Association of aldosterone synthase (CYP11B2) -344 T/C polymorphism with diabetic nephropathy: A meta-analysis

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Abstract

Introduction: Studies on the relation between aldosterone synthase -344 T/C polymorphism and diabetic nephropathy showed controversial conclusions. This meta-analysis aimed to systematically summarize the association between aldosterone synthase (CYP11B2) gene polymorphism and diabetic nephropathy risk.

Methods: Embase, PubMed, ScienceDirect, Web of Science, Wanfang Data, VIP Database, China Knowledge Resource Integrated Database and SinoMed have been searched. A total of five studies including 825 cases and 910 controls were included.

Results: In overall analysis, significant increased risk was found in recessive comparison (OR = 1.27, 95% CI 1.05–1.55), homozygote comparison (OR = 1.39, 95% CI 1.04–1.88) and allele comparison (OR = 1.20, 95% CI = 1.05–1.39). No significant association was detected in dominant comparison (OR = 1.27, 95% CI 0.97–1.66) and heterozygote comparison (OR = 1.17, 95% CI 0.88–1.56). In subgroup analysis, significant increased risk existed in Asian population in allele comparison (OR = 1.45, 95% CI = 1.17–1.79), dominant comparison (OR = 1.78, 95% CI 1.11–2.87), homozygote comparison (OR = 2.11, 95% CI 1.29–3.47), recessive comparison (OR = 1.54, 95% CI 1.17–2.03), except for heterozygote comparison (OR = 1.44, 95% CI 0.87–2.38).

Conclusions: Our meta-analysis indicates that aldosterone synthase (CYP11B2) gene polymorphism may contribute to diabetic nephropathy development, especially in Asian group, with the T allele acting as a risk factor.

Introduction

As a common microvascular complication of diabetes, diabetic nephropathy (DN) is the leading cause of end stage renal disease.[1] Diabetes clustering in families suggests that genetic factors play an important role on occurrence and development of DN.[2–4] It has been confirmed renin-angiotensin-aldosterone system (RAAS) has an important influence on the occurrence and development of diabetic nephropathy.[5] As an important component of RAAS, aldosterone synthase gene has received more and more attention. But whether aldosterone synthase (CYP11B2) polymorphism is related to diabetic nephropathy is still controversial. Up to now, there is no meta-analysis investigating the association between them. To estimate the overall risk of aldosterone synthase (CYP11B2) polymorphism associated with diabetic nephropathy and to quantify the potential between-study heterogeneity, we conducted this comprehensive meta-analysis.

Materials and methods

Publication search

Two independent investigators searched the relevant studies in Embase, PubMed, Science Direct, Web of Science, Wanfang Data, VIP Database, China Knowledge Resource Integrated Database and SinoMed with the last search update on 31 August 2015. The following terms were used: "diabetes mellitus OR diabetic patients" AND "diabetic

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nephropathy OR diabetic kidney complications OR diabetic kidney damage" AND "aldosterone synthase polymorphism OR CYP11B2 gene polymorphism". References cited in recruited studies were also searched. As to some researches without sufficient data, we sent emails to the corresponding authors for request.

Inclusion and exclusion criteria

Inclusion criteria: (a) case-control study; (b) evaluation of the association between aldosterone synthase polymorphism with DN; (c) detailed data of genotypes distribution could be acquired or calculated.

Exclusion criteria: (a) reviews, meeting abstracts, editorials and commentaries; (b) study did not meet the inclusion criteria; (c) duplication of previous publications.

Data extraction and synthesis

Two investigators extracted data independently and reached a consensus by discussing or consulting a third party. The following contents were extracted from the studies: the first author's name, publication year, ethnicity of the study population, the characteristics of cases and controls, the genotyping method, controls source, sample size of cases and controls. The alleles frequencies and genotypic distributions in both cases and controls were extracted or calculated. In addition, Hardy-Weinberg equilibrium (HWE) status in controls were tested for each research.

Statistical analyses

Odd ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated to evaluate the strength of the association between aldosterone synthase CYP11B2 polymorphism and diabetic nephropathy risk. The genetic models evaluated for pooled ORs of the polymorphisms were allele comparison (T vs. C), homozygote comparison (TT vs. CC), heterozygote comparison (TC vs. CC), dominant comparison (TC+TT vs. CC) and recessive comparison (TT vs. TC+CC), respectively. Heterogeneity among studies was checked by the chi-square-based Q statistic and was considered statistically significant at $P < 0.10$.[6] According to the heterogeneity, the OR was calculated by using a fixed effects model or a random effects model.[7] When $P > 0.10$, the pooled OR was calculated by using the fixed effects model, otherwise, the random effects model was used. The significance of the pooled OR was determined by a Z-test and $P < 0.05$ was considered statistically significant. Sensitivity analysis was performed to evaluate the effect of each study on the combined ORs. Subgroup analyses were stratified to evaluate the ethnicity specific effects. Potential publication bias was analyzed by Begg's funnel plots[8] and Egger's test.[9] All statistical tests were performed using STATA 12.0 software.

Results

Characteristics of studies

The research selection process is shown by the flow diagram (Figure 1). A total of 79 potentially eligible studies were acquired from the databases. According to the inclusion and exclusion criteria, 74 articles were excluded and five relevant studies concerning aldosterone synthase CYP11B2 polymorphism and diabetic nephropathy risk were included in our meta-analysis.[10–14] The characteristics of each study included in the meta-analysis are shown in Table 1. The genotype and allele distributions in each study and HWE status in controls were also summarized in Table 1. The included studies containing 825 cases and 910 controls were finally analyzed in our meta-analysis.

Meta-analysis

This is the first meta-analysis about the association between aldosterone synthase CYP11B2 polymorphism and diabetic nephropathy susceptibility. No significant heterogeneity was identified by *Q*-test and *I*-squared statistic in dominant comparison, recessive comparison, homozygote comparison and heterozygote comparison. Therefore, the fixed-effects model was used in above comparisons. Significant between-study heterogeneity only existed in allele comparison, so the random-effects model was chosen. As the result, a significant increased risk was found in recessive comparison (TT vs. TC+CC: OR = 1.27, 95% CI 1.05–1.55), homozygote comparison (TT vs. CC: OR = 1.39, 95% CI 1.04–1.88) and allele comparison (T vs. C: OR = 1.20, 95% CI = 1.05–1.39) (Figure 2). No significant association was found in dominant comparison (TC+TT vs. CC: OR = 1.27, 95% CI 0.97–1.66) and heterozygote comparison (TC vs. CC: OR = 1.17, 95% CI 0.88–1.56) (Table 2).

Next, subgroup analysis was conducted according to ethnicity. Only one study was about Caucasian, so we only did descriptive analysis. The research revealed -344T/C polymorphism of the aldosterone synthase gene was not associated with initiation or progression of diabetic nephropathy in Caucasian type 1 diabetic patients.[10] The rest of the four studies were all about Asian population, having no significant heterogeneity. The fixed-effects model was chosen and the pooled analysis results showed significant increased risk in allele comparison (T vs. C: OR = 1.45, 95% CI = 1.17–1.79), dominant comparison (TC+TT vs. CC: OR = 1.78, 95% CI 1.11–2.87), homozygote comparison (TT vs. CC: OR = 2.11, 95% CI 1.29–3.47), recessive comparison (TT vs. TC+CC: OR = 1.54, 95% CI 1.17–2.03) (Figure 3). Only in heterozygote comparison (TC vs. CC: OR = 1.44, 95% CI 0.87–2.38) no significant association was found (shown in Table 2).
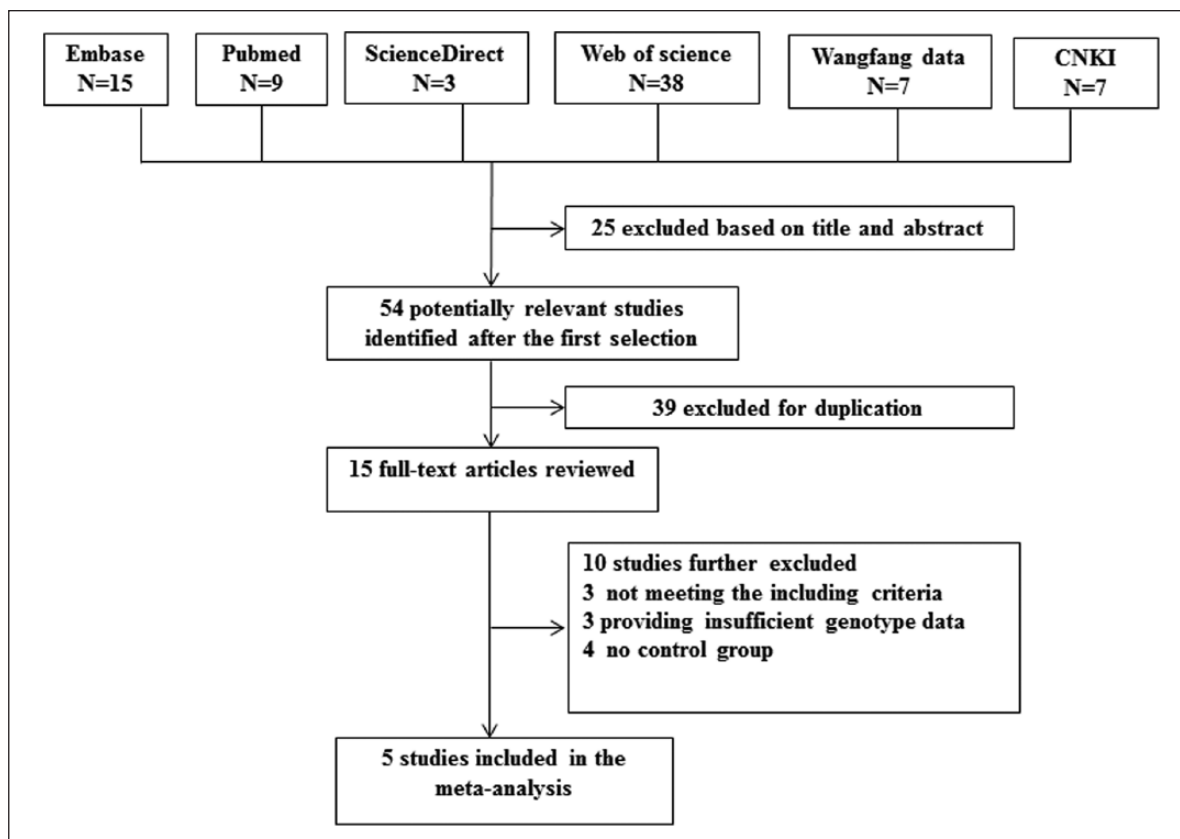
Figure 1. Search flow diagram for studies included in the meta-analysis.

Table 1. The characteristics of each study included in the meta-analysis.

First author	Year	Ethnicity	Case						Control					
			Sample size	Age (year)	Definition (renal status)	TT	CT	CC	Sample size	Age (year)	Definition (renal status)	TT	CT	CC	HWE
Lajer M	2006	Caucasian	422	43 ± 11	UAE median 558 mg/24 h	139	203	80	479	47 ± 12	Normoalbuminuria, with DM > 15 years	153	230	96	0.57
Prasad P	2006	Indian	196	57 ± 12.8	UAER median 864 mg/l; GFR 27.83 ± 24 ml/min/1.73 m²	106	74	16	225	60.6 ± 11.5	Normoalbuminuria, with DM ⩾ 10 years	90	106	29	0.8
Sun WH	2009	China	73	mean 59.8	Microalbuminuria, Proteinuria, Renal insufficiency	46	23	4	72	mean 61.9	Normoalbuminuria	35	24	13	0.02
Ko GJ	2008	Korea	102	55.5 ± 11.5	Microalbuminuria, Overt proteinuria	53	43	6	71	55.7 ± 10.8	Normoalbuminuria	33	32	6	0.65
Feng CS	2007	China	32	53.1 ± 17.6	UAER > 20 ug/min	12	17	3	63	52.0 ± 15.1	Normoalbuminuria	25	33	5	0.19

HWE: Hardy-Weinberg equilibrium; GFR: Glomerular filtration rate; DM: Diabetes mellitus; UAE: Urinary albumin excretion; UAER: Urinary albumin excretion rate.

Heterogeneity analysis

In the present meta-analysis, significant heterogeneity only existed in the allele comparison (for T vs. C: $P_Q = 0.057$, $I^2 = 56.3\%$). To clarify the sources of heterogeneity, we conducted the subgroup analyses based on ethnicity (Asian or Caucasian), and sensitivity analyses based on HWE status. The heterogeneity was significantly reduced after subgroup analyses ($P_Q = 0.259$, $I^2 = 25.4\%$). But it could not be effectively removed after sensitivity analyses based on HWE status ($P_Q = 0.085$, $I^2 = 59.5\%$). Then meta-regression was also performed to explore the other potential sources of heterogeneity under the allele genetic model. The confounding factors included publication year, sample size, quality score, HWE status and genotyping method. The controls source in each study was similar, so it was not included. The meta-regression results revealed that none of these five factors could explain significant between-study heterogeneity:publication year ($P = 0.724$), sample size ($P = 0.565$), quality score ($P = 0.587$) and HWE status ($P = 0.604$). In addition, we replaced the fixed effects model for the random effects model to calculate pooled ORs, and the results were not materially altered.
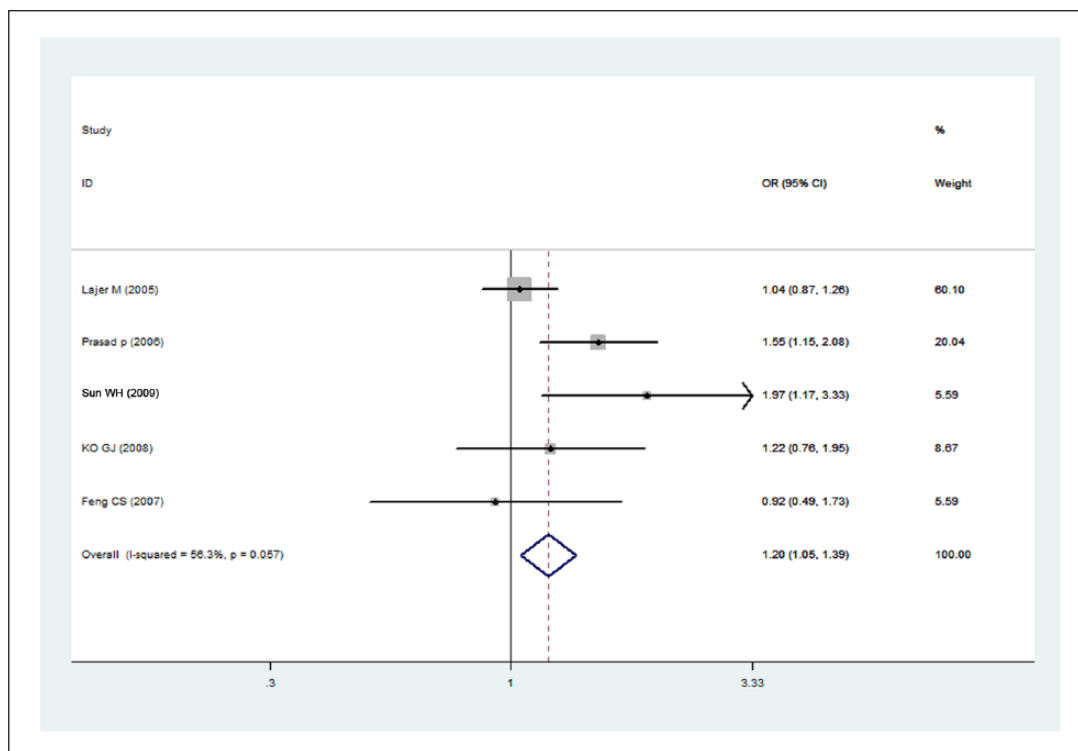
Figure 2. Forest plot for the overall analysis for aldosterone synthase *CYP11B2* polymorphism and diabetic nephropathy risk for allele comparison (T vs. C).

Table 2. Meta-analyses of aldosterone synthase CYP11B2 polymorphism and diabetic nephropathy risk.

Category	Sample size	T vs. C	TT vs. TC+CC	TC+TT vs. CC	TT vs. CC	TC vs. CC
	(case/control)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Overall	825/910	1.20 [1.05, 1.39][a]	1.27 [1.05, 1.55]	1.27 [0.97, 1.66]	1.39 [1.04, 1.88]	1.17 [0.88, 1.56]
Asian	403/431	1.45 [1.17, 1.79]	1.54 [1.17, 2.03]	1.78 [1.11, 2.87]	2.11 [1.29, 3.47]	1.44 [0.87, 2.38]

[a]Significant heterogeneity existing, the random-effects model was chosen to summarize the result.

Sensitivity analysis

Sensitivity analysis was performed by omitting one study at a time and calculating the pooled ORs for the remaining studies (data were shown in Figure 4). This procedure was used to explore whether individual study was entirely responsible for the combined results. We found only one study had greater effect on the combined results.[10] But after omitting this study, the results were not materially altered in every genetic model except for dominant comparison.

Publication bias

Begg's funnel plot and Egger's regression test were performed to assess the publication bias in allele comparison (T vs. C). No publication bias was identified by Begg's funnel plot ($P = 0.806$) or Egger's regression test ($P = 0.474$). The funnel plots in all genetic models were symmetrical (Figure 5, T vs. C).

Discussion

Aldosterone synthase (CYP11B2) gene is located on chromosome 8 (8q22), and it contains eight introns and nine exons.[15] Studies have shown that aldosterone synthase -344 T/C polymorphism was associated with essential hypertension, stroke and cardiovascular function.[16–18] But studies concerning relations between aldosterone synthase -344 T/C polymorphism and diabetic nephropathy showed controversial conclusions. Prasad et al.[11] found that T > C (-344) polymorphisms in aldosterone synthase were significantly associated with diabetic chronic renal insufficiency. Lajer et al.[10] maintained the -344T/C polymorphism of the aldosterone synthase gene was not associated with initiation or progression of diabetic nephropathy in Caucasian. So we conducted this meta-analysis to evaluate the association. And our results were not exactly the same as previous research results.

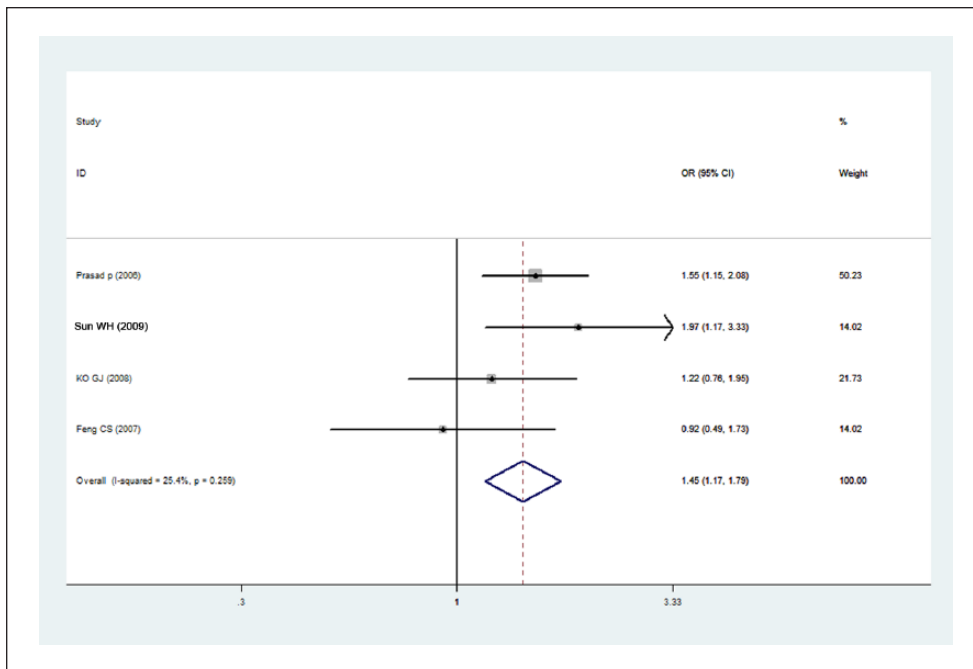As the first meta-analysis focused on the association between aldosterone synthase -344 T/C polymorphism

Figure 3. Forest plot for the subgroup analysis in Asian population for aldosterone synthase *CYP11B2* polymorphism and diabetic nephropathy risk for allele comparison (T vs. C).
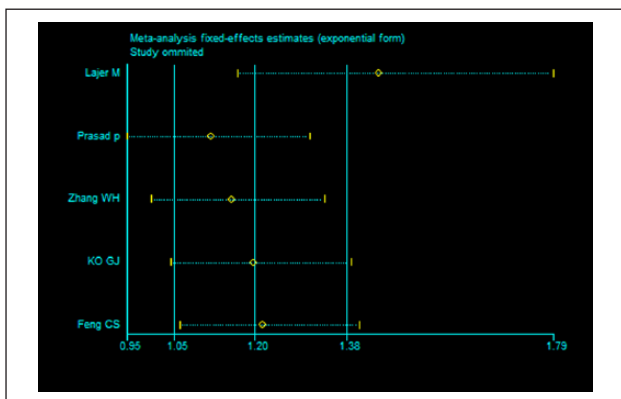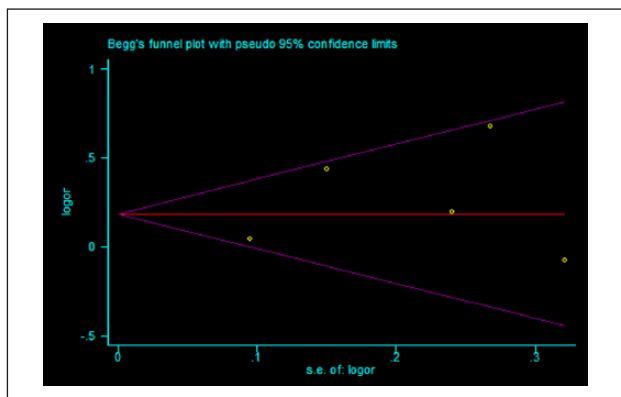

Figure 4. Result of sensitivity analysis.

Figure 5. Begg's funnel plot for publication bias test of the association between aldosterone synthase *CYP11B2* polymorphism and diabetic nephropathy risk.

and the susceptibility to diabetic nephropathy, our research analyzed the available data, including a total of 825 cases and 910 controls. In overall population, a significant increased risk was found in recessive comparison, homozygote comparison and allele comparison. No significant association existed in dominant comparison and heterozygote comparison. Subgroup analyses according to ethnicity were conducted. The results in Asian population revealed significant increased risk in allele comparison, dominant comparison, homozygote comparison and recessive comparison, but not in heterozygote comparison. In the only Caucasian study, aldosterone synthase -344 T/C polymorphism was found not associated with diabetic nephropathy in type 1 diabetic patients. The different results between Asians and Caucasians may be accounted for in a number of ways. Firstly, different genetic and environmental background in different races may play an important role on gene phenotypes. Secondly, only one research may not be able to explain the genotype distribution of aldosterone synthase gene polymorphism in Caucasus diabetic nephropathy patients.

In this meta-analysis, significant heterogeneity only existed in the allele comparison (T vs. C). After subgroup analyses the heterogeneity was significantly reduced. According to the meta-regression result, none of the five confounding factors including publication year, sample size, quality score, HWE status and genotyping method could explain the between-study heterogeneity. So the heterogeneity may derive from racial differences mainly. Then, sensitivity analysis was conducted by omitting one

study at a time. We found one study had greater effect on the combined results.[10] But after omitting the research, the results were not materially altered in every genetic model except for in dominant comparison. Moreover, we replaced the fixed effects model for the random effects model to calculate pooled OR, and the results were not materially altered too. No publication bias was identified by Begg's funnel plot or Egger's regression test. The funnel plots in all the genetic models were symmetrical. But owing to the limited number of included studies, power of these two tests was small. The conclusion needs further support of larger sample size studies.

When interpreting the results of this meta-analysis, some limitations should still be considered. Firstly, our meta-analysis only contained studies in Caucasians and Asians. We cannot know the genotype distributions in other ethnic groups. Secondly, the number of included studies limited further analysis due to shortage of original studies. Thirdly, the heterogeneity existed in the allele comparison (T vs. C) should be noted. Ethnicity and sample size might contribute to the heterogeneity.

In conclusion, the present meta-analysis suggests that aldosterone synthase -344 T/C polymorphism may be associated with increased risks of diabetic nephropathy, especially among Asian populations. However, larger sample size studies conducted in different ethnic populations are required to further evaluate our conclusion in the future.

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