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REVIEW ARTICLE

An association between IL-10 promoter polymorphisms and diabetic nephropathy: a meta-analysis of case-control studies

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Abstract

Background This study aimed to synthesize evidence on the association between IL-10 gene (−819 C/T, −1082 A/G, −592 A/C) polymorphisms and the risk of developing diabetic nephropathy.

Methods A systematic literature search was done in health-related electronic databases. The search was limited to studies published in English until September 2017. We also checked the references of retrieved articles and relevant reviews for any additional studies. The methodological quality of the studies included in this review was assessed using the 'Scales for Quality Assessment'. The I^2 test was used to quantify between-study heterogeneity. A value of $I^2 > 50\%$ indicated substantial heterogeneity. For the pooled analysis, summary odds ratio (OR) and its 95% confidence interval (CI) in random effect model were used.

Results Eight case-control studies (1192 cases with diabetic nephropathy and 2399 controls) met the inclusion criteria. Three groups of people namely Africans, Asians and Caucasians were included in this review. There were significant protective effects of SNP -819 C/T in overall population (OR 0.32, 95% CI 0.26–0.4) and − 1082 A/G SNP in the Asian population (OR 0.64, 95% CI 0.47–0.86) on diabetic nephropathy in the recessive model. There was no significant effect of −592 A/C on diabetic nephropathy.

Conclusion The findings suggest the protective effects of −1082A/G and -819G/A polymorphisms on the risk of developing diabetic nephropathy in type 2 diabetes mellitus, especially in the Asian population. Well- designed, prospective studies with sufficient number of participants are recommended to substantiate these findings.

Keywords Interleukin-10 · Diabetes mellitus · Nephropathy · Association · Meta-analysis

Norah Htet Htet and Arun Kumar Basavaraj contributed equally to this work.

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Background

Type 2 diabetes mellitus (T2DM) is the most common type of glucose intolerance, constituting 90% of all cases. This complex disorder might be related to an interaction between genes and environment [1]. Inflammatory markers like cytokines have been proposed in the development of T2DM. Of these cytokines, interleukin (IL)-10, a potent anti-inflammatory and immunosuppressive cytokine, is produced mainly by macrophages apart from numerous other cells such as Th2 cells, dendritic cells, B-cells, monocytes, neutrophils, eosinophils, and mast cells [2]. IL-10 is essential for the regulation of immune responses [3] by promoting the widespread suppression of immune responses through its pleiotropic effects [4]. It is known that dysregulation of IL-10 is associated with an enhanced immunopathological response to infection as well as an increased risk for the development of many autoimmune diseases [5].

Although about 99% of human genes are shared across the same population, variations in sequence may have significant predictive relevance. Single nucleotide polymorphisms

(SNPs) are sequence variations that occur when a single nucleotide in the genome is altered [6, 7]. It is known that the IL-10 locus is highly polymorphic, and more polymorphic elements may well exist [8]. Several IL-10 genes implicated to affect IL-10 transcription and secretion include −819 C/T, −1082 A/G and − 592 C/A promoter SNPs [9–11].

More than half of the individuals with diabetes mellitus will develop overt kidney disease over time [12, 13], suggesting that host genetic susceptibility may play an important role in diabetic nephropathy risk among different ethnic groups. Diabetic nephropathy is the primary cause of end stage renal disease and is broadly associated with a state of inflammation. As such, IL-10 is thought to play a key role because a significant difference is found between serum levels of IL-10 in T2DM patients compared to the healthy controls [14].

There has been a recent increase in published studies, assessing the association between IL-10 polymorphisms and the risk of diabetic nephropathy. However, individual studies were done with relatively small samples and variation in ethnicity of participants, SNPs targeted and results. This has stimulated us to conduct a meta-analysis, as described elsewhere [15]. Taken together, the objectives of the present study was to synthesize evidence on the association between IL-10 gene polymorphisms (−1082 A/G, −819 C/T, −592 C/A) and the risk of developing diabetic nephropathy.

Methods

Search strategy

One investigator searched the relevant studies in health-related electronic database such as MEDLINE, EMBASE, Web of Science, Google Scholar, the Latin American and Caribbean Health Sciences Literature (LILACS), African Journals online (AJOL) and BIOSIS databases. We used the following Medical Subject Heading (MeSH) AND/OR text words in any field, "(interleukin-10 OR IL-10 OR IL-10 gene OR -1082A/G OR -592C/A OR -819 C/T)" AND "(type 2 diabetes OR diabetes mellitus OR diabetes OR T2DM OR diabetic nephropathy)." Search strategy was slightly adjusted according to the requirement of different databases. The search was limited to studies published in English until September 2017. We also checked the references of retrieved articles and relevant reviews for any additional studies.

Selection criteria

Studies assessing IL-10 SNPs in patients with T2DM were included in the present meta-analysis if:

i) it was a case-control or nested case-control study,
ii) these were human cases with diabetic nephropathy compared with controls (healthy controls or T2DM without diabetic nephropathy),
iii) there were sufficient data to assess genotype frequencies for cases and controls,
iv) there was sufficient information to extract an odds ratio (OR) and its 95% confidence intervals (CI) (or raw data to compute OR and its 95%CI were provided).

Studies were excluded, if they did not meet the inclusion criteria.

Data extraction

Two investigators (CN and NHH) independently screened the titles, abstracts and assessed the full-text, if deemed relevant for this review. Any discrepancy was resolved by discussion. The selected full-text articles were reviewed to determine their eligibility for the current review. The key information from the included studies were extracted using a piloted data extraction sheet. Information collected were first author, year of publication, country, ethnic descent, percentage of male participants, number of cases and controls, genotype frequency, duration of diabetes and co-morbid illness.

The methodological quality of the studies included in the present review was assessed using the 'Scales for Quality Assessment' [16, 17] with necessary modification. The criteria consists of credibility of controls, representativeness of cases, consolidation of diabetic nephropathy, genotyping examination and association assessment. Total scores ranged from 0 (the worst) to 15 (the best). Studies with score ≥10 were regarded as 'high quality'.

Statistical analysis

The exact test for goodness of fit was used to inspect whether genotype frequencies of the control population conformed to Hardy-Weinberg equilibrium (HWE) [17, 18]. For dichotomous outcome (i.e. with diabetic nephropathy vs without diabetic nephropathy or the healthy controls), data from each study were extracted as the number of cases corresponding to each genotype (e.g. AA, AC, CC for −592 A/C) in cases and control groups. Described elsewhere [17], the strength of the association between each polymorphism and the risk of diabetic nephropathy was estimated using pooled OR and its 95% CI.

We considered the recessive model (as any trait, which expressed in a homozygote; two copies of that allele are necessary to manifest its effect), the dominant model (as described any trait, which expressed in a heterozygote; one copy of that allele is sufficient to manifest its effect) and the allele contrast model (one of several variants of a gene, usually referring to a specific site within the gene). Detailed

descriptions of these genetic models are available elsewhere [17, 19]. Using a recessive model as an example, data from AC and CC were collapsed and compared to AA group for −592 A/C. For −1082 A/G, AG and GG were collapsed and compared to AA group, while CT and TT were collapsed and compared to CC group in −819 C/T.

Statistical heterogeneity of the included studies was assessed with the I^2 test [15]. The value of I^2 test greater than 50% was regarded as substantial heterogeneity. For pooling of the studies, we used random effect model (DerSimonian-Laird method), if there were substantial between-study heterogeneity. Otherwise, fixed effect model (Mantel-Haenszel method) was used [15]. Considering the variation among ethnic descent, we stratified the analyses by three groups of people (i.e. Caucasians, Asians, and African populations) and further stratified on the basis of comparators (i.e. diabetes without nephropathy or healthy controls). We also performed cumulative meta-analysis to inspect the trend and stability of risk effect as evidence accumulated [20]. For sensitivity analysis, leave-one-out meta-analysis was done by removing one study at a time [15]. Publication bias was qualitatively assessed by visual inspection of a funnel plot and quantitatively with the Egger's test [21]. Meta-analysis was done with *R* version 3.4.3 (*R* Foundation for Statistical Computing, Vienna) and RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen).

Availability of data and material Data supporting the results were reported in the manuscript.

Results

The four-phase study selection process is presented in Fig. 1. An initial search yielded 266 citations. After screening of titles/abstracts and removal of duplicates, 15 studies were potentially relevant, and a final of 8 case-control studies (with 12 datasets) [22–29] met the pre-specified criteria. The agreement between the two investigators was substantial (kappa statistics 0.87). The excluded studies were those which did not provide sufficient data on SNPs [30, 31], did not give a separate data on diabetic nephropathy or did not assess diabetic nephropathy [32–35] and was a duplicate study [36].

Characteristics of the included studies (Table 1)

These studies included a total of 1192 cases with diabetic nephropathy and 2399 controls (i.e. diabetes without nephropathy and healthy controls) and all participants were adults with male predominance (62%). The publication year of the individual studies in this review spanned from 2006 to 2016. Two studies were done in China [27, 28], one study each was in Iran [26], Turkey [25], Taiwan [24], Egypt [29], Tunisia [24] or Germany [22]. Only five studies provided information on diagnosis of T2DM; three studies [23, 27, 28] used the WHO 1999 criteria [37], while the remaining two studies [25, 29] used the criteria of American Diabetes Association [38]. All these eight studies confirmed diabetic nephropathy based on proteinuria and glomerular filtration rate.

Four studies (905 cases and 1862 controls) assessed the associations between −819 C/T and diabetic nephropathy [23, 24, 27, 28]. Six studies (992 cases and 2199 controls) assessed the association between −1082 A/G and diabetic nephropathy [22–25, 27, 28]. Six studies (1105 cases and 2062 controls) assessed the association between −592 A/C and diabetic nephropathy [23, 24, 26–29].

In general, the methodological quality of these studies was moderate to high. The majority of studies included (62.5%) were in the category of high quality studies [22, 23, 26–28] (Additional File 1).

Quantitative data synthesis

All, except three studies [23–25] had HWE (Table 2). Quantitative synthesis was possible for four studies with IL-10 gene −819 G/A polymorphism [23, 24, 27, 28], six studies each with −1082 A/G [22–25, 27, 28] or − 592 A/C polymorphisms [23, 24, 26–29].

Allele contrast model

For −819 C/T, four studies [23, 24, 27, 28] assessed the association between the allele contrast (allele C vs T) and the risk of diabetic nephropathy. Overall, there was no significant association between this SNP and diabetic nephropathy (pooled OR: 1.17, 95% CI: 0.91–1.51 (Fig. 2a). However, a subset of three studies with the Asian population group showed a significant association; an increase of 36% increase in the risk of diabetic nephropathy (pooled OR: 1.36, 95% CI: 1.14–1.61). Six studies provided data for −1082 G/A [22–25, 27, 28]. Overall, there was no significant association between this SNP and diabetic nephropathy, regardless of population group (pooled OR: 0.97, 95% CI:0.97–1.24) (Fig. 2b). Six studies provided data on −592 A/C [23–25, 27–29]. Overall, there was no significant association of the allele contrast with the risk of diabetic nephropathy, regardless of population group (pooled OR: 0.99 , 95% CI:0.84 –1.17) (Fig. 2c).

SNP (−819 C/T)

Four studies assessed this SNP [23, 24, 27, 28]. In the dominant model, overall, there was no significant association between this SNP and diabetic nephropathy, regardless of population group (pooled OR: 0.93, 95% CI: 0.74–1.18) and in the absence of heterogeneity (I^2: 0%). In the recessive model, overall, there was a moderate level protective effect on the risk of diabetic nephropathy (pooled OR: 0.32, 95% CI: 0.26–0.4)

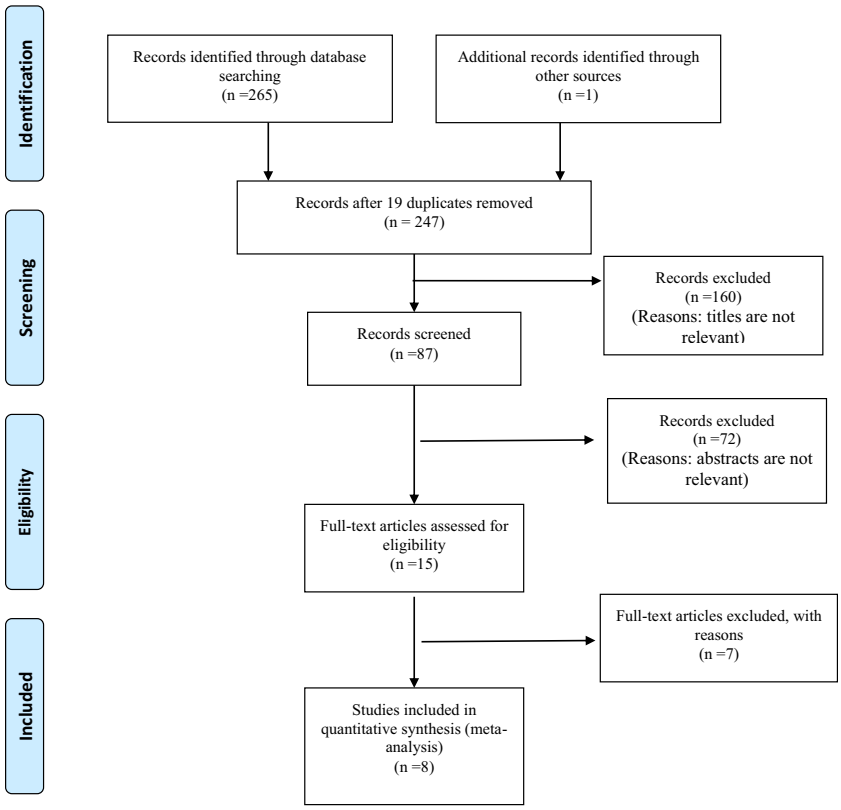

Fig. 1 Study selection flow diagram

with substantial heterogeneity (I^2: 97%); however, no significant association was found in a subset of three studies [24, 27, 29] with the Asian population (pooled OR: 1.06, 95% CI: 0.75–1.49) (Table 3).

SNP (−1082 A/G)

Six studies provided data for this SNP [22–25, 27, 28]. Using the dominant model, there was no significant association

Table 1 Characteristics of the studies included in meta-analysis

Study [Ref No]	Country	Study period	Age group	Ethnicity	Cases[a]/controls	Female %	Diagnosis[b]	Diagnosis of DN	IL-10 SNP	Genotyping methods
Babel 2006 [22]	Germany	NA	adults	Caucasian	44/ (DWN: 59)/ (H:118)	39	NA	NA	-1082 A/G	PCR-RFLP
Ezzidi 2009 [23]	African	NA	adults	African	515/(DWN:402)/(H: 748)	50.1	WHO,1999	AER	All 3 SNPs	PCR-ASA
Kung 2010 [24]	Taiwan	NA	adults	Asian	24/(DWN:23)/(H:25)	37.5	BG, Hb A1c	NA	All 3 SNPs	PCR-RFLP
Erdogan 2011 [25]	Turkey	NA	adults	Asian	43/ (DWN: 48)/ (H:112)	NA	ADA	AER	-1082 A/G	PCR-RFLP
Arababadi 2011 [26]	Iran	NA	adults	Asian	100/(DWN100/(H:100)	59	BG	PTU, GFR	-592 A/C	PCR-RFLP
Yin 2015 [27]	China	3/2012–10/2014	adults	Asian	172/(H: 344)	62.8	WHO 1999	PTU, GFR	All 3 SNPs	PCR-RFLP
Ma 2016 [28]	China	5/2012–8/2014	adults	Asian	194/(H: 320)	39.2	WHO 1999	PTU, GFR	All 3 SNPs	PCR-RFLP
Mahmoud 2016 [29]	Egypt	NA	adults	African	100/(DWN 100)	40%	ADA	GFR	-592 A/C	PCR-RFLP

HT, hypertension in patients with diabetes mellitus; *PTU*, proteinuria <500 mg/24; *GFR*, glomerular filtration rate <25 ml/min; *Diagnosis,* Diagnostic criteria for diabetes mellitus; *Duration,* mean year of duration (±standard deviation) of diabetes; *ADA,* Criteria of the American Diabetes Association; *AER,* Albumin excretion rate; *ASA,* Allele-specific Amplification; *BG,* Blood glucose >130 mg/dl; *DWN,* diabetes without nephropathy; *DN,* diabetic nephropathy; *H,* healthy controls; *Hb A_{1c}*, Glycosylated haemoglobin A1c; *RELP,* Restriction fragment length polymorphism

[a] cases with diabetic nephropathy

[b] diagnosis of type 2 diabetes mellitus

Table 2 Distribution of IL-10 gene polymorphisms included in the meta-analysis

Study [ref no]	IL-10	Cases				Controls				HWE, *p* value[b]	Remark
	-1082A/G	GG	GA	AA	N	GG	GA	AA	N		
Yin 2015 [27]		66	80	26	172	163	153	27	343	0.28	DN vs controls with free of diabetes mellitus
Ma 2016 [28]		71	94	29	194	154	141	25	320	0.35	DN vs healthy controls
Erdogan 2011 [25]		0	31	12	43	0	38	10	48	<0.001	DN vs DWN
Kung 2010 [24]		–	24	0	24	–	25	0	25	<0.001	DN vs healthy controls
Kung 2010 [24]		–	24	0	24	–	21	2	23	<0.001	DN vs DWN
Babel 2006 [22]		24	8	12	44	42	42	30	118	0.006	DN vs healthy controls
Babel 2006 [22		24	8	12	44	36	12	11	59	<0.001	DN vs DWN[a]
Ezzidi 2009 [23]		217	239	59	515	316	326	106	748	0.14	DN vs healthy controls
Ezzidi 2009 [23]		217	239	59	515	153	187	62	402	0.7	DN vs DWN
	-819 T/C	TT	TC	CC	N	TT	TC	CC	N		
Kung 2010 [24]		–	24	0	24	0	24	1	25	<0.001	DN vs healthy controls
Kung 2010 [24]		–	24	0	24	0	23	0	23	<0.001	DN vs DWN
Yin 2015 [27]		57	77	38	172	127	150	67	344	0.062	DN vs controls with free of diabetes mellitus
Ma 2016 [28]		65	90	39	194	121	142	57	320	0.18	DN vs healthy controls
Ezzidi 2009 [23]		32	184	299	515	32	228	488	748	0.41	DN vs healthy controls
Ezzidi 2009 [23]		32	184	299	515	30	173	199	402	0.36	DN vs DWN
	-592 A/C	AA	AC	CC	N	AA	AC	CC	N		
Kung 2010 [24]		7	13	4	24	–	24	1	25	<0.001	DN vs healthy controls
Kung 2010 [24]		7	13	4	24	–	23	0	23	<0.001	DN vs DWN
Mahmoud 2016 [29]		52	38	10	100	48	40	12	100	0.42	DN vs DWN
Ezzidi 2009 [23]		54	214	247	515	47	298	403	748	0.41	DN vs healthy controls
Ezzidi 2009 [23]		54	214	247	515	43	181	178	402	0.45	DN vs DWN
Yin 2015 [27]		67	79	26	172	132	155	57	344	0.32	DN vs controls with free of diabetes mellitus
Ma 2016 [28]		69	90	35	194	126	144	50	320	0.41	DN vs healthy controls
Arababadi 2011 [26]		6	47	47	100	4	36	60	100	0.62	DN vs DWN

DN, Diabetic with nephropathy; *DWN*, Diabetes without nephropathy; *HWE*, Hardy-Weinberg equilibrium; IL-10 = IL-10 polymorphisms

[a] chronic glomerulonephritis

[b] for control group

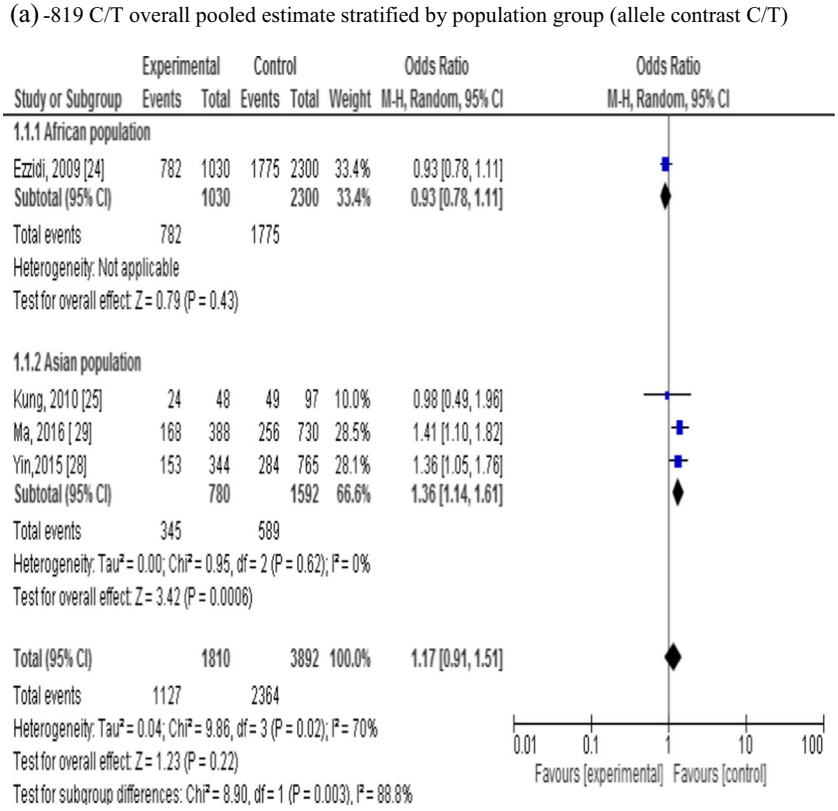

Fig. 2 Allele contrast models assessing IL-10 polymorphisms and the risk of diabetic nephropathy

b) -1082 A/G overall pooled estimate stratified by population group (allele contrast A/G)

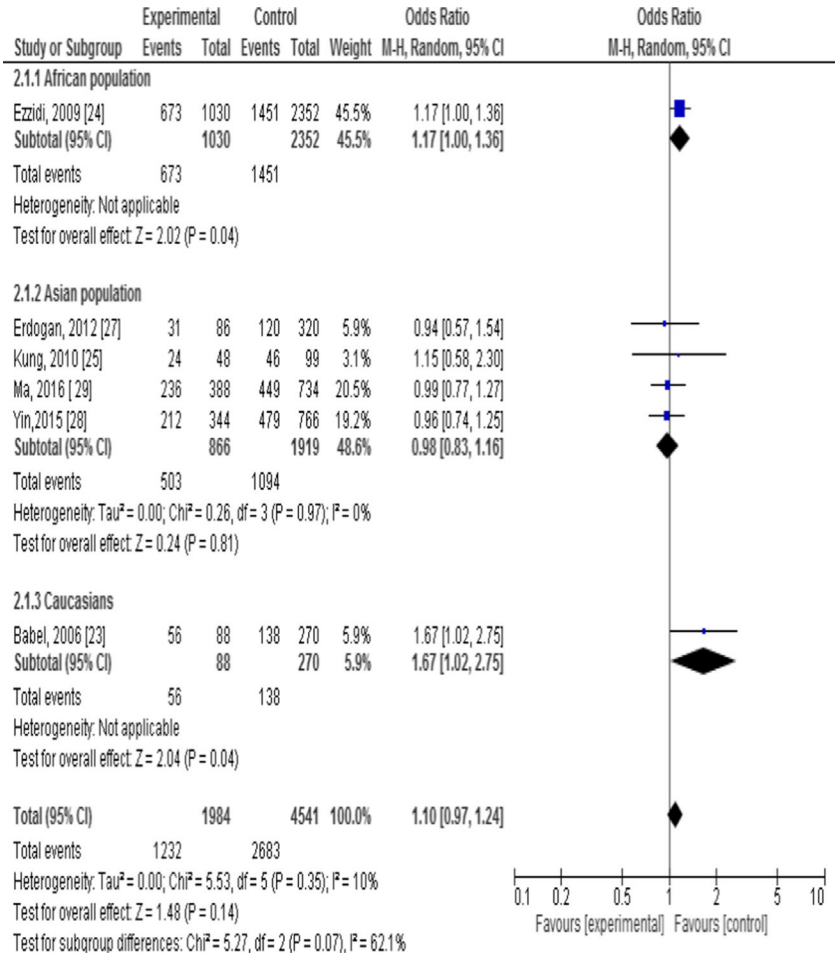

Fig. 2 (continued)

between this SNP and the risk of developing diabetic nephropathy, regardless of population group (pooled OR: 0.9, 95% CI: 0.43–1.91). Using the recessive model, there was significant protective effect of this SNP on diabetic nephropathy in the Asian group (pooled OR: 0.64, 95% CI: 0.47–0.86) with I^2 14.7% (Table 3).

SNP (−592 A/C)

Six studies with 9 datasets assessed this SNP [23, 24, 26–29]. Using the dominant model, there were no significant associations between this SNP and the risk of diabetic nephropathy compared to those without nephropathy or healthy controls (pooled OR: 1.31, 95% CI: 0.83–2.07), regardless of population group. So was the recessive model (pooled OR: 1.06, 95% CI: 0.71–1.58) (Table 3).

Cumulative meta-analyses of polymorphism association was conducted with all studies included in this review in the light of publication time and total number of sample size. As shown in Fig. 3 for −1082 G/A recessive model, there was a trend of association between diabetic nephropathy and comparators (diabetes without nephropathy/healthy controls) as evidence accumulates. A leave-one-out meta- analysis with −1082 A/G in the dominant model remained with the status of no significant association between this SNP and the risk of diabetic nephritic (Additional File 2). This was also true for −819 C/T and − 592 A/C SNPs (not shown). This implied that the results seems to be stable.

For −1082 A/G, its funnel plot (Fig. 4) showed that larger studies were published later, suggesting there was a publication bias. This was also true for −819 C/T and − 592 A/G (not shown).

Discussion

The current study has attempted to provide evidence on the relationship between the selected SNPs (−819 C/T, −1082

c) -592 A/C overall pooled estimate stratified by population group (allele contrast A/C)

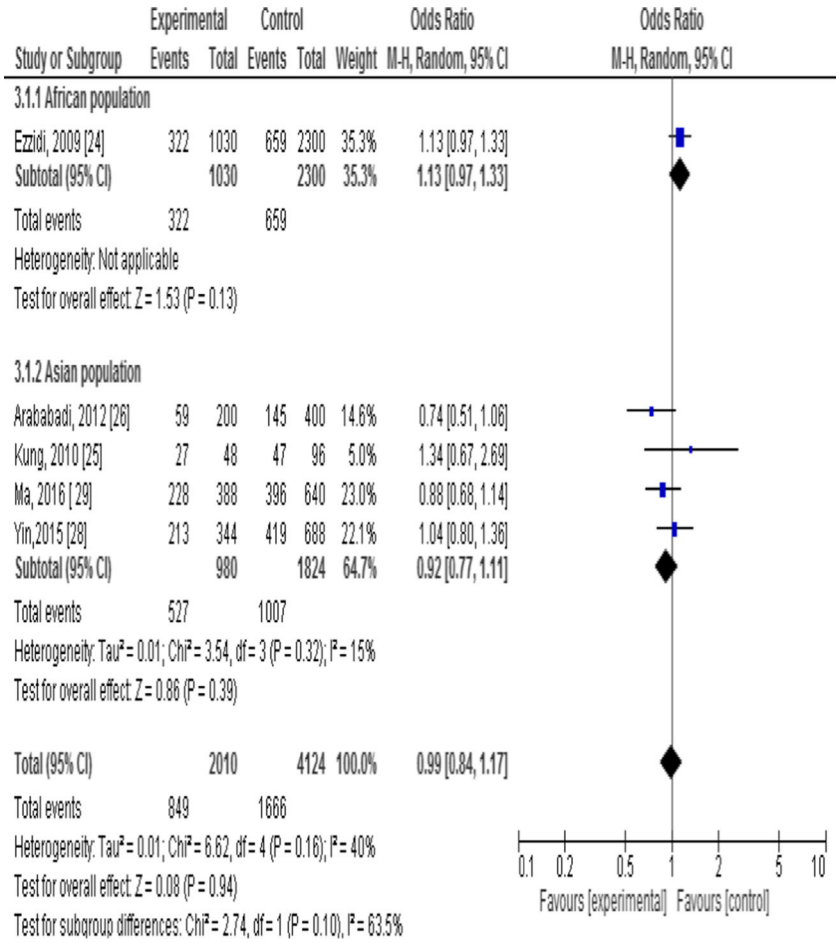

Fig. 2 (continued)

A/G, −592 A/C) and the risk of diabetic nephropathy. The impact of dominant, recessive and allele genetic models were evaluated.

The major observations were

i. Three categories of population group i.e. Africans, Asians and Caucasians were included in this meta-analysis.
ii. There were significant protective effects of SNP -819 C/T in overall population and − 1082 G/A SNP in the Asian population on diabetic nephropathy in the recessive model.
iii. Allele contrast models showed a significant association of SNPs −1082 G/A with increase in the risk of diabetic nephropathy in the Asian group.

Since cytokine genetic variability of IL-10 leads to a diverse immune and inflammatory responses, a detailed analysis of polymorphisms in cytokine genes may be crucial for understanding the mechanisms underlying initiation and progression of renal disease and eventual kidney failure [22]. The findings of an association between the IL-10 (−1082 A/G, −819 C/T) polymorphisms and diabetic nephropathy pertinent to the Asian group support that genetic diversity among ethnicities do exist. However, environmental factors may also play an important role in etiology as T2DM is a multifactorial disease. Thus, the association may also be linked to climate, diet, lifestyle and economic status [20] other than genetic diversity. However, this potential confounding was less likely as we may assume similar baseline levels of lifestyle factors among participants in the particular ethnic group.

An earlier review showed −1082 G/A and − 819 C/T in the IL-10 gene had potential protective effects in the development of T2DM [39]. The present analysis focused on the development of an end stage renal disease in T2DM, pertinent to diabetic nephropathy, and the pooled analyses showed the similar protective effect with −1082 A/G and − 819 C/T SNPs, using the recessive model for the Asian people. A protective effect of −1082 G/A (as well as −819 C/T in this case) might be due to the regulation of serum IL-10 concentrations often "track" pathogen burdens [40]. No significant associations between −592 C/A polymorphism and diabetic nephropathy could be related to a production property of IL-10.

Table 3 Subgroup analysis of the association between the three SNPs and the risk of diabetic nephropathy

Description	Genetic model	Reference no. of the included studies	Pooled odds ratio	95% CI	I^2 value	Remarks
SNP −819 C/T						
Overall	Dominant	23, 24, 27, 28	0.93	0.74–1.18	0%	Absence of between -study heterogeneity
Asian population		24, 27, 28	0.86	0.65–1.12	0%	Absence of between -study heterogeneity
Overall	Recessive	23, 24, 27, 28	0.32	0.26–0.4	97%	Pooled effect estimate of all four included studies Substantial between -study heterogeneity
Asian population		24, 27, 28	1.06	0.75–1.49	87.1%	Pooled effect estimate of three included studies Substantial between -study heterogeneity
SNP −1082 A/G						
Overall	Dominant	22–28	0.9	0.43, 1.91	87%	Pooled effect estimate of all six included studies, regardless of ethnic groups. Substantial between -study heterogeneity
Asian population		24,25,27,28	1.1	0.44–2.76	80.2%	Pooled effect estimate of four included studies Substantial between -study heterogeneity
Overall	Recessive	22–28	0.46	0.12–2.13	95.6%	Pooled effect estimate of all six included studies, regardless of ethnic groups. Substantial between -study heterogeneity
Asian population		25, 27, 28	0.64	0.47–0.86	14.7%	Pooled effect estimate of three included studies. Very low substantial between -study heterogeneity
SNP -592 A/C						
Overall	Dominant	23,24,26,27,28,29	1.31	0.83–2.07	81.7%	Pooled effect estimate of all six included studies, regardless of the type of controls and ethnic groups. Substantial between -study heterogeneity
Compared with healthy controls		23,24,26,27,28	2.25	0.9–5.6	89.3%	Pooled effect estimate of five included studies, regardless of ethnic groups. Substantial between -study heterogeneity
Compared with those who had not diabetes nephropathy		23,24,26,29	0.93	0.55–1.57	57.9%	Pooled effect estimate of four included studies, regardless of ethnic groups. Substantial between -study heterogeneity
Overall	Recessive	23,24,26,27,28,29	1.06	0.71–1.58	71.6%	Pooled effect estimate of all six included studies, regardless of the type of controls and ethnic groups. Substantial between -study heterogeneity
Compared with healthy controls		23,24,26,27,28	0.94	0.51, 1.73	83%	Pooled effect estimate of five included studies, regardless of ethnic groups. Substantial between -study heterogeneity
Compared with those who had not diabetes nephropathy		23,24,26,29	1.19	0.74–1.91	33%	Pooled effect estimate of four included studies, regardless of ethnic groups. Low between -study heterogeneity

A published review by Zhang and associates showed that −592 C/A SNP was not associated with the risk of T2DM [40]. In the current meta-analysis, −592 A/C was also not associated with the risk of developing diabetic nephropathy. To a certain extent, we could summarize that −592 A/C had neither the causative nor protective role in the development of diabetic nephropathy in these population groups. This can be partly explained by the fact that the immune activation in diabetic nephropathy does not seem to be dependent on antigenic stimulation, rather a consequence of chronic state of hyperglycemia. The advanced glycation end products induce inflammatory immune responses that contribute to the growth of ~~the~~ cortical fibroblasts, collagen synthesis and damage to the proximal tubular epithelial cells [41]. Moreover, cytokines do not act in isolation but regulate both themselves and each other, and thus the net cytokine milieu is the product of many interacting proteins. [22]. It is likely that this cytokine or interactions with other cytokines has not attained significant thresholds among these participants. Another possible reason is that participants in the primary studies had good renal function/renal reserves at the time of analysis, prior to development of subsequent pathological events on kidneys. Diabetic nephropathy is recognized as a devastating disease, persists for a long time as relatively mild, and is a systematic inflammatory process [42]. A study had reported that patients with prolonged diabetic nephropathy had relatively well preserved renal function in relation to the protective role of high concentrations of IL-10 [41].

Study limitations

This study has several limitations. If cases and controls have been genotyped in separate batches in the primary studies, differential misclassification of exposure is a concern. Due to small sample sizes with a few number of included studies, it was under powered to detect statistically significant

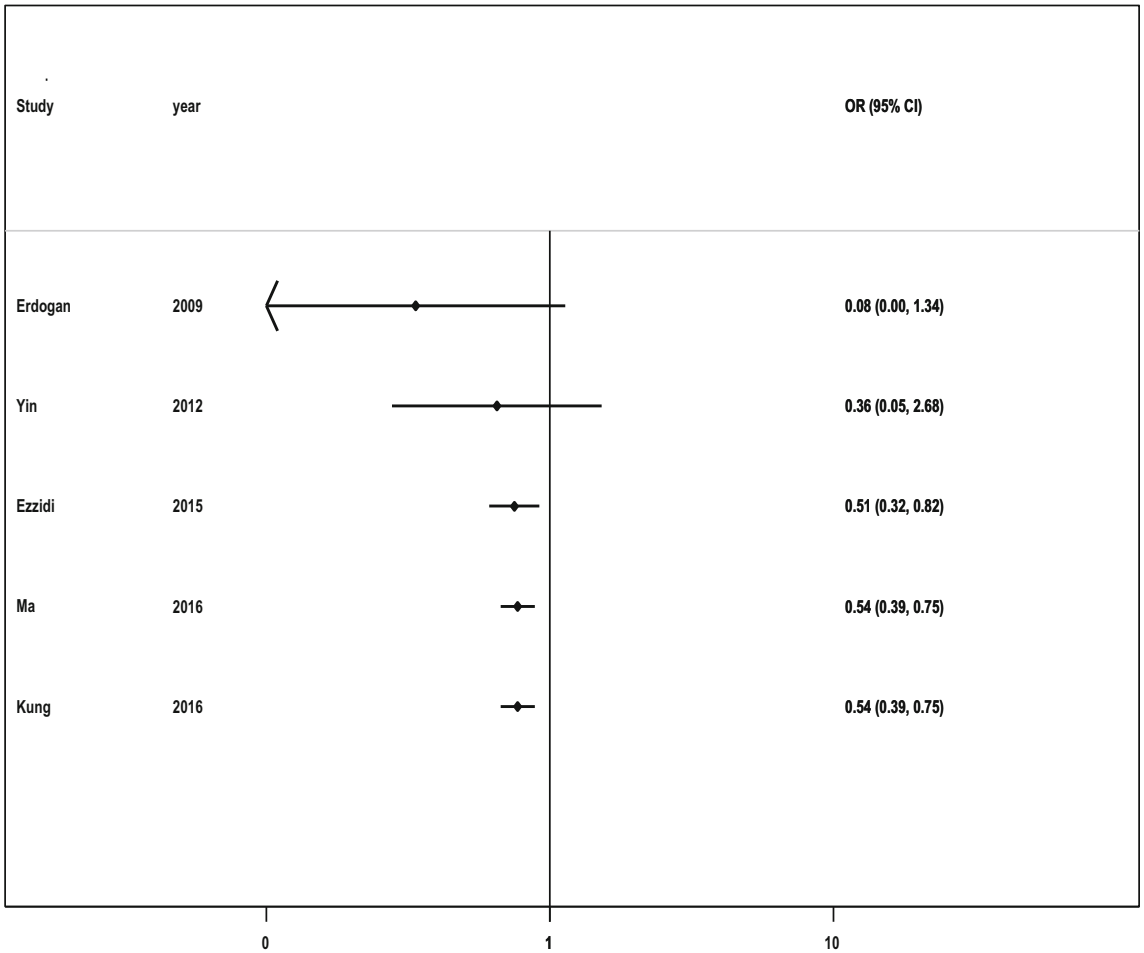

Fig. 3 Cumulative meta-analysis of association between −1082 A/G and the risk of diabetic nephropathy

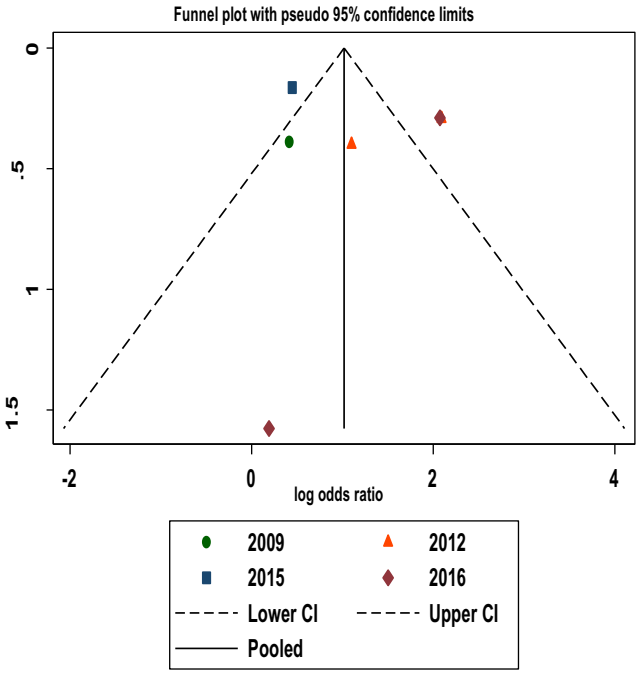

Fig. 4 Funnel plot using data from −1082 A/G in diabetic nephropathy

differences between the groups [20]. In the presence of publication bias in this analysis, non-published studies and/or studies in other language might have been missed in the current review. We had planned to do stratified analysis by studies, which deviated from HWE, by gender, and by duration of diabetes. Due to insufficient data, we were not able to do so. On the whole, findings in the current meta-analysis should be interpreted with caution.

Nevertheless, we have performed intensive search for published studies, using explicit methods for study selection, data extraction and statistical analyses with appropriate genetic model and stratification with ethnicity. The pooled estimates in this review were shown in the absence of statistical heterogeneity. The HWE was found almost in the controls of the studies included. All these points reinforced our confidence in the current findings.

The findings of the current analysis have clinical implications. Clinicians and researchers should be aware of the putative risks associated with these SNPs. In the future, genetic counselling may play one part of advice about risks of diabetes and its renal complications, and may help target participants for primary and secondary prevention of T2DM and its

consequences. As inflammation plays a pivotal role in pathological events in the kidney, modulation of inflammation are now being evaluated as being useful in prevention.

Conclusion

The findings suggest the protective effects of −819 C/T and −1082 A/G polymorphisms on the risk of developing diabetic nephropathy in T2DM in certain ethnicity such as the Asian population. To substantiate these findings, well- designed, prospective studies with sufficient number of participants are recommended.

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Authors' contribution SN: conceptualized and coordinated the study; CN, NHH, AKB: designed; CN, NHH: extracted data; AKB: checked data accuracy; CN, NHH, AKB: assessed quality of studies; CN, NHH: analyzed; SN, CN, AKB, NHH: interpreted; CN: wrote the first draft; CN, NHH, AKB, SN: revised the manuscript; All authors approved the final version of the revised manuscript.

Compliance with ethical standards

Ethics approval and consent to participate Ethics approval and consent were waived by the Joint Research and Ethics Committee at the International Medical University in Kula Lumpur of Malaysia as this study was exclusively performed with the published data.

Consent for publication Not applicable.

Competing interest The authors declare that they have no competing interests.

Abbreviations *AJOL*, African Journals online; *CI*, confidence intervals; *HWE*, Hardy-Weinberg equilibrium; *IL*, interleukin; *LILACS*, Latin American and Caribbean health sciences literature; *MeSH*, medical subject heading; *OR*, odds ratios; *SNP*, single nucleotide polymorphism; *T2DM*, type 2 diabetes mellitus

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