International Archives of Allergy and Immunology

Clinical Immunology – Research Article

Int Arch Allergy Immunol 2021;182:158–165
DOI: 10.1159/000510250

Received: January 30, 2020
Accepted: January 31, 2020
Published online: December 7, 2020

Cytokine Polymorphisms and Predisposition to Diabetic Nephropathy: A Meta-Analysis

Suqin Wang[a] Jiazhi Dong[a] Lingling Huang[b]

[a]Department of Nephrology, Huai'an TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Huai'an, China; [b]Department of Nephrology, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huai'an, China

Keywords
Diabetic nephropathy · Tumor necrosis factor-α · Interleukin-1 · Interleukin-4 · Interleukin-8 · Interleukin-18 · Gene polymorphisms · Meta-analysis

Abstract
Background: Cytokine polymorphisms might influence the predisposition to diabetic nephropathy (DN), but the results of already published related studies are still controversial and ambiguous. ***Objectives:*** The authors designed this meta-analysis to more precisely estimate relationships between *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms and DN by pooling the results of already published related studies. ***Methods:*** The authors searched Pubmed, Embase, Web of Science and CNKI for already published studies. Thirty already published studies were pooled and analyzed in this meta-analysis. ***Results:*** The overall pooled meta-analysis results showed that distributions of *TNF-α* –238 G/A, *TNF-α* –308 G/A, *TNF-α* –1031 C/T, *IL-1A* –889 C/T, *IL-1B* –511 C/T and *IL-18* –137 G/C polymorphisms among patients and controls differed significantly. Additionally, we also found that distributions of *TNF-α* –308 G/A, *IL-1B* –511 C/T and *IL-18* –137 G/C polymorphisms among patients and controls from Asians differed significantly, and the distribution of the *IL-1B* –511 C/T polymorphism among patients and controls from Caucasians also differed significantly. ***Conclusion:*** The meta-analysis results demonstrated that *TNF-α* –238 G/A, *TNF-α* –308 G/A, *TNF-α* –1031 C/T, *IL-1A* –889 C/T, *IL-1B* –511 C/T and *IL-18* –137 G/C polymorphisms might influence predisposition to DN in the overall pooled population. Moreover, *TNF-α* –308 G/A, *IL-1B* –511 C/T and *IL-18* –137 G/C polymorphisms might influence predisposition to DN in Asians, whereas the *IL-1B* –511 C/T polymorphism might also influence predisposition to DN in Caucasians.

Introduction

Diabetic nephropathy (DN) is a chronic and progressive microvascular complication of diabetes mellitus, which affects 30–40% of the patients, and it is also the leading cause of end-stage renal disease in grown-ups [1,

Edited by: H.-U. Simon, Berne. Suqin Wang and Jiazhi Dong contributed equally to this work.

karger@karger.com
www.karger.com/iaa

Suqin Wang
Department of Nephrology
Huai'an TCM Hospital Affiliated to Nanjing University of Chinese Medicine
No. 3 Heping Road, Huai'an 223001, Nanjing (China)
wangsiuqin2@163.com

2]. Although its definite etiologies and pathogenesis mechanisms are still ambiguous, accumulating evidence suggests that genetic architecture greatly influences its development. Firstly, the incidences of DN in different populations differ significantly [3–5], and the genetic background is probably one of the underlying reasons of this phenomenon. Secondly, previous association studies have also detected numerous predisposing gene loci of DN in different populations [6, 7]. However, the etiologies and pathogenesis mechanisms of DN are extremely sophisticated, and genetic factors that contribute to the development of DN still need intensive explorations.

Cytokines play vital roles in modulating immune responses and are involved in the pathogenesis of various inflammatory disorders [8, 9]. Previous studies have demonstrated that DN shares similar properties with many chronic inflammatory disorders, and classical inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) have also been found to be elevated in patients with DN [10, 11]. Moreover, proinflammatory cytokines and their associated overactivated immune responses have also been shown to be associated with development and progression of DN [12, 13]. Therefore, if a polymorphism can impact gene expression or protein structure of cytokines, it is likely that this polymorphism might alter inflammation status and influence predisposition to DN.

In the last two decades, investigators across the world have extensively explored the relationship between cytokine polymorphisms and DN, particularly for polymorphisms of *TNF-α*, *IL-1*, *IL-4*, *IL-8* and *IL-18*, yet the relationships between *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms and DN are still controversial and ambiguous. Thus, we designed this meta-analysis to get a more statistically reliable conclusion regarding relationships between *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms and DN by pooling the results of already published studies.

Materials and Methods

The PRISMA guideline was followed by the authors when conducting this meta-analysis [14].

Literature Search and Inclusion Criteria

A literature search of Pubmed, Web of Science, Embase and CNKI was performed by the authors using the following terms: (Tumor necrosis factor-α or TNF-α or interleukin-1 or IL-1 or interleukin 1 or IL 1 or interleukin-4 or IL-4 or interleukin 4 or IL 4 or interleukin-8 or IL-8 or interleukin 8 or IL 8 or interleukin-18 or IL-18 or interleukin 18 or IL 18) and (polymorphism or variant or variation or mutation or SNP or genome-wide association study or genetic association study or genotype or allele) and (diabetic nephropathy or DN). The authors also checked the references of obtained articles for additional related studies.

Eligible studies must meet all of three inclusion criteria: (I) formally published studies evaluating relationships between *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms and DN; (II) provide sufficient genotypic data of *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms in patients with DN and controls; (III) the whole manuscript is available in English or Chinese. Articles were excluded when at least one of the following three conditions was fulfilled: (I) studies not concerning *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms and DN; (II) reviews or expert comments; (III) case series only involving participants with DN. When duplicate reports were observed during literature searching, only the most complete one was included for pooled meta-analyses.

Data Extraction and Quality Assessment

We extracted the following items from included studies: (I) surname of the first author; (II) year of online publication; (III) country and ethnicity of involved participants; (IV) number of patients and controls; (V) genotypic distributions of *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms in patients and control subjects. We also calculated *p* values of Hardy-Weinberg equilibrium based on genotypic distributions of *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms.

The authors used the Newcastle-Ottawa scale to assess the quality of included studies [15]. Its score range is from zero to 9, and the methodology quality of an article is considered to be good if it can get a score of more than 7.

Data extraction and quality assessment of included studies were performed by two authors separately. We would write to the corresponding authors for additional data if we failed to extract the necessary information from included studies.

Statistical Analyses

The authors used Review Manager to pool meta-analysis results. The authors used the *Z* test to evaluate the relationship between *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms and the predisposition to DN. The authors set the statistically significant threshold at 0.05. The authors used I^2 statistics to estimate heterogeneity. The authors used the DerSimonian-Laird method to pool the results if I^2 was larger than 50%. Otherwise, the authors used the Mantel-Haenszel method to pool the results. The authors also conducted subgroup analyses by ethnicity. The authors examined stabilities of pooled results through omitting one study each time and pooling the results of the other studies. The authors examined publication biases through funnel plots.

Results

Characteristics of Included Studies

Two hundred and eighteen articles were retrieved by the authors through our literature search strategy. The authors assessed 41 articles for eligibility after omitting unrelated and repeated reports. Nine reviews and 2 studies with incomplete data were further excluded by the au-

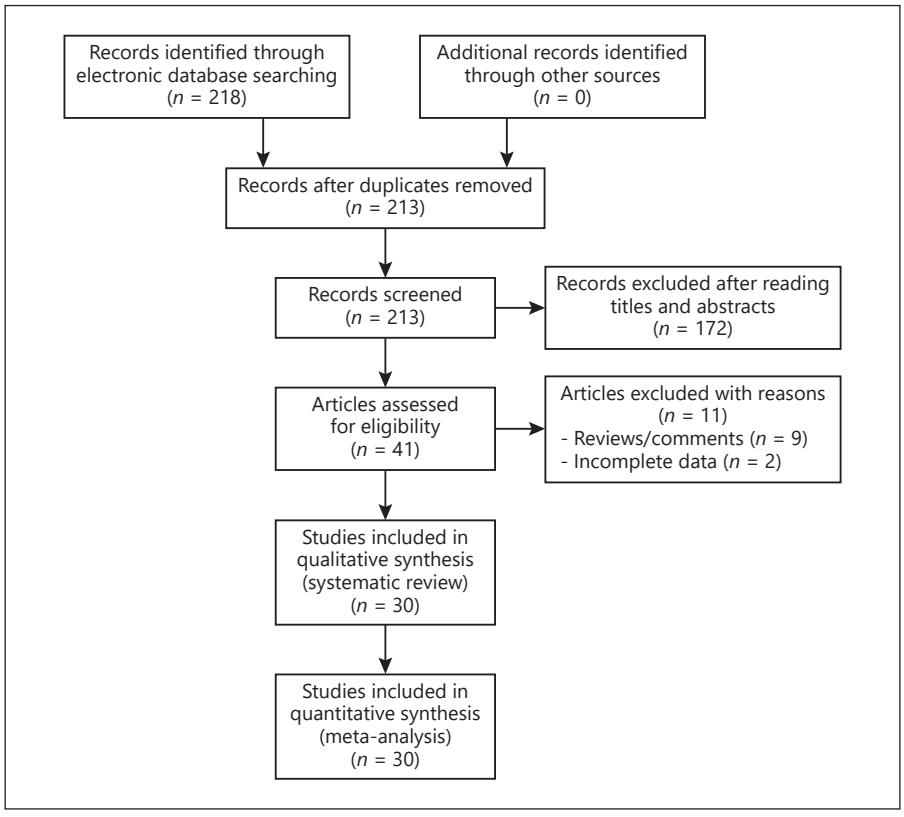

Fig. 1. Flowchart of the study selection for this meta-analysis.

thors. Totally 30 studies were finally pooled in our meta-analyses (Fig. 1). Extracted data of eligible studies are summarized in Table 1.

Meta-Analyses of TNF-α Polymorphisms and DN

Nineteen studies were eligible for estimation of the relationship between *TNF-α* polymorphisms and DN. *TNF-α* –238 G/A (dominant comparison: odds ratio, OR = 0.35, $p < 0.0001$; recessive comparison: OR = 3.57, $p < 0.0001$; overdominant comparison: OR = 2.37, $p < 0.0001$; allele comparison: OR = 0.40, $p < 0.0001$), –308 G/A (recessive comparison: OR = 1.68, $p < 0.0001$) and –1031 T/C (dominant comparison: OR = 0.52, $p < 0.0001$; overdominant comparison: OR = 1.60, $p < 0.0001$; allele comparison: OR = 0.51, $p = 0.02$) polymorphisms were all found to be significantly associated with DN in the overall pooled population. The pooled meta-analyses also revealed a similar positive association for –308 G/A polymorphism and DN in Asians, but not in Caucasians (Table 2).

Meta-Analyses of IL-1 Polymorphisms and DN

Eight studies were eligible for estimation of the relationship between *IL-1* polymorphisms and DN. *IL-1B* −511 C/T (dominant comparison: OR = 0.65, $p = 0.001$; recessive comparison: OR = 1.54, $p < 0.0001$; allele comparison: OR = 0.75, $p < 0.0001$) and *IL-1A* −889 C/T (dominant comparison: OR = 0.39, $p < 0.0001$; overdominant comparison: OR = 2.77, $p < 0.0001$; allele comparison: OR = 0.51, $p < 0.0001$) polymorphisms were found to be significantly associated with DN in the overall pooled population. The pooled meta-analyses also revealed a similar positive association for *IL-1B* −511 C/T polymorphism and DN in both Asians and Caucasians, but the pooled meta-analyses did not reveal any significant association for *IL-1B* –31 C/T polymorphism and DN (Table 2).

Meta-Analyses of IL-4 Polymorphisms and DN

Two studies were eligible for estimation of the relationship between the *IL-4* –590 C/T polymorphism and DN. The pooled meta-analyses did not reveal any significant association for the *IL-4* –590 C/T polymorphism and DN (Table 2).

Meta-Analyses of IL-8 Polymorphisms and DN

Two studies were eligible for estimation of the relationship between the *IL-8* –251 A/T polymorphism and

Table 1. The characteristics of included studies in this meta-analysis

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*p* value for HWE	NOS score
					cases	controls		
TNF-α –238 G/A rs361525					GG/GA/AA			
Fathy, 2019 [24]	Egypt	Mixed	DN	67/92	66/1/0	90/2/0	0.916	7
Hameed, 2018 [25]	India	Mixed	DN	448/878	228/184/36	660/197/21	0.174	7
TNF-α –308 G/A rs1800629					GG/GA/AA			
Babel, 2006 [26]	Germany	Caucasian	DN	44/113	34/7/3	76/33/4	0.859	7
Buraczynska, 2003 [27]	Poland	Caucasian	DN	37/115	22/13/2	86/24/5	0.066	8
Dabhi, 2015 [28]	India	Mixed	DN	188/235	160/24/4	191/44/0	0.113	8
Fathy, 2019 [24]	Egypt	Mixed	DN	67/92	48/16/3	79/12/1	0.488	7
Hameed, 2018 [25]	India	Mixed	DN	448/878	228/184/36	660/192/26	0.011	7
Krayenbuehl, 2007 [29]	Switzerland	Caucasian	DN	39/37	30/9/0	28/9/0	0.400	7
Kung, 2010 [30]	Taiwan	Asian	DN	24/48	24/0/0	48/0/0	n.a.	7
Lee, 2005 [31]	Korea	Asian	DN	122/125	116/6/0	108/17/0	0.415	7
Lindholm, 2008 [32]	Sweden	Caucasian	DN	427/780	254/152/21	443/292/45	0.732	7
Peng, 2015 [33]	China	Asian	DN	86/94	52/28/6	72/18/4	0.057	7
Prasad, 2007 [34]	India	Mixed	DN	196/224	178/16/2	195/27/2	0.336	8
Sikka, 2014 [35]	India	Mixed	DN	145/358	124/21/0	315/42/1	0.747	7
Song, 2018 [36]	China	Asian	DN	300/600	159/83/58	415/116/69	<0.001	7
Umapathy, 2018 [37]	India	Mixed	DN	342/414	181/95/66	288/79/47	<0.001	7
Wang, 2015 [38]	China	Asian	DN	388/323	326/62/0	261/62/0	0.056	7
Zhang, 2017 [39]	China	Asian	DN	113/108	38/53/22	25/63/20	0.079	7
TNF-α –1031 T/C rs1799964					TT/TC/CC			
Gupta, 2015 [40]	India	Mixed	DN	100/200	65/30/5	167/33/0	0.203	8
Hameed, 2018 [25]	India	Mixed	DN	448/878	170/215/63	463/331/84	0.030	7
IL-1A –889 C/T rs1800587					CC/CT/TT			
Dabhi, 2015 [28]	India	Mixed	DN	188/449	114/74/0	367/77/5	0.672	8
Loughrey, 1998 [41]	UK	Caucasian	DN	95/96	39/51/5	56/34/6	0.784	7
IL-1B –511 C/T rs16944					CC/CT/TT			
Buraczynska, 2019 [42]	Poland	Caucasian	DN	506/354	162/268/76	165/145/44	0.173	8
Hameed, 2018 [25]	India	Mixed	DN	448/878	220/188/40	443/380/55	0.025	7
Lee, 2004 [43]	Korea	Asian	DN	95/123	15/51/29	30/70/23	0.116	7
Lin, 2014 [44]	China	Asian	DN	262/327	50/131/81	76/180/71	0.067	8
Loughrey, 1998 [41]	UK	Caucasian	DN	95/96	44/44/7	63/31/2	0.415	7
Stefanidis, 2014 [45]	Greece	Caucasian	DN	173/186	71/77/25	104/66/16	0.243	7
IL-1B –31 C/T rs1143634					CC/CT/TT			
Hameed, 2018 [25]	India	Mixed	DN	448/878	196/200/52	394/369/115	0.054	7
Wang, 2014 [46]	China	Asian	DN	132/124	40/76/16	28/60/36	0.753	8
IL-4 –590 C/T rs2243250					CC/CT/TT			
Arababadi, 2010 [47]	Iran	Mixed	DN	100/150	69/29/2	108/38/4	0.766	7
Završnik, 2018 [48]	Slovenia	Caucasian	DN	276/375	186/81/9	236/129/10	0.119	8
IL-8 –251 A/T rs4073					AA/AT/TT			
Ahluwalia, 2009 [49]	India	Mixed	DN	240/255	103/96/41	130/107/18	0.525	7
Yahya, 2019 [50]	Malaysia	Asian	DN	131/125	45/66/20	45/66/14	0.162	7
Yahya, 2019 [50]	China	Asian	DN	108/95	43/57/8	35/50/10	0.202	7
IL-18 –137 G/C rs187238					GG/GC/CC			
Chen, 2013 [51]	China	Asian	DN	160/360	94/59/7	275/99/6	0.386	7
Kang, 2015 [52]	China	Asian	DN	170/400	96/61/13	279/106/15	0.223	7
Zhu, 2011 [53]	China	Asian	DN	52/155	28/14/10	117/33/5	0.175	7

HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; DN, diabetic nephropathy; n.a., not available.

Int Arch Allergy Immunol 2021;182:158–165
DOI: 10.1159/000510250

Table 2. Pooled meta-analysis results of the current study

Polymorphisms	Population	Sample size	Dominant comparison		Recessive comparison		Overdominant comparison		Allele comparison	
			p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
TNF-α –238 G/A	Overall	515/970	*<0.0001*	*0.35 (0.27–0.44)*	*<0.0001*	*3.57 (2.06–6.19)*	*<0.0001*	*2.37 (1.86–3.03)*	*<0.0001*	*0.40 (0.33–0.49)*
TNF-α –308 G/A	Overall	2,966/4,544	0.32	0.85 (0.61–1.17)	*<0.0001*	*1.68 (1.38–2.05)*	0.56	1.09 (0.81–1.47)	0.17	0.83 (0.64–1.09)
	Asian	1,033/1,298	0.95	0.98 (0.54–1.90)	*0.004*	*1.61 (1.17–2.22)*	0.82	0.94 (0.56–1.59)	0.87	0.96 (0.58–1.59)
	Caucasian	5,47/1,045	0.47	1.08 (0.87–1.34)	0.81	0.94 (0.58–1.52)	0.53	0.93 (0.75–1.16)	0.49	1.06 (0.89–1.27)
TNF-α –1031 T/C	Overall	548/1,078	*<0.0001*	*0.52 (0.42–0.64)*	0.29	4.04 (0.31–52.43)	*<0.0001*	*1.60 (1.29–1.98)*	*0.02*	*0.51 (0.29–0.89)*
IL-1A –889 C/T	Overall	283/545	*<0.0001*	*0.39 (0.28–0.53)*	0.37	0.61 (0.21–1.79)	*<0.0001*	*2.77 (2.01–3.81)*	*<0.0001*	*0.51 (0.39–0.67)*
IL-1B –511 C/T	Overall	1,579/1,964	*0.001*	*0.65 (0.50–0.84)*	*<0.0001*	*1.54 (1.26–1.89)*	0.26	1.17 (0.89–1.55)	*<0.0001*	*0.75 (0.68–0.83)*
	Asian	357/450	0.07	0.72 (0.51–1.02)	*0.001*	*1.69 (1.22–2.32)*	0.20	0.83 (0.63–1.10)	*0.002*	*0.74 (0.60–0.90)*
	Caucasian	774/636	*<0.0001*	*0.53 (0.43–0.66)*	*0.03*	*1.45 (1.04–2.02)*	*<0.0001*	*1.60 (1.29–1.99)*	*<0.0001*	*0.65 (0.55–0.76)*
IL-1B –31 C/T	Overall	580/1,002	0.86	1.02 (0.82–1.26)	0.23	0.56 (0.22–1.43)	0.15	1.17 (0.95–1.44)	0.35	1.26 (0.78–2.02)
IL-4 –590 C/T	Overall	376/525	0.45	1.11 (0.84–1.48)	0.82	1.10 (0.49–2.44)	0.39	0.88 (0.66–1.18)	0.56	1.08 (0.84–1.37)
IL-8 –251 A/T	Overall	479/475	0.21	0.85 (0.65–1.10)	0.30	1.49 (0.70–3.17)	0.61	0.94 (0.72–1.21)	0.31	0.85 (0.62–1.17)
IL-18 –137 G/C	Overall (Asian)	382/915	*<0.0001*	*0.48 (0.38–0.62)*	*<0.0001*	*3.01 (1.76–5.16)*	*0.001*	*1.52 (1.18–1.97)*	*<0.0001*	*0.43 (0.30–0.63)*

OR, odds ratio; CI, confidence interval. The italicized values represent there is statistically significant differences between cases and controls.

DN. The pooled meta-analyses did not reveal any significant association for the *IL-8* –251 A/T polymorphism and DN (Table 2).

Meta-Analyses of IL-18 Polymorphisms and DN

Three studies were eligible for estimation of the relationship between the *IL-18* –137 G/C polymorphism and DN. The *IL-18* –137 G/C polymorphism was found to be significantly associated with DN in Asians (dominant comparison: OR = 0.48, $p < 0.0001$; recessive comparison: OR = 3.01, $p < 0.0001$; overdominant comparison: OR = 1.52, $p < 0.0001$; allele comparison: OR = 0.43, $p < 0.0001$) (Table 2).

Sensitivity Analyses

Stabilities of pooled meta-analysis results were examined by omitting one study each time and pooling the results of the other studies. The trends of associations remained unchanged in sensitivity analyses, indicating that our pooled meta-analysis results were statistically stable.

Publication Biases

Publication biases were examined by funnel plots. Funnel plots were overall symmetrical, suggesting that our pooled meta-analysis results were not likely to be severely influenced by publication biases.

Discussion

The meta-analysis results demonstrated that *TNF-α* –238 G/A, *TNF-α* –308 G/A, *TNF-α* –1031 C/T, *IL-1A* −889 C/T, *IL-1B* −511 C/T and *IL-18* –137 G/C polymorphisms might influence susceptibility to DN in the overall pooled population. Moreover, we found that *TNF-α* –308 G/A, *IL-1B* −511 C/T and *IL-18* –137 G/C polymorphisms might influence susceptibility to DN in Asians, whereas the *IL-1B* −511 C/T polymorphism might also influence susceptibility to DN in Caucasians. The trends of associations remained unchanged in sensitivity analyses, suggesting that our pooled meta-analysis results were statistically quite stable.

A few points need to be considered when interpreting our findings. First, previous experimental studies have demonstrated that all investigated polymorphisms are correlated with altered gene expression or protein structure of corresponding cytokines [16, 17]. Thus, it is likely that these variations might influence normal functioning of *TNF-α/IL-1/IL-4/IL-8/IL-18*, lead to immune dysfunction and influence predisposition to DN. In this meta-analysis, we did not observe positive findings for *IL-4* and *IL-8* polymorphisms. Nevertheless, since only 2 studies were pooled and analyzed, maybe our pooled meta-analyses were still not statistically sufficient to detect the real associations between *IL-4/IL-8* polymorphisms and DN, and future studies in larger populations are still needed so as to get a statistically more robust finding. Second, the etiologies and pathogenesis mechanisms of DN are extremely sophisticated, so further association studies also need to investigate the potential influence of gene-gene interactions on predisposition to DN [18]. Third, we also aimed to analyze gene polymorphisms of other cytokines such as IL-6 and IL-10 at the beginning. However, since recent published meta-analyses already covered these polymorphisms, we did not perform repeated works for *IL-6* and *IL-10* polymorphisms in this meta-analysis [19, 20].

Like all meta-analyses, a few limitations of our pooled meta-analyses have to be acknowledged. Firstly, our pooled meta-analysis results were derived from pooling unadjusted findings since the authors did not have raw data of eligible studies [21]. Secondly, environmental factors might also influence relationships between *TNF-α/IL-1/IL-4/IL-8/IL-18* polymorphisms and DN. However, most investigators only focused on genetic associations in their works, so genetic-environmental interactions were not explored in this meta-analysis [22]. Thirdly, we did not consider gray literatures. Therefore, despite the fact that funnel plots were overall symmetrical, publication biases might still affect the robustness of our pooled results [23].

Conclusions

This meta-analysis demonstrated that *TNF-α* –238 G/A, *TNF-α* –308 G/A, *TNF-α* –1031 C/T, *IL-1A* −889 C/T, *IL-1B* −511 C/T and *IL-18* –137 G/C polymorphisms might influence predisposition to DN. These results also suggested that TNF-α, IL-1 and IL-18 might be involved in the development of DN, and they may serve as potential therapeutic targets for DN.

Statement of Ethics

Ethical approval and informed consent are not applicable to meta-analyses.

Disclosure Statement

There is no conflict of interest.

Author Contributions

Suqin Wang and Jiazhi Dong designed this meta-analysis. Suqin Wang and Jiazhi Dong searched the literature. Lingling Huang analyzed data. Suqin Wang and Jiazhi Dong wrote the manuscript. All authors approved the final paper as submitted.

References

1 Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, et al. Diabetic kidney disease. Nat Rev Dis Primers. 2015 Jul;1:15018.
2 Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017 Dec;12(12):2032–45.
3 Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016 Feb;12(2):73–81.
4 Tomino Y, Gohda T. The Prevalence and Management of Diabetic Nephropathy in Asia. Kidney Dis (Basel). 2015 May;1(1):52–60.
5 Gupta R, Misra A. Epidemiology of microvascular complications of diabetes in South Asians and comparison with other ethnicities. J Diabetes. 2016 Jul;8(4):470–82.
6 Sandholm N, Groop PH. Genetic basis of diabetic kidney disease and other diabetic complications. Curr Opin Genet Dev. 2018 Jun;50:17–24.
7 Florez JC. Genetics of Diabetic Kidney Disease. Semin Nephrol. 2016 Nov;36(6):474–80.
8 Dinarello CA. Role of pro- and anti-inflammatory cytokines during inflammation: experimental and clinical findings. J Biol Regul Homeost Agents. 1997 Jul-Sep;11(3):91–103.
9 Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest. 2007 May;117(5):1175–83.
10 Macisaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis. 2014 Feb;63(2 Suppl 2):S39–62.
11 Sangoi MB, de Carvalho JA, Tatsch E, Hausen BS, Bollick YS, Londero SW, et al. Urinary inflammatory cytokines as indicators of kidney damage in type 2 diabetic patients. Clin Chim Acta. 2016 Sep;460:178–83.
12 Hickey FB, Martin F. Diabetic kidney disease and immune modulation. Curr Opin Pharmacol. 2013 Aug;13(4):602–12.
13 Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. Clin Sci (Lond). 2013 Feb;124(3):139–52.
14 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009 Aug;151(4):264–9.
15 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010 Sep;25(9):603–5.
16 Smith AJ, Humphries SE. Cytokine and cytokine receptor gene polymorphisms and their functionality. Cytokine Growth Factor Rev. 2009 Feb;20(1):43–59.
17 Feitosa RN, Vallinoto AC, Vasconcelos PF, Azevedo RS, Azevedo VN, Machado LF, et al. Gene Polymorphisms and Serum Levels of Pro- and Anti-Inflammatory Markers in Dengue Viral Infections. Viral Immunol. 2016 Sep;29(7):379–88.
18 Nishi A, Milner DA Jr, Giovannucci EL, Nishihara R, Tan AS, Kawachi I, et al. Integration of molecular pathology, epidemiology and social science for global precision medicine. Expert Rev Mol Diagn. 2016;16(1):11–23.
19 Cui ZH, Lu XT, Xiao KL, Chen Y, Li HQ. Association of Interleukin-6 -174G/C Polymorphism with the Risk of Diabetic Nephropathy in Type 2 Diabetes: A Meta-analysis. Curr Med Sci. 2019 Apr;39(2):250–8.
20 Naing C, Htet NH, Basavaraj AK, Nalliah S. An association between IL-10 promoter polymorphisms and diabetic nephropathy: a meta-analysis of case-control studies. J Diabetes Metab Disord. 2018 Sep;17(2):333–43.
21 Yin F, Liu J, Fan MX, Zhou XL, Zhang XL. Association between the vitamin D receptor gene polymorphisms and diabetic nephropathy risk: A meta-analysis. Nephrology (Carlton). 2018 Feb;23(2):107–16.
22 Lin Z, Huang G, Zhang J, Lin X. Adiponectin gene polymorphisms and susceptibility to diabetic nephropathy: a meta-analysis. Ren Fail. 2014 Apr;36(3):478–87.
23 Ahmad N, Jamal R, Shah SA, Gafor AH, Murad NA. Renin-Angiotensin-Aldosterone System Gene Polymorphisms and Type 2 Diabetic Nephropathy in Asian Populations: An Updated Meta-analysis. Curr Diabetes Rev. 2019;15(4):263–76.
24 Fathy SA, Mohamed MR, Ali M A M. EL-Helaly A E, Alattar A T. Influence of IL-6, IL-10, IFN-γ and TNF-α genetic variants on susceptibility to diabetic kidney disease in type 2 diabetes mellitus patients. Biomarkers. 2018;32:1–38.
25 Hameed I, Masoodi SR, Malik PA, Mir SA, Ghazanfar K, Ganai BA. Genetic variations in key inflammatory cytokines exacerbates the risk of diabetic nephropathy by influencing the gene expression. Gene. 2018 Jun;661:51–9.
26 Babel N, Gabdrakhmanova L, Hammer MH, Schoenemann C, Skrypnikov V, Poliak N, et al. Predictive value of cytokine gene polymorphisms for the development of end-stage renal disease. J Nephrol. 2006 Nov-Dec;19(6):802–7.
27 Buraczynska K, Koziol-Montewka M, Majdan M, Ksiazek A. Polymorphisms of tumor necrosis factor and myeloperoxidase genes in patients with chronic renal failure on peritoneal dialysis. Mol Diagn. 2003;7(3-4):175–80.
28 Dabhi B, Mistry KN. Oxidative stress and its association with TNF-α-308 G/C and IL-1α-889 C/T gene polymorphisms in patients with diabetes and diabetic nephropathy. Gene. 2015 May;562(2):197–202.
29 Krayenbuehl PA, Wiesli P, Schmid M, Schmid C, Ehses JA, Hersberger M, et al. TNF-alpha -308G[{GT}]A polymorphism modulates cytokine serum concentrations and macrovascular complications in diabetic patients on aspirin. Exp Clin Endocrinol Diabetes. 2007 May;115(5):322–6.
30 Kung WJ, Lin CC, Liu SH, Chaung HC. Association of interleukin-10 polymorphisms with cytokines in type 2 diabetic nephropathy. Diabetes Technol Ther. 2010 Oct;12(10):809–13.
31 Lee SH, Lee TW, Ihm CG, Kim MJ, Woo JT, Chung JH. Genetics of diabetic nephropathy in type 2 DM: candidate gene analysis for the pathogenic role of inflammation. Nephrology (Carlton). 2005 Oct;10(s2 Suppl):S32–6.
32 Lindholm E, Bakhtadze E, Cilio C, Agardh E, Groop L, Agardh CD. Association between LTA, TNF and AGER polymorphisms and late diabetic complications. PLoS One. 2008 Jun;3(6):e2546.
33 Peng Y, Li LJ. TNF-α-308G/A polymorphism associated with TNF-α protein expression in patients with diabetic nephropathy. Int J Clin Exp Pathol. 2015 Mar;8(3):3127–31.
34 Prasad P, Tiwari AK, Kumar KM, Ammini AC, Gupta A, Gupta R, et al. Association of TGFbeta1, TNFalpha, CCR2 and CCR5 gene polymorphisms in type-2 diabetes and renal insufficiency among Asian Indians. BMC Med Genet. 2007 Apr;8(1):20.
35 Sikka R, Raina P, Matharoo K, Bandesh K, Bhatia R, Chakrabarti S, et al. TNF-α (g.-308 G [{GT}] A) and ADIPOQ (g. + 45 T [{GT}] G) gene polymorphisms in type 2 diabetes and microvascular complications in the region of Punjab (North-West India). Curr Eye Res. 2014 Oct;39(10):1042–51.

36 Song SX. Association between rs1800629 polymorphism of TNF - α gene and risk of diabetic nephropathy. Chinese PLA J Prev Med. 2018;36:343–6.
37 Umapathy D, Krishnamoorthy E, Mariappanadar V, Viswanathan V, Ramkumar KM. Increased levels of circulating (TNF-α) is associated with (-308G/A) promoter polymorphism of TNF-α gene in Diabetic Nephropathy. Int J Biol Macromol. 2018 Feb;107 Pt B: 2113–21.
38 Wang Y, Ng MC, So WY, Ma R, Ko GT, Tong PC, et al. Association between tumour necrosis factor-α G-308A polymorphism and risk of nephropathy in obese Chinese type 2 diabetic patients. Nephrol Dial Transplant. 2005 Dec;20(12):2733–8.
39 Zhang L, Li Y, Jia PJ, Du JC. Association between TNF-α G-308A gene polymorphism and type 2 diabetic nephropathy. J Trop Med. 2017;17:1465–8.
40 Gupta S, Mehndiratta M, Kalra S, Kalra OP, Shukla R, Gambhir JK. Association of tumor necrosis factor (TNF) promoter polymorphisms with plasma TNF-α levels and susceptibility to diabetic nephropathy in North Indian population. J Diabetes Complications. 2015 Apr;29(3):338–42.
41 Loughrey BV, Maxwell AP, Fogarty DG, Middleton D, Harron JC, Patterson CC, et al. An interluekin 1B allele, which correlates with a high secretor phenotype, is associated with diabetic nephropathy. Cytokine. 1998 Dec; 10(12):984–8.
42 Buraczynska M, Ksiazek K, Wacinski P, Zaluska W. Interleukin-1β Gene (IL1B) Polymorphism and Risk of Developing Diabetic Nephropathy. Immunol Invest. 2019 Aug; 48(6):577–84.
43 Lee SH, Ihm CG, Sohn SD, Lee TW, Kim MJ, Koh G, et al. Polymorphisms in interleukin-1 β and Interleukin-1 receptor antagonist genes are associated with kidney failure in Korean patients with type 2 diabetes mellitus. Am J Nephrol. 2004 Jul-Aug;24(4):410–4.
44 Lin NB, Tang XP, Cao Y, Chen Z, Wan Q. The relationship between interleukin-1-511 (C / T) gene polymorphism and early diabetic nephropathy. Chinese. J Diabetes. 2014;5:407–11.
45 Stefanidis I, Kreuer K, Dardiotis E, Arampatzis S, Eleftheriadis T, Hadjigeorgiou GM, et al. Association between the interleukin-1β Gene (IL1B) C-511T polymorphism and the risk of diabetic nephropathy in type 2 diabetes: a candidate-gene association study. DNA Cell Biol. 2014 Jul;33(7):463–8.
46 Wang YX, Bian C, Chi XM, Zhao Y, Suo LN. Relationship between interleukin-1 gene rsl143627c / T polymorphism and type 2 diabetic nephropathy. Med Clin Res. 2014;39: 1684-6.
47 Kazemi Arababadi M. Interleukin-4 gene polymorphisms in type 2 diabetic patients with nephropathy. Iran J Kidney Dis. 2010 Oct;4(4):302–6.
48 Zavrnik M, Letonja J, Makuc J, Seruga M, CilenSek L, Petrovic D. Interleukin-4 (IL4) -590C/T (rs2243250) gene polymorphism is not associated with diabetic nephropathy (DN) in Caucasians with type 2 diabetes mellitus (T2DM). Bosn J Basic Med Sci. 2018;18: 347-51.
49 Ahluwalia TS, Khullar M, Ahuja M, Kohli HS, Bhansali A, Mohan V, et al. Common variants of inflammatory cytokine genes are associated with risk of nephropathy in type 2 diabetes among Asian Indians. PLoS One. 2009; 4(4):e5168.
50 Yahya MJ, Ismail PB, Nordin NB, Akim AB, Yusuf WS, Adam NL, et al. Association of CCL2, CCR5, ELMO1, and IL8 Polymorphism with Diabetic Nephropathy in Malaysian Type 2 Diabetic Patients. Int J Chronic Dis. 2019 Jan;2019:2053015.
51 Chen JN. Study on the relationship between IL18 genotype and serum level and type 2 diabetic nephropathy. J Guilin Med Univ. 2013: 1-50.
52 Kang L. Relationship between interleukin-18, interleukin-6 gene polymorphism and type 2 diabetic nephropathy. J Hebei Med Univ. 2015:1-30.
53 Zhu LL. Association between 137c / G polymorphism of IL18 gene promoter and type 2 diabetic nephropathy. J Guilin Med Univ. 2011:1-38.