCT	20	12/8	50 (42–60)	13 (9–15)	Pitava-statin 10	–	4.7 ± 0.8	–	–	–	12	4	Statins	UAE
49	2005	Ger-many	RCT	1255	677/578	65.7 ± 8.3	18.1 ± 8.8	Atorva-statin 619	-	5.66 ± 1.09	2.98 ± 1.87	0.93 ± 0.36	3.26 ± 0.78	48	7	Statins	All-cause mortality
30	2003	multi coun-tries	Prospective cohort[a]	1513	956/557	60 ± 7	–	–	–	5.9 ± 1.4	2.5 ± 2.2	1.2 ± 0.4	3.7 ± 1.2	40.8 (27.6–55.2)	5	TC, TG, HDL-C, LDL-C	ESRD
34	2002	UK	Retrospective cohort	170	117/53	58.2 ± 10.6	4.9 ± 2.7	–	–	6.5 ± 2.0	–	–	–	61.2 ± 31.9	7	TC	All-cause mortality
32	2001	UK	Case-control	56	36/20	60.8 ± 12.1	12 (3.5, 20.5)	–	–	6.48 ± 1.78	–	–	–	36	5	TC	All-cause mortality
39	2001	Japan	RCT	60	38/22	56.5 ± 9.6	–	Ceriva-statin 30	–	6.7 ± 1.1	2.3 ± 0.4	0.6 ± 0.3	5.4 ± 1.1	6	4	Statins	SCr, UAE
44	1997	Italy	RCT	19	14/5	61 ± 5	9.5 ± 2.5	Simva-statin 10	–	6.5 ± 0.4	1.6 ± 0.2	1.3 ± 0.2	4.8 ± 0.4	12	4	Statins	UAE
50	1997	Japan	Prospective cohort	182	124/58	57 ± 11	–	–	–	6.31 ± 1.71	1.99 (1.43–2.83)	1.24 ± 0.47	–	–	6	TC, HDL-C	ESRD
40	1993	Den-mark	RCT	18	12/6	65.0 ± 1.5	10.6 ± 2.0	Simva-statin 8	96.9 ± 21.2	6.7 ± 0.3	1.92 ± 0.41	1.37 ± 0.18	4.51 ± 0.31	9	4	Statins	eGFR

Sex (M/F) – males to females ratio, DN – diabetic nephropathy, eGFR – estimated glomerular filtration rate, ESRD – end-stage renal disease, FU – follow up, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, RCT – randomized controlled trial, SCr – serum creatinine, TC – total cholesterol, TG – triglycerides, UAE – urinary albumin excretion. [a] Qualitative article.

Data analysis

Effect of blood lipids on ESRD. – Upon analyzing the blood lipid indices as continuous variables, an analysis of the effect of blood lipids on ESRD was conducted in this study (Table II). For TC and LDL-C, a total of 569 patients across two studies were considered respectively, both given the heterogeneity test yielded an I^2 = 0.0 %, Thereby, a fixed-effects model was employed for the analysis. The pooled results were as follows: for TC, the WMD was 0.517 with a 95% CI of (0.223, 0.812), and the *p*-value was 0.001; for LDL-C, WMD: 0.449, 95%CI: (0.200, 0.698), $p < 0.001$ (Fig. 2a,b), implying that the levels of TC and LDL-C were higher in patients with DN who developed ESRD. For the continuous type variables TG and HDL-C, both included 569 patients from two separate publications. Heterogeneity tests for both were low, therefore, fixed effect model analysis was used (TG: I^2 = 24.9 %; HDL-C: I^2 = 0.0 %). The results indicated that there was no significant difference between TG or HDL-C levels and DN patients with or without ESRD [TG: WMD: –0.220, 95%CI: (–0.534, 0.096), p = 0.721; HDL-C: WMD: 0.091, 95%CI: (–0.020, 0.202), p = 0.108] (Fig. 2c,d).

However, this study subdivided the four blood lipid indices that were counted in the literature and analyzed as HR and found that it was not possible to consider changes in TC, TG, HDL-C, and LDL-C levels to influence the prevalence of ESRD in patients with DN (Fig. 3, Table II).

Effect of blood lipids on all-cause mortality. – Since the included literature only partially reported the relationship between blood lipid indices and all-cause mortality, this part of the present study was analyzed only for the continuous variable TC and all-cause mortality.

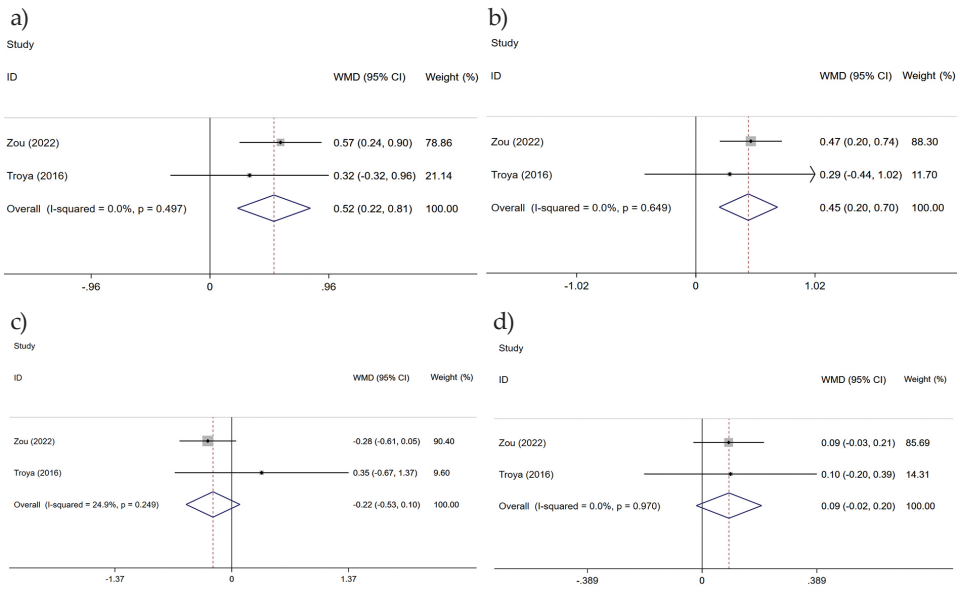

Fig. 2. Effect of blood lipids on ESRD (continuous variable): a) TC; b) LDL-C; c) TG; d) HDL-C.

Table II. Effect of blood lipids on ESRD and all-cause mortality

Outcome	Variables	Number of studies	Sample size	WMD/HR (95%CI)	*p*	I^2
ESRD	TC (mmol L^{-1})					
	overall	2	569	0.517 (0.223, 0.812)	0.001	0.0
	LDL-C (mmol L^{-1})					
	overall	2	569	0.449 (0.200, 0.698)	< 0.001	0.0
	TG (mmol L^{-1})					
	overall	2	569	–0.220 (–0.534, 0.096)	0.721	24.9
	HDL-C (mmol L^{-1})					
	overall	2	569	0.091 (–0.020, 0.202)	0.108	0.0
	TC, HR					
	overall	3	1047	1.059 (0.962, 1.167)	0.244	80.9
	LDL-C, HR					
	overall	2	4374	1.123 (0.980, 1.286)	0.096	80.4
	TG, HR					
	overall	2	865	0.986 (0.924, 1.053)	0.681	38.3
	HDL-C, HRl					
	overall	2	518	1.113 (0.854, 1.451)	0.428	77.1
All-cause mortality	TC (mmol L^{-1})					
	overall	3	426	0.006 (–0.293, 0.304)	0.969	0.0

ESRD – end-stage renal disease, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, RCT – randomized controlled trial, SCr – serum creatinine, TC – total cholesterol, TG – triglycerides, UAE – urinary albumin excretion, WMD – weighted average difference, HR – hazard ratio.

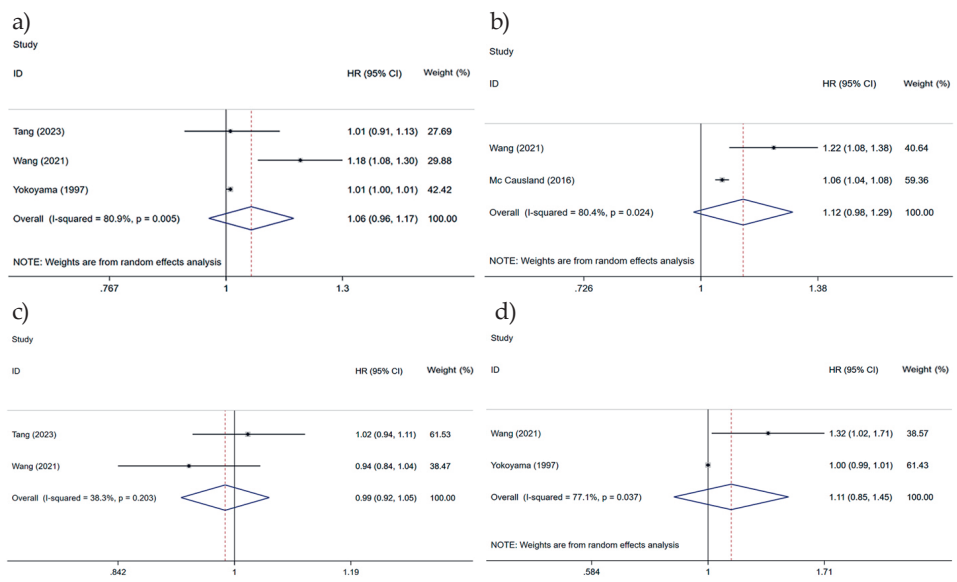

Fig. 3. Effect of blood lipids on ESRD (Hazard ratio): a) TC; b) LDL-C; c) TG; d) HDL-C.

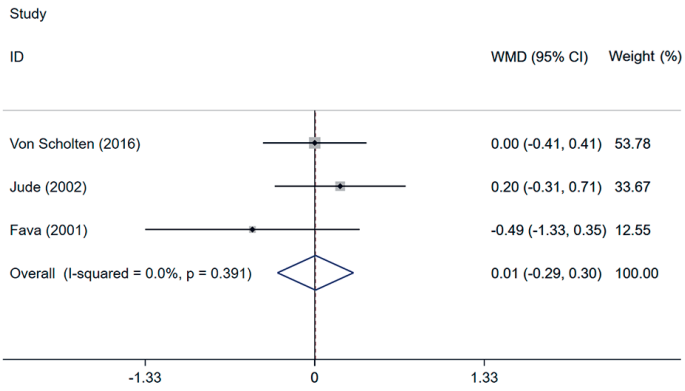

Fig. 4. Effect of TC on all-cause mortality (continuous variable).

A meta-analysis was conducted, incorporating data from 426 patients across three studies, utilizing a fixed-effect model due to the absence of significant heterogeneity among the studies (I^2 = 0.0 %). The findings indicated that there was no statistically significant difference in TC levels between patients with DN who experienced all-cause mortality and those who did not [WMD: 0.006, 95%CI: (–0.293, 0.304), p = 0.969] (Fig. 4, Table II).

Effect of statins on eGFR. – Pooled data from four studies (including 405 patients with DN) demonstrated that statins could not be considered to affect changes in eGFR, with a WMD change in eGFR of 1.913 [95%CI: (–0.313, 4.139), p = 0.092, I^2 = 0.0 %] (Fig. 5a, Table III).

Effect of statins on UAE. – Three literature enrolled for analysis, including 99 patients. In this analysis, due to the large results of the heterogeneity test (I^2 = 66.7 %), a random effects model was used for the next step of the evaluation. The results of the study recommended that the effect of statins on UAE was beneficial and may reduce the level of UAE in patients with DN [WMD: –46.814, 95%CI: (–71.767, –21.861), p < 0.001] (Fig. 5b). In addition, because of the large heterogeneity, the study was analyzed in subgroups according to race (Asian, Caucasian), intervention/length of follow-up (≥ 12, < 12 months), and the results, shown in Fig. 6, were found to be consistent.

Effect of statins on SCr. – In analyzing the effect of statins on SCr, 206 patients from three literature enrolled. As shown in Fig. 5c, the WMD change in SCr was –0.003 [95%CI: (–0.313, –0.057, 0.050), p = 0.900, I^2 = 0.0 %], which revealed that statins may not significantly influence changes in SCr levels for patients with DN.

Effect of statins on ESRD. – In the investigation of the effect of statins on the progression of ESRD in patients with DN, the HR index of statins was included as a variable. Three surveys were taken into account, including 13031 patients. A fixed effects model was used for the purpose of the study based on the results of the heterogeneity test (I^2 = 12.1 %). The HR: 0.884 for ESRD was statistically significant [95%CI: (0.784, 0.998), p = 0.045], meaning that statins may be able to attenuate the incidence of ERSD in patients with DN (Fig. 7a, Table III).

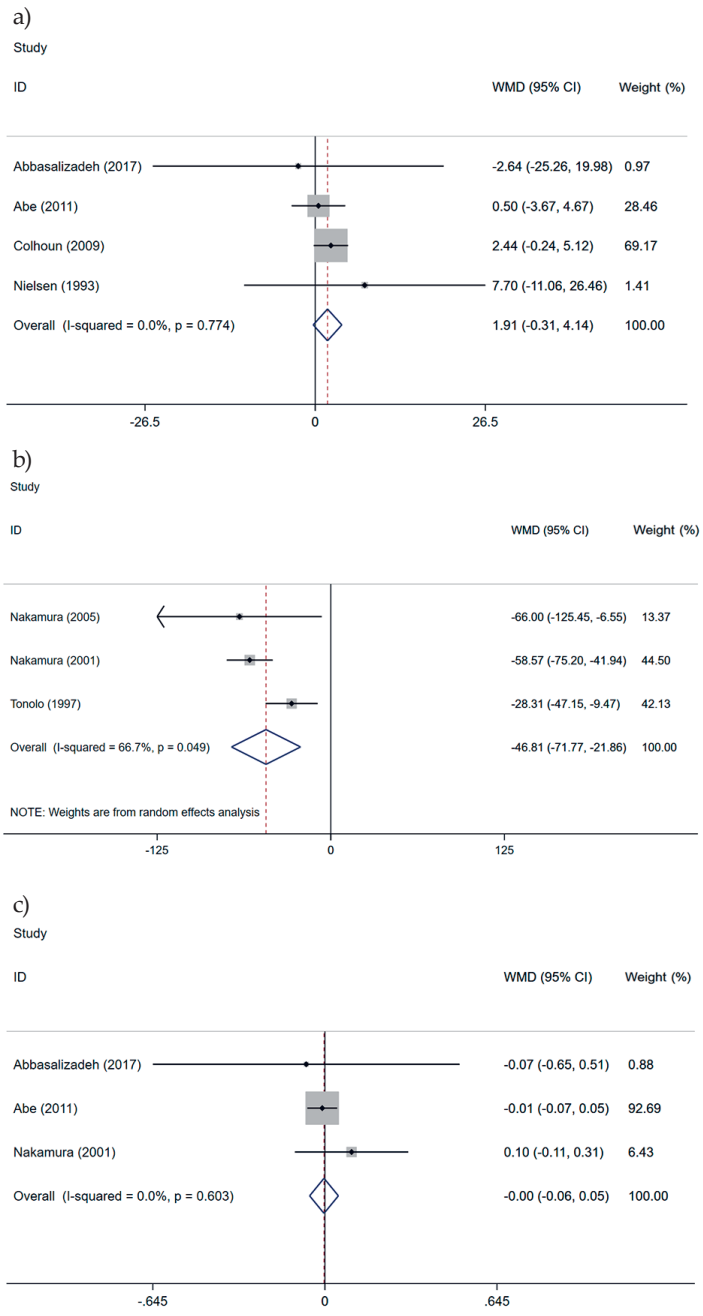

Fig. 5. Effect of statins on: a) eGFR; b) UAE; c) SCr.

Table III. Effect of statins on eGFR, UAE, SCr, ESRD, and all-cause mortality

Outcome	Variables	Numbers of studies	Sample size	WMD/HR/RR (95%CI)	*p*	I^2
eGFR	Statins					
	overall	4	405	1.913 (–0.313, 4.139)	0.092	0.0
UAE	Statins					
	overall	3	99	–46.814 (–71.767, –1.861)	<0.001	66.7
	Ethnicity					
	Asian	2	80	–59.109 (–75.129, –3.090)	< 0.001	0.0
	Caucasian	1	19	–28.310 (–47.154, –9.465)	0.003	NA
	Treatment duration					
	≥ 12 months	2	39	–36.177 (–66.197, –6.156)	0.018	28.7
	< 12 months	1	60	–58.570 (–75.204, –1.936)	< 0.001	NA
SCr	Statins					
	overall	3	206	–0.003 (–0.057, 0.050)	0.900	0.0
ESRD	Statins, HR					
	overall	3	13031	0.884 (0.784, 0.998)	0.046	12.1
All-cause mortality	Statins, classification					
	overall	4	2870	0.916 (0.834, 1.006)	0.066	17.4
	Statins, HR					
	overall	2	1492	0.973 (0.754, 1.253)	0.831	0.0

eGFR – estimated glomerular filtration rate, ESRD – end-stage renal disease, SCr – serum creatinine, UAE – urinary albumin excretion, WMD – weighted average difference, HR – hazard ratio, RR – relative risk.

Effect of statins on all-cause mortality. – In conducting a study to explore whether statins affected the occurrence of all-cause mortality in patients with DN, statins as a categorical number as well as HR, respectively. When statins were used as a categorical number, 2870 patients from four studies were collected. Based on the outcomes of the heterogeneity test (I^2 = 17.4 %), a fixed-effects model was employed for the analysis, and the results were shown below: RR: 0.916, 95%CI: (0.834, 1.006), p = 0.066 (Fig. 7b). Moreover, this investigation included 2870 patients from 4 studies when statins were used as HR. The results

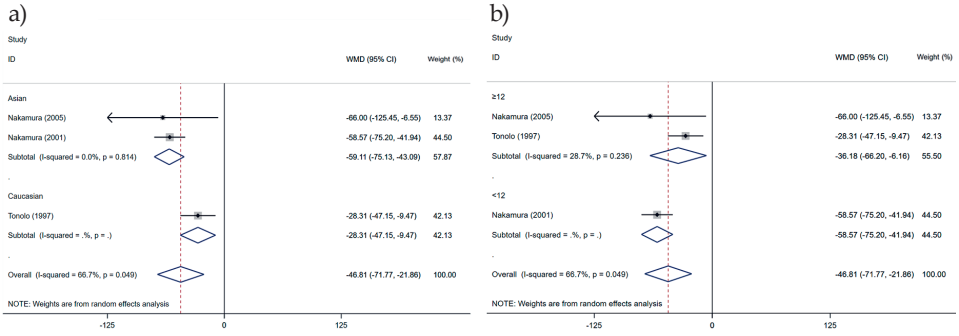

Fig. 6. Subgroup analysis of the effect of statins on UAE: a) ethnicity; b) intervention length of follow-up.

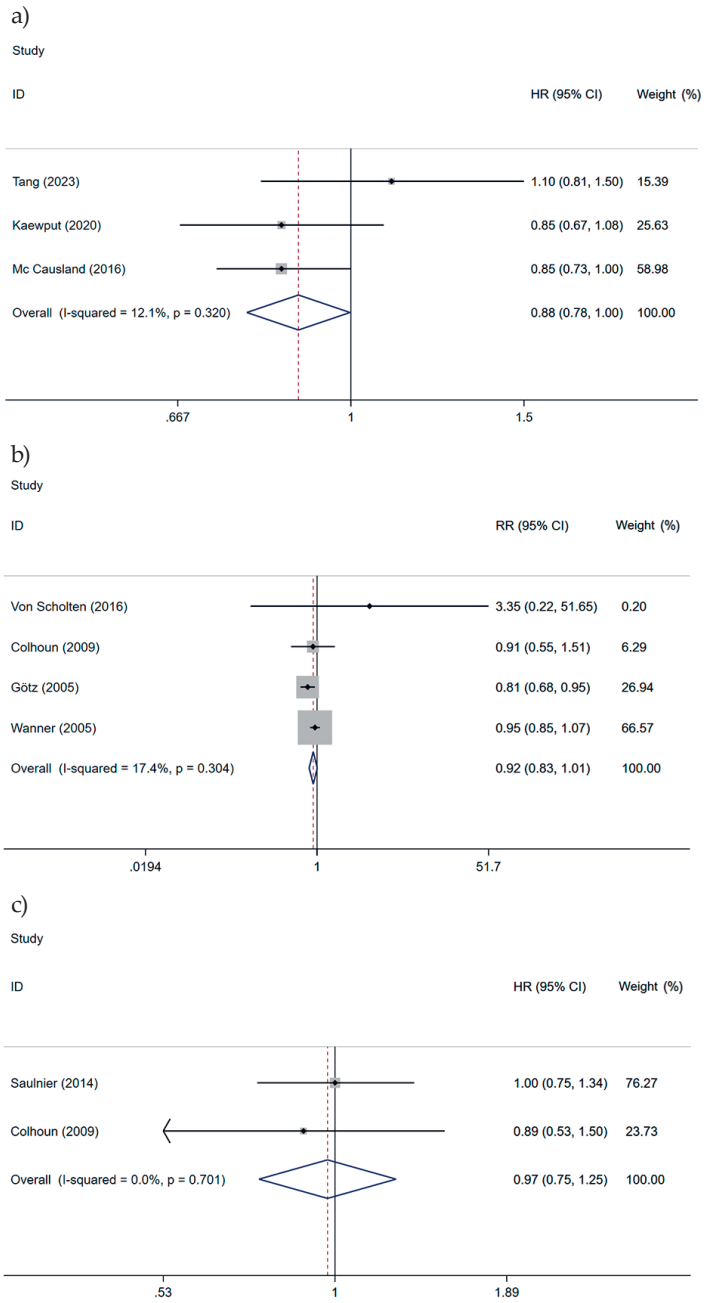

Fig. 7. Effect of statins on: a) ESRD-hazard ratio; b) all-cause mortality-relative ratio; c) all-cause mortality-hazard ratio.

likewise displayed that statins could not be considered to affect the incidence of all-cause mortality in patients with DN [HR: 0.973, 95%CI: (0.754, 1.253), $p = 0.831$] (Fig. 7c).

Sensitivity analysis. – All associations in this study were analyzed for sensitivity. The results illustrated that the findings were similar overall after excluding any of the individual studies. The above outcomes suggested that the results of our statistical analysis were relatively robust and reliable (Supplementary Table 2).

Systematic review

In Appel's study, the risk of ESRD was strongly associated with baseline TC (96% increase in risk per 100 mg dL^{-1}, $p < 0.001$) and LDL-C (47 % increase in risk per 50 mg dL^{-1}, $p < 0.001$), while HDL and TG were not associated with the risk of ERSD (30). The study by Zhao *et al.* showed that statins also did not affect the incidence of ESRD (61 % statins treatment in the ESRD group, 58 % statins treatment in the non-ESRD group, $p = 0.57$) (51).

Subsequently, in the investigation targeting all-cause mortality as an outcome variable, Seki's study indicated that LDL-C and HDL-C did not affect all-cause mortality [HR: 1.025, 95%CI: (0.979, 1.072) and HR: 0.973, 95%CI: (0.903, 1.048)] (42). Similarly, there was no difference in LDL-C levels between the death and survival groups in von Scholten's study (1.9 ± 0.8 *vs.* 1.8 ± 0.8 mmol L^{-1}) (47). However, in März's study all-cause mortality was found to be higher in the highest LDL-C quartile than in the lowest quartile group [HR: 1.62, 95%CI: (1.05, 2.50)], and in the highest quartile group, atorvastatin was able to significantly reduce all-cause mortality [HR: 0.72, 95%CI: (0.52, 0.99)] (36).

DN stands as a leading etiology of ESRD globally. Recognizing its substantial impact on public health and the significant economic ramifications it imposes, there is a growing awareness and concern regarding this condition on a global scale (1, 3, 8). In this study, a comprehensive analysis was conducted, encompassing a total of 25 papers that reported data on 21,411 patients with DN. The principal findings derived from this analysis of research were as follows: elevated levels of TC and LDL-C had been observed in patients with DN who possessed progressed to ESRD; statins significantly decreased UAE in patients with DN; statins may reduce the incidence of ESRD in patients with DN, and the underlying mechanisms were worthy of further exploration.

During the past several decades, the pivotal role of dyslipidemia in the etiopathogenesis of DN has gained extensive recognition and underscored the significance of lipid metabolism in the progression of renal complications associated with diabetes (18, 53). In a study by Retnakaran *et al.*, utilizing data from the United Kingdom Prospective Diabetes Study (UKPDS), a significant and independent correlation was observed between plasma levels of LDL-C and the degree of proteinuria in diabetic patients, and elevated LDL-C levels were identified as a predictive factor for the development of renal dysfunction (54). Analogously, our study observed elevated levels of LDL-C in patients with DN who progressed to ESRD, which may be able to suggest a potential causal or exacerbating role of higher LDL-C in the deterioration of renal function. Concurrently, the survey identified a higher concentration of TC in DN patients with ESRD, revealing a potential correlation between elevated TC levels and the progression to ESRD in this patient population. Corroborating our findings, a study conducted by Cusick *et al.* demonstrated a significant association between raised TC levels and adverse renal outcomes, establishing TC as an

independent risk factor for poor renal prognosis (55). The above results of this study were all based on the TC and LDL-C as continuous variables and did not lead to conclusions with similar statistical significance when analyzing both HR variables. Simultaneously, it was imperative to consider that incorporating HR as a variable in the analysis might potentially diminish the statistical power to discern differences among groups. In addition, Liu *et al.* used a Mendelian randomization (MR) study to explore the causal relationship between lipid parameters and DN did not validate the above findings, and they found that elevated HDL-C may have a potentially protective effect and high levels of TG may have a negative effect, but did not observe a corresponding trend for LDL-C and TC (56). While in the research, no differences in HDL-C as well as TG levels in patients suffering from DN patients with ESRD were observed for the time being, either when analyzed as continuous or HR variables on the other hand. The unwanted discrepancy might be ascribed to the following factors. The DN patients enrolled in the study had different medical conditions, including a history of other diseases, race, and other conditions. For example, the patients' history of other diseases as well as medication history were not taken into account in this study, and these may have exacerbated kidney damage. In short, dyslipidemia may be involved in the progression of pathological states such as inflammation, fibrosis, and apoptosis, and high levels of TG can cause lipid accumulation or lipotoxicity thereby affecting the normal functioning of the kidney (57–59). From the above findings, it was reasonable to assume that lipid levels might be the independent risk factors for DN that should be controlled early in diabetic patients to avoid the development of renal function-related diseases, and in DN patients, the development of ESRD and other related diseases can be delayed or even avoided by controlling blood lipids.

Given the impact of dyslipidemia on DN as discussed, many scholars then have commenced to take heed of the effects of applying lipid-lowering drugs on the prognosis of DN (60). Currently, most of the research was on the clinical use of statins in the protection of renal function in patients with DN, as statins have been shown to have a positive protective effect on renal function (22, 61). In the present study, the effect of statins on eGFR and SCr was not remarkable, but Nikolic *et al.*' investigations identified a notable effect of statins on SCr, particularly a significant increase in eGFR after 1–3 years of statin use, suggesting a clear renoprotective operation of statins (62). However, statins were significantly negatively correlated with eGFR in the study by Zhao *et al.* (63). Nikolic's study illustrated the importance of the duration of statin use, yet in this study only the number of people applying statins and no data on the duration of use were collected, which may be one of the reasons for the conflicting conclusions. Besides, evidence suggested that recurrent elevations in UAE may be associated with the diagnosis of DN (61). In the present investigation, the results of the analyses suggested that statins may be able to significantly reduce UAE levels. Nakamura *et al.* also came to a similar conclusion (39). Atthobari's study presents a different conclusion, stating in his RCT study data that statins do not decrease UAE, and in the cohort study data statins were not associated with a decrease in UAE, which increased instead (64). Sorof also believed that statins did not have a clinically meaningful effect on UAE (65). For the study conducted by Atthobari, the study population was the general population, whereas both this study and Nakamura were patients with DN. In addition, Sorof's study focused on rosuvastatin or atorvastatin, whereas Nakamura studied cerivastatin and this study did not focus on the type of statins. The difference in the design of the two studies might be the main reason for the different results and suggested

that the type of statins and the applicable population need to be carefully considered when applying statins in the future.

In addition to looking at the role of statins on a range of short-term outcomes such as eGFR, UAE, and SCr as described above. There has also been more focus on the effect of statins on ESRD and all-cause mortality in patients. In this study, the results of our data analysis indicated that statins reduce the risk of ESRD in patients with DN, while the systematic review did not reach a comparable conclusion (51). Inconsistent conclusions also remained in currently published articles. For example, Nemerovski *et al.* reviewed a series of trials on the effects of statins in ESRD patients and suggested that statins didn't show a strong advantage in ESRD patients, instead recommending caution in the use of statins in ESRD patients with concomitant LDL-C elevation (66); Baigent *et al.* also found that simvastatin combined with ezetimibe treatment did not significantly reduce the risk of ESRD (67). A case-control study indicated that statins may be associated with an increased risk of ESRD too (68). However, in fact, some studies have reached conclusions similar to our research, suggesting that statins were associated with favorable outcomes in patients with ESRD. A good example of this was a multicenter study by Soohoo, where statins were associated with favorable outcomes for early ESRD (69). Besides, statins have been found to improve prognosis in ESED patients in several observational studies (70, 71). Baber's study agrees and recommends the application of statins in patients with kidney disease (72). With regard to the effect of statins on all-cause mortality in DN patients, although neither the number of categories nor the risk ratios in the quantitative analyses of the present investigation yielded the conclusion that statins could influence the incidence of all-cause mortality, in the qualitative analyses, März's study found that atorvastatin reduces all-cause mortality (36). Soohoo's survey identified statins as being associated with lower all-cause mortality and cardiovascular mortality by the same token (69). Comparable observations were reported in Mason and Seliger's study (70, 71). Overall, there is still a conflict over the renoprotective effects of statins. For instance, in the same toxicological study in diabetic rats, the study by Huang *et al.* concluded that long-term administration of statins exacerbates DN through ectopic fat deposition (73). In contrast, Zhou *et al.* showed that atorvastatin may have a protective effect on the kidneys by improving glucose and fat metabolism and enhancing antioxidant capacity (19). Zhang *et al.* supported the idea that it contributed to the protection of DN by statins and also assumed that atorvastatin may ameliorate DN by inhibiting oxidative stress and iron death signaling (74). Our investigation likewise provided new evidence in favor of statins protection against DN. Through the above in-depth discussion, however, future research is more certain that the impact of statins on the protection of renal function and the prognosis of DN needs to be interpreted more cautiously. All of the above studies remind us that different types of statins, the duration of statins usage, and the population for which they are prescribed can lead to different outcomes and that more authoritative studies are needed to demonstrate the true role and contraindications of statins.

Against the backdrop of existing research, to fill the lacuna in this area of research to some extent, this study aims to achieve a more thorough understanding of the effects of blood lipids and statins on renal function and mortality in patients with DN. Not to mention, we hope the present study may contribute to the improvement of the health status and quality of life of patients with DN, and help to achieve early prevention and monitoring

of relevant diseases, reduce healthcare costs thereby addressing significant social and economic challenges.

But in common with any study, there were some limitations to our analyses. First, this study did not include data on the use and duration of different classes of statins. Second, most of the outcome literature was sparse, resulting in high heterogeneity that precludes subgroup analyses, and therefore may affect the stability of the results. Third, when the variables in this study were analyzed as continuous data and HR, the results were inconsistent and caution is needed in interpreting and extrapolating the results. Fourth, this study did not incorporate the history of other diseases as well as the medication history of the patients analyzed, and these may have an impact on renal damage.

CONCLUSIONS

This meta-analysis found that the blood lipid markers TC and LDL-C were associated with ESRD, and also suggested that statins may reduce UAE levels and the risk of ESRD, which was associated with all-cause mortality. Our findings provided new evidence-based scientific support to sustain the view that blood lipids and statins were protective of renal function and attenuated the risk of mortality. Our findings are encouraging, but there is still a need for larger and more authoritative ones to confirm the above views.

Abbreviations. – Cis – confidence intervals, DN – diabetic nephropathy, eGFR – estimated glomerular filtration rate, ESRD – end-stage renal disease, HDL-C – high-density lipoprotein cholesterol, HR – hazard ratio, LDL-C – low-density lipoprotein cholesterol, MR – Mendelian randomization, PRISMA – preferred reporting items for meta-analyses, RCT – randomized controlled trial, RR – relative risk, SCr – serum creatinine, TC – total cholesterol, TG – triglycerides, UAE – urinary albumin excretion, WMD – weighted mean difference, UKPDS – United Kingdom Prospective Diabetes Study.

Availability of data and materials. – The datasets used and/or analyzed during the current study were publicly available from PubMed, https://pubmed.ncbi.nlm.nih.gov; Embase, https://www.embase.com; Web of Science, https://www.webofscience.com/wos/; and Cochrane Library, Cochrane Reviews | Cochrane Library; database.

Conflict of interests. – All authors declare that they have no conflict of interest.

Funding. – None.

Authors contributions. – Conceptualization, D.T.; collecting the data, D.T., Q.C., L.Z. and Y.H.; analysis, D.T., Q.C., L.Z. and Y.H.; writing, original draft preparation, D.T.; investigation, D.T., Q.C., L.Z. and Y.H.; writing, review and editing, D.T., Q.C., L.Z. and Y.H. All authors have read and agreed to the published version of the manuscript.

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