REVIEW ARTICLE

Association of microRNA gene polymorphisms with Type 2 diabetes mellitus: A systematic review and meta-analysis

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Background: Type 2 diabetes mellitus (T2DM) is a metabolic disorder with growing prevalence and increasing economic burden. Based on the role of genetics and epigenetic factors on T2DM, we aimed to carry a systematic review and meta-analysis for all miRNA gene polymorphisms and risk of T2DM. **Materials and Methods:** A computerized literature search was carried out on PubMed, Web of Science, Scopus, Embase, as well as references of relevant review/meta-analysis. Key search terms were "Diabetes Mellitus, Type 2," "MicroRNAs," and "Polymorphism, Single Nucleotide." All types of observational studies from January 1, 1992, to November 30, 2019, were included, without language restriction. Data analysis was performed using R programming language (3.5.2). Level of heterogeneity was obtained by Cochran's Q test ($P<0.05$), and subgroup analysis was performed based on ethnicity. **Results:** Thirty-two polymorphisms from fifteen articles were included. Meta-analysis was carried out based on minor allele frequencies. Seven studies with 2193 cases and 3963 controls were included for rs2910164 polymorphism. In subgroup analysis, there were significant results in Caucasian population in dominant model (odds ratio [OR] =1.12; 95% confidence interval [CI]: 0.83–1.51), homozygote model (OR = 1.78; 95% CI: 1.06–3.00), heterozygote model (OR = 1.77; 95% CI: 1.03–3.05), and recessive model (OR = 1.78; 95% CI: 1.07–2.96). Four studies with 2085 cases and 1933 controls were included for rs895819 polymorphism. Overall, there was no significant result for association with rs895819, but subgroup analysis revealed that minor allele significantly decreased the risk of T2DM in Caucasians by recessive model (OR = 0.34; 95% CI: 0.18–0.66), dominant model (OR = 0.70; 95% CI: 0.52–0.94), homozygote model (OR = 0.32; 95% CI: 0.16–0.62), heterozygote model (OR = 0.37; 95% CI: 0.19–0.74), allelic model (OR = 0.67; 95% CI: 0.52–0.85). **Conclusion:** The minor allele of rs2910164 may increase the risk of T2DM by leading to lower level of miR-146a. In contrast, minor allele of rs895819 may decrease the risk of T2DM by leading to higher level of miR-27a.

Key words: MicroRNAs, polymorphism, Type 2 diabetes

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) as a metabolic disorder is caused by insulin resistance and beta-cell dysfunction.[1,2] The prevalence of diabetes is rapidly growing, especially in middle- and low-income countries. In 2014, 422 million people had diabetes, which means 8.5/100 persons,[3,4] which may increase to 592 million till 2035. More than 90% of these patients develop type-2 diabetes.[5,6] In recent years, diabetes leads to approximately 4 million deaths, as direct or indirect cause each year, and it is proclaimed as the seventh cause of death by the World Health Organization.[7] T2DM micro- and macrovascular complications obligate increasing financial and social burden on communities. The world direct annual cost of T2DM is estimated over 800 billion dollars.[3] Several

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factors including genetic, family history, diet, low physical activity, smoking, high body mass index, and aging are responsible for the increasing prevalence of T2DM.[3,4] Majority of T2DM patients suffer from obesity. High level of FFA in obese individuals correlates with beta-cell dysfunction and insulin resistance in T2DM.[8] Both genetics and environmental factors are involved in the development of diabetes mellitus.[9] In many studies, various candidate genes are proposed which are involved in the development of T2DM such as peroxisome proliferator-activated receptor gamma, glycogen synthase, insulin receptor substrate 1, insulin, potassium voltage-gated channel subfamily J member 1, ATP-binding cassette subfamily C member 8, and solute carrier family 2 member 1.[10] These genes play roles in diabetes by several mechanisms.

MicroRNAs are small, conserved ncRNA molecules that are involved in most cellular processes through interaction with 3′-UTR region of the genes.[11-13] miRNAs are important small noncoding RNAs that regulate RNAs and gene expression in various common diseases such as T2DM.[14] miRNAs seem to play a role in the development of pancreatic islets and differentiation of insulin-producing cells.[15-18] For instance, mir-375 is involved in insulin secretion by interaction with myotrophin gene and development of islets.[16,19,20] The interaction of *FoxA2* and *Rab27A* genes with miR-124a has also been proven influential in the development of islet cells.[15,21] On the other hand, polymorphisms in miRNAs may be functionally important by regulation of target genes or transcription of miRNAs.[22,23] These polymorphisms may affect the risk, development, progress, or morbidity associated with diabetes, by further effect on miRNA target genes.[24,25] There are several studies on the role of miRNA polymorphisms in T2DM, but no systematic review or meta-analysis was performed yet. Only two reviews in 2017 and 2018 have been conducted on this subject. In 2017, Zhuang and Wang studied the polymorphisms related to diabetes mellitus and its complications in miRNA genes or their target sites.[26] In 2018, Zhang *et al*. reviewed the miRNA polymorphisms associated with diabetes mellitus and its complications.[27] However, their studies did not accomplish with all requirements. For instance, they included only few polymorphisms, from Ciccacci *et al*.,[28] while this study contains more miRNA polymorphism. Furthermore, some studies were inadequately added in their report including the study by Alipoor *et al*.[29] with MAF 0.25 which was designed to investigate the role of miRNA variant on miR-146a expression, or the study by Hara *et al*.[30] in Zhang review that was a GWA study and should be excluded in our systematic review.

The aim of the current study was to systematically search all miRNA polymorphism-related documents and further meta-analysis of results for their association with T2DM.

MATERIALS AND METHODS

Data sources (electronic and hand-searching)

The strategy has been developed based on the PRISMA-P 2015 checklist.[31] Figure 1, the PRISMA 2009 flow diagram,[32] shows the review process.

We systematically searched literatures in Web of Science, PubMed, Embase, and Scopus databases. Syntax definition was performed by combining Medical Subject Headings (MeSH) and free text. Key search terms were "Diabetes Mellitus, Type 2," "MicroRNAs," "Polymorphism, Single Nucleotide," and their equivalents. We also did a search on key journals and references of relevant review/meta-analysis. The second search was performed after first data collections; the search was based on included polymorphisms to find all relevant documents.

Types of studies and participants

Primary documents were screened according to this review strategy. We included case–control, cohort, and cross-sectional studies as three types of observational studies, with data being related to the association between miRNA polymorphisms and T2DM. All other studies were excluded. Studies that their controls were healthy people were included and others were excluded. Studies with insufficient data or with deviation from Hardy–Weinberg equilibrium[33] were excluded. Insufficient data were resolved by contact with the corresponding author. If we had not received any response after three E-mails, the data were excluded from meta-analysis. Search was performed for documents restricted to publication dates from January 1, 1992, to November 30, 2019, to find the most recent documents which were more reliable. Documents in all languages were included. There was also no restriction about the age, gender, race, or genotyping methods. Documents with diabetes complications such as nephropathy, retinopathy, and other traits were excluded. The quality assessment has been applied by Newcastle–Ottawa Scale method.[34]

Data collection

Data collection was carried out in three steps: first, removing duplications; second, three reviewers (M.Z., S.A., and A.V.) independently checked title/abstract to find included studies and studies with uncertainty. Disagreements and uncertainties were resolved by both consensus strategy and third-person strategies; at the final step, full texts were investigated by three reviewers (M.Z., S.A., and A.V.). Data extraction was performed by two reviewers (M.G. and M.M.A.) for the following data: first author name, country of study, publication year, study design, ethnicity, gender, polymorphisms, miRNAs, and genotyping methods.

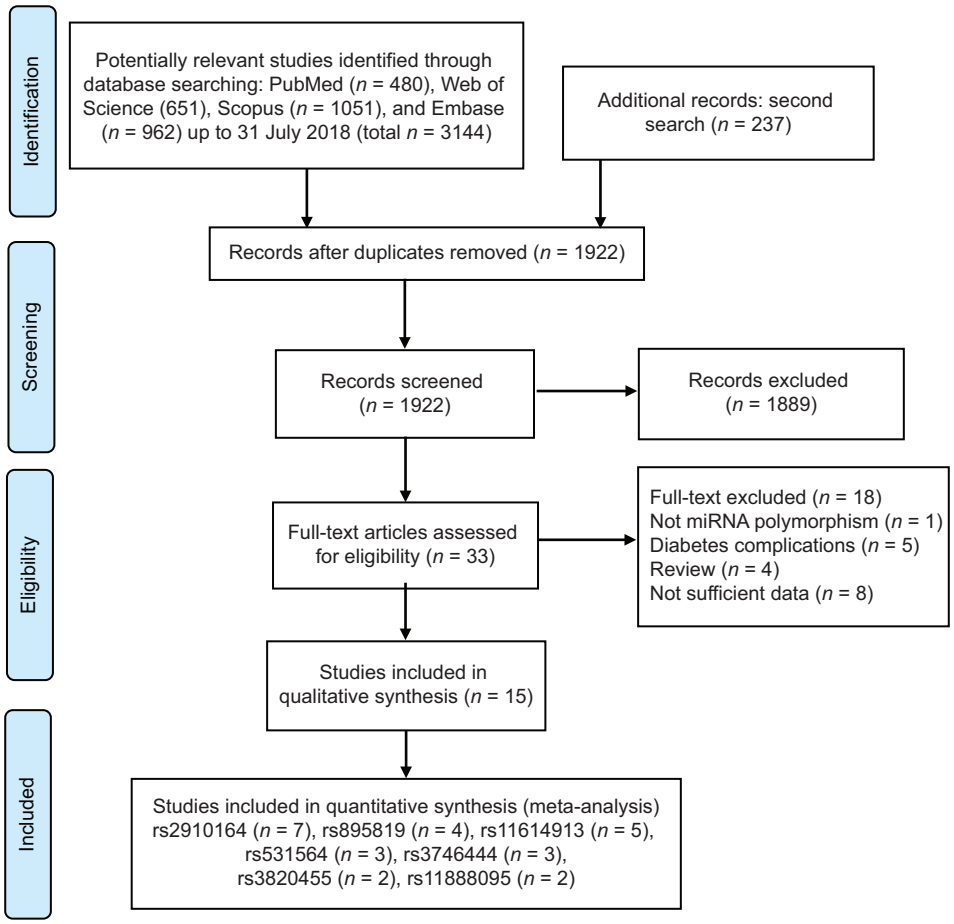

Figure 1: The flow diagram of systematic review

Disagreements between reviewers were resolved by previously described strategies.

Statistical analysis

Data analysis was performed using R programming language 3.5.2 (R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; URL http://www.R-project.org/.)[35] and STATA software V.13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP).[36] The associations between included polymorphisms and T2DM were assessed by odds ratio (OR) and confidence interval (95% CI) for OR. The meta-analysis was performed based on allelic, homozygous, heterozygote, dominant, and recessive genetic models. All genetic models were analyzed in both two random and fixed models. Heterogeneity was assessed by the Cochran's Q test. We used random effects model if Q test was $P < 0.05$ and the I^2 statistic was more than 50% in forest plots. For each polymorphism, if sufficient studies were included, subgroup analysis was performed based on ethnicity. To find publication bias in primary studies, we assessed Egger's and Begg's tests. The results were depicted by funnel plots. Sensitivity analysis was carried out by leave-one-out method, based on omit studies one by one.

RESULTS

Study selection

Based on our double systematic searching and after removing duplication, 1922 articles were included. The flow diagram and data related to screening are shown in Figure 1. Among 15 included studies[28,37-50] (32 polymorphisms), we found two articles for two single-nucleotide polymorphisms (rs3820455 and rs11888095), three studies were included for rs3746444 and rs531564 polymorphisms, and also more than three studies were included for each of the following polymorphisms (rs895819, rs11614913, and rs2910164). These data are summarized in Table 1.

Meta-analysis

When we combined data related to polymorphisms with two included articles, it was observed that C and T alleles of rs3820455 and rs11888095, respectively, may increase the risk of T2DM, but the results were not significant (data are not shown). Furthermore, analysis of three included

Table 1: Basic characteristics of included studies

First author	Year	Country	Ethnicity	Study design	Quality score	Gender	Source	Genotyping method	miRNAs	Single-nucleotide polymorphism	Sample size (case/control)
Alipoor *et al.*[38]	2016	Iran	Caucasian	Case/control	8	Male/female	PB	PCR-RFLP	miR-146a	rs2910164	183/192
									miR-149	rs2292832	183/192
Buraczynska *et al.*[39]	2014	Poland	Caucasian	Case/control	8	Male/female	PB	PCR-RFLP	miR-196a2	rs11614913	920/834
Ciccacci *et al.*[28]	2017	Italy	Caucasian	Case/control	7	Male/female	PB	Sequencing	miR-375	rs6715345	100/75
									miR-27a	rs895819	148/147
									miR-27a	rs11671784	148/147
									miR-130b	rs861843	161/145
									miR-124a	rs531564	162/178
									miR-124a	rs73662598	163/178
									miR-128a	rs11888095	108/85
									miR-194a	rs3820455	144.92
									miR-146a	rs2910164	153/181
Ghaedi *et al.*[40]	2016	Iran	Caucasian	Case/control	8	Male/female	HB	PCR-RFLP	miR-27a	rs895819	204/209
Li *et al.*[41]	2015	China	ESA	Case/control	7	Male/female	PB	TaqMan	miR-27a	rs895819	738/610
									miR-124a	rs531564	738/610
									miR-128a	rs11888095	738/610
									miR-194a	rs3820455	738/610
									miR-146a	rs2910164	738/610
Sun *et al.*[42]	2018	China	ESA	Case/control	6	Male/female	PB	Sequencing	miR-34a	rs12128240	130/117
									miR-34a	rs2666433	130/117
									miR-34a	rs6577555	130/117
Wang *et al.*[37]	2015	China	ESA	Case/control	7	Male/female	PB	SNPscan Kit	miR-27a	rs895819	995/967
									miR-146a	rs2910164	995/967
									miR-124a	rs531564	995/967
Zhou *et al.*[43]	2013	China	ESA	Case/control	7	Male/female	PB	PCR-RFLP	let-7a-2	rs1143770	104/62
									let-7a-2	rs547008	104/62
Chen *et al.*[44]	2014	China	ESA	Case/control	5	Male/female	PB	PCR-LDR	miR-149	rs71428439	33/856
									miR-146a	rs2910164	33/856
									miR-218	rs11134527	33/856
									miR-196a2	rs11614913	33/856
									mir-499	rs3746444	33/856
Huang *et al.*[45]	2015	China	ESA	Case/control	5	Male/female	HP	TaqMan	miR-146a	rs2910164	46/485
									miR-196a2	rs11614913	46/485
Zhi *et al.*[46]	2012	China	ESA	Case/control	5	Male/female	HP	PCR-RFLP	miR-196a2	rs11614913	38/252
									miR-499	rs3746444	38/252
Huang *et al.*[47]	2015	China	ESA	Case/control	7	Male/female	HP	TaqMan	miR-146a	rs2910164	45/672
									miR-196a2	rs11614913	45/675
Li *et al.*[48]	2019	China	ESA	Case/control	7	Male/female	PB	MassArray	miR-135a-2	rs10459194	784/846
									let-7d	rs10993081	784/846
									let-7d	rs7045890	784/846
									miR-107	rs2296616	784/846
									miR-96	rs2402959	784/846
									miR-96	rs6965643	784/846
									miR-29a	rs24168	784/846
									miR-23a	rs3745453	784/846
									miR-126	rs4636297	784/846
									miR-133a-1	rs8089787	784/846
									miR-133a-1	rs9948906	784/846
									miR-106b	rs999885	784/846
Mohsen *et al.*[49]	2018	Iraq	Caucasian	Case/control	5	Male/female	PB	PCR-RFLP	miR-499	rs3746444	80/40
Moudi and Zohour[50]	2018	Iran	Caucasian	Case/control	6	Male/female	PB	PCR-RFLP	miR-605	rs2043556	300/300

articles for rs531564 and rs3746444 polymorphisms showed no significant results (data are not shown).

Seven studies were included for rs2910164.[28,37,38,41,44,45,47] Seven studies with 2193 cases and 3963 controls were included for rs2910164 polymorphism. In overall analysis, the meta-analysis showed no significant association. Subgroup analysis for ethnicity showed that in Caucasians, there was a significant association in homozygote model (OR = 1.78; 95% CI: 1.06–3.00; I^2 = 35%, Q test P = 0.22), heterozygote model (OR = 1.77; 95% CI: 1.03–3.05; I^2 = 0%, Q test P = 0.57), and recessive model (OR = 1.78; 95% CI: 1.07–2.96; I^2 = 4%, Q test P = 0.31). The plots are shown in Figure 2.

Five studies were included in the meta-analysis[39,44-47] for rs11614913. Five studies with 1082 cases and 3102 controls were included for rs11614913 polymorphism. The results showed that T allele significantly decreased risk of T2DM in four genetic models: overdominant model (OR = 0.83; 95% CI: 0.70–0.97; I^2 = 32%, Q test P = 0.21), dominant model (OR = 0.73; 95% CI: 0.62–0.88; I^2 = 57%, Q test P = 0.05), homozygote model (OR = 0.76; 95% CI: 0.59–0.98; I^2 = 52%, Q test P = 0.08), and heterozygote model (OR = 0.75; 95% CI: 0.62–0.90; I^2 = 51%, Q test P = 0.09). However, subgroup analysis for rs11614913 in Chinese population showed no significant results [Figure S1].

Four studies with 2085 cases and 1933 controls were included for rs895819 polymorphism. Meta-analysis for rs895819 showed no significant association with the C allele, but subgroup analysis revealed significantly decreased risk of T2DM in Caucasians with recessive model (OR = 0.34; 95% CI: 0.18–0.66; I^2 = 0%, Q test P = 0.32), dominant model (OR = 0.70; 95% CI: 0.52–0.94; I^2 = 0%, Q test P = 0.44, I^2 = 13%), heterozygote model (OR = 0.37; 95% CI: 0.19–0.74; I^2 = 0%, Q test P = 0.43), allelic model (OR = 0.67; 95% CI: 0.52–0.85; I^2 = 0%, Q test P = 0.39). The plots are shown in Figure 3. The results for publication bias and sensitivity analysis are presented in Figures S2 and S3, receptively.

DISCUSSION

Main findings and interpretation

This study aimed to systematically investigate the role of miRNA gene polymorphisms on the risk of T2DM. For this purpose, we performed an overall meta-analysis and subgroup analysis for eligible studies.

Our results showed that C allele of rs2910164 polymorphism increased the risk of T2DM in subgroup analysis, as the risk effect was stronger in Caucasians. This polymorphism is located on miR-146a gene. The conversion of G to C in rs2910164 causes a mispairing in pre-microRNA structure and maturation process, which leads to decrease of both pre/mature miR-146a.[51] Furthermore, the decreased expression of this miR-146a has been reported in the serum of patients with diabetes compared to the healthy control group.[52] On the other hand, miRNA-mRNA interaction

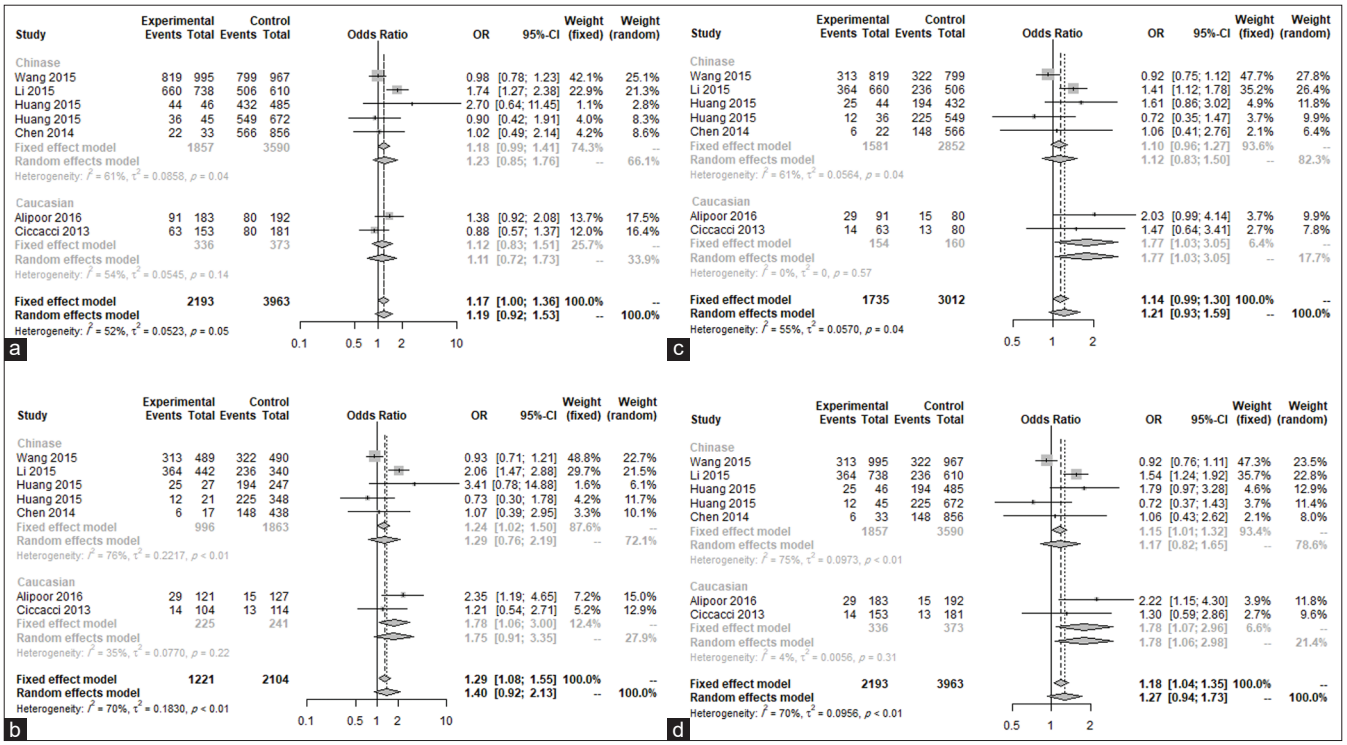

Figure 2: Forest plot related to rs2910164 and risk of Type 2 diabetes mellitus. (a) Dominant model, (b) homozygote model, (c) heterozygote model, and (d) recessive model

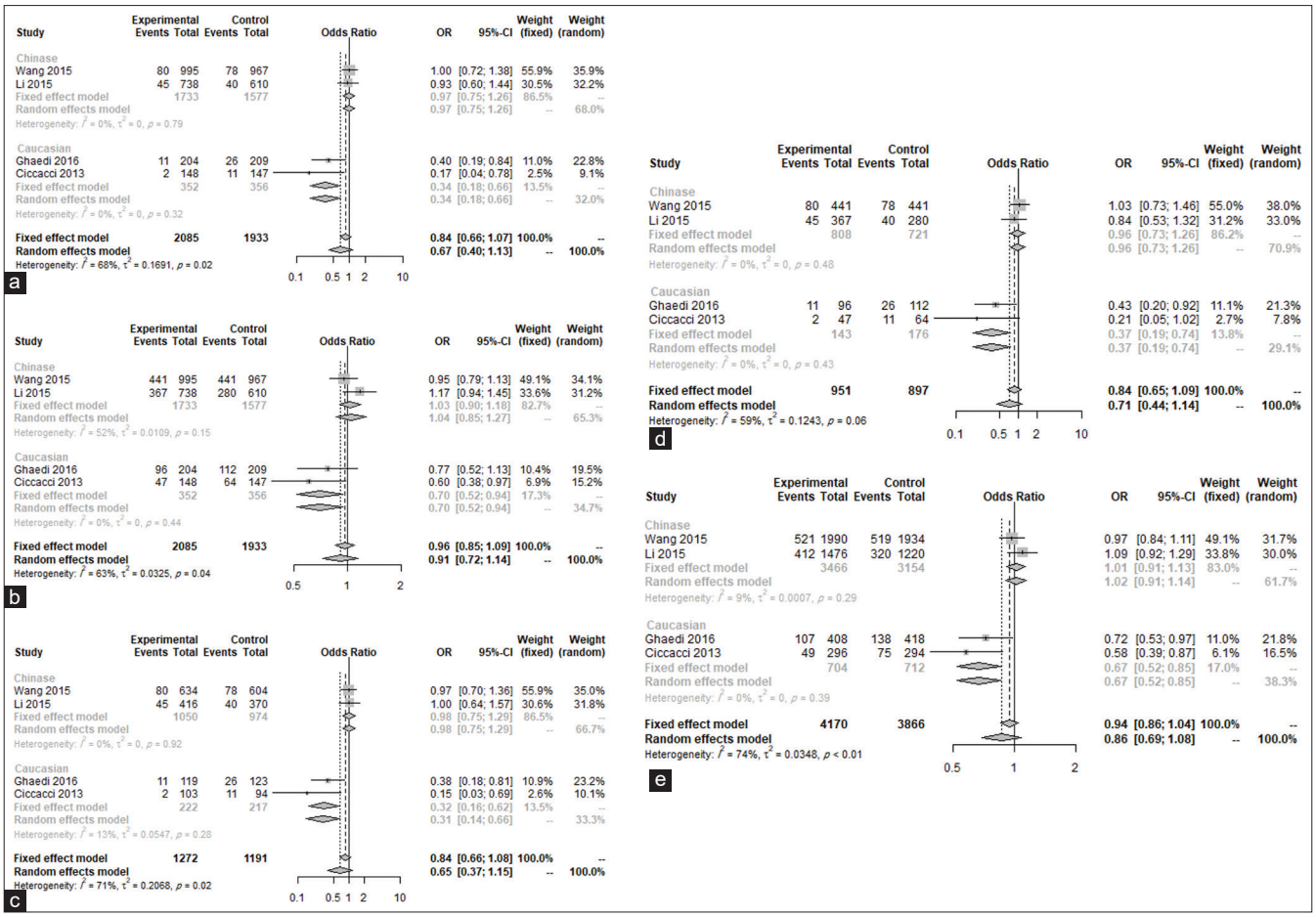

Figure 3: Forest plot related to rs895819 and risk of Type 2 diabetes mellitus. (a) Recessive model, (b) dominant model, (c) homozygote model, (d) heterozygote model, and (e) allelic model

can play a role in disease-related gene expression or gene regulations. In T2DM, it is shown that this miRNA has interaction with inflammatory genes including *TRAF6*, *NFκB TNFα*, and *IL-6*, which are involved in the pathogenesis of T2DM. Lower expression of miR-146a is associated with higher expression of inflammatory markers, insulin resistance, poor glycemic control, and the overall progression to diabetes.[53] The reduced level of miR-146a, caused by C allele, may be an important factor for induction of inflammatory mechanism involved in T2DM. These causal relationships may justify the higher frequency of allele C and the role of rs2910164 polymorphism in T2DM patients.

The rs11614913 polymorphism in miR-196a is located on chromosome 17 between *HOX* genes and also has interaction with *HOX* genes.[54,55] Hox genes play an important role in the initial development of fetal organs including pancreas.[56] In addition, miR-196a can activate the *AKT* signaling pathway, which is involved in the development and treatment of type 2 diabetes,[55,57,58] elucidating the importance of miR-196 in the pathology of diabetes. Converting C to T allele in rs11614913 polymorphism influences the processing of miR-196a2 and its function.[59] Meta-analysis in this study showed that the T allele of this polymorphism has a protective effect on the risk of T2DM, which is similar to the study by Buraczynska *et al.* on Caucasians.[39] No such association was observed in the subgroup analysis (Chinese studies), and even, it seems that in Chinese population, the T allele was tended to increase the risk of T2DM. The reason for the discrepancy in the total and subgroup analysis may be the result of the larger sample size in Caucasian study. Furthermore, previous studies such as gnomAD-Exomes and 1000 Genomes determined that the frequency of allele T was considerably different between East Asian and other parts of the world and C allele frequency was higher in East Asian population. Therefore, it may affect result for association between T allele and T2DM in this population. However, these results should be interpreted with cautious and nondecisively. Based on the important role of miR-196a and inconclusive results for the role of rs11614913 polymorphism in T2DM, additional observational studies on different ethnic populations seem to be essential.

We did not find a significant relation between rs895819 and T2DM. It may be related to few studies included and also ethnicity differences between groups. Based on subgroup

analysis, we found significant associations in different genetic models, and variant allele seemed to decrease risk of T2DM in Caucasians, which suggests the protective effect for this allele. Most of the previous studies for this polymorphism were related to its role in cancers. Previously, a meta-analysis showed the ethnic effect on the role of this polymorphism in risk of cancers,[60] which may approve the role of ethnic variation for association with this polymorphism. The miR-27a has high expression in high glycemic condition in adipose tissue.[61] Higher level of this miRNA increases expression of pro-inflammatory cytokines and plays positive roles in inflammatory response.[62] The rs895819 in pri-miR-27a may be involved in processing and function of this miRNA.[63] In this study, the association with this polymorphism was merely affirmed in two included studies.

The rs531564 polymorphism in the pri-miRNA influences the expression of miR-124.[64] However, we did not observe any correlation between rs531564 and T2DM, which can be as a result of an insufficient number of studies, small sample size, and various ethnicities.

Strengths and limitations

The strengths of our study are as follows: first, this is the first systematic review and meta-analysis, on the role of miRNA polymorphisms on T2DM, and has been performed without any language limitation. Second, we included four main databases as well as hand-searching. Third, three steps of title/abstract screening, full-text eligibility, and data extraction are done by two researchers independently. The limitations of our study are as follows: one of the main causes of heterogeneity in our study was different ethnic populations. Because of the small number of included studies in some cases, subgroup analysis was done by only two included articles. Furthermore, meta-analysis was performed for some included polymorphisms.

CONCLUSION

In this meta-analysis, we found that minor alleles of polymorphisms in miR-146a (rs2910164) and miR-27a (rs895819) inversely affect T2DM susceptibility, especially in Caucasian population. The minor allele of rs2910164 may increase the risk of T2DM by leading to lower level of miR-146a and consequently higher expression of inflammatory markers involved in T2DM. In contrast, minor allele of rs895819 may decrease the risk of T2DM by leading to higher level of miR-27a increasing the effect of inflammatory genes involved in T2DM.

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Conflicts of interest

There are no conflicts of interest.

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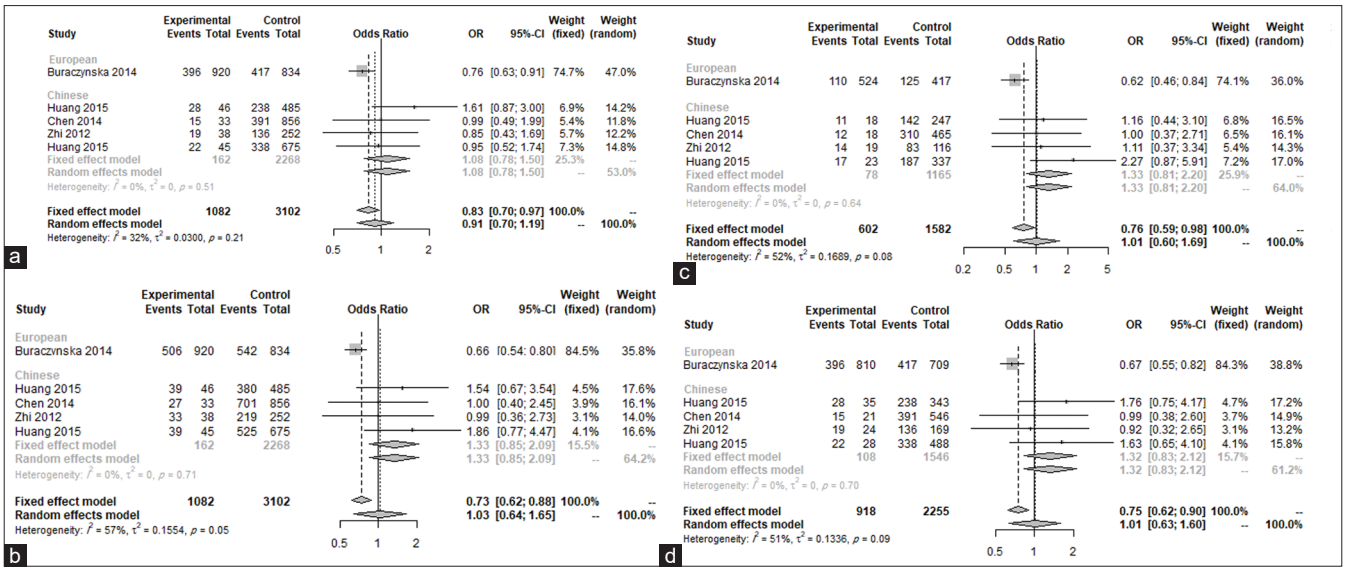

Figure S1: Forest plot related to rs11614913 and risk of Type 2 diabetes mellitus. (a) Overdominant model, (b) dominant model, (c) homozygote model, and (d) heterozygote model

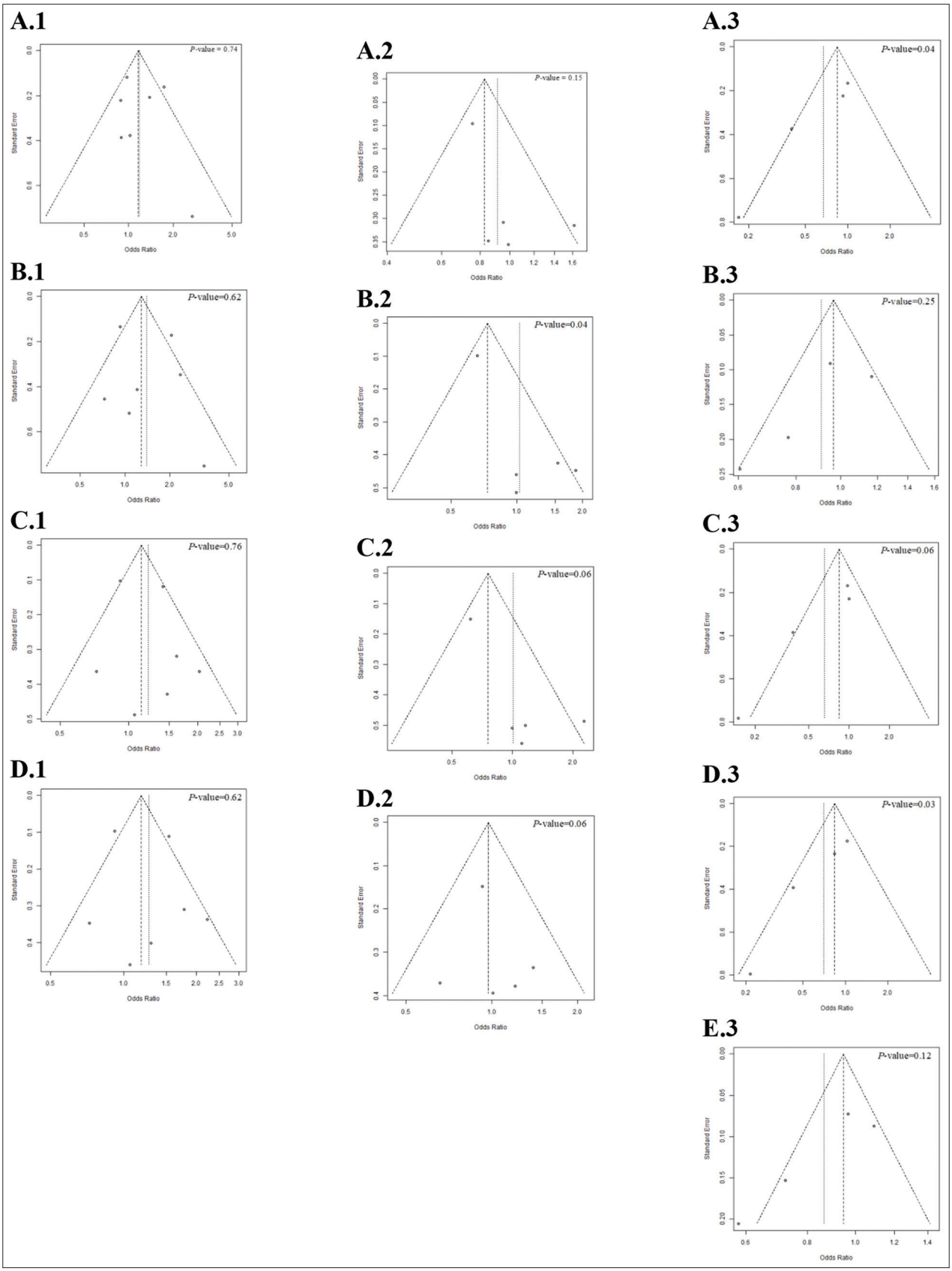

Figure S2: Funnel plots of publication bias for the relation between polymorphism and risk of Type 2 diabetes mellitus. rs2910164: (a1) dominant model, (b1) homozygote model, (c1) heterozygote model, and (d1) recessive model. rs11614913: (a2) overdominant model, (b2) dominant model, (c2) homozygote model, and (d2) heterozygote model. rs895819: (a3) recessive model, (b3) dominant model, (c3) homozygote model, (d3) heterozygote model, and (e3) allelic model

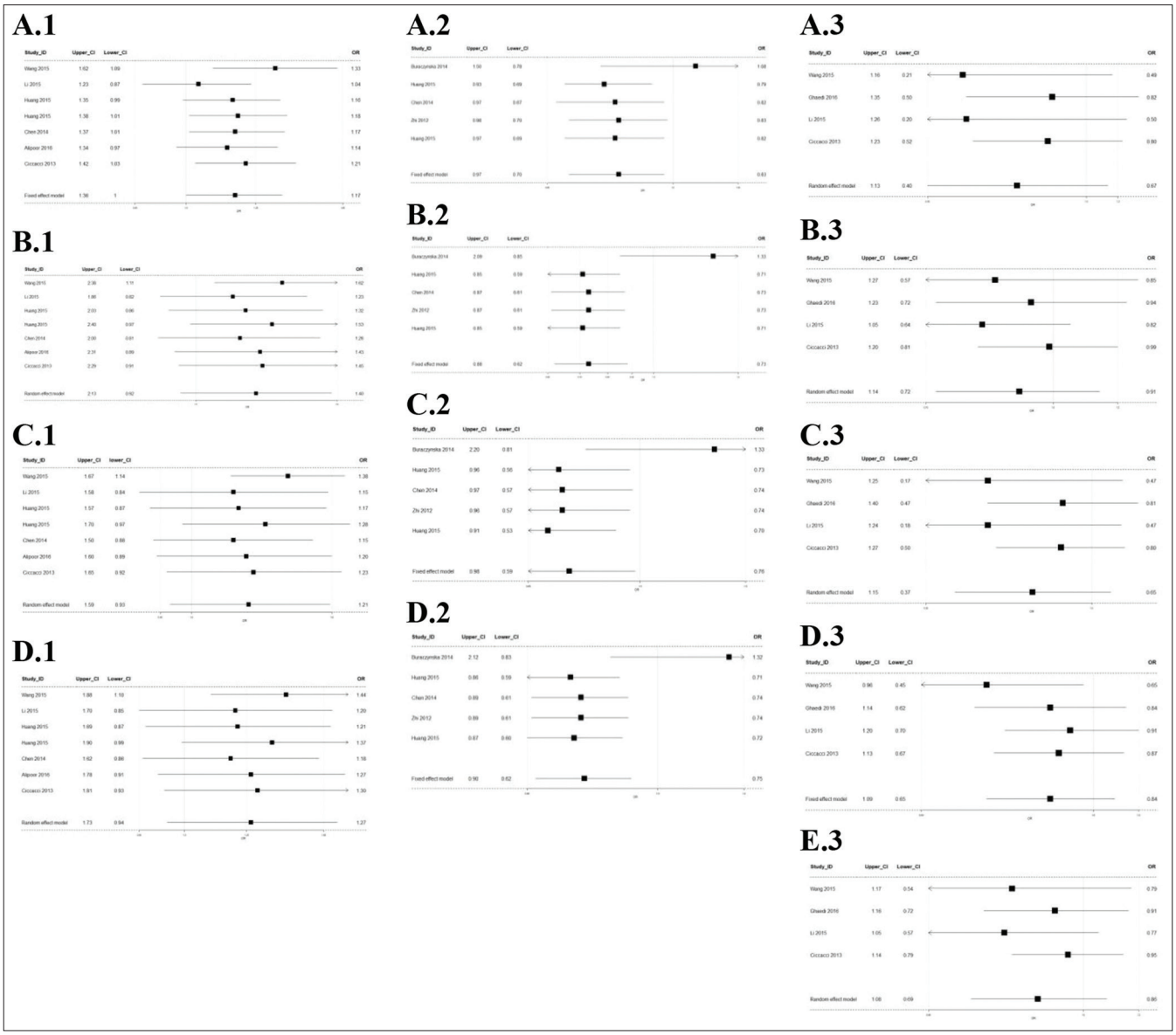

Figure S3: Sensitivity forest plots for the relation between polymorphism and risk of Type 2 diabetes mellitus. rs2910164: (a1) dominant model, (b1) homozygote model, (c1) heterozygote model, and (d1) recessive model. rs11614913: (a2) overdominant model, (b2) dominant model, (c2) homozygote model, and (d2) heterozygote model. rs895819: (a3) recessive model, (b3) dominant model, (c3) homozygote model, (d3) heterozygote model, and (e3) allelic model