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Review

Genetic determinants of variable anti-diabetic therapy responses across diverse populations with type 2 diabetes mellitus: a systematic review and meta-analysis

Fikry Ahmad [a], Suhaili Abubakar [a,*], Sharifah Sakinah Syed Alwi [a], Ng Ooi Chuan [b]

[a] Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang 43400, Malaysia
[b] Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang 43400, Malaysia

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ABSTRACT

Aim: This study explores the relationship between gene polymorphisms and glycemic responses across ethnic populations and identifies optimal therapy combinations for glycemic control. However, the definition of glycemic response varied across included studies (e.g., HbA1c <7 %, or >0.5 % reduction), which may affect the comparability and interpretation of pooled data.

Methods: Pooled odds ratios (ORs) with 95 % CI were used for binary glycemic outcomes, while pooled standardized mean differences (SMDs) with 95 % CI were applied to continuous glycemic outcomes. Heterogeneity was assessed with I^2 and Cochran Q tests.

Results: Of 43 articles screened, 36 studies involving 10 genes and 34 SNPs were included. Significant associations were found between improved glycemic response and the following variants: *SLC22A1* rs622342, *SLC47A2* rs12943590, *TCF7L2* rs7903146, *SLC22A1* rs12208357, and *ABCC8* rs757110 ($p < 0.05$). In treatment analysis, Arabian, Indian, Mestizo, and Persian populations showed significant HbA1c reductions with biguanide monotherapy ($p < 0.05$). Arabian populations also exhibited significant reductions with biguanide-sulfonylurea combination therapy.

Conclusion: Glycemic responses to anti-diabetic drugs vary across ethnic groups and are influenced by genetic variants. These findings support the need for personalised, genotype-guided therapy to improve glycemic control. Further research is necessary to explore broader drug classes and demographic factors.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes and is often initially managed with metformin, alongside lifestyle changes such as exercise, diet, and weight management [1]. As diabetes progresses, treatment regimens become more complex due to varying responses to therapy [2]. Common oral anti-diabetic drugs (OADs), such as biguanides, sulfonylureas (SU), sodium-glucose transport protein 2 inhibitors (SGLT-2i), and dipeptidyl-peptidase 4 inhibitors (DPP4i), aim to reduce blood glucose, improve insulin sensitivity, and enhance insulin secretion [3,4]. T2DM pathogenesis is complex, as it is shaped by metabolic factors, genetic predisposition, and gene-environment interactions, contributing to differences in OAD responses [5].

Ethnic disparities in T2DM prevalence and treatment responses have been attributed to genetic variations, along with dietary, environmental, and socioeconomic factors [6]. Gene variations that are shaped by migration, mating patterns, and genetic drift could influence allele frequencies and affect drug pharmacokinetics and pharmacodynamics [7]. Gene polymorphisms related to drug transport, metabolism, and insulin sensitivity can alter protein function, leading to diverse therapeutic responses across populations [8]. Despite extensive studies, inconsistent findings have been found due to small sample sizes, varied treatment protocols, and population heterogeneity [8]. Notably, glycemic response was inconsistently defined across studies, including thresholds such as HbA1c <7 %, or a reduction >0.5 %, which represents a limitation in data harmonization for *meta*-analysis.

This systematic review and *meta*-analysis aim to examine the relationship between gene polymorphisms and OADs treatment responses

* Corresponding author at: Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor Darul Ehsan, Malaysia.
E-mail address: suhaili_ab@upm.edu.my (S. Abubakar).

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across diverse ethnic groups in identifying effective therapy combinations for glycemic control and providing insights into personalized, gene-oriented approaches for managing T2DM.

2. Methods

2.1. Design

The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [9], and the review protocol was registered at PROSPERO (CRD42024531355) on April 13, 2024.

2.2. Literature search strategy

A search was conducted across five databases, including Scopus, PubMed, Cochrane, CINAHL, and Medline, covering publications from January 2018 to July 2024. The search aimed to identify studies examining the genetic variants that influence glycemic levels and therapy responses in different populations. Literature search keywords can be found in **Supplementary Table S1**. Two independent reviewers (MFA, SAB) performed the search and screening. All retrieved records were exported to Mendeley Reference Manager (version 2.115.0, Mendeley, London, United Kingdom) and Microsoft Excel (version 2406 Build 16.0.17726.20078) for eligibility assessment, screening, and cross-referencing.

2.3. Eligibility criteria

Eligible studies underwent a systematic screening of titles, abstracts, and full texts, considering population, intervention, comparison, and outcomes. Studies included were: 1) T2DM cases (18–69 years); 2) genetic association studies on gene polymorphisms and therapy response; 3) treated with any OAD class; 4) involved multiple populations; 5) used HbA1c as an outcome. Exclusions included *in vitro/in vivo* animal studies, reviews, case studies, editorials, conference papers, guidelines, and non-English full-text studies published more than five years ago. Two co-authors (MFA, SAB) independently assessed eligibility using Mendeley Reference Manager and Microsoft Excel. Duplicate studies were removed, and disagreement was resolved by a third author (SSA).

2.4. Data Extraction

Information included the first author, study design, number of participants and their demographic (ethnicity, gender, age, BMI), biochemical parameters (HbA1c), gene polymorphisms (SNPs), OAD dosage, genotyping techniques, and outcome measures were recorded in Microsoft Excel following a full-text screening. Statistical data (mean, standard deviation (SD) of HbA1c, and allelic frequencies) were collected for *meta*-analysis. Datasets were summarised in Table 1 and **Supplementary Table S2**. Genotyping methods included TaqMan assays, PCR-RFLP, MassARRAY, Sanger Sequencing, RT-PCR, HRM Analysis, TETRA-ARMS and ARMS-PCR (**Supplementary Table S2**). Most studies applied quality control such as replicate concordance, call rate thresholds (>95 %), Hardy-Weinberg Equilibrium tests to ensure data integrity and additional genotyping protocol for random samples to ensure data accuracy (**Supplementary Table S2**).

2.5. Risk of bias

The risk of bias was assessed by two reviewers using the Q-Genie tool **(Supplementary Table S3),** designed for evaluating genetic association studies in systematic reviews [10]**.** The tool includes 11 criteria, such as research rationale, comparison group selection (i.e. case and controls), genetic variant testing, outcome classification, potential sources of bias, sample size, statistical analyses, statistical measures, testing assumptions in the genetic studies (e.g., Hardy-Weinberg equilibrium), and the reliability of results interpretation. Each criterion was scored from 1 (poor) to 7 (excellent), with total scores ≤35 indicating low quality, 35–45 medium quality, and >45 high quality.

2.6. Statistical analysis

Meta-analysis was performed using SPSS statistical software (version 29.0) on genetic variants reported in at least two studies. Three *meta*-analysis strategies were used: 1) **Strategy A** for continuous glycemic measurement (HbA1c mean and SD), pooling standardized mean differences (SMD) with 95 % confidence interval (CI) [13–15,17–21,24,26,27,30,31,35,41–52]**;** 2) **Strategy B** for binary glycemic responses (responder/non-responder), pooling odds ratios (ORs) with 95 % CI [11,12,16,22,23,25,28,29,39,40]**;** 3) **Strategy C** to examine treatment efficacy across populations, pooling SMD with 95 % CI. [13–15,17–21,24,26,27,30–32,34–38,41–53]**.** Heterogeneity was assessed using I^2 Test and *Cochran's Q* test. A fixed-effect model was applied when heterogeneity was insignificant. Results were presented using forest plots with single-study genetic variants described narratively.

3. Results

3.1. Characteristics of the included studies

A total of 1920 studies were identified from Scopus (n = 1513), PubMed (n = 137), Cochrane (n = 85), CINAHL (n = 73), and Medline (n = 112). After removing 505 duplicates, 1415 studies were screened, and 75 articles were eligible. Following risk bias assessment and outcome relevance, 32 studies were excluded, leaving 43 studies, with 36 included in the *meta*-analysis (Fig. 1).

The 43 studies comprised 9 case-control, 23 cohorts, and 11 cross-sectional studies from 25 populations. These populations were grouped into 10 study populations: Indian, Persian, Mestizo, Chinese, African, Arabian, European, Pakistani, Thailand and Ethiopian. Participants received monotherapy or combination therapies (biguanides, sulfonylureas, DPP4i, TZD, α-GI, meglitinides, GLP-1Ra). A total of 10 genes with 34 SNPs were investigated for glycemic response and anti-diabetic drug efficacy **(**Table 1**),** with studies classified by gene, SNPs, and outcome type (continuous or binary). Quality assessment using Q-Genie revealed 9 high, 34 moderate, and 1 low-quality study, the latter excluded **(Supplementary Table S3).**

3.2. The impact of gene polymorphism on glycemic response to oral antidiabetic drugs

From all 43 included studies, 10 genes were investigated: *SLC22A1, SLC22A2, SLC22A3, SLC47A1, SLC47A2, ATM, CYP2C9, TCF7L2, KCNJ11*, and the *ABCC8* gene. In the result section, every gene will be reported by each study's findings first, followed by *meta*-analysis results, if any.

3.2.1. SLC22A1 gene polymorphism

From Table 1**, 20** out of 43 studies [11–30] evaluated the effects of six (6) *SLC22A1* SNPs (rs628031, rs622342, rs72552763, rs12208357, rs594709, and rs2282143) on glycemic levels across nine (9) populations: Indian, Persian, Mestizo, Chinese, African, Arabian, European, Pakistani, and Ethiopian. From 20 studies, 9 studies assessed the rs622342 variant and its association with glycemic response [18–26]**,** of which 4 studies reported a significant association in Arabian [19,21,23] and African [25] populations, while five (5) studies found no significant association in Mestizo, Indian, Arabian, and European [18,20,22,24,26] populations**.**

Meta-analysis of continuous outcome studies (strategy A) [18,20,21,24] revealed that the CC genotype of rs622342 was

Table 1
Summary of Outcomes Measures.

Gene	SNP	Chromosome position	Population	MAF	*(P)** with HWE	OAD	Clinical effects	References
SLC22A1	rs628031	A > G	India	A = 0.18	>0.05	Biguanides + SU	No significant association.	Rizvi et al. [11]*
			Russia	A = 0.36	>0.05	Biguanides	No significant association	Nasykhova et al. [12]*
			India	A = 0.32	>0.05	Biguanides	No significant association with HbA1c reduction.	Singh et al. [13]
			China	A = 0.21	>0.05	Biguanides	No significant effects in HbA1c changes.	Chen et al. [14]
			Indonesia	A = 0.05	>0.05	Biguanides	No correlation with glycemic levels.	Ningrum et al. [15]
			Egypt	A = 0.39	>0.05	Biguanides + SU	Variants were not associated with therapy response.	Ahmed et al. [16]*
			Mexico	A = 0.12	0.750	Biguanides + SU	Positive correlation between A allele with HbA1c.	Zepeda-Carrillo et al. [17]
	rs622342	C > A	Mexico	C = 0.41	0.138	Biguanides + SU	No significant association	Ortega-Ayala et al. [18]
			Lebanon	C = 0.41	>0.05	Biguanides + SU	A significant interaction between AC/AA genotype and HbA1c reduction.	Naja et al. [19]
			Mexico	A = 0.15	>0.05	Biguanides + SU	No significant association.	Sanchez-Ibarra et al. [20]
			Lebanon	C = 0.17	>0.05	Biguanides	There was a significant reduction in HbA1c.	Naja et al. [21]
			India	A = 0.47	>0.05	Biguanides	No significant association.	Phani et al. [22]*
			Egypt	C = 0.19	0.396	Biguanides + SU	Significant association between AA genotype with metformin-glimepiride therapy.	Ebid et al. [23]*
			Jordan	C = 0.23	0.040	Biguanides	No significant association.	Al-Eitan et al. [24]
			South Africa	C	0.021	Biguanides + SU	Significant association between CC genotype and poor response.	Masilela et al. [25]*
			Netherland	C = 0.4	0.420	Biguanides	No significant association.	Out et al. [26]
	rs72552763	160139853delGAT	Mexico	Del = 0.35	0.984	Biguanides + SU	Significant association with lower HbA1c.	Ortega-Ayala et al. [18]
			Iraq	Del = 0.26	>0.05	Biguanides	A significant association with poor glycemic control.	Aladhab et al. [27]
			Ethiopia	Del = 0.09	>0.05	Biguanides	Significant association with metformin response.	Degaga et al. [28]*
			Mexico	Del = 0.38	>0.05	Biguanides + SU	No significant association with HbA1c reduction.	Sanchez-Ibarra et al. [20]
			Indonesia	A = 0.51	>0.05	Biguanides	Extremely weak correlation with metformin concentration.	Ningrum et al. [15]
			Egypt	Del = 0.17	>0.05	Biguanides + SU	No significant association.	Ahmed et al. [16]*
	rs12208357	C > T	Russia	T = 0.02	>0.05	Biguanides	Significant impact with response to metformin ($p < 0.05$).	Nasykhova et al. [12]*
			South Africa	T = 0.4	0.966	Biguanides	No significant association.	Xhakaza et al. [29]*
			Egypt	T = 0.39	>0.05	Biguanides	A significant association between genotype and glucose level.	Mostafa-Hedeab et al. [30]
			Netherland	T = 0.06	0.520	Biguanides	No significant association with HbA1c reduction.	Out et al. [26]
			Mexico	T = 0.03	>0.05	Biguanides + SU	No significant association.	Sanchez-Ibarra et al. [20]
	rs594709	G > A	South Africa	G = 0.27	0.148	Biguanides	No association with metformin response ($p > 0.05$).	Xhakaza et al. [29]*
	rs2282143	C > G/T	South Africa	T = 0.07	0.361	Biguanides	No significant association.	Xhakaza et al. [29]*
			Jordan	T = 0.02	0.810	Biguanides	No significant association.	Al-Eitan et al. [24]
SLC22A2	rs316019	A > C/T	Mexico	A = 0.04	0.265	Biguanides + SU	No significant association with HbA1c level.	Ortega-Ayala et al. [18]
			China	A = 0.22	>0.05	Biguanides	No significant effects against glycemic level.	Chen et al. [14]
			India	T = 0.12	>0.05	Biguanides	A significant association with metformin response.	Phani et a. [22]*
			Mexico	A = 0.06	>0.05	Biguanides + SU	No significant association with HbA1c reduction.	Sanchez-Ibarra et al. [20]

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Table 1 (*continued*)

Gene	SNP	Chromosome position	Population	MAF	*(P)** with HWE	OAD	Clinical effects	References
	rs662301	C > T	Saudi Arabia	T = 0.04	>0.05	Biguanides	A significant association with elevated HbA1c.	Alharbi et al. [31]
			Jordan	T = 0.05	0.610	Biguanides	No significant association.	Al-Eitan et al. [24]
	rs315978	T > A/C	Saudi Arabia	T = 0.16	>0.05	Biguanides	Significant association with elevated HbA1c.	Alharbi et al. [31]
	rs316009		South Africa	T = 0.04	0.595	Biguanides	Significant association with good response.	Abrahams – October et al. [32]
SLC22A3	rs2292334	G > A/C/T	India	A = 0.45	>0.05	Biguanides + SU	A significant association with better response.	Rizvi et al. [11]*
			Jordan	T = 0.28	0.320	Biguanides	No significant association with HbA1c level.	Al-Eitan et al. [24]
	rs12194182	T > C	Jordan	C = 0.09	0.290	Biguanides	A significant association with lower mean HbA1c.	Al-Eitan et al. [24]
	rs2076828	C > G	Mexico	G = 0.14	0.280	Biguanides + SU	No significant association.	Ortega-Ayala et al. [18]
			South Africa	G = 0.34	0.03	Biguanides	No significant association.	Xhakaza et al. [29]*
	rs3088442	G > A/C	Pakistan	G = 0.40	>0.05	Biguanides + SU	Significant association with better response.	Moeez et al. [33]*
	rs543159	C > A	Iran	A = 0.46	>0.05	Biguanides	A significant association with glycemic reduction.	Taheri et al. [34]
SLC47A1	rs2289669	G > A	Russia	A = 0.32	>0.05	Biguanides	No significant association.	Nasykhova et al. [12]*
			South Africa	A = 0.02	0.725	Biguanides	No significant association with good response.	Xhakaza et al. [29]*
			China	A = 0.45	>0.05	Biguanides	Significant correlations with HbA1c reduction	Chen et al. [14]
			India	A = 0.5	3.173	Biguanides	No significant association.	Raj et al. [35]
			India	A = 0.58	>0.05	Biguanides	No significant association	Phani et al. [22]*
			Indonesia	A = 0.61	>0.05	Biguanides	A significant association with glycemic changes.	Ningrum et al. [15]
			Egypt	A = 0.42	>0.05	Biguanides + SU	Significant association with glycemic response.	Ahmed et al. [16]*
			Netherlands	A = 0.40	0.340	Biguanides	Significant association with glycemic reduction.	Out et al. [26]
	rs2252281	T > C	Egypt	C = 0.42	>0.05	Biguanides	Significant association with HbA1c reduction.	Mostafa-Hedeab et al. [30]
	rs77630697	G > A	Pakistan	A = 0.27	>0.05	Biguanides	Significant association with HbA1c reduction.	Hakim et al. [36]
	rs2250486	T > C	Iran	Responder C = 0.13	0.295	Biguanides	A significant association with better response.	Semnani et al. [37]
				Non – responder C = 0.23	0.367			
	rs67238751	C > T	Iran	Responder T = 0.13	0.947	Biguanides	No significant association.	Semnani et al. [37]
				Non – responder T = 0.15	0.731			
	rs8065082	C > T	India	T = 0.28	>0.05	Biguanides	No significant association.	Phani et al. [22]*
	rs2453580	T > C	Mexico	C = 0.17	>0.05	Biguanides + SU + DPP4i + TZD	Significant association with changes to HbA1c level.	Gonzalez-Covarrubias et al. [38]
SLC47A2	rs12943590	G > A	South Africa	A = 0.16	0.305	Biguanides	Significant association with lower response.	Xhakaza et al. [29]*
			Egypt	A = 0.39	>0.05	Biguanides	A significant difference with HbA1c changes.	Mostafa-Hedeab et al. [30]
			China	A = 0.41	>0.05	Biguanides	Significant association with glycemic level.	Chen et al. [14]
			India	A = 0.48	2.535	Biguanides	No significant association.	Raj et al. [35]
			India	A = 0.35	>0.05	Biguanides	A significant association with better response.	Phani et al. [22]*
ATM	rs11212617	C > A	Russia	C = 0.45	0.718	Biguanides	No significant association.	Nasykhova et al. [12]*

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Table 1 (*continued*)

Gene	SNP	Chromosome position	Population	MAF	*(P)** with HWE	OAD	Clinical effects	References
			Netherlands	C = 0.46	0.910	Biguanides	A significant association with metformin plasmatic concentration.	Out et al. [26]
CYP2C9	CYP2C9*2 rs1799853	C > A/T	Mexico	T = 0.05	>0.05	Biguanides + SU	No significant association.	Castelán-Martínez et al. [39]*
			Lebanon	T = 0.32	>0.05	Biguanides + SU	No significant interaction.	Naja et al. [19]
			Slovenia	T	>0.05	Biguanides + SU	No significant association.	Klen et al. [40]*
			Iran	T = 0.15	>0.05	Biguanides + SU	No significant correlation.	Saberi et al. [41]
			Iraq	T = 0.14	>0.05	Biguanides + SU	No association with the HbA1c.	Rasool et al. [42]
	CYP2C9*3 rs1057910	A > C/G	Mexico	C = 0.03	>0.05	Biguanides + SU	A significant association with better glycemic control.	Castelán-Martínez et al. [39]*
			Mexico	C = 0.03	0.848	Biguanides + SU	No association with HbA1c reduction.	Ortega-Ayala et al. [18]
			Lebanon	C = 0.31	>0.05	Biguanides + SU	No significant interaction.	Naja et al. [19]
			Slovenia	C	>0.05	Biguanides + SU	No significant association.	Klen et al. [40]*
			Iran	C = 0.05	>0.05	Biguanides + SU	No significant correlation with HbA1c level.	Saberi et al. [41]
			Iraq	C = 0.05	>0.05	Biguanides + SU	No significant association.	Rasool et al. [42]
			Iran	A = 0.14	>0.05	Biguanides + SU	No significant interaction with HbA1c changes.	Didari et al. [43]
	IVS8-109 A > T rs1934969	A > T	Mexico	T = 0.19	0.197	Biguanides + SU	No association with HbA1c.	Ortega-Ayala et al. [18]
			Mexico	T = 0.16	>0.05	Biguanides + SU	Significant association with reduction of HbA1c.	Cuautle-Rodríguez et al. [44]
TCF7L2	rs7903146	C > G/T	Mexico	T = 0.19	>0.05	Biguanides + SU	No significant association with good glycemic.	Castelán-Martínez et al. [39]*
			Thailand	T = 0.06	0.267	Biguanides + SU + TZD	A significant association with lower FPG.	Teerawatta −napong et al. [45]
			India	T = 0.6	>0.05	Biguanides + SU + α-GI	A significant association with HbA1c changes.	Kumar et al. [46]
			Iran	T = 0.3	>0.05	Biguanides + SU	No significant association with HbA1c changes.	Dianatshoar et al. [47]
			Slovakia & Czech	T = 0.31	0.63	DPP4i	No significant association with improved HbA1c.	Urgeová et al. [48]
			Bosnia	T = 0.37	>0.05	Biguanides	Significant association with glycemic response.	Dujic et al. [49]
	rs12255372	G > A/T	Mexico	T = 0.15	>0.05	Biguanides + SU	No significant association with good glycemic control.	Castelán-Martínez et al. [39]*
KCNJ11	rs5219	T > A /C/G	Mexico	T = 0.42	>0.05	Biguandies + SU	No significant association with good glycemic control.	Castelán-Martínez et al. [39]*
			Slovenia	T = 0.37	>0.05	Biguanides + SU	No significant association with glycemic changes.	Klen et al. [40]*
			Slovakia	K = 0.4	0.84	SU	Significant association with HbA1c reduction.	Javorsky et al. [50]
			Italy	K = 0.36	>0.05	Biguanides + SU	Significant association with secondary failure of SU treatment.	Sesti et al. [51]
			Egypt	K = 0.36	>0.05	Biguanides + SU	Significant association with good response.	Ahmed et al. [16]*
			Mexico	T = 0.38	>0.05	Biguanides + SU	Significant association with good response to SU.	Sanchez-Ibarra et al. [20]
	rs5215	C > T	Slovenia	C = 0.38	>0.05	Biguanides + SU	No significant association with glycemic changes.	Klen et al. [40]*
ABCC8	rs757110	C > A/T	Mexico	G = 0.42	>0.05	Biguanides + SU	No significant association with good glycemic control.	Castelán-Martínez et al. [39]*
			Iran	C = 0.17	>0.05	SU	No significant association with HbA1c level.	Azimi et al. [52]
			Slovenia	C = 0.38	>0.05	Biguanides + SU	No significant association.	Klen et al. [40]*
			Mexico	C = 0.39	>0.05	Biguanides + SU	Significant association with HbA1c reduction.	Sanchez-Ibarra et al. [20]

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Table 1 (*continued*)

Gene	SNP	Chromosome position	Population	MAF	*(P)** with HWE	OAD	Clinical effects	References
			Egypt	C = 0.27	0.867	Biguanides + SU	No significant association with response to therapy.	Ebid et al. [23]*
	rs1799854	G > A/C	Iran	A = 0.36	>0.05	SU	No significant association with HbA1c.	Azimi et al. [52]
	rs1801261	G > A/T	China	T = 0.2	>0.05	Meglitinides	Significant association with HbA1c.	Zhou et al. [53]

SLC: Solute Carrier; ATM: Ataxia Telangiectasia; CYP: Cytochrome; TCF: Transcription Factor; KCNJ: Potassium Channel Subfamily J; ABC: ATP-binding Cassette; HWE: Hardy-Weinberg Equilibrium; MAF: Minor allele frequency; OAD: oral anti-diabetic drugs; author*: study that reported binary glycemic outcome (responder/non-responder).

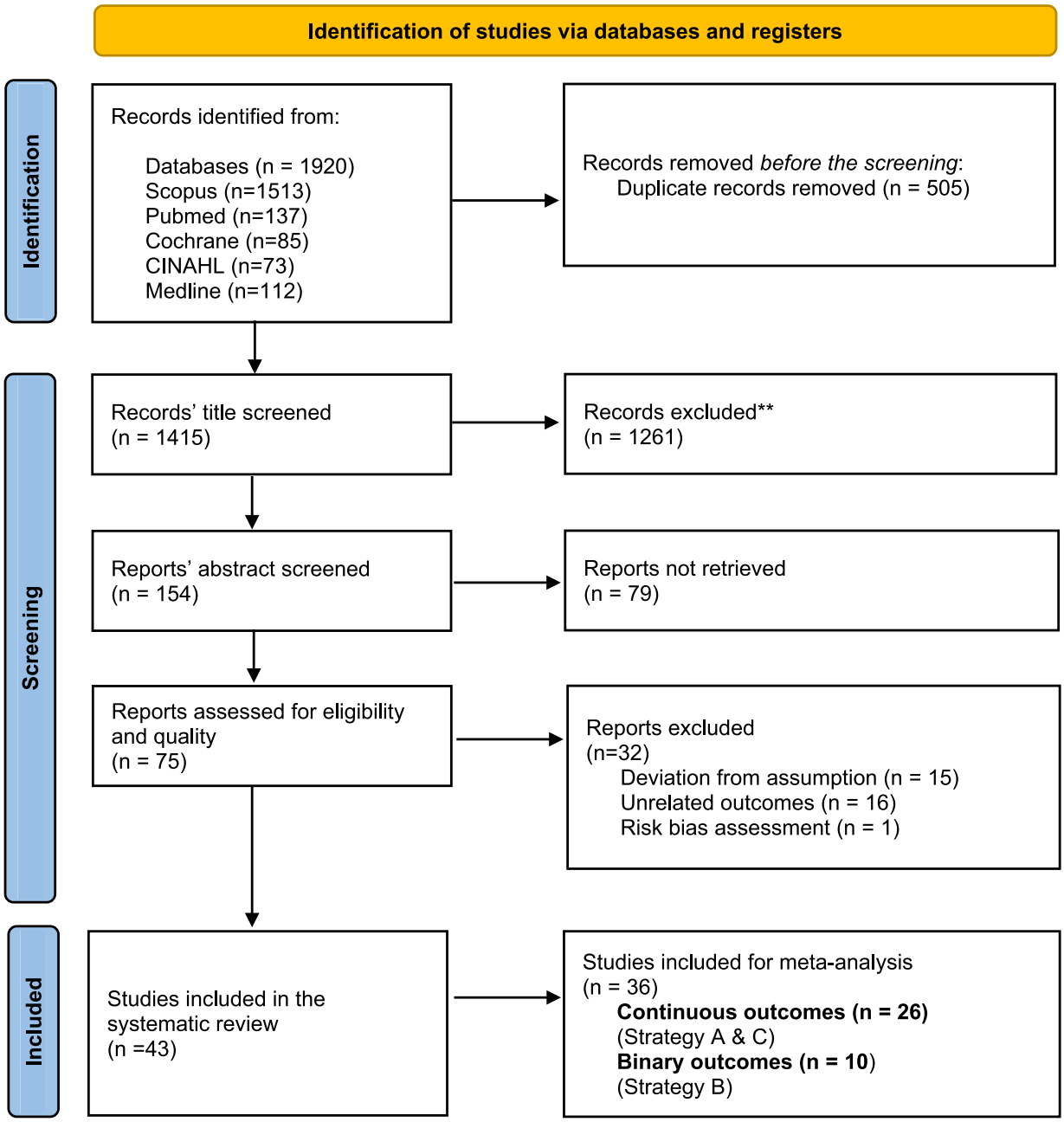

Fig. 1. PRISMA flow diagram for the selection of included studies.

significantly associated with a reduction in HbA1c compared to the AA genotype [SMD (95 % CI) = 0.94 (0.46, 1.42); P = 0.001; P^Q = 0.191; I^c2 = 36.8 %] (Fig. 2**A**) and the AC genotype [SMD (95 % CI) = 0.73 (0.24, 1.22); P = 0.003; P^Q = 0.791; I^2 = 0.0] (Fig. 2**B**, **Supplementary Table S4**). However, a *meta*-analysis based on binary outcome studies (strategy B) found no association between rs622342 and the

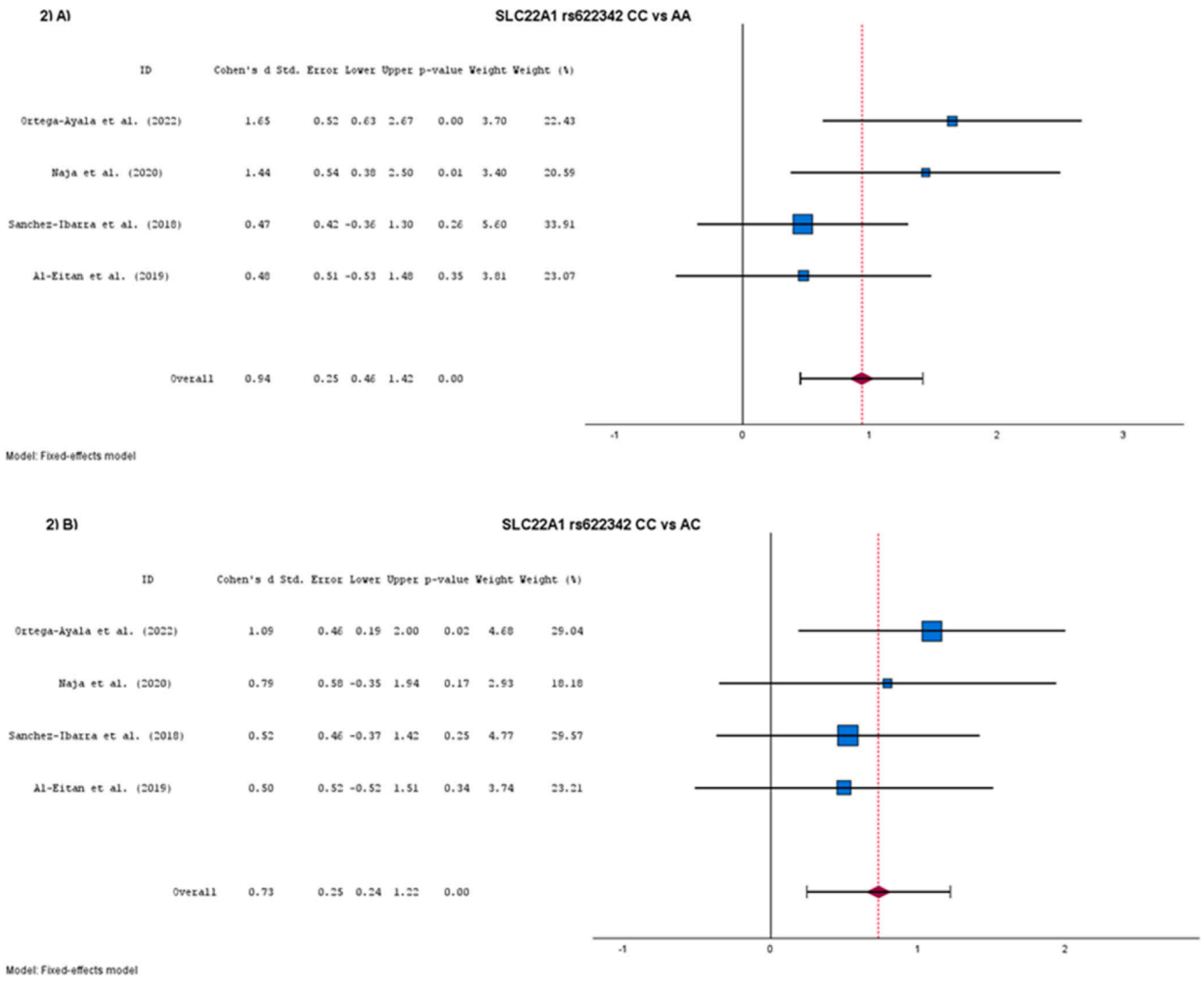

Fig. 2. The forest plots of *meta*-analysis strategy A for the association between *SLC22A1* polymorphisms and glycemic response. **(A)** Forest plots of *SLC22A1* rs622342 (CC vs. AA) and **(B)** rs622342 (CC vs. AC).

glycemic response to OAD.

Seven (7) studies [11–17] evaluated rs628031 polymorphism. Only one (1), conducted among the Mestizo population [17], reported a positive correlation with HbA1c level, while six (6) others (Indian, European, Chinese, Indonesian, and Arabian) [11–16] reported no significant result. Strategy A of continuous *meta*-analysis cannot be calculated due to insufficient HbA1c data for every genotype. Meta-analysis of strategy B [11,12,16] found no significant association with glycemic response **(Supplementary Table S4).**

Two (2) studies examining rs12208357 [12,30] identified significant findings with improved glycemic response in European and Arabian populations, while the others [20,26,29] found no association in African, Mestizo, and European populations. Meta-analysis of strategy A [20,30] reported no significant association was observed between rs12208357 and HbA1c reduction. However, strategy B [12,29] reported a significant association for the dominant model AA + Aa vs. aa $\left[OR(95\%CI) = 4.89(1.09, -21.98); P = 0.038; P^{Q} = 0.265; I^{2} = 19.5\%\right]$ **(**Fig. 3**A)** and additive model AA vs. aa $\left[OR(95\%CI) = 5.16(1.14, -23.30); P = 0.033; P^{Q} = 0.255; I^{2} = 22.8\%\right]$ **(**Fig. 3**B)** indicating improved glycemic response to OADs **(Supplementary Table S4).** One (1) study [26] was excluded due to the unavailability of HbA1c measurement.

Two (2) studies [27,28] evaluating rs72552763 conducted among Arabians and Ethiopians found a significant association with the glycemic level, while two (2) others [16,20] in Arabian and Mestizo populations reported non-significant findings. One (1) study in Indonesia [15] observed an extremely weak correlation, while the Mestizo [18] found significance only with biguanide monotherapy but not with combined therapy. However, a *meta*-analysis of strategies A [18,20,27] and B [16,28] reported no significant result. One (1) study [15] was not included in the *meta*-analysis due to the unavailability of HbA1c data.

No significant associations were reported regarding glycemic response for rs594709 in African [29] and rs2282143 in African and Arabian populations [24,29] **(**Table 1**).** No *meta*-analyses were carried out due to inadequate reported studies.

3.2.2. *SLC22A2 gene polymorphism*

Out of 43 studies, seven (7) [14,18,20,22,24,31,32] assessed the effects of four (4) SNPs (rs316019, rs662301, rs315978, rs316009) on glycemic levels **(**Table 1**).** Four (4) studies assessed rs316019 polymorphism, where one (1) study involving Indians [22] reported significant findings with glycemic response, while three (3) studies (Mestizo and Chinese) [14,18,20] found no association. Meta-analysis of strategy A [18,20] showed no significant results between rs316019 and glycemic responses. Meta-analysis of strategy B [22] cannot be calculated due to insufficient studies. Two (2) studies examined rs662301 in Arabian, with one (1) reporting a significant association with HbA1c [31], while the other showed no association [24]. A single study investigated

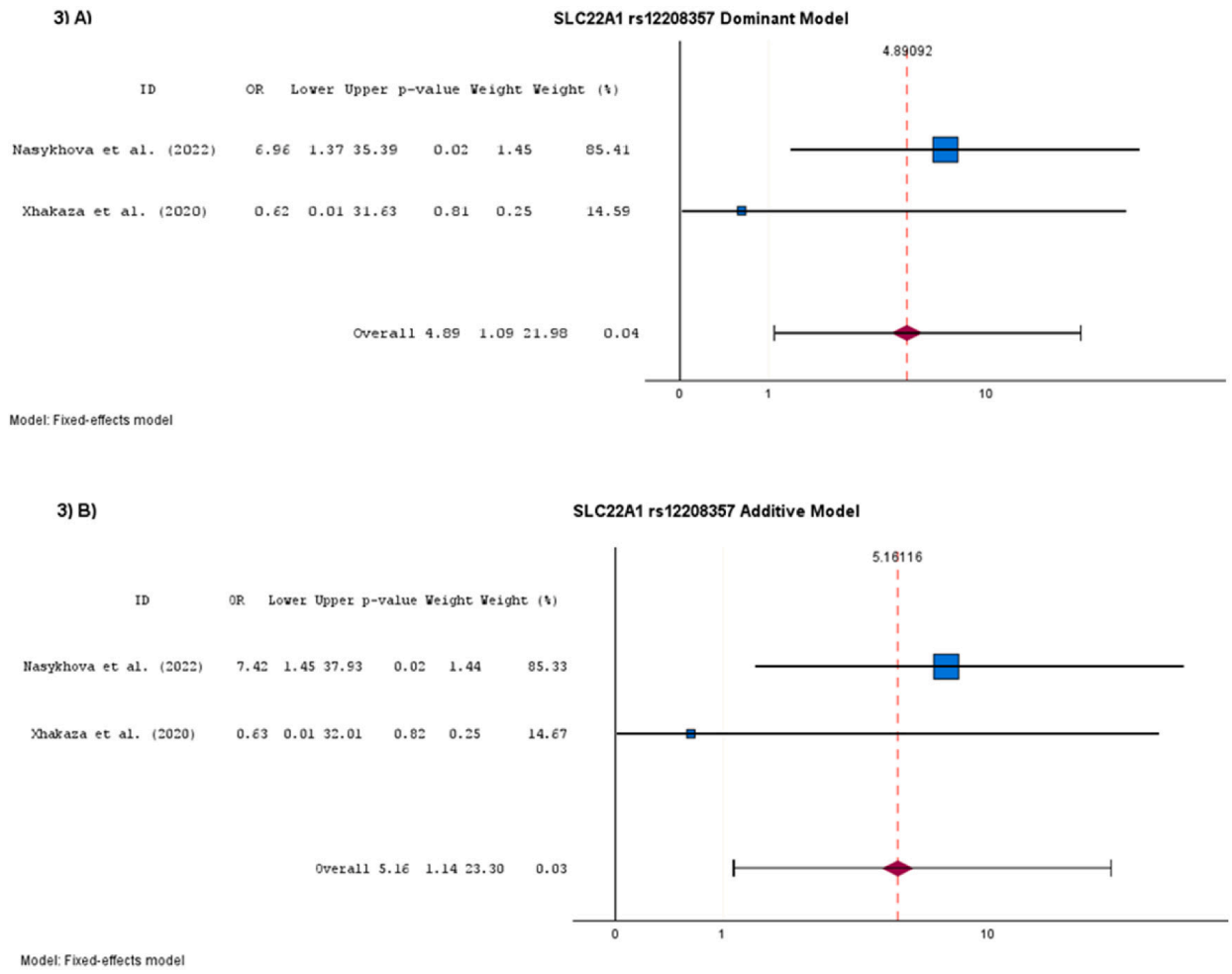

Fig. 3. The forest plots of *meta*-analysis strategy B for the association between *SLC22A1* and the glycemic response of OAD. **(A)** Forest plots of *SLC22A1* rs12208357 and glycemic response of OAD in the dominant model (AA + Aa vs aa) and **(B)** additive model (AA vs aa).

rs315978 (Arabian) [31] and rs316009 (African) [32], both reporting an association with glycemic control. No *meta*-analysis was carried out due to the lack of studies for every SNP.

3.2.3. *SLC22A3 gene polymorphism*

Out of 43 studies, six (6) studies [11,18,24,29,33,34] examined the effects of five (5) SNPs (rs2292334, rs12194182, rs2076828, rs3088442, rs543159) on glycemic levels (Table 1). rs12194182 [24], rs543159 (Arabian) [34], and rs3088442 among Pakistanis [33] were analysed in one (1) study, respectively. All showed significant associations with improved glycemic responses. rs2292334 showed a significant association in Indians [11] but not in Arabians [24]. Two (2) studies on rs2076828 (African and Mestizo) [18,29] reported no significant results in relation to improved glycemic control. No *meta*-analyses were calculated due to an inadequate number of studies for every SNP.

3.2.4. *SLC47A1 gene polymorphism*

Out of 43 studies, 12 studies [12,14,15,16,22,26,29,30,35,36,37,38] examined the effects of seven (7) SNPs (rs2289669, rs2252281, rs77630697, rs2250486, rs67238751, rs80650821, rs2453580) on glycemic levels. Four (4) studies found no association between rs2289669 and glycemic responses, particularly among European, African, and Indian [12,22,29,35] (Table 1). The remaining four (4) studies among Chinese, Indonesians, Arabians and Europeans showed significant results [14,15,16,26]. Strategy A of *meta*-analysis cannot be carried out due to the limited glycemic data reported. Strategy B of *meta*-analysis [12,16,22,29] revealed no significant association between rs2289669 and glycemic response to OADs (**Supplementary Table S4**). Significant findings were reported for rs2252281 [30] and rs2250486 [37] in Arabian, rs77630697 in Pakistan [36], and rs2453580 in Mestizo [38] populations, but no *meta*-analysis was performed due to an inadequate amount of data.

3.2.5. *SLC47A2 gene polymorphism*

From 43 studies, five (5) studies [14,22,29,30,35] assessed the effects of rs12943590 on glycemic levels. Out of five (5), four (4) studies involving Chinese, African, Arabian and Indian [14,22,29,30] reported significant findings between rs12943590 with glycemic response, depicted by a reduction in HbA1c. Strategy A of *meta*-analysis [30,35] validated a significant association for HbA1c $\left[AGvs.AA : SMD(95\%) = -0.53(-0.94, -0.13); P = 0.01; P^{Q} = 0.208; I^{2} = 37.0\%\right]$ (Fig. 4, **Supplementary Table S4**) though in strategy B [22,29], no association was observed with glycemic response to OADs across all genetic models.

3.2.6. *ATM gene polymorphism*

Two (2) studies [12,26] on the European population investigated the rs11212617 polymorphism of the *ATM* gene in relation to the OAD glycemic response. One study [26] demonstrated a significant association, while the other did not [12]. Due to the insufficient number of studies, no *meta*-analysis was conducted.

3.2.7. *CYP2C9 gene polymorphism*

Out of 43 studies, eight (8) studies [18,19,39,40,41,42,43,44]

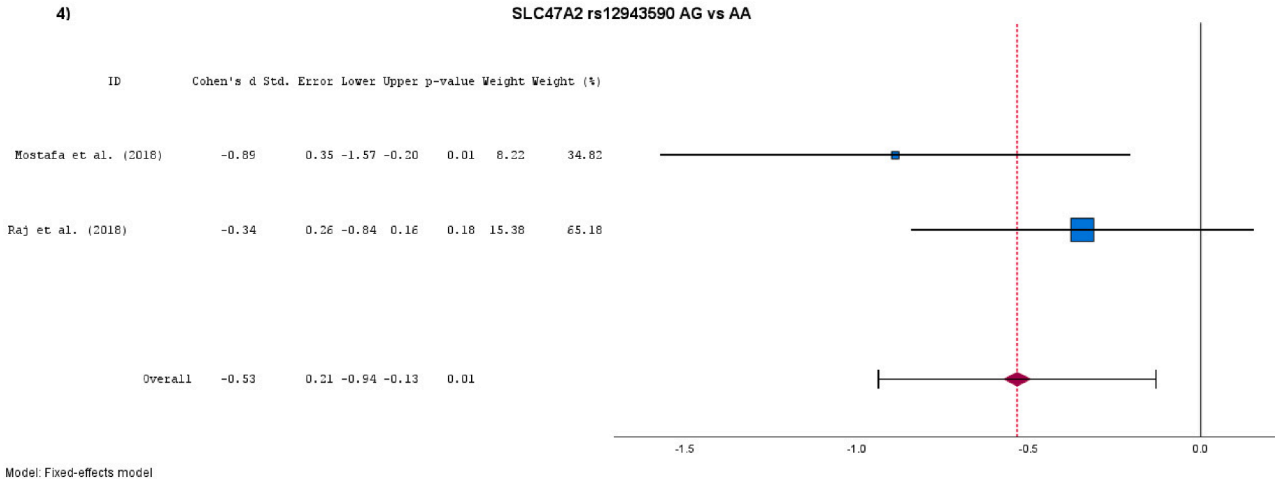

Fig. 4. Forest plots of *meta*-analysis strategy A for the association between *SLC47A2* rs12943590 and the changes of HbA1c (AG vs. AA).

examined the effects of three (3) SNPs (CYP2C9*2, CYP2C9*3 and IVS8-109 A > T) on glycemic levels **(**Table 1**).** The CYP2C9*2 (rs1799853) polymorphism was widely studied with five (5) studies [19,39,40,41,42] across Mestizo, Arabian and European populations showing no significant association with glycemic control. Similarly, seven (7) studies [18,19,39,40,41,42,43] on CYP2C9*3 (rs1057910) revealed only one significant finding in the Mestizo population [39]**.** Our *meta*-analysis strategies A [18,43] and B [39,40] for both SNPs

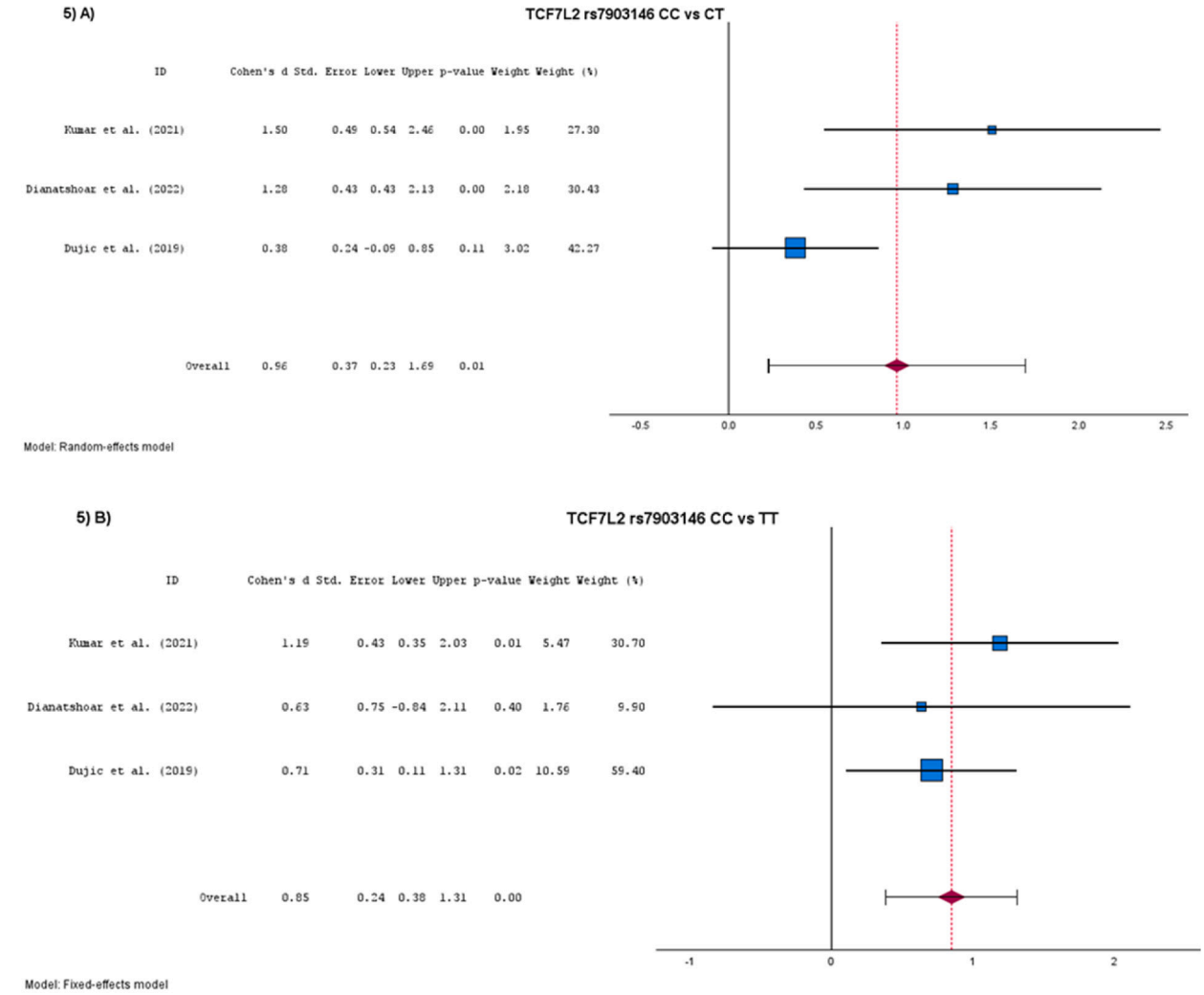

Fig. 5. The forest plots of *meta*-analysis strategy A for the association between *TCF7L2* and the changes of HbA1c. **(A)** Forest plots of *TCF7L2* rs7903146 and HbA1c changes (CC vs. CT) and **(B)** rs7903146 (CC vs. TT).

demonstrated no significant findings regarding glycemic control (**Supplementary Table S4**). Two (2) studies [18,44] on *CYP2C9*IVS8-109A > T (rs1934969) in the Mestizo population found only one (1) [44] reporting a significant association. Due to the small number of studies, no analysis was carried out.

3.2.8. *TCF7L2 gene polymorphism*

Out of 43 studies, six (6) studies [39,45–49] examined the effects of two (2) SNPs (rs7903146, rs12255372) on glycemic levels. Three (3) studies in Thailand, India, and Europe [45,46,49] demonstrated significant findings between rs7903146 with glycemic changes, while the three (3) others [39,47,48], involving Mestizo, Persian, and European groups, report no significant results. Strategy A of *meta*-analysis [46,47,49] confirmed that the CC genotype significantly improved HbA1c compared to CT $[SMD(95\%CI) = 0.96(0.23, 1.69); P = 0.010; P^Q = 0.045; I^2 = 65.5\%]$ (Fig. 5**A**) and TT genotype $[SMD(95\%CI) = 0.85(0.38, 1.31); P = 0.001; P^Q = 0.629; I^2 = 0.0]$ (Fig. 5**B**) (**Supplementary Table S4**). Strategy B cannot be calculated due to an inadequate binary outcomes study. One study (1) on *TCF7L2* rs12255372 involved the Mestizo population [39] and reported no significant association with glycemic control, and no *meta*-analysis can be carried out due to the lack of studies.

3.2.9. *KCNJ11 gene polymorphism*

Out of 43 studies, six (6) studies [16,20,39,40,50,51] examined two (2) SNPs (rs5219, rs5215) on glycemic levels. Several studies found a significant association between rs5219 polymorphism and glycemic control in Arabian [16], parts of the European [50,51] and Mestizo population [20], while others [39,40] did not. Based on strategies A [20,50,51] and B [16,39,40] of *meta*-analysis, there is no significant result between rs5219 and glycemic response (**Supplementary Table S4**). Additionally, a study on rs5215 in the European population [40] also reported no significant findings, which means no *meta*-analysis can be carried out.

3.2.10. *ABCC8 gene polymorphism*

Out of 43 studies, six (6) studies [20,23,39,40,52,53] examined three (3) SNPs (rs757110, rs1799854, rs1801261) on glycemic responses (Table 1). Notably, a study involving the Mestizo population [20] revealed a significant association between rs757110 with glycemic response. In contrast, the remaining four (4) studies involving Persian, European and Arabian people did not demonstrate any statistically significant findings [23,39,40,52]. Strategy A of *meta*-analysis [20,52] showed no association with HbA1c changes. Meanwhile, our strategy B of *meta*-analysis [23,39,40] under the dominant model indicated a significant association between rs757110 and glycemic response to OADs $[OR(95\%CI) = 0.60(0.39, -0.93); P = 0.023; P^Q = 0.733; I^2 = 0.0]$ (Fig. 6, **Supplementary Table S4**). Another study in the Arabian population [52] found no significant result between rs1799854 and glycemic response whereas rs1801261 polymorphism in the Chinese population [53] showed a significant relationship with HbA1c levels. No *meta*-analysis was carried out due to inadequate studies for both SNPs.

3.3. *Impact of treatment regimens on continuous HbA1c changes across populations*

Strategy C was implemented using continuous *meta*-analysis of pooled SMD with a 95 % confidence interval to examine the efficacy of different treatment regimens in several distinct populations. No *meta*-analysis was able to be carried out involving African, Thai, Ethiopian, Chinese and Pakistani populations due to an inadequate number of studies reporting treatment regimens.

3.3.1. *Arabian population*

Nine (9) studies evaluated OAD affecting HbA1c levels in Arabians [16,19,21,23,24,27,30,31,42]. Biguanides monotherapy showed significant HbA1c reduction [SMD (95 % CI) = -1.30 (−2.46, −0.15); P = 0.026; P^Q = 0.00; I^2 = 98.3 %], as did biguanides plus sulphonylureas [SMD (95 % CI) = -1.76 (−2.97, −0.55); P = 0.004; P^Q = 0.00; I^2 = 96.9 %] (**Supplementary Table S5**).

3.3.2. *Indian population*

Five (5) studies [11,13,22,35,46] examined Indian patients on biguanide monotherapy, revealing a significant HbA1c reduction $[SMD(95\%CI) = -0.99(-1.49, -0.49); P = 0.001; P^Q = 0.00; I^2 = 89.0\%]$ (**Supplementary Table S5**).

3.3.3. *Mestizo population*

Six (6) studies [17,18,20,38,39,44] focused on Mestizos involving biguanides monotherapy [SMD (95 % CI) = -1.13 (−1.17, −0.50); P = 0.001; P^Q = 0.00; I^2 = 94.6 %], showing significant HbA1c reduction. However, the combination therapy yielded no statistically significant results (**Supplementary Table S5**).

3.3.4. *Persian population*

Six (6) studies [34,37,41,43,47,52] conducted among Persians, where biguanides monotherapy demonstrated a significant HbA1c reduction [SMD (95 % CI) = -2.27 (−2.53, −2.02); P = 0.001; P^Q = 0.365; I^2 = 5.7 %], while no significant results were found for combination therapy or sulfonylureas monotherapy (**Supplementary Table S5**).

3.3.5. *European population*

Seven (7) studies [26,40,42,48,49,50,51] involving European population where no significant HbA1c reduction was observed in European patients for either biguanides monotherapy or combination therapy (**Supplementary Table S5**).

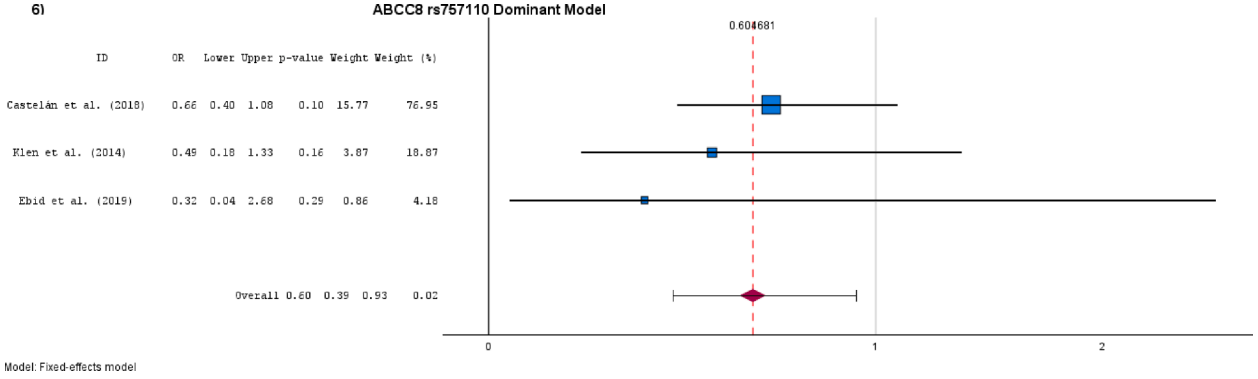

Fig. 6. The forest plots of strategy B for the association between *ABCC8* rs757110 and the glycemic response of OAD in the dominant model (AA + Aa vs aa).

4. Discussion

Pharmacological intervention is crucial in managing T2DM [1], with OAD efficacy influenced by genetic heterogeneity [54,55]. This review assessed gene polymorphism affecting glycemic responses to OADs, revealing significant association for *SLC22A1* rs622342, *SLC22A1* rs12208357, *SLC47A2* rs12943590, *TCF7L2* rs7903146 and *ABCC8* rs757110 with HbA1c reduction. Inconsistencies arose between continuous (strategy A) and binary (strategy B) in *meta*-analyses due to different outcome definitions where some studies indicate HbA1c readings of < 7 % as good responders [11,16], while other study indicate good responders have ≥ 0.5 % HbA1c reduction from the baseline [28], and sample size imbalances (continuous 26 studies; binary 10 studies) leading to varied conclusions.

SLC22A1 encodes Organic Cation Transporter 1 (OCT1), vital for metformin hepatic uptake, renal excretion and intestinal absorption [26,56]. The rs622342 C minor allele was correlated with the reduction of OCT1 function, which led to diminishing metformin efficacy [23]. Strategy A found the CC genotype linked to HbA1c reduction, contradicting with previous studies showing the A allele carriers benefit more from metformin, suggesting that C allele polymorphism causes a diminished transporter function [23,57]. However, a study reported that rs622342 does not influence glucose-lowering effects in metformin-treated patients [58]. Similarly, rs12208357 polymorphisms, which has been correlated with declined transportation, reducing metformin uptake and thus lowering OAD efficacy [59] was linked to better OAD responses in the dominant model (wild-type C allele) [12,30] in agreement with the current *meta*-analysis. Several other SNPs (e.g., rs628031 and rs72552763) have been reported to be associated with glycemic responses [17,18], though *meta*-analysis failed to show a significant glycemic effect.

SLC22A2 encodes Organic Cation Transporter 2 (OCT2), which regulates renal metformin uptake [22] with rs316019 could significantly influence metformin distribution and elimination [14], though strategy A found no significant association. SNPs rs662301, rs315978, and rs316009 were also studied in Arabian and African populations but require further validation [24,31,32]. The *SLC22A3* gene is responsible for encoding the OCT3 protein, which is widely distributed in adipocytes, muscle and intestinal cells [33]: thus, OCT3 variants were associated with alteration of expression, affecting metformin uptake, and thus reducing its efficacy [34]. However, *SLC22A3* polymorphisms (rs2292334, rs12194182, rs2076828, rs3088442, rs543159) have only been examined in a few populations and have insufficient data for *meta*-analysis, hindering conclusions on glycemic response.

SLC47A1 and *SLC47A2* encoding for multidrug and toxic extrusion 1 (MATE1) and MATE 2 proteins, respectively [18] influence metformin excretion in hepatic and renal [35]. rs2289669 is known to reduce MATE expression prolonging metformin activity and lowering HbA1c levels [14,15,16] though strategy B of *meta*-analysis showed no significant association in improving glycemic levels consistent with other studies [12,35] possibly due to gene frequency differences. Other SNPs reported to have significant results previously (e.g., rs2252281, rs77630697, rs2250486, rs67238751) [30,36,37,38] but no *meta*-analyses were carried out due to insufficient data. Similarly, the *SLC47A2* rs12943590 AG genotype was linked to HbA1c reduction [14,22,29], though other studies showed conflicting results on metformin bioavailability [35].

The *ATM* gene, which is responsible for DNA repair and cell cycle control [12] shows the rs11212617 variant is correlated with metformin efficacy, though the mechanism remains unclear [26] and insufficient studies prevented *meta*-analysis.

The CYP2C9 enzyme, encoded by the *CYP2C9* gene, is responsible for metabolising SU in the liver [39]. The present *meta*-analysis found no significant associations, but a study reported that the CYP2C9*3 allele improved response in Mexicans and not the CYP2C9*2 allele [39]. Another study reported that CYP2C9*1*3 and CYP2C9*1*2 variants enhanced glycemic response in Indians compared to wild-type CYP2C9*1*1 [60]. The CYP2C9*2 and CYP2C9*3 allele variants may have higher SU plasma concentrations due to the lower enzymatic activity compared to the wild-type alleles (*1/*1) [41]; thus, higher SU levels enter β cells and maximise their effect in the glycemic response [25].

The *TCF7L2* gene is responsible for insulin production with the rs7903146 risk allele able to reduce insulin secretion [39] demonstrated a significant HbA1c reduction among patients with the CC genotype compared to heterozygous CT and homozygous variant TT in strategy A, consistent with previous findings [45,46,49].

KCNJ11 encodes for a component of the KATP channel that is involved in insulin secretion [39] was extensively studied with several conflicting results [16,40,50,51] with no significant association in our *meta*-analysis.

ABCC8 rs757110 affects the SUR1 protein, a component of the KATP channel [39] influencing SU binding sensitivity [52] with strategy B showing a significant association with improved glycemic response [20,62], contradicting previous studies that showed no effect [40,52].

Discrepancies in genetic association studies may stem from population genetic differences, outcome definition variations, sample size imbalances, and treatment variability. Population-specific analyses showed significant HbA1c reductions in Arabians [19,23] and Indians with metformin [22,63] but limited data prevented combination therapy analysis. The Mestizo population showed glycemic improvement with metformin and similar results were found in Mexicans with the GAT/GAT genotype of *SLC22A1* rs72552763 [17,18]. Persians also showed improved response, though findings require cautious interpretation due to small sample sizes and study design differences [34]. Nevertheless, this present analysis found no significant HbA1c reduction in European studies, likely due to limited research. Another limitation is the geographical concentration of studies, with limited or no representation from the United States and European populations. This restricts the generalizability of the current findings to those populations.

Monotherapy significantly influences glycemic levels compared to combination therapy though uneven study designs and dosage variability should be considered. Inconsistent glycemic response definitions across studies, where some studies classify responders based on achieving HbA1c levels below 7 %, and others define response as a reduction of at least 0.5 % from baseline, contribute to observed heterogeneity, highlighting the need for a standardized definition of glycemic response to ensure comparability across populations in future studies. High I^2 values suggest underlying differences in study protocols and population characteristics, and subgroup analyses could further elucidate genetic influences. Nevertheless, genetic heterogeneity likely accounts for varied glycemic responses, with certain SNPs like *SLC22A1* rs628031 showing higher alternate allele frequencies across populations, explaining the lack of association with glycemic responses in some studies [11–16]. Variability in findings for *SLC22A2* rs316019 also points to the population-specific differences in allele frequency, which influence the drug response [14,18,20,22]. Given the consistent associations observed between certain gene polymorphisms and glycemic response, particularly *SLC22A1* rs622342 [56] and *TCF7L2* rs7903146 [61], implementing targeted pharmacogenomic screening in clinical settings may be worth considering, pending further studies on cost-effectiveness and ethical aspects. Incorporating targeted genetic testing for the above genes represents a promising step toward advancing precision medicine in diabetes care, especially for high-risk subgroups with strong familial predisposition, early-onset T2DM, or poor glycemic control despite standard therapy.

5. Conclusions

This *meta*-analysis highlights the impact of gene polymorphisms on glycemic response to OADs in T2DM patients, identifying key variants in *SLC22A1, SLC22A2, SLC22A3, SLC47A1, SLC47A2, ATM, CYP2C9,*

TCF7L2, KCNJ11, and *ABCC8* genes that influence metformin and sulfonylurea efficacy. Polymorphisms like *SLC22A1* rs622342, *SLC22A1* rs12208357, *SLC47A2* rs12943590, *TCF7L2* rs7903146, and *ABCC8* rs757110 were linked to HbA1c reduction, although inconsistencies due to study designs, sample sizes, and population-specific genetic backgrounds were noticed.

Monotherapy generally showed greater glycemic improvement than combination therapy, though this finding requires caution due to study imbalances and treatment variations. Population-based analyses revealed significant heterogeneity, with notable responses in Arabians, Indians, Mestizos, and Persians, while European cohorts showed inconclusive results.

These findings underscore the importance of personalized medicine, advocating for genetic profiling to optimize OAD selection and improve therapeutic outcomes. Further large-scale, multiethnic studies with standardized methods are required to validate and refine precision medicine approaches for diabetes management. Screening for key SNPs, such as *SLC22A1* rs622342 or *TCF7L2* rs7903146, could support the development of genotype-guided treatment algorithms. Integrating such pharmacogenetic data into clinical workflows and electronic health records may improve drug efficacy and reduce adverse outcomes through more precise OAD prescribing.

CRediT authorship contribution statement

Fikry Ahmad: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Suhaili Abu bakar:** Validation, Data curation, Funding acquisition, Writing – review & editing, Formal analysis, Supervision, Conceptualization. **Sharifah Sakinah Syed Alwi:** Writing – review & editing. **Ng Ooi Chuan:** Writing – review & editing.

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Author contribution

During the preparation of this work, the author(s) used ChatGPT tool (https://chatgpt.com/) in order to shorten the text as the word count in the original write-up was above 7000. After using this tool/service, the author(s) reviewed and edited the content as needed and took(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2025.112337.

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