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RESEARCH

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Adiponectin gene polymorphisms and risk of type 2 diabetes: an updated evidence for meta-analysis

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Abstract

Background: Growing body of evidence suggest the association between SNP − 11377 C > G and SNP + 276 G > T polymorphisms of adiponectin gene with type 2 diabetes (T2D). However, these findings have not been conclusive and consistent. The present study quantitatively evaluates the data on the association between DIPOQ − 11377C/G, and + 276G/T polymorphisms and risk of T2D through a meta-analysis.

Methods: A systematic search was performed in the PubMed, Web of science, Scopus and Cochrane library databases to extract published studies according to the inclusion criteria. Among the 741 studies, 391 of them were screened as full text and 31 studies were finally included in the meta-analysis. Analysis of data was performed using random-effects model. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to analyze the strength of association. Subgroup and meta-regression analyses were performed to identify the potential source of heterogeneity.

Results: The pooled analysis showed that there was no statistically significant association between genotypes of CC (OR = 0.76, 95% CI: 0.53–1.09, *P* = 0.14), CG (OR = 0.93, 95% CI: 0.72–1.20, P = 0.58) and GG (OR = 1, 95% CI: 0.80–1.26, P = 0.94) ADIPO − 11377 polymorphism with increased risk of T2D. In addition, the results revealed a trend toward an increased risk of T2D for the SNP + 276 TT genotype (OR = 0.87, 95% CI: 0.77–0.98, P = 0.026) as compared with the GT and GG genotypes. Subgroup analysis by ethnicity indicated significant association between the TT genotype of the SNP + 276 and increased risk of T2D among Europeans. Met-regression demonstrated significant association between the GT genotype of + 276 polymorphism with risk of T2D in male individuals (slope: 0.0006; 95% CI: 0.0002–0.0009; P < 0.001).

Conclusions: Collectively, our findings demonstrated a positive association between ADIPOQ + 276 G > T polymorphism with increased risk of T2D in male individuals with European ethnicity.

Highlights

Adiponectin (ADIPOQ) plays an important role in the development of type 2 diabetes and previous studies regarding the association between ADIPOQ polymorphisms and T2D risk reported conflicting results.

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We performed a meta-analysis to assess the association between two ADIPOQ polymorphisms [− 11377C/G (rs266729), and +276G/T (rs1501299)] and risk for T2D.

Odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were pooled to assess the association between four aforementioned polymorphisms and susceptibility to T2D.

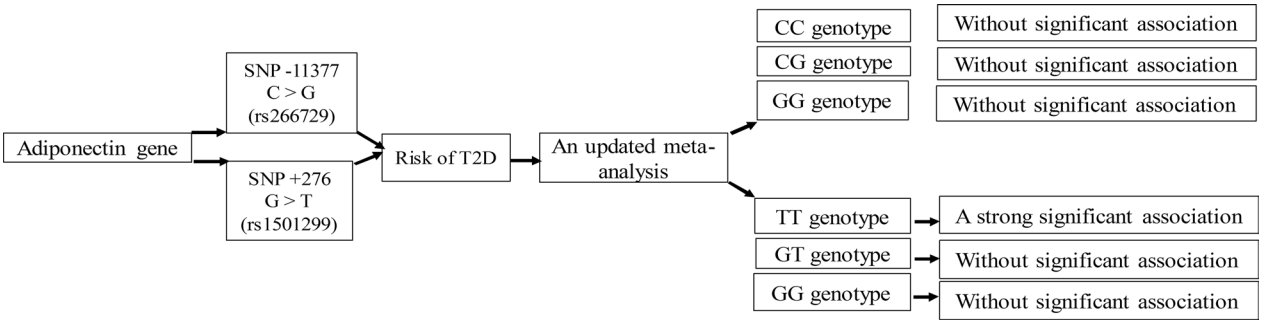
Overall, there was an association between ADIPOQ +276 G > T with increased T2D risk.

Subgroup by ethnicity suggested significant association between +276G/T polymorphism and T2D risk among European ethnicities.

Our findings evidence a positive association between ADIPOQ +276 G > T polymorphism with increased risk of T2D in male individuals with European ethnicity.

Keywords: Adiponectin, Type 2 diabetes, SNP − 11377, SNP + 276, Single nucleotide polymorphism

Graphical Abstract



Background

Type 2 diabetes (T2D), a metabolic disorder with severe complications, is a growing public health problem all over the world [1]. According to the latest statistics published by the International Diabetes Federation (IDF), about 500 million people worldwide have confirmed or diagnosed diabetes. It's predicted that approximately 693 million people will be affected by the disease by 2045[2]. Although insulin resistance is the main property of patients with T2D, some grade of insulin resistance has been observed in nondiabetic individuals [3]. It has been suggested that insulin resistance in T2D is caused by a combination of genetic and environmental factors [4]. Environmental risk factors contributing to T2D include central obesity, low exercise, high fat nutrition, hypertension, and impaired glucose tolerance [5, 6]. Furthermore, genetic factors play a potential role in the development of the disease among different populations. Individuals with genetic susceptibility have a higher risk of developing T2D than other people [4]. Several polymorphisms have been reported to be associated with T2D risk. Accumulating reports have revealed the main role of adiponectin gene polymorphism in the development of T2D [7]. The circulating levels of adiponectin, an adipose tissue-extracted protein (~30 kDa), have been shown to be decreased in patients with metabolic syndrome including T2D, and insulin resistance [8]. It is known that adiponectin has anti-inflammatory, anti-atherosclerotic, and antidiabetic properties [9]. Furthermore, it has been reported that plasma levels of adiponectin are also decreased in T2D condition. The ADIPOQ, adiponectin-coding gene, which is located in chromosome 3q27, proposed as a genomic locus for the T2D using genome-wide scans [7, 8]. The association of two common single nucleotide polymorphisms (SNPs) of ADIPOQ gene, rs266729 and rs1501299 with risk of T2D have been investigated in different populations worldwide [10, 11]. Given the many contradictions in the effect of adiponectin gene polymorphism in rs266729 and rs1501299 locus on T2D, we designed a study to find out the association of ADIPOQ gene polymorphism, rs266729 and rs1501299, with risk of T2D using meta-analysis.

Methods

Search strategy

This study was outlined according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [12]. To find the full texts related to this topic, our search was performed on PubMed, Scopus, Web of Science, and Embase databases up to July 15, 2021. The above databases were searched based on the following queries as key terms in the title and abstract: (Adiponectin gene polymorphism OR single nucleotide polymorphism (SNP) − 11377

C > G OR SNP − 11365 C > G AND type 2 diabetes), (Adiponectin gene polymorphism OR SNP + 276 G > T AND type 2 diabetes), (SNP + 276 OR rs1501299 of adiponectin gene AND type 2 diabetes), (SNP − 11377 OR rs266729 of adiponectin gene AND type 2 diabetes). The wild-card term "*" was used to improve the sensitivity of the search strategy. We enhanced this search by scanning the reference lists of relevant articles. The search was limited to previous studies published in English language. Two researches (MA and MT. G) assessed the full text independently, Disagreements were resolved by consensus-based discussion by third party (M. N).

Inclusion and exclusion criteria

According to the topic of this study, inclusion criteria included: (1) observational (cohort, case –control) studies which evaluated the association between the polymorphisms of SNP − 11377 and SNP + 276 of adiponectin gene in patients with T2D and healthy controls, (2) studies providing relevant information with topic such as genotype frequency for assessment of odds ratio (ORs) and 95% confidence intervals (95% CI), (3) studies with human subjects, (4) the control group with healthy individuals. The following items were excluded from the study: (1) animal and in vitro studies, (2) observational studies were not related to the association between the polymorphism of adiponectin gene and T2D, (3) conference abstracts, reviews, case reports, or editorials; (4) lack of sufficient information on adiponectin gene polymorphisms and susceptibility to T2D, and (5) studies with insufficient details of study methodology.

Study selection

To find the original articles associated with this subject, titles and abstracts of all retrieved studies were screened separately by two reviewers to identify the relevant articles. According to the predefined inclusion and exclusion criteria, the articles were selected for the meta-analysis.

Data extraction

Selected articles were reviewed and data were independently retrieved by two researches using a standardized electronic form. The following information was extracted: (1) first author name, (2) publication year, (3) study location (country), (4) study designs which were classified into case–control and cohort, (5) genotyping methods, (6) ethnicity, (7) target population which was categorized as Asian, American, African and European, (8) sample sizes of case and controls (cases are individuals with T2D), (9) genotype and/or allele frequencies in case and control groups, (10) P-value of Hardy–Weinberg equilibrium (HWE) and (11) Newcastle Ottawa Scale (NOS) score. Above data were extracted for two polymorphisms of SNP − 11377 and SNP + 276 separately.

Quality assessment

The quality of all eligible studies was assessed by two researches using the Newcastle Ottawa Scale (NOS) [13]. The NOS is composed of 3 items: selection, comparability, and exposure, with a total score of 9. Based on the final score, the studies could be classified into high quality (score more than 6), medium quality (score between 4 and 6), and low quality (score less than 4). Any disagreements were adjudicated through discussion.

Statistical analysis

The data were analyzed based on random-effect model. Effect size was expressed as odds ratio with 95% CIs to evaluate the associations between SNP − 11377 C > G (rs266729) and SNP + 276 G > T (rs1501299) of adiponectin gene and risk of T2D. Higgin's index and Cochrane's Q test were applied to evaluate heterogeneity among included studies. If the Higgin's index revealed a P-value of $I^2 < 50\%$, the fixed-effects model (the Mantel–Haenszel method) was selected to pool the data. Otherwise, the random effects model (the DerSimonian and Laird method) was used. Potential publication bias was calculated using Begg's funnel plot, the funnel plot of the study precision (inverse standard error) by effect size (log OR) and Egger's weighted regression tests [14, 15]. If publication bias observed, Duval and Tweedie "trim and fill" method was used to adjust pooled OR and 95% CI. Sensitivity analysis was performed using "leave-one-out" method with removing one study in turn and reporting the analysis. Subgroup and random-effect meta-regression were conducted. Subgroup analyses were performed based on subgroups of study design (cohort and case–control), ethnicity (Asian, American, European and African) and sex (male and female). To find significant heterogeneity, meta-regression was performed using unrestricted maximum likelihood method to assess the association between estimated effect size of the polymorphisms of adiponectin gene and risk of T2D with variables of sex, age and ethnicity. Statistical analyses were conducted using the Comprehensive the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [16].

Results

Process of study selection

The search provided 741 records. 350 items were removed from the study because of the duplication. After screening of the title and abstract of full text, 31 studies were identified according to the inclusion criteria. 25 relevant studies were included in − 11,377 C > G (rs266729) analysis and 20 articles were included in + 276

G > T (rs1501299) analysis. Some articles included in this meta-analysis was common for these SNPs. The reasons for excluding the remaining 360 articles were: articles that were reviews, editorial, conference abstract and brief report (n = 80), articles that were performed in animal and in vitro models (n = 50), articles evaluating adiponectin gene polymorphisms in patients without T2D (n = 90), articles didn't assess SNPs of − 11377 and + 276 in T2D patients (n = 80), articles didn't provide sufficient information on the numbers of genotypes (n = 60). A summary of the study selection process according to the PRISMA flowchart is shown in Fig. 1.

Characteristics of included studies

In total, 31 studies were included according to the inclusion criteria. Out of these 31 studies, 25 studies were allocated to evaluation of SNP − 11377 C > G (rs266729) in subjects with T2D and 20 studies to SNP + 276 G > T (rs1501299) analysis. Of 20 studies for the analysis of SNP + 276, only 6 studies were different. In the 25 studies associated with − 11377 C > G, 11,963 cases and 15,527 controls were included. Of 11,963 cases, 6098 cases were males and 5865 cases were females. In the 20 studies involved in + 276 G > T analysis, 8658 cases and 16,498 controls were included. In the cases group of SNP + 276 analysis, 4130 cases were males and 4528 cases were

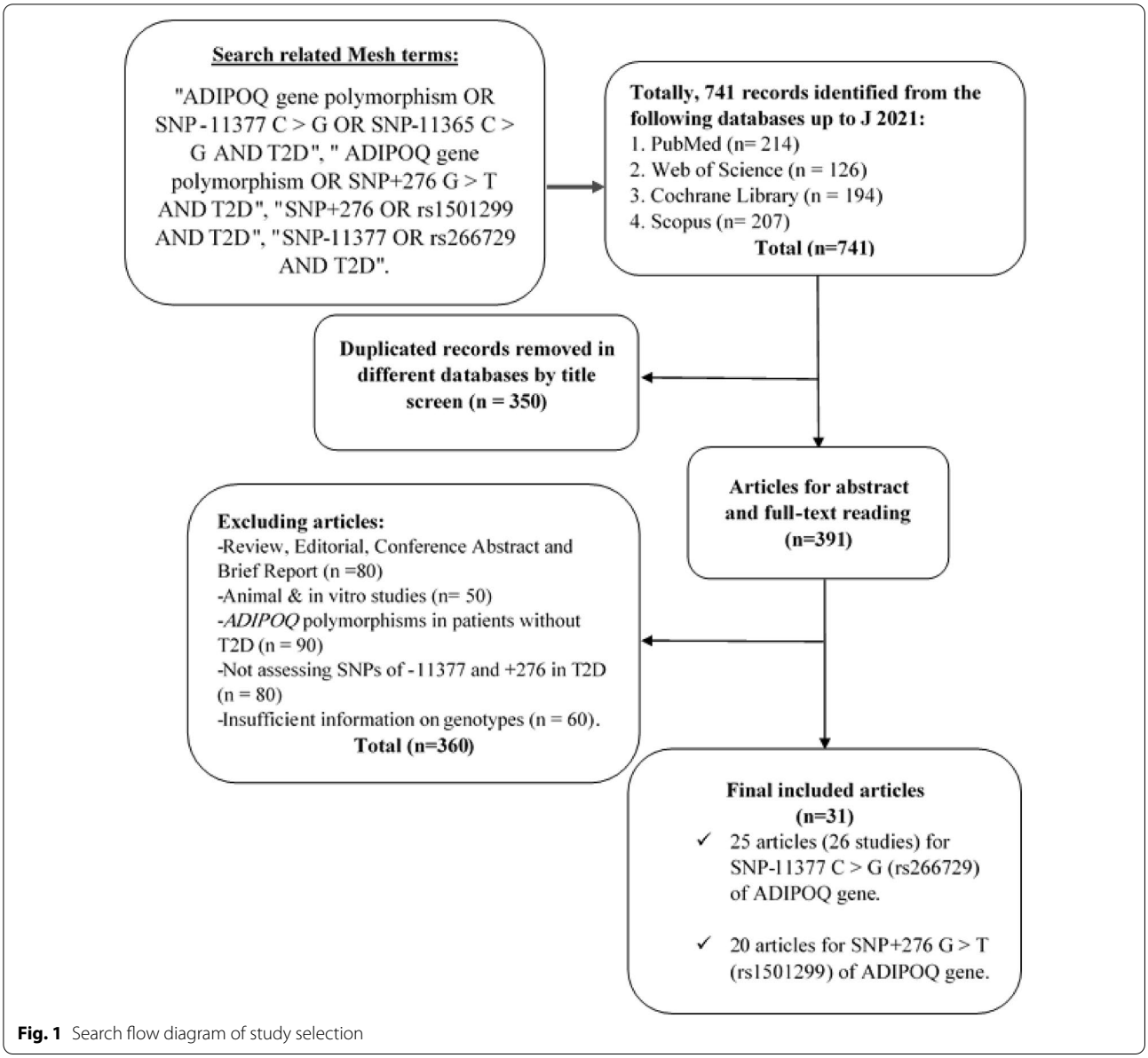


Fig. 1 Search flow diagram of study selection

females. Of the 25 studies for analysis of SNP − 11377 C > G, 18 were case–control studies and seven were cohort studies. Among 20 studies for SNP + 276 G > T analysis, 13 studies were case–control studies, six studies were cohort studies and one study was a cross-sectional. Selected studies were conducted in individuals with T2D. Included articles were published between 2002 and 2021. The examined races were Asian, American, European and African. The baseline and demographic characteristic of the eligible studies were summarized in Tables 1 and 2.

Quality assessment

Evidence quality scores were summarized in Tables 1 and 2 as a column. According to the NOS score, quality scores ranged from 7 to 9. The seven demonstrates a moderate score and 9 means a strong score. The quality of the included studies was moderate to strong in all studies.

Meta-analysis results

Association between the SNP − 11337 C > G polymorphism of adiponectin gene and risk of T2D

Meta-analysis of data showed a significant heterogeneity among the included studies of genotyping frequencies of CC ($I^2 = 97.7\%$, $P < 0.001$), CG ($I^2 = 95.3\%$, $P < 0.001$) and GG ($I^2 = 75.7\%$, $P < 0.001$) of − 11377 C > G polymorphism of adiponectin gene and risk of T2D. Thus, the random-effects model was used. The results revealed that there were no significant association between genotypes of CC (OR = 0.76, 95% CI: 0.53–1.09, $P = 0.14$) (Fig. 2), CG (OR = 0.93, 95% CI: 0.72–1.20, $P = 0.58$) (Fig. 3) and GG (OR = 1, 95% CI: 0.80–1.26, $P = 0.94$) (Fig. 4) of − 11377 C > G polymorphism and risk of T2D. In addition, we performed sensitivity analysis using "leave-one-out" method to assess the stability of overall results. The effect sizes obtained from three genotypes were robust and removing any of the studies in turn did not change the effect on estimated overall results significantly.

Association between the SNP + 276 G > T polymorphism of adiponectin gene and risk of T2D

With respect to the presence of obvious heterogeneity among the genotypes of GT ($I^2 = 93.8\%$, $P < 0.001$) and GG ($I^2 = 96.7\%$, $P < 0.001$). The random-effects model was adopted, whereas for the analysis of the genotype of TT ($I^2 = 38\%$, $P = 0.05$), the fixed- effects model was used. In the whole populations including SNP + 276 G > T polymorphism, a significant association was found between the genotype TT of SNP + 276 G > T polymorphism of adiponectin gene and susceptibility to T2D (OR = 0.87, 95% CI: 0.77–0.98, $P = 0.026$) (Fig. 5). There was no statistical significant association between the genotypes of GT and GG of SNP + 276 G > T polymorphism of adiponectin gene and risk of T2D (OR = 0.79, 95% CI: 0.60–1.02, $P = 0.07$) (Fig. 6) and (OR = 0.76, 95% CI: 0.56–1.04, $P = 0.09$) (Fig. 7), respectively. We performed sensitivity analysis using "leave-one-out" method by removing the studies by sequence. The results showed that omission of the studies did not have a significant effect on pooled ORs. These results indicating that our meta-analysis had reliable and stable results.

Publication bias

Funnel plot, Begg's rank correlation and Egger's regression tests were performed to find the potential publication bias among the studies. Visual inspection of the funnel plots of genotypes in polymorphisms of − 11377 and + 276 showed no significant publication bias among included studies (Fig. 8). Begg's rank correlation test for genotype of CC (P = 0.62), CG (P = 1) and GG (P = 0.42) of − 11377 C > G polymorphism and for genotypes of TT (P = 0.58), CG (P = 0.29) and GT (P = 0.25) of + 276 G > T polymorphism were not significant. In addition, the results of Egger's regression test also showed no evidence of significant publication bias for genotypes of − 11377 polymorphism (P = 0.49 for CC, P = 0.51 for CG and P = 0.80 for GG) and for genotypes of + 276 polymorphism (P = 0.30 for TT, P = 0.27 for GG and P = 0.49 for GT). The observed publication bias was imputed using trim-and-fill method. 23 missing studies for the genotypes of CC, CG and GG of − 11377 polymorphism were imputed leading to correct pooled analysis that less than the overall effect size (OR: 0.54; 95% CI: 0.40–0.73), (OR: 0.75; 95% CI: 0.60–0.94) and (OR: 0.95; 95% CI: 0.76–1.17), respectively. The classic fail-safe N method showed that collectively 898 theoretically missing studies for − 11377 polymorphism would be needed to determine the pooled calculated effect size significantly. In addition, eight potentially missing studies were imputed for the genotypes of TT, GT and GG of + 276 polymorphism that equal with the initial estimate (OR: 0.84; 95% CI: 0.72–0.98), (OR: 0.54; 95% CI: 0.40–0.73) and (OR: 0.54; 95% CI: 0.40–0.73), respectively. The classic fail-safe N method for + 276 polymorphism indicated that 457 theoretically missing studies were required to bring P-value to < 0.05 (Figs. 8, 9).

Subgroup analyses

Subgroup analyses were conducted to find the possible source of significant heterogeneity among the included studies in − 11377 C > G and + 276 G > T polymorphisms of adiponectin gene using the following subgroups: sex (male *vs.* female), study design (case–control *vs.* cohort) and ethnicity (American vs. European vs. Asian vs. African).

Table 1 Main characteristics of studies included for investigation of association between SNP − 11377 (rs266729) and risk of type 2 diabetes

Author's name	Country	Study design	Sex ratio (M/F)	Genotyping method	Ethnicity	Target population	Disease	Sample size (Diabetes)	Sample size (control)	Case			Control			P-value for HWE	NOS score
										GG	CG	CC	GG	CG	CC		
Zhang et al. [17]	Sweden	Cohort	313/265	DASH	Caucasian	American	T1D	578	599	35	232	310	29	230	340	0.022	7
Hara et al. [18]	Japan	Case–control	267/117	SNaPshot ddNTP	Asian	Japanese	T2D	384	480	24	127	233	37	178	265	0.77	8
Vasseur et al. [19]	France	Case–control	604/769	Ampli-Fluor	Caucasians	French	T2D	1373	743	46	274	300	45	264	382	0.71	8
Gu et al. [20]	Sweden	Case–control	56/50	DASH	Caucasians	Swedish	T2D	106	497	11	34	58	53	186	247	0.25	8
Hu et al. [21]	USA	Nested Case–control	642F	TaqMan	Caucasians	Caucasians	T2D	642	995	41	244	357	59	379	557	0.75	9
Gibson et al. [22]	UK	Case–control	390/422	Ampli-Fluor	Caucasians	French	T2D	812	1044	59	320	433	70	402	572	0.003	7
Vasseur et al. [23]	France	Case–control	115/329	TaqMan	Caucasians	French	T2D	444	535	10	98	123	13	90	167	0.04	8
Tso et al. [24]	Hong Kong	Cohort	76/82	PCR–RFLP	Chinese	Chinese	T2D	50	104	10	62	86	8	44	52	0.1	7
Schwarz et al. [25]	Germany	Cohort	224/191	TaqMan	Caucasians	German	T2D	365	323	35	143	187	20	120	183	0.003	7
Gable et al. [26]	UK	Cohort	169 M	TaqMan	Caucasians	European	T2D	169	2767	15	60	83	175	1038	1440	0.43	6
Olckers et al. [27]	South Africa	Cohort	31/196	TaqMan	Black	South African	T2D	227	226	1	60	166	5	60	161	0.05	6
Sun et al. [28]	China	Case–control	138/117	PCR–RFLP	Chinese	Chinese	T2D	255	120	14	119	122	5	41	74	0.05	7
Hivert et al. [29]	USA	Cohort	515/580	MS	white	white	T2D	1095	1448	11	98	124	146	784	1259	2.52	7
Wang et al. [30]	China	Case–control	394/591	TaqMan	Han Chinese	Han Chinese	T2D	985	1050	79	379	479	61	408	529	2.31	7
Yang et al. [31]	China	Case–control	75/137	PCR–RFLP	Han Chinese	Han Chinese	T2D	212	585	22	90	100	50	210	325	3.6	7
Wang et al. [32]	China	Case–control	196/142	PCR–RFLP	Chinese	Chinese	T2D	338	460	21	101	165	15	161	243	3.53	8
Chiodini et al. [33]	Italy	Cohort	285/218	TaqMan	Italians	Italians	T2D	503	503	22	159	322	22	160	321	0.72	9
Karimi et al. [34]	Iran	Case–control	36/44	PCR–RFLP	Iranian	Iranian	T2D	80	80	2	32	441	1	29	50	0.65	6
Palit et al. [35]	India	Case–control	142/143	PCR–RFLP	Gujarat	Indian	T2D	285	286	148	148	137	131	131	155	0.2	7

Table 1 (continued)

Author's name	Country	Study design	Sex ratio (M/F)	Genotyping method	Ethnicity	Target population	Disease	Sample size (Diabetes)	Sample size (control)	Case			Control			P-value for HWE	NOS score
										GG	CG	CC	GG	CG	CC		
Palit et al.	India	Case–control	217/174	PCR–RFLP	Jand K	Indian	T2D	503	290	194	194	309	139	139	151	0.2	8
Ramya et al. [36]	India	Case–control	497/603	PCR–RFLP	South Indian	Indian	T2D	1073	1053	71	71	572	49	383	621	0.004	6
Mtiraoui et al. [37]	Tunisia	Case–control	422/495	TaqMan	Cauca-sian	Tunisia	T2D	917	748	89	89	4231	50	279	419	5.1	9
Cui et al. [4]	China	Case–control	85/118	IMLDR	Chinese	Chinese	T2D	203	203	10	10	110	15	83	105	0.47	7
Nomani et al. [38]	Iran	Case–control	43/57	PCR–RFLP	Iranian	Iranian	T2D	100	95	3	3	61	1	28	66	0.35	8
Alimi et al. [11]	Iran	Case–control	57/43	Tetra ARMS-PCR	Iranian	Iranian	T2D	100	110	9	9	33	9	46	55	0.041	8
Populaire et al. [39]	Japan	Case–control	82/82	PCR–RFLP		Japanese	T2D	164	183	11	11	105	10	87	86	0.002	6

Subgroup analysis of − 11377 polymorphism

The results of subgroup analyses for genotypes of CC, CG and GG of − 11377 C > G polymorphism of adiponectin gene based on sex, study design and ethnicity showed that there was no significant association between sex, study design and ethnicity and susceptibility to T2D compared to healthy control (Table 3).

Subgroup analysis of + 276 polymorphism

In the + 276 G > T polymorphism with genotypes of TT, GT and GG, subgroup analyses were performed according to the sex, study design and ethnicity. No statistically significant between SNP + 276 (rs1501299) and risk of T2D was found neither in sex (males and females) nor in the study design (case–control and cohort studies). On the other hand, the results of the ethnicity subgroup revealed that + 276 (rs1501299) dominant model (TT *vs.* CG + GG) of European ethnicity relative to other ethnicities could be associated with the risk of T2D. The results of sex subgroup showed no significant association between male and female and the risk of T2D in genotypes reported for + 276 polymorphism of adiponectin gene (Table 4).

Meta-regression analysis

Random-effects meta-regression showed no significant association between genotypes of SNPs of − 11377 with potential confounding factors such as male (slope: 0.0001; 95% CI: − 0.0005 to 0.0007; P = 0.69), female (slope: − 0.0001; 95% CI: − 0.0007 to 0.0004; P = 0.61), age (slope: − 0.43; 95% CI: − 0.82 to 0.91; P = 0.60) and genotyping method (slope: 0.013; 95% CI: − 1.53 to 1.37; $P = 0.94$). On the other hand, for the genotypes of SNP of + 276, no statistical significant association with age and genotyping method was found. While, there was a significant positive association between GT genotype and male individuals (slope: 0.0006; 95% CI: 0.0002 to 0.0009; P < 0.001) in comparison with female individuals (slope: 0.0002; 95% CI: -0.0001 to 0.0005; P = 0.06)]. The analysis of moderator variables showed that they were not the main cause of heterogeneity in the included studies, however sex may modify this association.

Discussion

This meta-analysis carried out to analyze the correlation between adiponectin (ADIPOQ) gene polymorphisms (SNP − 11377 C > G and SNP + 276 G > T) and risk of T2D among included studies. There are many fundamental mechanisms involved in T2D pathogenesis. However, adiponectin gene polymorphisms have been associated with T2D. In this regard, several studies demonstrated a significant difference in the risk of T2D among individuals with genotypes of adiponectin gene [48, 49]. The adiponectin gene is located on human chromosome 3q27, which is composed of three exons with span 17 kb as a susceptibility locus for T2D [50]. Previous studies have reported conflicting and inconsistent results on the association of ADIPOQ gene − 11377 C > G and + 276 G > T polymorphisms and the risk of T2D. Therefore, we designed this meta-analysis to determine whether these SNPs in the adiponectin gene were correlated with T2D risk in the whole population. In the present meta-analysis, we found a significant association between the TT genotype of + 276 G > T rs1501299 and increased risk of T2D. On the other hand, this meta-analysis demonstrated that the genotypes of (CC, CG and GG) of − 11377 C > G (rs266729) of ADIPOQ gene was no associated with T2D risk.

We performed subgroup analyses according to ethnicity, study design and sex. Subgroup analyses by ethnicity and sex suggested significant association between + 276 G > T polymorphism and T2D risk among male individuals in European population compared to other ethnicities and female individuals. Moreover, we did not find any correlation between T2D risk and ADIPOQ − 11377 C > G polymorphism in the whole population. The obtained results in this study were similar to several previous studies with populations of different ethnicities [24, 51], while, some studies have reported the inconsistent results such that there was no significant association of SNP − 11377 C > G and SNP + 276 G > T with risk of T2D [52–54]. The absence of significant association between genotypes and allele of G and C − 11377 C > G of ADIPOQ gene and risk of T2D might be due to the following results: Differences in the ADIPOQ − 11377 G > C genotype distribution in the ethnic background, location of these SNPs on the ADIPOQ gene, as such SNP − 11377 C > G is located in the ADIPOQ gene promoter region, whereas + 276 G > T is located in the intron 2 region. Thus, studies suggested that genetic variation in the promoter region of this gene with SNP − 11377 could reduce ADIPOQ promoter transcription activity leading to the loss of the relationship between SNP − 11377 and T2D disease. In addition, the ethnicities involved in these two SNPs were different, the majority of populations for − 11377 C > G were Asian, while, those for + 276 G > T were European or Asian.

In order to find the observed heterogeneity, subgroup analyses were performed. Firstly, we analyzed the association between the genotypes (TT, GT, GG and allele C vs. allele G) of + 276 G > T with risk of T2D by subgroup of ethnicity (Asian, European, American and African). The results showed no significant association

Table 2 The baseline information of studies included for assessment of association between SNP + 276 (rs1501299) and risk of type 2 diabetes

Author's name	Country	Study design	Sex ratio of case (M/F)	Genotyping method	Ethnicity	Target population	Sample size (Diabetes)	Sample size (Control)	Case			Control			P-value for HWE	NOS score
									TT	GT	GG	TT	GT	GG		
Hara et al. [18]	Japan	Case–control	267/117	SNaPshot ddNTP	Asian	Japanese	384	480	18	142	224	41	203	236	0.08	8
Menzaghi et al. [40]	Italy	Case–control	167/143	PCR-hydridization	Caucasian	Italian Caucasian	310	304	28	124	158	27	117	160	0.7	8
Populaire et al. [39]	Japan	Case–control	82/82	PCR–RFLP	Asian	Japanese	164	177	22	55	87	18	80	79	0.12	9
Gu et al. [20]	Sweden	Case–control	56/50	DASH	Caucasian	Swedish Caucasians	106	497	101	46	50	42	206	249	0.004	8
Fumeron et al. [41]	France	Cohort	150/79	fluorogenic	Caucasian	French Caucasian	229	3072	15	64	97	305	1773	2419	0.67	7
Hu et al. [21]	USA	Nested Case–control	642F	TaqMan	Caucasian	Caucasians	642	995	54	266	322	73	399	523	0.07	9
Gibson et al. [22]	UK	Case–control	390/422	Ampli-Fluor	Caucasian	French Caucasian	701	893	51	276	374	75	368	450	0.0003	7
de Courten et al. [42]	USA	Cohort	496/584	PCR–RFLP	Indian	Pima Indians	1080	1080	26	200	371	24	133	249	1.2	7
Lee et al. [43]	Korea	Case–control	237/256	SNaPshot ddNTP	Korean	Korean population	493	427	38	231	224	35	167	225	0.26	6
Sanchez et al. [44]	Finland	Cross-sectional	356/391	PCR-SnaPshot	Spanish	Spanish	747	747	5	35	24	39	231	260	1.61	6
Vasseur et al. [23]	France	Case–control	115/329	LightCycler technology	Caucasians	French Caucasians	444	535	23	89	97	23	93	132	0.34	8
Tso et al. [24]	Hong Kong	Cohort	76/82	PCR–RFLP	Chinese	Chinese	137	125	17	59	82	15	40	49	2	7
Gable et al. [26]	UK	Cohort	169 M	TaqMan	Caucasians	European Caucasian	169	2767	10	59	87	175	1015	1470	0.92	6
Yang et al. [45]	China	Case–control	75/137	SEQUENOM genotyping system	Chinese	Chinese	637	801	42	206	191	661	408	499	2.04	8
Hivert et al. [29]	USA	Cohort	515/580	Mass spectroscopy	White	White	282	1448	15	61	100	111	641	864	0.28	7

Table 2 (continued)

Author's name	Country	Study design	Sex ratio of case (M/F)	Genotyping method	Ethnicity	Target population	Sample size (Diabetes)	Sample size (Control)	Case			Control			P-value for HWE	NOS score
									TT	GT	GG	TT	GT	GG		
Magdalena et al. [46]	Poland	Case–control	217/278	PCR–RFLP	Caucasian	Polish Caucasian	495	435	11	131	353	11	150	274	0.024	9
Mohammadzadeh et al. [47]	Iran	Case–control	26/24	PCR–RFLP	Iranian	Iranian	50	52	2	19	29	4	21	27	0.41	8
Wang et al. [32]	China	Case–control	394/591	TaqMan	Han	Han Chinese	985	1050	66	397	451	72	398	496	0.41	7
Chiodini et al. [33]	Italy	Cohort	285/218	TaqMan	Italians	Italians	503	503	52	206	245	66	198	239	0.02	9
Alimi et al. [11]	Iran	Case–control	57/43	Tetra ARMS-PCR	Iranian	Iranian	100	110	8	45	47	8	44	58	0.3	6

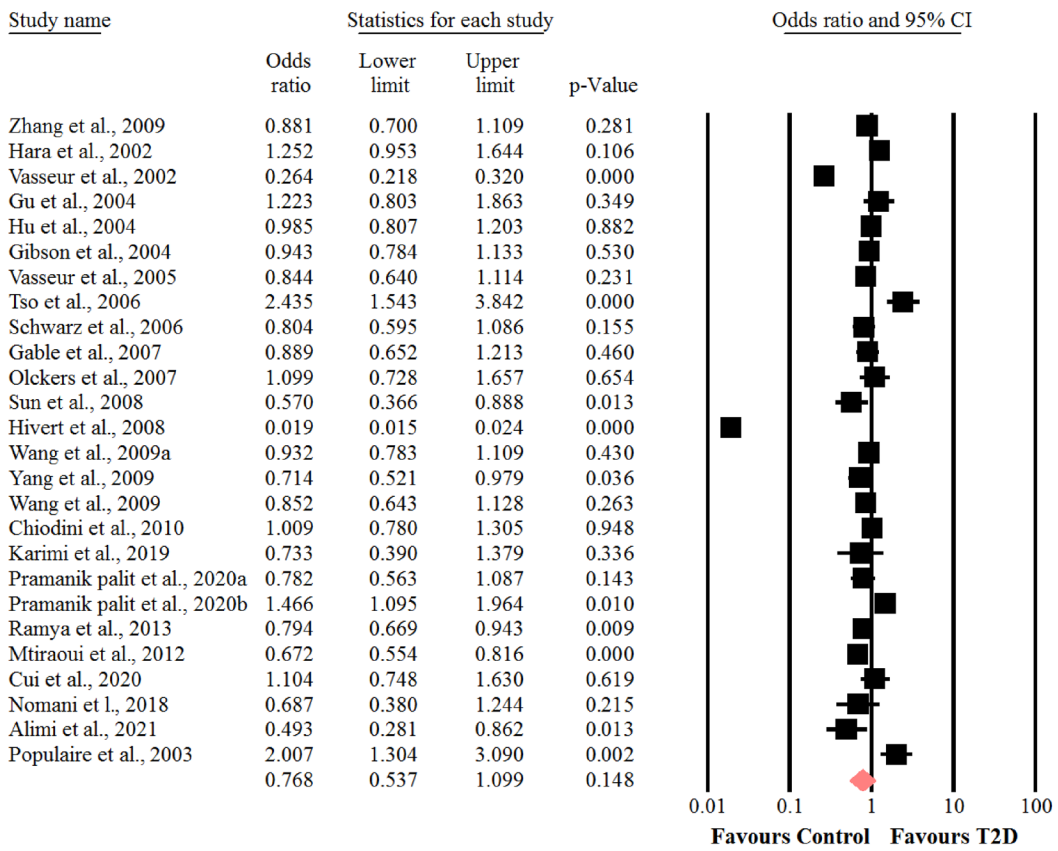


Fig. 2 Forest plot for the association between the GG genotype of SNP − 11377 C > G and risk of T2D in the whole populations

between genotypes of − 11377 C > G and the risk of T2D, whereas, the TT genotype of + 276 G > C in European population is significantly associated with increased risk of T2D. In the next step, we analyzed this association in subgroups of sex and study design. The pooled results from two SNPs indicated no significant correlation between these SNPs and the risk of T2D in subgroups stratified to sex and study design. For confirming these results, meta-regression was conducted. We found a strong association between susceptibility to T2D and sex in the GT genotype of + 276 G > T. Our meta-analysis data have suggested that males are significantly susceptibility to T2D. This provides some evidence that the association between + 276 (TT and GT) and T2D might be mediated by sex. Therefore, sex may modify this association.

In 2011, Hara et al. have reported that SNP + 276 GG genotype of ADIPOQ gene was associated with T2D in the Japanese population [55]. This result agreed with our meta-analysis data. In contrast to our finding, Hara et al. was found that G vs. C allele of − 11377 C > G rs266729 might be associated with T2D risk. In this regard, there are several explanations for this inconsistency. First, the difference may be owing to the small sample size and the low number of studies in the meta-analysis by Hara et al. relative to our study. Second, the rs266729 polymorphism in the adiponectin gene is not considerable SNP in the whole population. Third, T2D is a complex disease

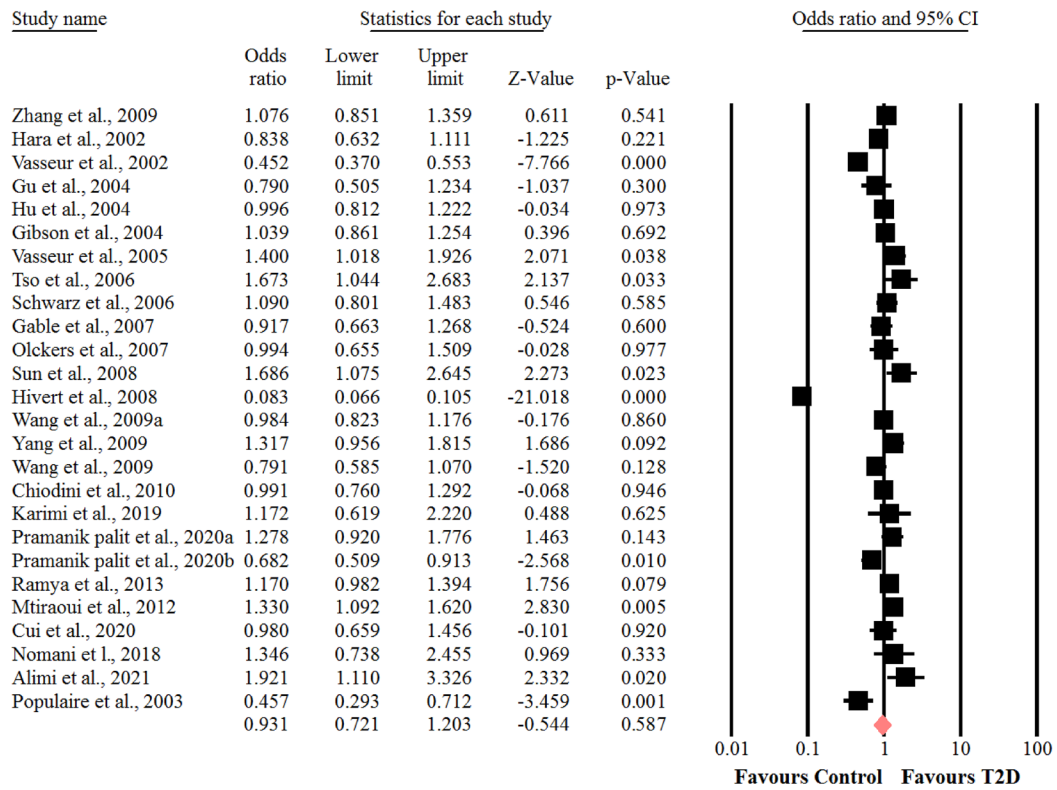


Fig. 3 Forest plot for the association between the CG genotype of SNP — 11377 C > G and risk of T2D in the whole populations

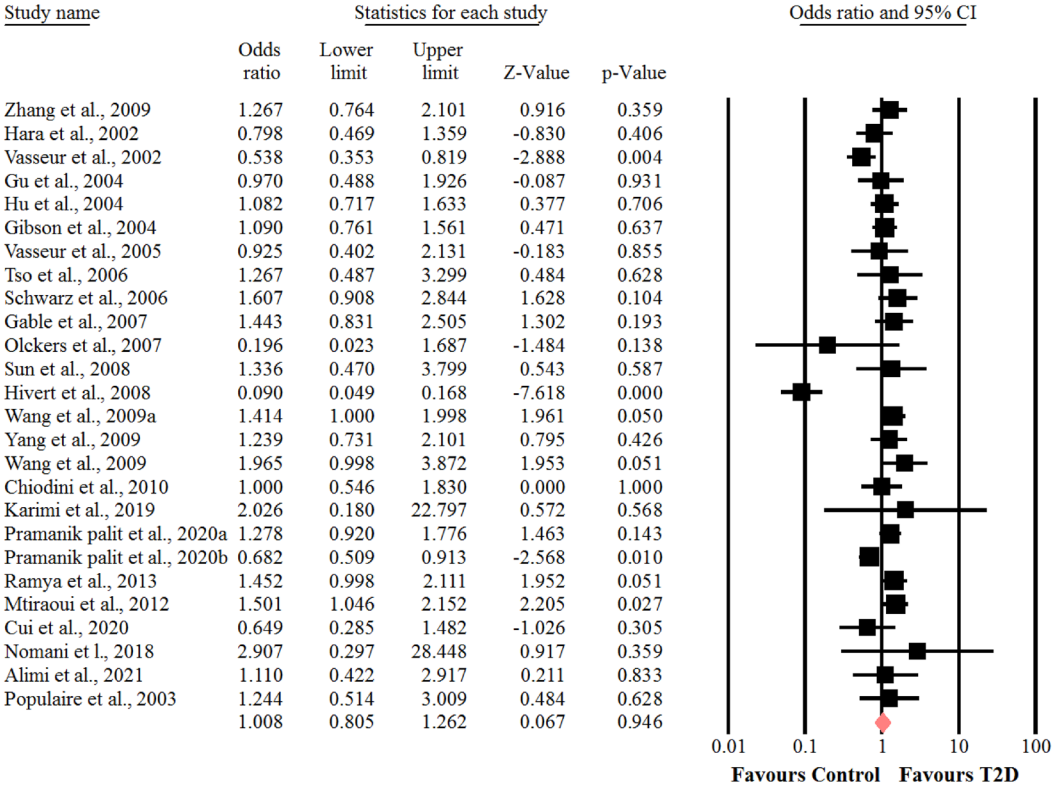


Fig. 4 Forest plot for the association between the GG genotype of SNP — 11377 C > G and risk of T2D in the whole populations

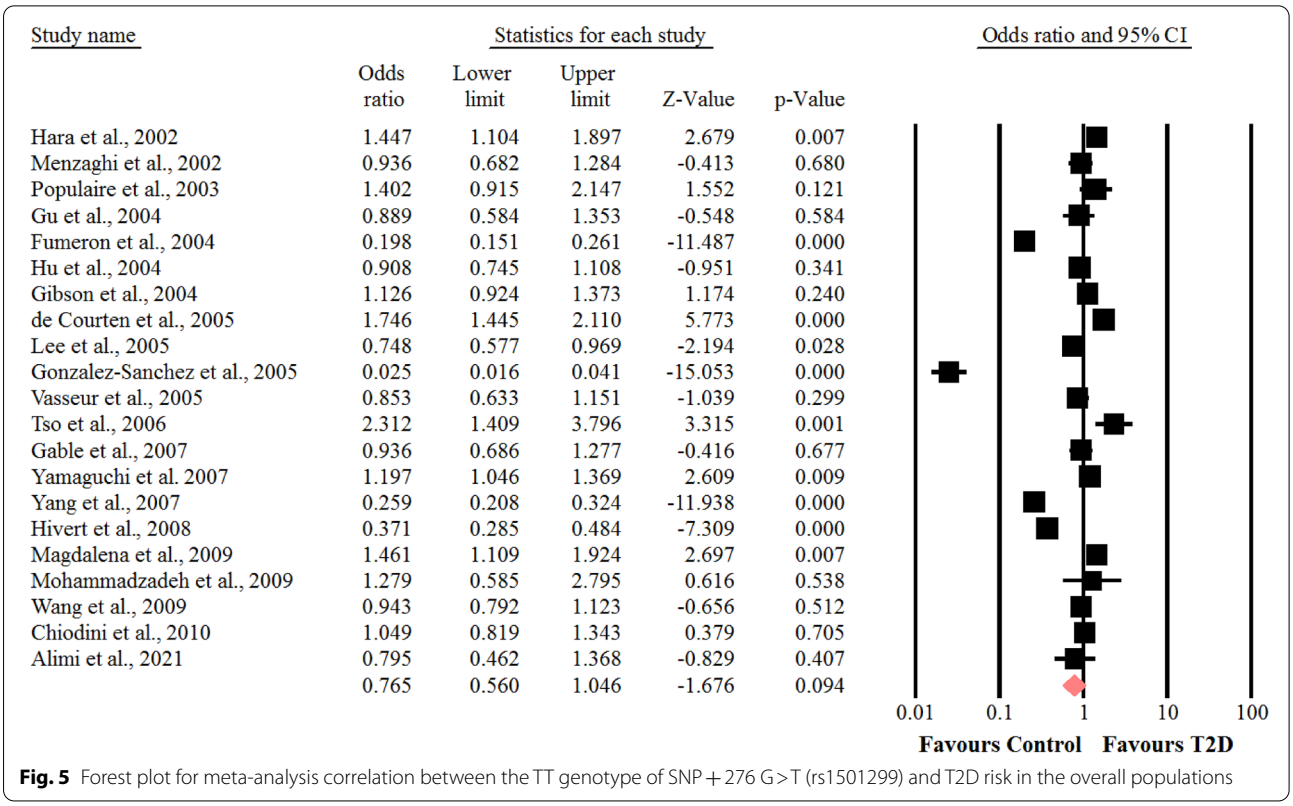


Fig. 5 Forest plot for meta-analysis correlation between the TT genotype of SNP + 276 G > T (rs1501299) and T2D risk in the overall populations

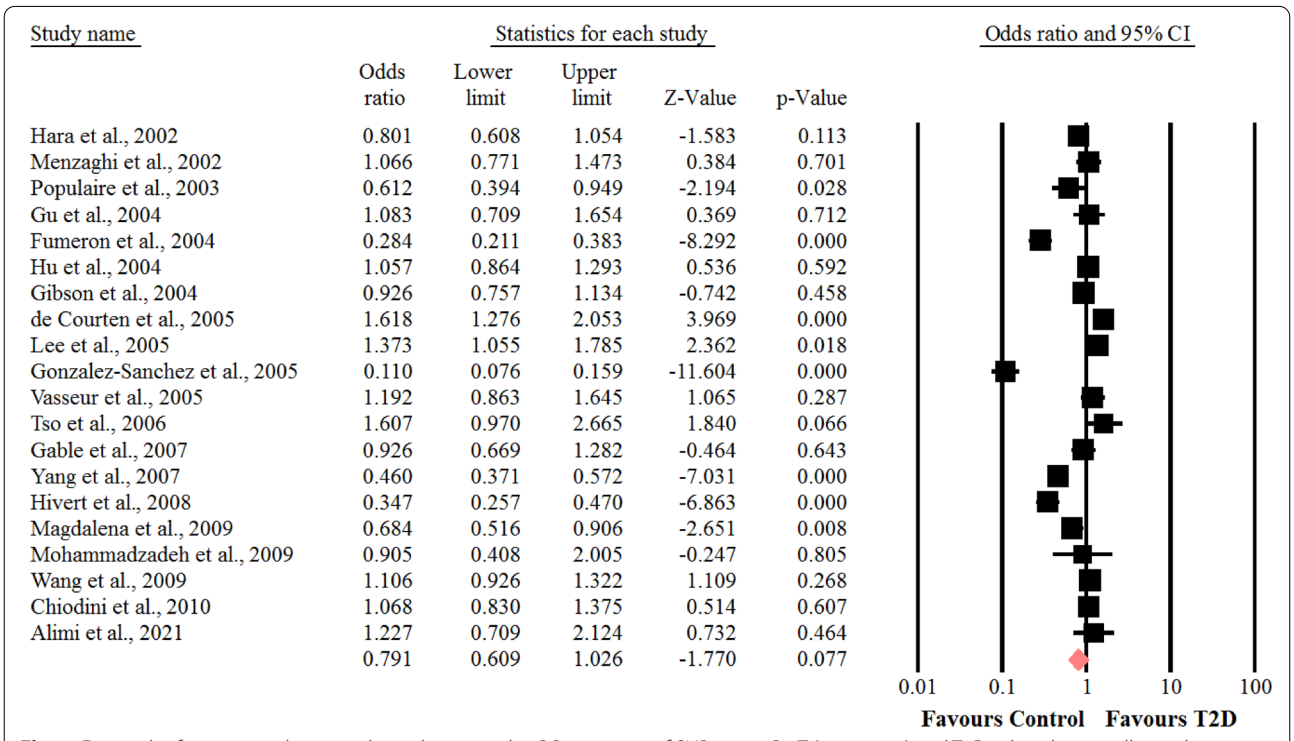


Fig. 6 Forest plot for meta-analysis correlation between the GG genotype of SNP + 276 G > T (rs1501299) and T2D risk in the overall populations

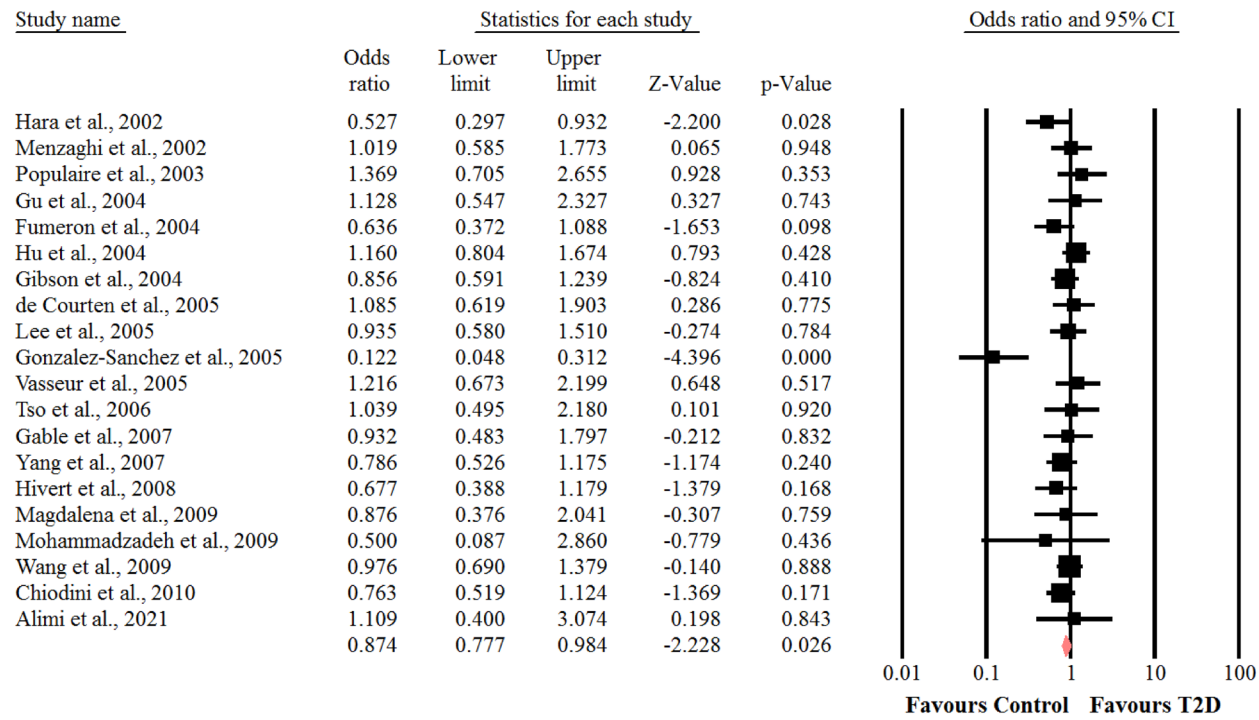


Fig. 7 Forest plot for meta-analysis correlation between the GT genotype of SNP + 276 G > T (rs1501299) and T2D risk in the overall populations

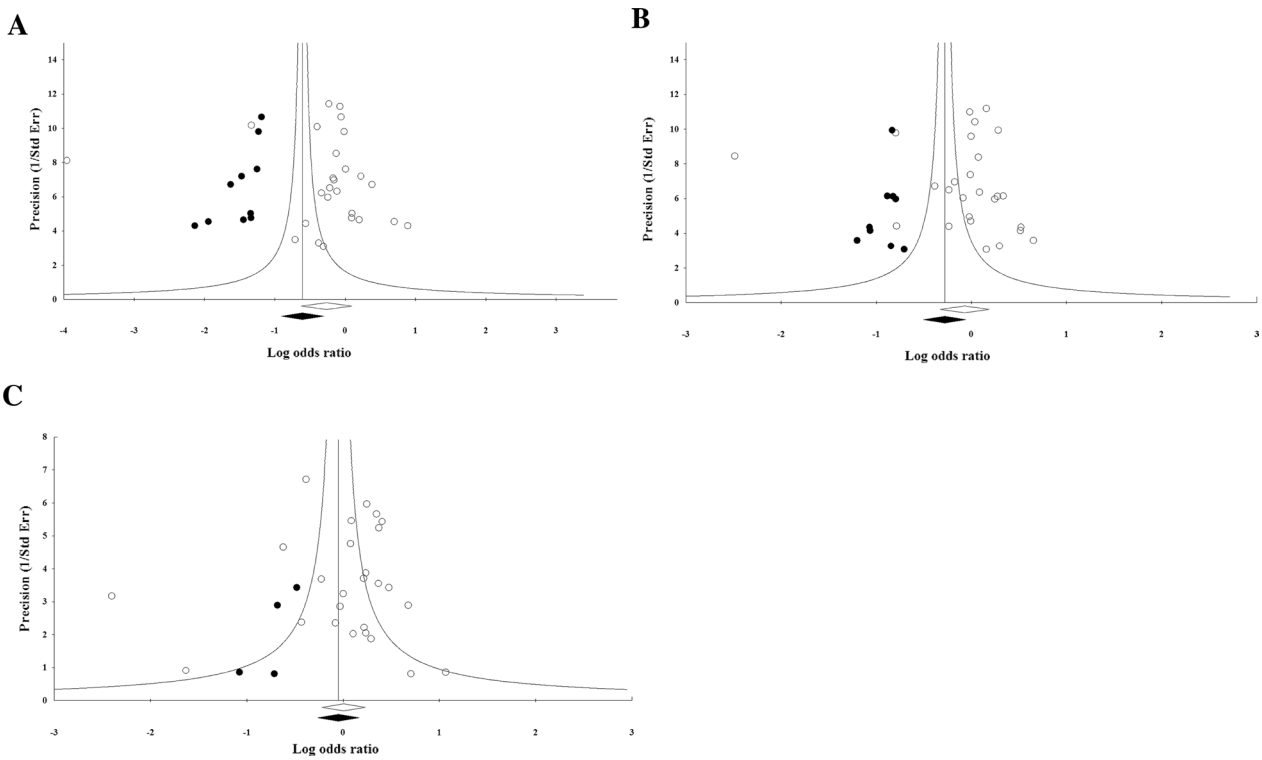


Fig. 8 Funnel plots for assessing publication bias in the studies investigating association between SNP − 11377 C > G (rs266729) and risk of T2D in the genotype models: **A** CC, **B** CG, **C** GG

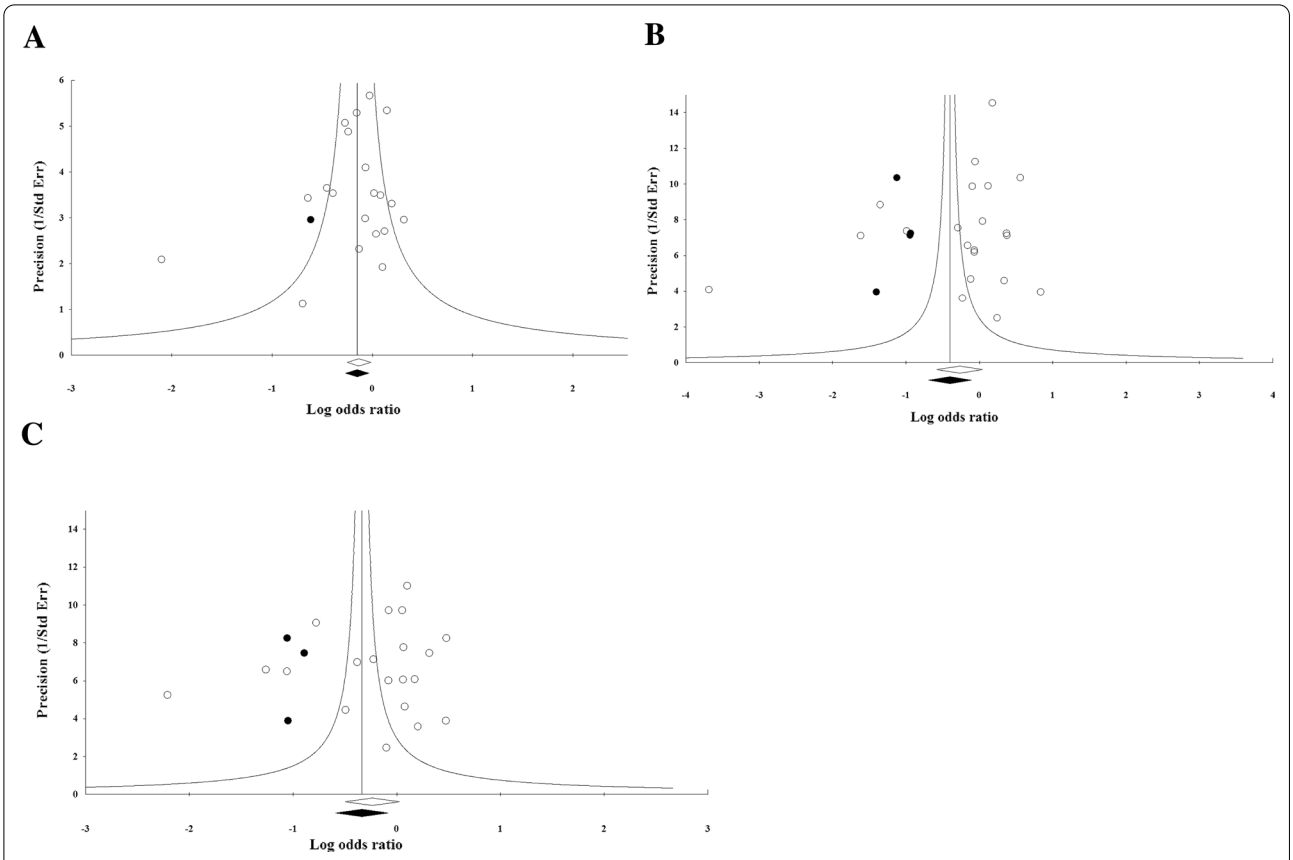


Fig. 9 Funnel plots for assessing publication bias in the studies investigating association between SNP + 276 G > T (rs266729) and risk of T2D in the genotype models: **A** TT, **B** GG, **C** GT

that is affected by environmental agents, life style, socioeconomic condition and individual's susceptibility [56, 57].

Our meta-analysis has several advantages. This study included the most recent published articles on the association between the two SNPs of adiponectin gene and T2D. To enhance the power of strategy search, we used precise inclusion and exclusion criteria and a predefined standard sheet for data extraction. Moreover, to find observed heterogeneity among included studies, we performed subgroup and meta-regression analyses according to the moderator variables of sex, ethnicity, study design and genotyping methods. A comprehensive quality assessment of included studies using NOS checklist detected that the most of the studies had moderate to high quality. In addition, having the high number of studies with large sample size has raised the statistical power of this study.

The limitations of this meta-analysis are that our search was restricted to published studies with English language, which potentially might lead to publication bias. With respect to significant heterogeneity among included studies, the findings of the present study should be interpreted with caution. Finally, the number of studies for subgroup analyses was relatively small, thus, further studies are needed for sex, study design and ethnicity to identify the precise relationship between these two SNPs and increased risk of T2D.

Table 3 Investigation of association between SNP − 11377 (rs266729) and type 2 diabetes risk using subgroup analyses

Subgroup	Number of studies	OR (95% CI)	Z-value	*P*-value	Test of heterogeneity	
					I^2 (%)	P
CC genotype	26	0.76 (0.53, 1.09)	− 1.44	0.14	< 0.001	97.7
Ethnicity						
Asian	14	0.96 (0.79, 1.16)	− 0.36	0.71	79.1	< 0.001
European	7	0.78 (0.49, 1.22)	− 1.08	0.27	95.2	< 0.001
American	3	0.25 (0.02, 2.9)	− 1.09	0.27	99.7	< 0.001
African	2	0.83 (0.51, 1.3)	− 0.76	0.44	77.6	0.03
Study design						
Case–control	20	0.69 (0.44, 1.07)	− 1.62	0.10	98.2	< 0.001
Cohort	6	1.04 (0.82, 1.34)	0.38	0.70	72.9	0.002
Sex						
Male	26	0.90 (0.65, 1.23)	0.64	0.52	96	< 0.001
Female	25	1.28 (0.88, 1.86)	1.29	0.19	97.6	< 0.001
CG genotype	26	0.93 (0.72, 1.20)	0.58	0.58	< 0.001	95.3
Ethnicity						
Asian	14	1.05 (0.89, 1.25)	0.64	0.52	71.9	< 0.001
European	7	0.90 (0.66, 1.23)	− 0.62	0.53	89	< 0.001
American	3	0.44 (0.08, 2.24)	− 0.97	0.32	99	< 0.001
African	2	1.2 (0.94, 1.58)	1.51	0.13	34.6	0.21
Study design						
Case–control	20	0.88 (0.64, 1.22)	− 0.72	0.47	96.3	< 0.001
Cohort	6	1.05 (0.93, 1.20)	0.37	0.37	0.00	0.44
Sex						
Male	25	0.99 (0.82, 1.19)	− 0.07	0.94	75.3	< 0.001
Female	24	1.003 (0.81, 1.23)	0.03	0.97	75.8	< 0.001
GG genotype	26	1.008 (0.80, 1.26)	0.067	0.94	< 0.001	75.7
Ethnicity						
Asian	14	1.10 (0.96, 1.27)	1.28	0.14	41.9	0.05
European	7	1.01 (0.75, 1.37)	0.09	0.92	53.6	0.04
American	3	0.50 (0.11, 2.22)	− 0.90	0.36	96.1	< 0.001
African	2	1.41 (0.99, 2.02)	− 0.33	0.05	70	0.06
Study design						
Case–control	20	0.96 (0.73, 1.25)	− 0.28	0.77	80.1	< 0.001
Cohort	6	1.27 (0.98, 1.66)	1.8	0.07	0.00	0.50
Sex						
Male	24	1.10 (0.91, 1.33)	1.05	0.29	0.00	0.50
Female	24	0.90 (0.75, 1.09)	− 1.05	0.45	0.00	0.51

OR odds ratio, I^2 Higgins index

Table 4 Assessment of association between SNP + 276 (rs1501299) and risk of type 2 diabetes using subgroup analyses

Subgroup	Number of studies	OR (95% CI)	Z-value	*P*-value	Test of heterogeneity	
					I^2 (%)	P
TT genotype	20	0.87 (0.77, 0.98)	1.84	0.026	38	0.05
Ethnicity						
Asian	9	0.90 (0.75, 1.08)	− 1.07	0.28	0.00	0.56
European	9	0.80 (0.67, 0.97)	− 1.58	0.023	60	0.01
American	2	0.98 (0.72, 1.33)	− 0.29	0.92	60.3	0.11
Study design						
Case–control	14	0.87 (0.70, 1.08)	− 1.22	0.22	52	0.012
Cohort	6	0.80 (0.64, 1)	− 1.93	0.05	0.00	0.71
Sex						
Male	19	0.78 (0.65, 1.03)	− 0.98	0.69	65	0.04
Female	19	0.82 (0.75, 1.21)	− 0.75	0.61	75	0.02
GT genotype	20	0.79 (0.60, 1.02)	− 1.77	0.07	93.8	< 0.001
Ethnicity						
Asian	9	0.99 (0.71, 1.3)	− 0.032	0.97	90.3	< 0.001
European	9	0.67 (0.42, 1.06)	− 1.70	0.08	95.3	< 0.001
American	2	0.61 (0.20, 1.81)	− 0.89	0.37	97.2	< 0.001
Study design						
Case–control	14	0.79 (0.59, 1.05)	− 1.5	0.11	93	< 0.001
Cohort	6	0.79 (0.43, 1.45)	− 0.75	0.45	95.9	< 0.001
Sex						
Male	19	0.76 (0.45, 1.93)	− 1.02	0.76	92	< 0.001
Female	19	0.64 (0.37, 1.78)	− 0.96	0. 45	95	< 0.001
GG genotype	21	0.76 (0.56, 1.04)	-1.6	0.09	96.7	< 0.001
Ethnicity						
Asian	10	1.04 (0.71, 1.24)	0.23	0.81	95.7	< 0.001
European	9	0.57 (0.30, 1.06)	− 1.75	0.08	97.5	< 0.001
American	2	0.58 (0.24, 1.40)	− 1.20	0.22	96.4	< 0.001
Study design						
Case–control	15	0.75 (0.52, 1.06)	− 1.59	0.11	96.3	< 0.001
Cohort	6	0.80 (0.38, 1.68)	− 0.56	0.57	97.7	< 0.001
Sex						
Male	20	0.85 (0.62, 1.75)	− 0.76	0.43	90	< 0.001
Female	20	0.77 (0.34, 1.32)	− 1.61	0.21	85.4	< 0.001

OR odds ratio, I^2 Higgins index

Conclusion

Regarding to the role of adiponectin level in the control of T2D, this meta-analysis of available studies suggests a strong significant association between the TT genotype of SNP + 276 G > T of adiponectin gene and increased risk of T2D in European population. Sex may modify this association. However, further studies with the higher quality are needed for confirming this association.

Abbreviations

SNP: Single nucleotide polymorphism; ADIPOQ: Adiponectin gene; T2D: Type 2 diabetes; OR: Odds ratio; CI: Confidence interval; HWE: Hardy–Weinberg equilibrium; NOS: Newcastle Ottawa scale; CMA: Comprehensive Meta-analysis; PRISMA: Preferred reporting items for systematic reviews and meta-analysis.

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Authors' contributions

MTG and MA conceptualized and designed the project. MA and MN had full access to all the data in the study and wrote the draft of manuscript. MA and MN independently extracted the data using a predefined standard sheet. All the authors contributed to the statistical analyses and data interpretation. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors consented to the publication of this article.

Availability of data and materials
The data used to support the findings of this study are included in the article. Additional data or information can be requested by contacting the corresponding author.

Competing interests
No potential competing interest relevant to this study were reported.

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