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Association between insulin receptor substrate 1 gene polymorphism rs1801278 and gestational diabetes mellitus: an updated meta- analysis

Lili Shen[1*], Junli Liu[1], Xiaolei Zhao[1], Aiqin Wang[1] and Xiaomei Hu[1]

Abstract

Objectives we performed this meta- analysis to investigate the impact of insulin receptor substrate 1 (IRS1) gene rs1801278 on susceptibility to gestational diabetes mellitus (GDM).

Methods The pooled odds ratio (OR) and 95% confidence interval (95% CI) were calculated, and *p* value is used to determine statistical significance. Sensitivity analysis was performed under three models (dominant, recessive and allele model), and the pooled ORs and 95%CI were calculated. Funnel plots and Begger's regression test were employed to test the publication bias.

Results The meta-analysis included 4777 participants (2116 cases and 2661 controls). The *IRS1* rs1801278 (C/T) were not significant associated with GDM risk under the dominant and allele models, OR (95%CI) = 1.22 (0.88–1.70) and 1.24 (0.91–1.68), respectively (both *p* values were more than 0.05). But we also found the *IRS1* rs1801278 (C/T) were significant associated with GDM risk under the recessive model, OR (95%CI) = 0.37 (0.16–0.86), *p* = 0.030. Our results showed that none of the studies affected the quality of the pooled OR. We also found no significant publication bias existed in this meta study for three genetic models, $P_{TT + CT\,vs.\,CC}$ = 0.445; $P_{CC+CT\,vs.\,TT}$ = 0.095; $P_{C\,vs.\,T}$ = 0.697.

Conclusion this meta-analysis indicated that *IRS1* rs1801278 (C/T) was associated with the GDM risk under the recessive model but was not associated with the GDM risk under dominant and allele models.

Keywords IRS1, Polymorphism, T2DM, Meta-analysis

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Introduction

Gestational diabetes (GDM) refers to abnormal glucose metabolism of different degrees that occurs or is first found during pregnancy, which is characterized by a potential defect in the response of pancreatic beta cells to insulin during pregnancy, which can have adverse effects on perinatal and maternal postpartum outcomes [1, 2]. In addition to these short-term risks, the risk of type 2 diabetes (T2DM) in women with a history of GDM during pregnancy will increase by 17–63% 5 to 16 years after delivery [3]. Both GDM and T2DM are characterized by insulin resistance, there are similarities in their pathogenesis [4], and there is a common genetic background between GDM and T2DM [5].

Insulin receptor substrate 1 (IRS1) gene, which located at chromosome 2q36, is a member of the IRS protein family. It also encodes IRS-1 protein, which plays an important role in signal transmission between insulin receptor and Phosphoinositide 3-kinase (PI3K) [6]. Previous studies have also shown that dysregulation of IRS-1 expression and function can affect the insulin signaling pathway, leading to the occurrence of IR and DM [7, 8]. Previously, several studies have suggested a significant association between IRS-1 gene single nucleotide polymorphisms (SNPs) and T2DM risk [9, 10]. Previous study [11] have confirmed that the substitution of glycine arginine in Gly972Arg (rs1801278) of IRS-1 gene has a statistical correlation with the high incidence rate of GDM. Several studies [12–16] were performed to investigate the relationship between rs1801278 and GDM susceptibility, however these studies concluded inconsistent results. Although, three meta- studies [17–19] have focused on this topic, and the fore- mentioned meta- analysis indicated that rs1801278 was associated with higher GDM risk, but in recent years, there have been new case-control studies [20–22] have been performed, and these new studies concluded inconsistent result with previous meta- analysis. Therefore, we performed this updated meta- analysis to investigate the relationship between IRS-1 gene (rs1801278) and susceptibility to GDM.

Methods

Publication search

We systematically searched articles published between 2004 and 2023 on databases of PubMed, Cochrane Library, Web of Science, Embase and China National Knowledge Infrastructure. The following terms were used: ("Gly972Arg" OR "Insulin receptor substrate 1" OR "Insulin receptor substrate" OR "rs1801278") AND ("pregnancy-induced diabetes" OR "gestational diabetes mellitus" OR "gestational diabetes" OR "pregnancy-induced diabetes mellitus" OR "GDM"). Two staff members independently searched for articles and screened and extracted relevant information from their content.

Selection criteria

All included studies need to meet the following requirements: (1) evaluation the association between IRS-1 gene rs1801278 and susceptibility to GDM. (2) the studies included should be case-control studies and the full text could be obtained; (3) genotype frequencies for IRS-1 gene rs1801278 could be obtained. The rules for excluding research are as follows: (1) duplication of previous publications; (2) the study was not case- control study; (3) we could not obtain the genotype frequencies for IRS-1 gene rs1801278. PRISMA statement as the preferred reporting rule for this meta-analysis [23].

Data extraction

The process of literature review and data extraction will be independently conducted by two researchers based on literature selection criteria simultaneously. Information was extracted from these articles, including author, publication year, country, frequencies of *IRS1* rs1801278 genotype and alleles in case and control group. Only articles with the largest sample amount, and the same data appears in multiple publications. To ensure the accuracy and objectivity of data extraction, the third researcher will verify the extracted data with the literature one by one. Any inconsistencies in the data will be publicly decided by the third researcher and the first two researchers together.

Study quality assessment

The two researchers conducted an independent quality assessment of each qualified article based on the NOS quantity table (NOS), which applied to the quality assessment of observation research. The third appraiser solves the different results of the two appraisers. The evaluation scores mainly include the following aspects: (1) Cases and control options (4 points); (2) the mass of confusion factor in cases and comparison with China correction (2 points); (3) exposure determination (3 points). The total score ranges from 0 to 9, and the score is higher than 6 for high quality.

Statistical analysis

The OR and 95% CI were calculated to estimate the relevance of *IRS1* rs1801278 (C/T) gene and GDM risk. The Chi-square based Q-test and I-squared test were performed to analyze heterogeneous ($P<$ recommended heterogeneity) [24, 25]. When there is no heterogeneity, estimate the combined OR using fixed effects models (Mantel Haenszel) or random effects models (DerSimonian and Laird) [26, 27]. Chi-square test was performed to examine Hardy–Weinberg equilibrium (HWE).

Sensitivity analysis was performed for three models (dominant, recessive and allele model) to estimate the influence of the pooled ORs. The publication bias was tested by Funnel plot and Begg's linear regression [28, 29], $p < 0.05$ was considered existing publication bias. Stata 15.0 was used for all analysis in this study. Two-sides p-values less than 0.05 were considered significant.

Results

Study characteristics

Figure 1 shows the process of literature search and inclusion. There were 75 publications searched in several electronic databases. After carefully reading the articles, a total of 67 studies were excluded, including 60 duplicate literatures, four meta- studies, two studies not involved in rs1801278 and one study have no sufficient data of rs1801278. Finally, a total of 8 articles were included in current meta-analysis. In these 8 case-control studies, 2 were conducted for Asian populations, 6 were Caucasian. The distribution of genotype for one study did not meet HWE balance ($P < 0.05$), but the distribution of genotype in controls of this study meet the HWE balance ($P > 0.05$). Table 1 shows the main characteristics and HWE test results of all included studies.

Meta-analysis results

The meta-analysis included 4777 participants (2116 cases and 2661 controls). The *IRS1* rs1801278 (C/T) were not significant associated with GDM risk under the dominant and allele models, OR (95%CI) = 1.22 (0.88–1.70) and 1.24 (0.91–1.68), respectively (both p values were more than 0.05). But we also found the *IRS1* rs1801278 (C/T) were

significant associated with GDM risk under the recessive models, OR (95%CI) = 0.37 (0.16–0.86), $p = 0.030$ (Fig. 2).

Sensitivity analysis

Sensitivity analyzes were performed by sequentially removing each eligible study one at a time to assess the effect of each study on the pooled OR. Our results showed that none of the studies affected the quality of the pooled OR (Fig. 3).

Publication bias

Publication bias was evaluated using the Begg's funnel plot. We found no significant publication bias existed in this meta study for three genetic models, $P_{TT + CT \, vs. \, CC} = 0.445$; $P_{CC+CT \, vs. \, TT} = 0.095$; $P_{C \, vs. \, T} = 0.697$ (Fig. 4).

Discussion

In current meta- study, we found that the *IRS1* rs1801278 (C/T) were not significant associated with GDM risk under the dominant and allele models, but the *IRS1* rs1801278 (C/T) were significant associated with GDM risk under the recessive models. Several studies [12–16] were performed to investigate the relationship between rs1801278 and GDM susceptibility, however these studies concluded inconsistent results. A case- control [12] study performed in Saudi women suggested that the IRS-1 rs1801278 variant may associated with increased risk of GDM under the dominant model. A study [13] for Greek population suggests that the risk of developing GDM is higher among female carriers of the minor allele within IRS1 gene rs1801278. But Shaat et al. [14] concluded inconsistent results, they found a negative result on relationship between IRS1 gene rs1801278 and GDM
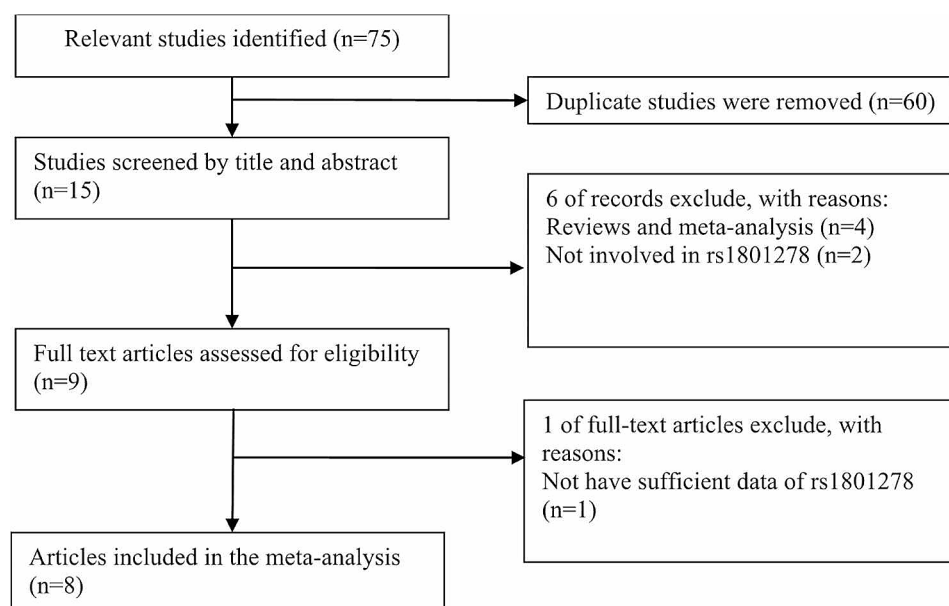
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│ Relevant studies identified (n=75) │
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              │─────────────▶│ Reviews and meta-analysis (n=4)   │
              │              │ Not involved in rs1801278 (n=2)   │
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│ (n=9)                            │
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              │─────────────▶│ reasons:                         │
              │              │ Not have sufficient data of rs1801278 │
              │              │ (n=1)                            │
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│ Articles included in the meta-analysis │
│ (n=8)                            │
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Fig. 1 The flow sheet of identification of eligible studies

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Table 1 Information for studies included in this meta-analysis

Author	Year	Country	Definition for GDM	Sample size		Case					Control					NOS score	HWE
				Case	Control	CC	CT	TT	C	T	CC	CT	TT	C	T		
Alharbi, et al.[1]	2014	Saudi	OGTT confirmed	200	300	189	10	1	388	12	295	5	0	595	5	6	0.022
Pappa, et al.[1]	2011	Greece	Fourth IWCGDM criteria	148	107	58	73	17	189	107	60	40	7	160	54	8	0.682
Tok, et al.[1]	2006	Turkey	NDDG criteria	62	100	53	9	0	115	9	89	11	0	189	11	6	0.402
Fallucca, et al.[1]	2006	Italy	OGTT confirmed	309	277	271	34	4	576	42	255	22	0	532	22	8	0.071
Shaat, et al.[1]	2005	Sweden	EASD-DPSG criteria	588	1189	534	49	4	1117	57	1078	111	0	2267	111	8	0.986
Popova, et al.[2]	2021	Russians	IADPSG criteria	319	318	292	27	0	611	27	284	34	0	602	34	6	0.204
Wu, et al.[2]	2021	Chinese	IADPSG criteria	213	191	205	8	0	418	8	184	7	0	375	7	6	0.704
Popova, et al.[2]	2017	Russians	IADPSG criteria	278	179	257	21	0	535	21	160	19	0	339	19	6	0.328

Note: 1: those articles were included in previous meta- analysis; 2: those articles were not included in previous meta- analysis. OGTT: the oral glucose tolerance test; IADPSG: the International Association of Diabetes in Pregnancy Study Groups; EASD-DPSG: the European Association for the Study of Diabetes-Diabetic Pregnancy Study Group; IWCGDM: International Workshop-Conferences on Gestational Diabetes Mellitus; NDDG: National Diabetes Data Group criteria
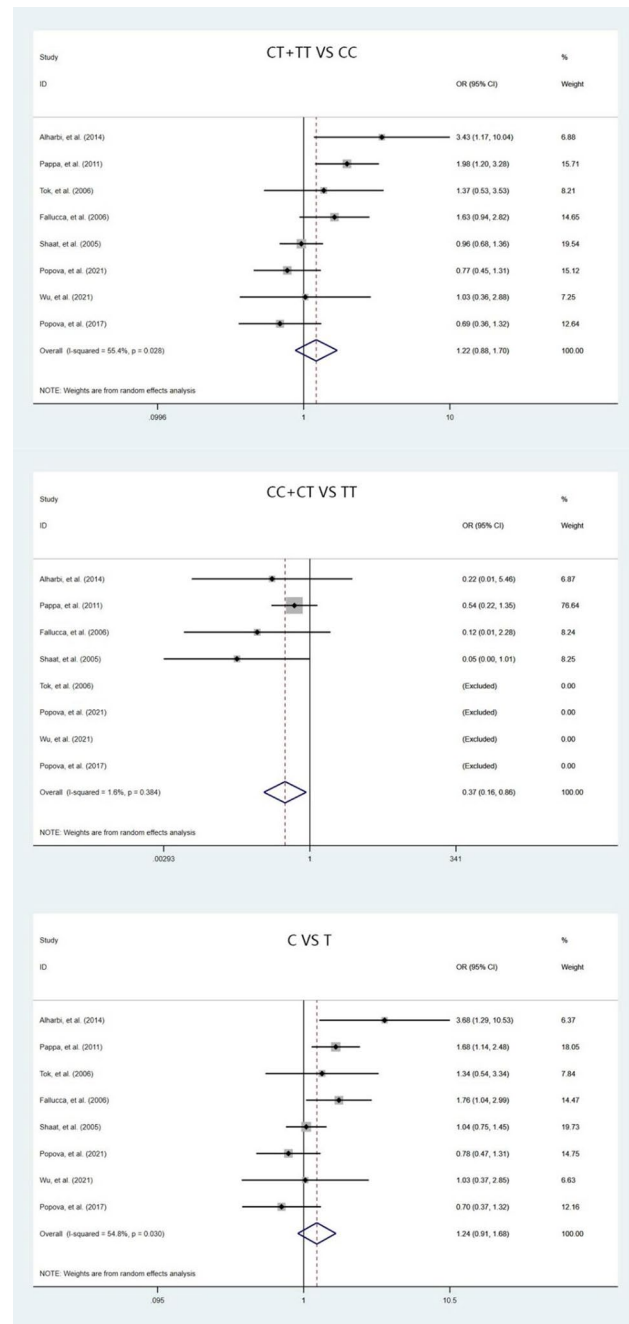

Fig. 2 Forest plots of the *IRS1 rs1801278 (C/T)* polymorphism under three genetic models (dominant, recessive and allele model)

risk. Although, three meta- studies [17–19] have focused on this topic, and the three meta- analyses indicated that rs1801278 was associated with higher GDM risk, but in recent years, there have been new case-control studies [20–22] have been performed, and these new studies concluded inconsistent result with previous meta- analysis. Wu et al. [19] conducted a meta study suggested that GDM was associated with rs1801278(IRS1), but this relationship was not significant in Asian populations. In
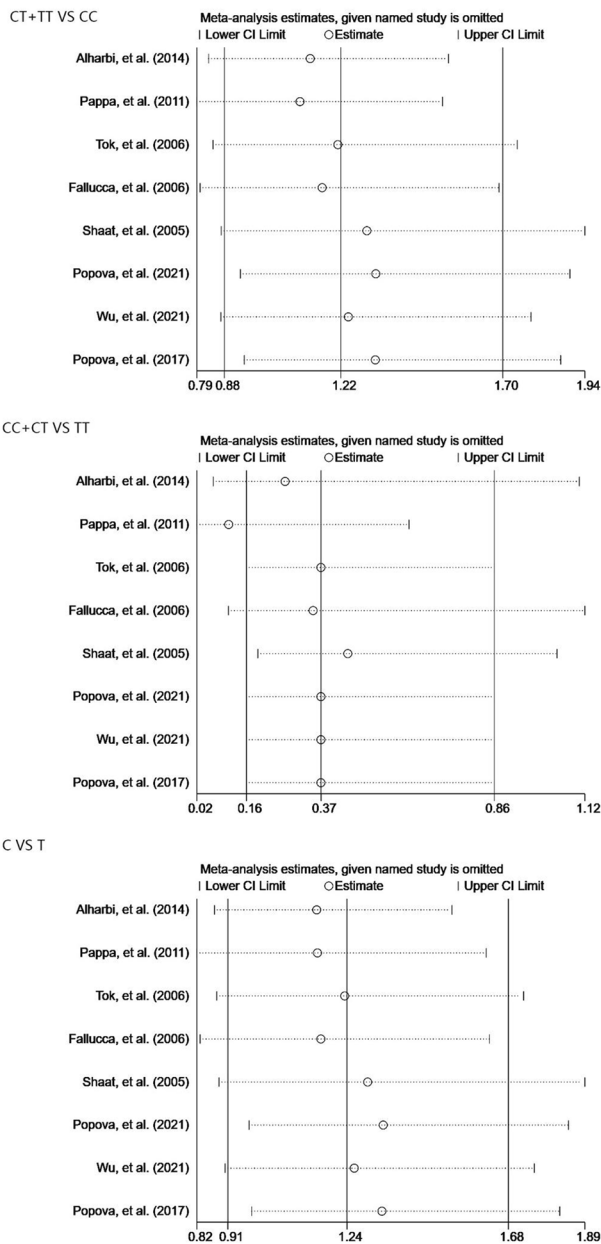
Fig. 3 Sensitivity analysis examining the association between the *IRS1 rs1801278 (C/T)* and risk of gestational diabetes mellitus under three genetic models (dominant, recessive and allele model)

Fig. 4 Begg's funnel plot for publication bias analysis under three genetic models (dominant, recessive and allele model)

addition, the IRS1- rs1801278 was significantly affected by OGTT protocol and genotyping methods. Zhang et al. [17] indicated that the minor alleles of IRS1- rs1801278 (Gly972Arg) were significantly associated with a higher risk of GDM, and another meta- study concluded similar results. From then on, additional case- control studies were performed. Popova et al. [20] suggested that the distribution of genotype frequencies was not significant different between cases and controls. In 2021, Popova et al. [21] conducted another case- control study in Russian
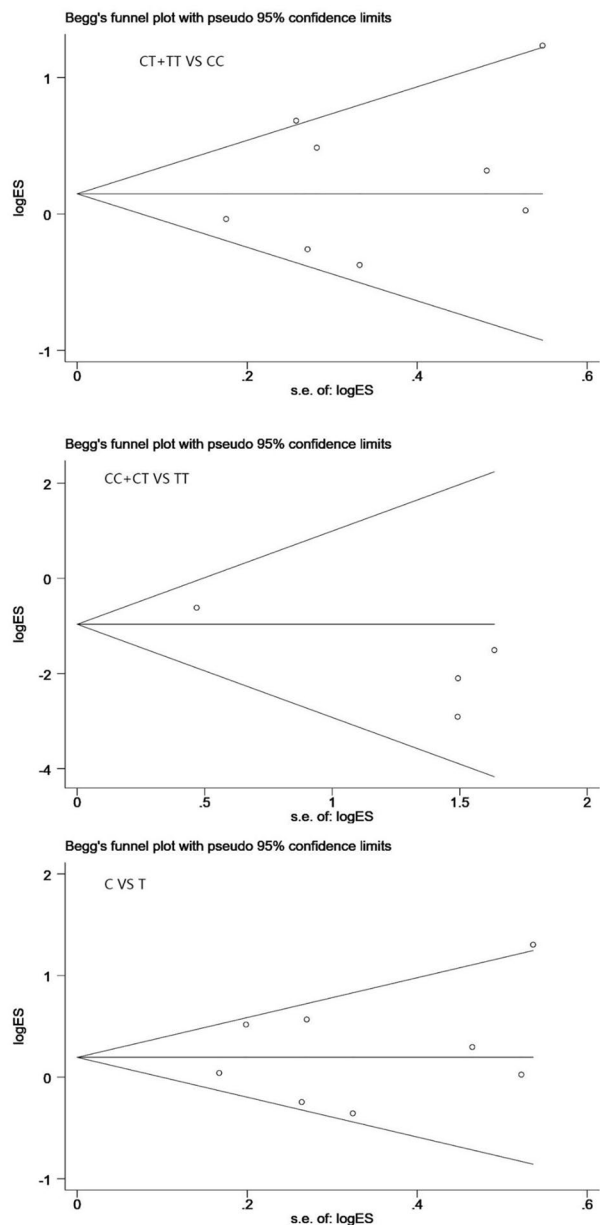
women and they obtained similar results. Wu et al. [22] performed a case- control study in Chinese females and found that there was no statistically significant difference in genotype frequency between the case and the control group.

Previous research [30, 31] suggests that IRS1 is a substrate of insulin receptor tyrosine kinase and plays a crucial role in insulin signaling pathways. IRS1 protein can be expressed in many insulins sensitive tissues, and its tyrosine phosphorylation can trigger activation of phosphatidylinositol 3-kinase (PI3K) and translocation of glucose transporter [32]. Evidence [14] have shown that

the IRS1 G972R polymorphism reduces insulin content in isolated human islets and impairs insulin secretion function.

Several limitations existed in this meta-analysis. Firstly, we could not analyze the data grouped by ethnic, because just two studies were conducted in Asian. Secondly, the pathogenesis of GDM is very complex, including genetic factors, environmental factors and the synergistic effects. Therefore, this study only analyzes the association between a single SNP and GDM, without involving gene-environmental synergistic effects.

In conclusion, this meta-analysis indicated that *IRS1* rs1801278 (C/T) was associated with the GDM risk under the recessive model but was not associated with the GDM risk under dominant and allele models.

Abbreviations
GDM	Gestational diabetes mellitus
HWE	Hardy–Weinberg equilibrium
IRS1	Insulin receptor substrate 1
PRISMA	Preferred Reporting Project
SNP	Single nucleotide polymorphism
T2DM	Type 2 diabetes

Author contributions
Manuscript writing, editing and review were conducted by Lili Shen and Xiaomei Hu; Lili Shen, Xiaolei Zhao and Aiqin Wang participated in the articles search; Junli Liu and Xiaomei Hu performed data analysis and evaluation the quality of the selected studies.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

References
1. Homayouni A, Bagheri N, Mohammad-Alizadeh-Charandabi S, Kashani N, Mobaraki-Asl N, Mirghafurvand M, Asgharian H, Ansari F, Pourjafar H. Prevention of gestational diabetes mellitus (GDM) and probiotics: mechanism of action: a review. Curr Diabetes Rev. 2020;16(6):538–45.
2. Juan J, Yang H. Prevalence, prevention, and lifestyle intervention of gestational diabetes mellitus in China. Int J Environ Res Public Health. 2020;17(24):9517.
3. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational diabetes mellitus: mechanisms, treatment, and complications. Trends Endocrinol Metab. 2018;29(11):743–54.
4. Huang S, Magny-Normilus C, McMahon E, Whittemore R. Systematic review of lifestyle interventions for gestational diabetes mellitus in pregnancy and the postpartum period. J Obstet Gynecol Neonatal Nurs. 2022;51(2):115–25.
5. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ. 2020;369:m1361.
6. Marushchak M, Krynytska I. Insulin receptor substrate 1 gene and glucose metabolism characteristics in type 2 diabetes mellitus with comorbidities. Ethiop J Health Sci. 2021;31(5):1001–10.
7. Bedair RN, Magour GM, Ooda SA, Amar EM, Awad AM. Insulin receptor substrate-1 G972R single nucleotide polymorphism in Egyptian patients with chronic hepatitis C virus infection and type 2 diabetes mellitus. Egypt Liver J. 2021;11:2.
8. Menting JG, Whittaker J, Margetts MB, Whittaker LJ, Kong GK, Smith BJ, Watson CJ, Záková L, Kletvíková E, Jiráček J, Chan SJ, Steiner DF, Dodson GG, Brzozowski AM, Weiss MA, Ward CW, Lawrence MC. How insulin engages its primary binding site on the insulin receptor. Nature. 2013;493:241–5.
9. Atmodjo WL, Larasati YO, Jo J, Nufika R, Naomi S, Winoto I. Relationship between insulin-receptor substrate 1 and Langerhans' islet in a rat model of type 2 diabetes mellitus. Vivo. 2021;35(1):291–7.
10. Htwe TN, Thein OM, Hmone SW, Thandar M. Prevalence of insulin receptor substrate-1 gene (G972R) polymorphism, insulin resistance, and determination of β-cell function among overweight and obese persons with type 2 diabetes mellitus. J ASEAN Fed Endocr Soc. 2021;36(1):25–30.
11. Khan IA, Jahan P, Hasan Q, Rao P. Genetic confirmation of T2DM meta-analysis variants studied in gestational diabetes mellitus in an Indian population. Diabetes Metab Syndr. 2019;13(1):688–94.
12. Alharbi KK, Khan IA, Abotalib Z, Al-Hakeem MM. Insulin receptor substrate-1 (IRS-1) Gly927Arg: correlation with gestational diabetes mellitus in Saudi women. Biomed Res Int. 2014;2014:146495.
13. Pappa KI, Gazouli M, Economou K, Daskalakis G, Anastasiou E, Anagnou NP, Antsaklis A. Gestational diabetes mellitus shares polymorphisms of genes associated with insulin resistance and type 2 diabetes in the Greek population. Gynecol Endocrinol. 2011;27(4):267–72.
14. Shaat N, Ekelund M, Lernmark A, Ivarsson S, Almgren P, Berntorp K, Groop L. Association of the E23K polymorphism in the KCNJ11 gene with gestational diabetes mellitus. Diabetologia. 2005;48(12):2544–51.
15. Tok EC, Ertunc D, Bilgin O, Erdal EM, Kaplanoglu M, Dilek S. Association of insulin receptor substrate-1 G972R variant with baseline characteristics of the patients with gestational diabetes mellitus. Am J Obstet Gynecol. 2006;194(3):868–72.
16. Fallucca F, Dalfrà MG, Sciullo E, Masin M, Buongiorno AM, Napoli A, Fedele D, Lapolla A. Polymorphisms of insulin receptor substrate 1 and beta3-adrenergic receptor genes in gestational diabetes and normal pregnancy. Metabolism. 2006;55(11):1451–6.
17. Zhang C, Bao W, Rong Y, Yang H, Bowers K, Yeung E, Kiely M. Genetic variants and the risk of gestational diabetes mellitus: a systematic review. Hum Reprod Update. 2013;19(4):376–90.
18. Zhang Y, Sun CM, Hu XQ, Zhao Y. Relationship between melatonin receptor 1B and insulin receptor substrate 1 polymorphisms with gestational diabetes mellitus: a systematic review and meta-analysis. Sci Rep. 2014;4:6113.
19. Wu L, Cui L, Tam WH, Ma RC, Wang CC. Genetic variants associated with gestational diabetes mellitus: a meta-analysis and subgroup analysis. Sci Rep. 2016;6:30539.
20. Popova PV, Klyushina AA, Vasilyeva LB, Tkachuk AS, Bolotko YA, Gerasimov AS, Pustozerov EA, Kravchuk EN, Predeus A, Kostareva AA, Grineva EN. Effect of gene-lifestyle interaction on gestational diabetes risk. Oncotarget. 2017;8(67):112024–35.
21. Popova PV, Klyushina AA, Vasilyeva LB, Tkachuk AS, Vasukova EA, Anopova AD, Pustozerov EA, Gorelova IV, Kravchuk EN, Li O, Pervunina TM, Kostareva AA, Grineva EN. Association of common genetic risk variants with gestational diabetes mellitus and their role in gdm prediction. Front Endocrinol (Lausanne). 2021;12:628582.
22. Wu L, Fang C, Zhang J, Ye Y, Zhao H. The association between maternal/fetal insulin receptor substrate 1 gene polymorphism rs1801278 and gestational diabetes mellitus in a Chinese population. Gynecol Obstet Invest. 2021;86(1–2):177–84.

23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.

24. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.

25. Zintzaras E, Lau J. Synthesis of genetic association studies for pertinent gene-disease associations requires appropriate methodological and statistical approaches. J Clin Epidemiol. 2008;61(7):634–45.

26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Res ed). 2003;327(7414):557–60.

27. McKenzie JE, Beller EM, Forbes AB. Introduction to systematic reviews and meta-analysis. Respirol (Carlton Vic). 2016;21(4):626–37.

28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical Res ed). 1997;315(7109):629–34.

29. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.

30. Sun XJ, Rothenberg P, Kahn CR, Backer JM, Araki E, Wilden PA, Cahill DA, Goldstein BJ, White MF. Structure of the insulin receptor substrate IRS-1 defines a unique signal transduction protein. Nature. 1991;352(6330):73–7.

31. Stephens JM, Lee J, Pilch PF. Tumor necrosis factor-alpha-induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT4 expression without a loss of insulin receptor-mediated signal transduction. J Biol Chem. 1997;272(2):971–6.

32. Kaburagi Y, Yamauchi T, Yamamoto-Honda R, Ueki K, Tobe K, Akanuma Y, Yazaki Y, Kadowaki T. The mechanism of insulin-induced signal transduction mediated by the insulin receptor substrate family. Endocr J. 1999;46(Suppl):25–34.

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