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Systematic Review

Association Between Angiotensinogen Gene M235T and Renin–Angiotensin System Insertion/Deletion Variants and Risk of Cardiovascular Disease in North African and Middle Eastern Populations: A Systematic Review and Meta-Analysis

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Abstract

Background: The renin–angiotensin system (RAS) is pivotal in regulating cardiovascular function, while cardio-genomics offers insights into genetic factors influencing cardiovascular disease (CVD) susceptibility. Aim: This study investigates the relationship between the angiotensin-converting enzyme insertion/deletion variant (ACE I/D) and the angiotensinogen gene M235T variant (AGT M235T) in Mediterranean, North African, and Middle Eastern populations. Methods: A systematic review and meta-analysis, encompassing studies until December 2023, were conducted utilizing the PubMed and Scopus databases. The study followed the PICO checklist to enroll in the review process. The meta-analysis results were obtained using CMA software V2. Results: An analysis of 12 studies (2984 participants) for ACE I/D and 7 studies (2275 participants) for AGT M235T revealed significant associations between these gene variants and increased CVD risk in Mediterranean and North African populations. Conclusions: These findings underscore the utility of cardio-genomics in delineating CVD susceptibility among these groups, emphasizing targeted interventions and personalized treatment strategies

Keywords: AGT; ACE insertion/deletion; cardiovascular; North Africa

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1. Introduction

Cardiovascular diseases (CVDs) represent the foremost global health challenge, accounting for 17.9 million deaths annually and reflecting a marked increase in mortality rates of 25.1% and 49% since 2000 and 1990, respectively [1]. While high-income countries have advanced CVD research and intervention, rapidly developing regions, particularly the Middle East and North Africa (MENA), continue to experience a dual burden: declining communicable diseases alongside a surge in noncommunicable conditions, such as cancer, diabetes, and mental disorders [2]. In nations like Tunisia and Morocco, these noncommunicable diseases have become primary contributors to morbidity. Despite the growing impact of CVD, genomics research in North African and Mediterranean populations remains limited. The emergence of cardiogenomics offers a promising avenue for precision medicine, yet implementation is nascent [3]. Initiatives like the Centre for Arab Genomic Studies' 'Catalogue of Transmission Genetics in Arabs' (CTGA) database have

begun to systematically document genetic disorders prevalent among Arab populations [4], although data remain geographically skewed, with 40% of entries from Tunisia, Lebanon, Morocco, and Saudi Arabia [5].

The renin–angiotensin system (RAS) is a key regulator of cardiovascular homeostasis, governing blood pressure, fluid balance, and vascular remodeling. Its chronic overactivation—primarily via angiotensin II—contributes to endothelial dysfunction, oxidative stress, inflammation, and myocardial remodeling, thereby promoting the development of hypertension, atherosclerosis, and heart failure [6]. Pharmacological inhibition of RAS, through ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists, remains a cornerstone of cardiovascular therapy [7]. In the Middle East and North Africa (MENA) region, where cardiovascular disease (CVD) is the leading cause of mortality, RAS-mediated hypertension is highly prevalent and influenced by metabolic risk factors, consanguinity, and region-specific genetic profiles [8]. Elevated serum levels of RAS components serve as important biomarkers and reflect the distinct pathophysiological patterns observed in MENA populations [8,9]. A comprehensive initial review was undertaken to assess the role of single nucleotide polymorphisms (SNPs) associated with cardiovascular disease in the Middle East and North Africa (MENA) region [7]. The analysis revealed that only variants within the renin–angiotensin system—specifically the ACE and AGT genes—were supported by adequate data for rigorous evaluation. In contrast, investigations into other candidate genes, including eNOS, MTHFR, cytochrome P450, and ApoE, did not yield sufficient evidence to justify their inclusion. This limitation highlights significant gaps in the regional genetic research landscape and directed the scope of the present study. Accordingly, this research centers on examining the association between the ACE I/D and AGT M235T polymorphisms and cardiovascular disease in MENA populations, with the goal of advancing precision medicine strategies in this underrepresented region.

2. Materials and Methods

A systematic search following the PRISMA diagram was conducted in Scopus using the following query: TITLE-ABS-KEY (Morocco OR Tunisia OR Algeria OR Egypt OR Arab AND Heart AND SNP). Additional keywords included the following: polymerase chain reaction, smoking, cardiovascular risk, case-control study, controlled study in adults, allele, ACE, M235T, polymorphism, mortality, and restriction fragment length polymorphism, among others. The search was designed to capture studies relevant to cardiovascular diseases and single nucleotide polymorphisms (SNPs) in Arab and North African populations [10,11].

2.1. Eligibility Criteria

Studies were included if they met the following criteria: observational design (case–control or cohort); focus on molecular genotyping of SNPs in both control and case groups; investigation of cardiovascular diseases, such as myocardial infarction, hypertension, ischemia, or cardiomyopathy; conducted in North African countries (Morocco, Algeria, Tunisia, Egypt, Libya, Mauritania) or selected Arab countries (United Arab Emirates, Saudi Arabia, Qatar); published in English or French.

Studies were excluded if the genotype distribution in control groups deviated from Hardy–Weinberg equilibrium ($p < 0.05$) or if they lacked relevant outcome measures or genotype data.

2.2. Outcome Measurement

The primary outcome was the association between specific SNPs (e.g., ACE I/D, AGT M235T) and the presence of cardiovascular disease. This was assessed using odds ratios (ORs) under different genetic models: allele contrast, homozygote, heterozygote, dominant, recessive, and over-dominant.

2.3. Data Sources and Search Strategy

Data were retrieved from three major electronic databases: PubMed, Scopus, and Clarivate Analytics, as well as additional sources, such as reference lists of included articles and the Global Burden of Disease database. The multi-source strategy aimed to ensure comprehensive coverage of eligible studies.

2.4. Data Extraction

Data extraction was performed independently by two reviewers using RedCap software (REDCap 15.4.3, 2025, Vanderbilt University). Duplicate records were removed, and eligible studies were selected through title and abstract screening followed by full-text review. Extracted data included study design, country, population characteristics, polymorphisms studied, genotype distribution, and reported effect sizes.

2.5. Quality Assessment

The methodological quality and potential for publication bias were assessed using the Begg and Egger tests. Studies not conforming to Hardy–Weinberg equilibrium in the control group were excluded from the meta-analysis to reduce genotyping bias or stratification effects.

2.6. Statistical Analysis

Associations between SNPs and cardiovascular outcomes were calculated using odds ratios (ORs) and 95% confidence intervals (CIs) across multiple genetic models. Between-study heterogeneity was assessed using I^2 and Cochran's Q statistics, with $I^2 > 50\%$ indicating substantial heterogeneity. When heterogeneity was present, random-effects models were applied. Hardy–Weinberg equilibrium was evaluated using Pearson's chi-square or Fisher's exact test. Sensitivity analyses involved the sequential omission of studies to evaluate result stability. Meta-analyses were conducted using the meta–Gen U platform and Comprehensive Meta-Analysis (CMA) software (version 02), which also generated forest plots and prediction intervals.

3. Results

3.1. Study Selection

Out of 250 studies initially retrieved from the databases, 152 articles remained for review after duplicates were removed. Of these, 75 papers did not meet the inclusion criteria, and 63 were excluded due to the unavailability of the full text. Ultimately, 17 articles focusing on the risk of restenosis and the use of drug-eluting stents were selected for analysis (Figure 1). These selected studies were analyzed following a standardized protocol. The extracted data were compiled into a table that included the following information: author, year, ethnicity, sample size, type of stent, genotyping method, gene studied, restenosis occurrence, control group, *p*-value, odds ratio, and confidence interval. A total of 12 studies on the ACE I/D polymorphism were identified among the eligible articles (n = 2038) [11–22].

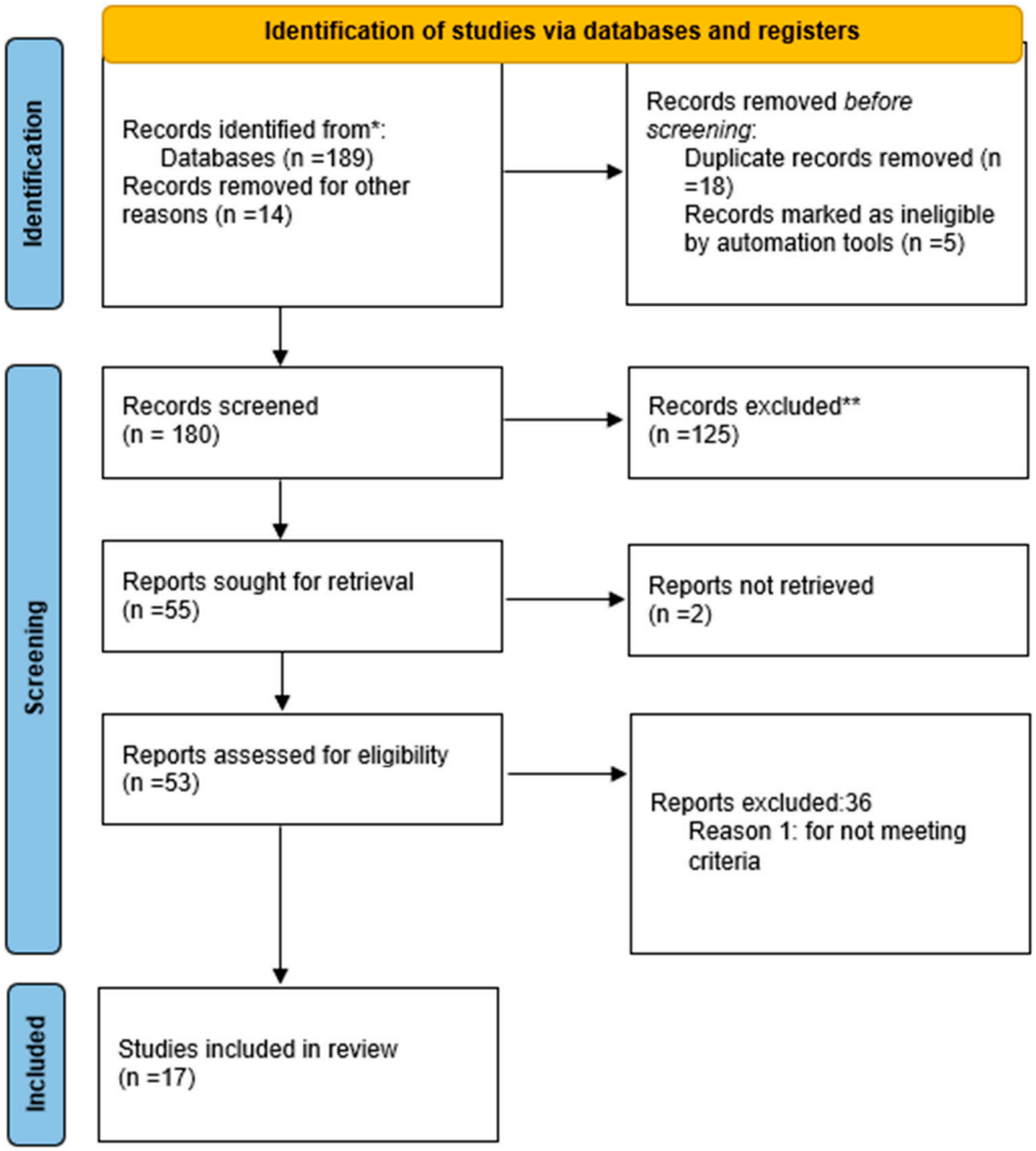

Figure 1. Diagram flow of the studies included in the study. * $p < 0.05$, ** $p < 0.01$.

Furthermore, seven studies on the AGT gene M235T polymorphism were included [16,19–21,23–25] (n = 1447). The characteristics are compiled and organized collectively in Table 1.

Table 1. Study characteristics included and sensitivity test results.

	Authors	Country	Year	DISEASE	Case	Control	Case			Control			Begg Test	Egger Test
							AA	Aa	aa	AA	Aa	aa		
AGT M273M	Saidi et al. [23]	TUNISIA	2008	Ischemia	320	444	49	149	122	37	172	235	0.4882	0.4882
	Frossard, et al. [25]	ABUDHABI	1998	Hypertension	154	109	56	74	24	34	43	32	0.0278	0.0621
	Mehri, S et al. [16]	TUNISIA	2011	Hypertension	142	191	52	67	23	60	82	49	0.0556	0.0778
	Amrani, A et al. [19]	ALGERIA	2015	Hypertension	75	70	14	13	48	15	25	30	0.0355	0.0621
	Al-Jafari, et al. [20]	SAUDI ARABIA	2017	Hypertension	169	97	52	70	47	35	40	22	0.1147	0.1338
	Imen et al. [24]	TUNSIAN	2015	Heart failure	126	108	74	32	20	24	36	48	0.0019	0.0133
	Saab, Y. et al. [21]	LIBANON	2012	Hypertension	124	146	18	72	34	49	59	38	0.0237	0.0621

Table 1. *Cont.*

	Authors	Country	Year	DISEASE	Case	Control	Case			Control			Begg Test	Egger Test
							AA	Aa	aa	AA	Aa	aa		
ACE	Abouelfath, R et al. [11]	Morocco	2018	Resistant hypertension	88	110	41	26	21	26	40	44	0.008	0.024
	Saleh, N.Y. et al. [12]	Egyptian	2020	Congenital heart disease	70	70	25	34	11	26	40	4	0.0249	0.0598
	Meroufel, D.N. et al. [13]	Algeria	2014	Hypertension	91	113	48	36	7	54	47	12	0.7114	0.8555
	Morsy, M.-M.F. et al. [14]	Egyptian	2011	CVD	139	79	37	59	43	11	39	29	0.7129	0.8555
	Mahjoub, S. et al. [15]	Tunisian	2010	Dilated cardiomyopathy	76	151	26	38	12	22	83	46	0.1162	0.2324
	Mehri, S. et al. [16]	Tunisian	2010	CVD	119	238	64	41	14	51	106	81	0.1433	0.2457
	Amara, A. et al. [17]	Tunisian	2016	Coronary artery disease	145	300	110	32	3	95	147	58	0.9329	0.9329
	Hmimech, W. et al. [18]	Morocco	2017	Myocardial infraction	140	182	87	45	8	113	52	17	0.005	0.02
	Enyioma N. OBINECHE et al. [22]	Abbu Dhabi emirate	2001	CVD	92	100	28	58	6	30	62	8	0.0024	0.0144
	Amrani, A et al. [19]	Algeria	2015	Resistant hypertension	75	70	10	40	25	43	25	2	0.4652	0.6978
	Al-Jafari, A.A. et al. [20]	SAUDI ARABIA	2017	Coronary artery disease	169	97	111	43	15	54	26	17	0.0002	0.0024
	Saab, Y. et al. [21]	LIBANEESE	2012	Hypertension	124	146	78	37	9	76	58	12	0.842	0.9185

3.2. Study Characteristics

The identified studies included nine studies on hypertension conducted between 1998 and 2017 in Tunisia, Algeria, Lebanon, and Abu Dhabi. There were seven additional studies on ischemia, myocardial infarction, and another coronary artery disease. In addition to the countries mentioned above, we found additional studies related to coronary heart disease in Morocco, Algeria, Lebanon, Tunisia, and Egypt.

3.3. Risk of Bias

For our meta-analysis, we performed both the Begg and Egger tests to assess publication bias among the studies included. The outcomes of these tests (illustrated in Table 2) indicate that there was no publication bias in any of the allele contrast, over-dominant, or AA vs. aa models, as their *p*-values were greater than 0.05. In contrast the rest had a risk of bias (Table 2).

3.4. Heterogeneity Test

A heterogeneity analysis was conducted on 12 studies assessing the association between the ACE gene polymorphism and cardiovascular disease. The pooled mean effect size was 1.391 (95% CI: 0.911–2.122), but this was not statistically significant (Z = 1.529, $p = 0.126$) (Figure 2). However, the Q-test revealed substantial heterogeneity (Q = 144.053, df = 11, $p < 0.001$), with an I^2 value of 92%, indicating that most of the variability in effect sizes was due to true differences across studies rather than random error. The between-study variance (τ^2) was 0.513, with a corresponding τ of 0.716. The 95% prediction interval ranged from 0.263 to 7.364, suggesting considerable uncertainty in estimating the effect size in future populations. For the AGT gene, the analysis of seven studies yielded a pooled mean effect size of 0.775 (95% CI: 0.559–1.074), with no statistically significant difference from the null (Z = −1.530, $p = 0.126$). Nonetheless, significant heterogeneity was observed (Q = 18.389, df = 6, $p = 0.005$), with an I^2 of 67%, reflecting moderate heterogeneity. The prediction interval (0.284–2.117) also suggests variation in true effect sizes across studies. As fewer than ten studies were included in the AGT analysis, the heterogeneity estimates should be interpreted with caution (Figure 3). Overall, both analyses indicated substantial

heterogeneity, particularly in the ACE group, limiting the confidence in pooled estimates and underscoring the need for further research to explore sources of variability and improve the robustness of future meta-analyses. The presence of significant heterogeneity in the AGT studies limits the strength of conclusions that can be drawn from the meta-analysis. This highlights the need for more homogeneous, well-designed studies and suggests that future research should aim to identify and adjust for sources of variability to improve the precision and applicability of genetic associations with cardiovascular risk.

Table 2. Heterogeneity test.

	Model	Test of Association			Test of Heterogeneity			Publication Bias
		OR	95% CI	*p*-Value	Model	*p*-Value	I^2	*p*-Value (Egger's Test)
ACE ID	Allele contrast (A vs. a)	1.3904	[0.9110; 2.1221]	0.1264	Random	0	0.9238	0.0018
	Recessive model (AA vs. Aa + aa)	1.5587	[0.9202; 2.6401]	0.098	Random	0	0.9044	0.086
	Dominant model (AA + Aa vs. aa)	1.5116	[0.9123; 2.5047]	0.108	Random	0	0.7678	0.1272
	Over-dominant (Aa vs. AA + aa)	0.799	[0.6114; 1.0441]	0.1002	Random	0.0009	0.6525	0.0545
	(AA vs. aa)	1.8062	[0.8963; 3.6401]	0.098	Random	0	0.8538	0.0293
	(AA vs. Aa)	1.4802	[0.9328; 2.3490]	0.095	Random	0	0.8574	0.1293
	(Aa vs. aa)	1.2645	[0.8631; 1.8524]	0.228	Random	0.0158	0.5288	0.1701
AGT M273T	Allele contrast (A vs. a)	1.3171	[1.1658; 1.4881]	9.73×10^{-6}	Fixed	0	0.9122	0.5076
	Recessive model (AA vs. Aa + aa)	1.2852	[1.0485; 1.5754]	0.015681	Fixed	0	0.8749	0.5584
	Dominant model (AA + Aa vs. aa)	1.5160	[1.2593; 1.8252]	1.11×10^{-5}	Fixed	0	0.838	0.523
	Over-dominant (Aa vs. AA + aa)	1.2042	[1.0144; 1.4295]	0.033678	Fixed	0.0045	0.6811	0.1335
	(AA vs. aa)	1.6291	[1.2763; 2.0793]	8.88×10^{-5}	Fixed	0	0.8767	0.3505
	(AA vs. Aa)	1.1017	[0.8824; 1.3756]	0.392214	Fixed	0	0.8067	0.8789
	(Aa vs. aa)	1.4493	[1.1849; 1.7727]	0.000305	Fixed	0.0023	0.7061	0.3579

3.5. AGT Gene MT237 Polymorphism with Hypertension

During the analysis of the AGT gene's correlation with CVD in Arab, Mediterranean, and North African populations, a significant association was identified using various models, including the allele contrast, recessive, dominant, and homozygote models, under the Random-effect fixed model (Figure 4). The comparison between the C and T alleles revealed an odds ratio (OR) of 1.3171 with a 95% confidence interval (CI) of [1.1658; 1.4881] and a *p*-value of 0.005. When comparing CC to CT+TT, the OR was 1.2852 with a 95% CI of [1.0485; 1.5754] and a *p*-value below 0.005. On the other hand, comparing CC+CT to TT resulted in an OR of 0.7116 with a 95% CI of [0.5487; 0.9228] and a *p*-value of 0.010280479. Additionally, comparing CC to TT yielded an OR of 1.5160 with a 95% CI of [1.2593; 1.8252]

and a *p*-value of 0.005, while comparing CC to CT resulted in an OR of 0.6583 with a 95% CI of [0.5171; 0.8379] and a *p*-value of 0.0006. Notably, these findings do not support the over-dominant and heterozygote hypotheses (Figures 4–6).

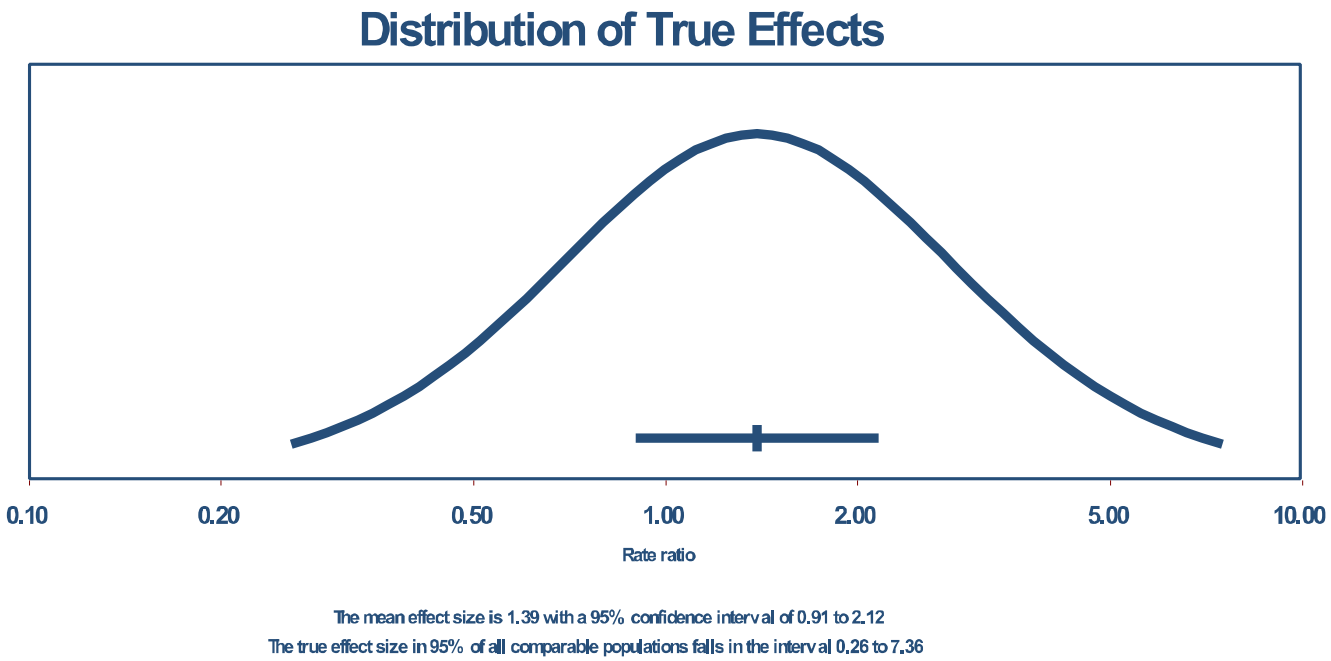

Figure 2. Heterogeneity test for the twelve studies included in the ACE meta-analysis.

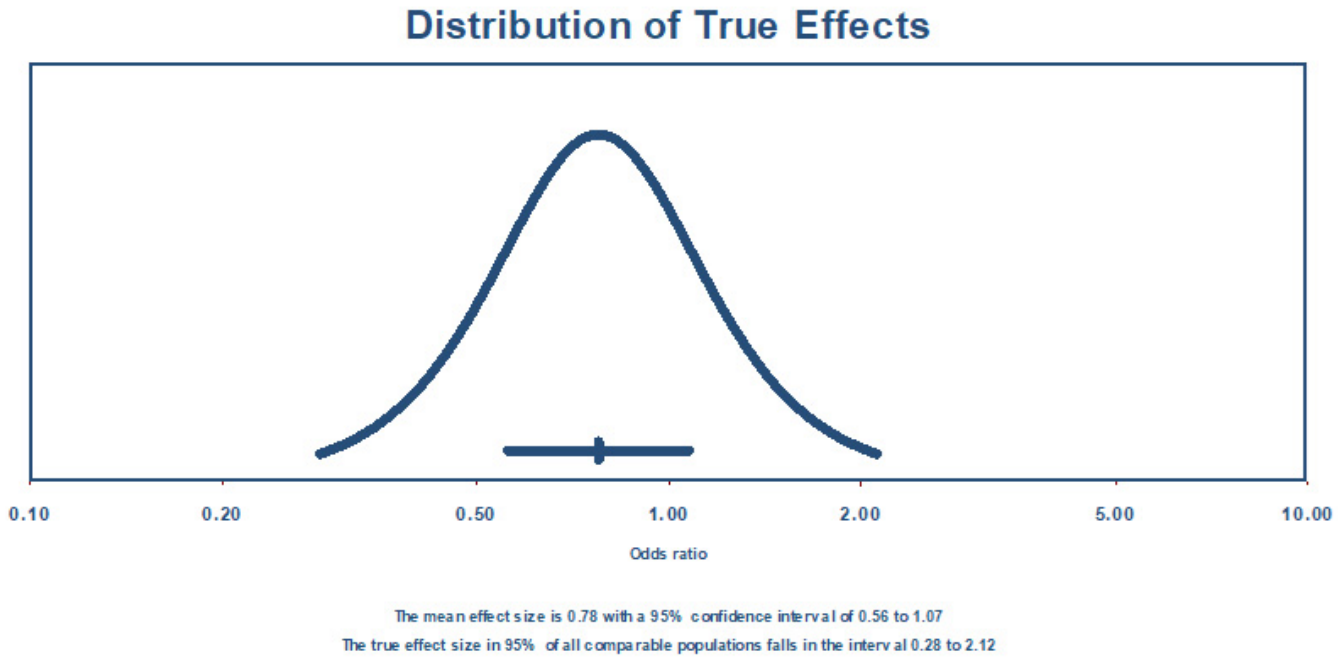

Figure 3. Heterogeneity analysis of AGT M235T polymorphism across seven studies in the meta-analysis.

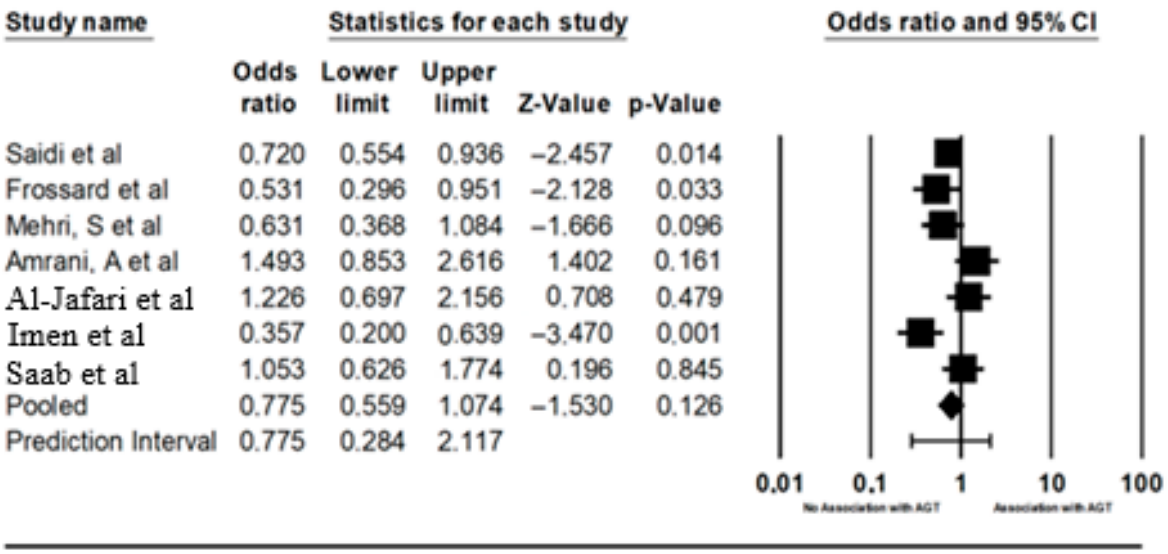

Figure 4. Forest plot illustrating the association between AGT M235T polymorphism and cardiovascular disease risk in the Middle East and North Africa regions [16,19–21,23–25].

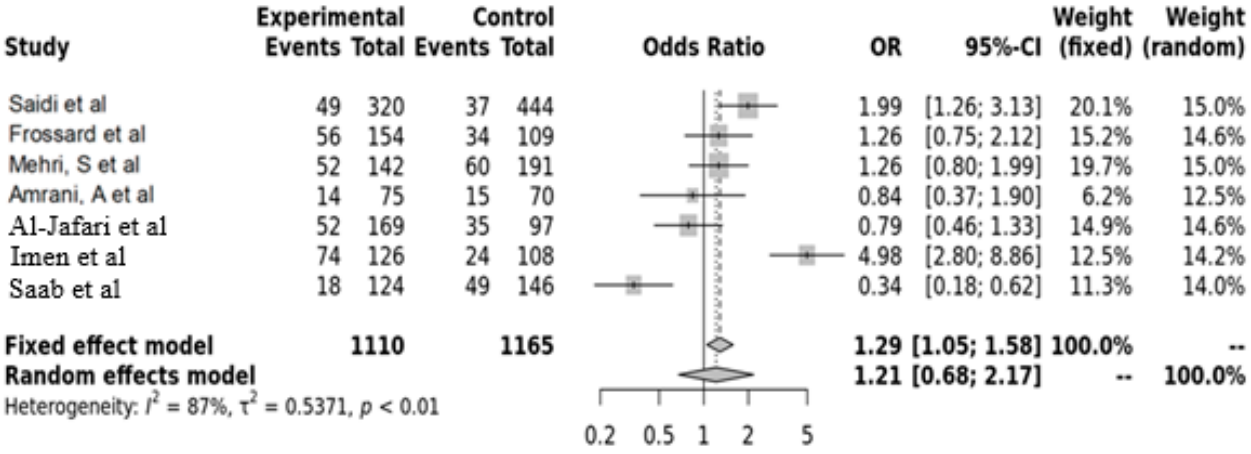

Figure 5. Forest plot of AGT polymorphism under recessive model [16,19–21,23–25].

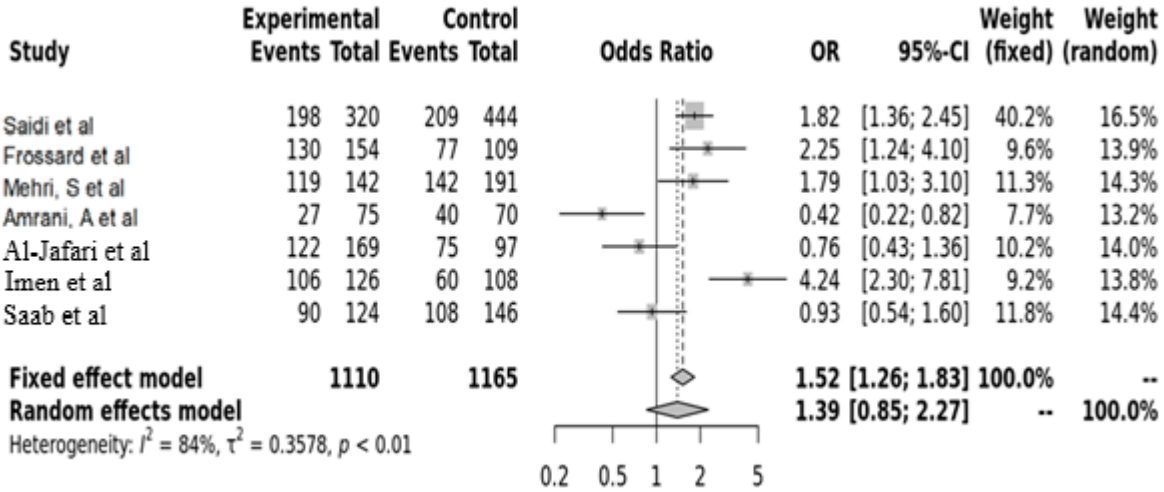

Figure 6. Odds ratio summary and forest plot of AGT polymorphism under dominant model [16,19–21,23–25].

3.6. The ACE Gene INSERTION/DELETION Polymorphism and CVD

Initially, there was no correlation observed in the random model between the fixed model and the D vs. I: OR of 1.3904, CI 95% [0.9110; 2.1221], and *p*-value of 0.127. Similarly, no significant association was found under the recessive model (DD vs. ID++II; OR of 1.5587, CI 95% [0.9202; 2.6401], and *p*-value of 0.098) or under the dominant model (OR of 1.5116, CI 95% [0.9123; 2.5047], and *p*-value of 0.108). However, studies in which the genotype distribution significantly deviated from Hardy–Weinberg equilibrium (HWE) in the control group ($p < 0.05$) were excluded from the meta-analysis. This criterion ensured population genetic consistency and reduced potential bias due to genotyping errors or population stratification. As such, the studies by Abouelfath, Hmimech, Al-Jafari, and Obineche [11,18,20,22] were excluded based on this criterion. As a result, a positive correlation was identified under the fixed model with the recessive model showing an OR of 2.1521 [1.7588; 2.6333], the dominant model indicating an OR of 1.6991, CI [1.2687; 2.2755], and a *p*-value of 0.0003, as well as the I vs. D allele with an OR of 1.6519, CI 95% [1.4309; 1.9070], and a non-significant *p*-value (Figure 7).

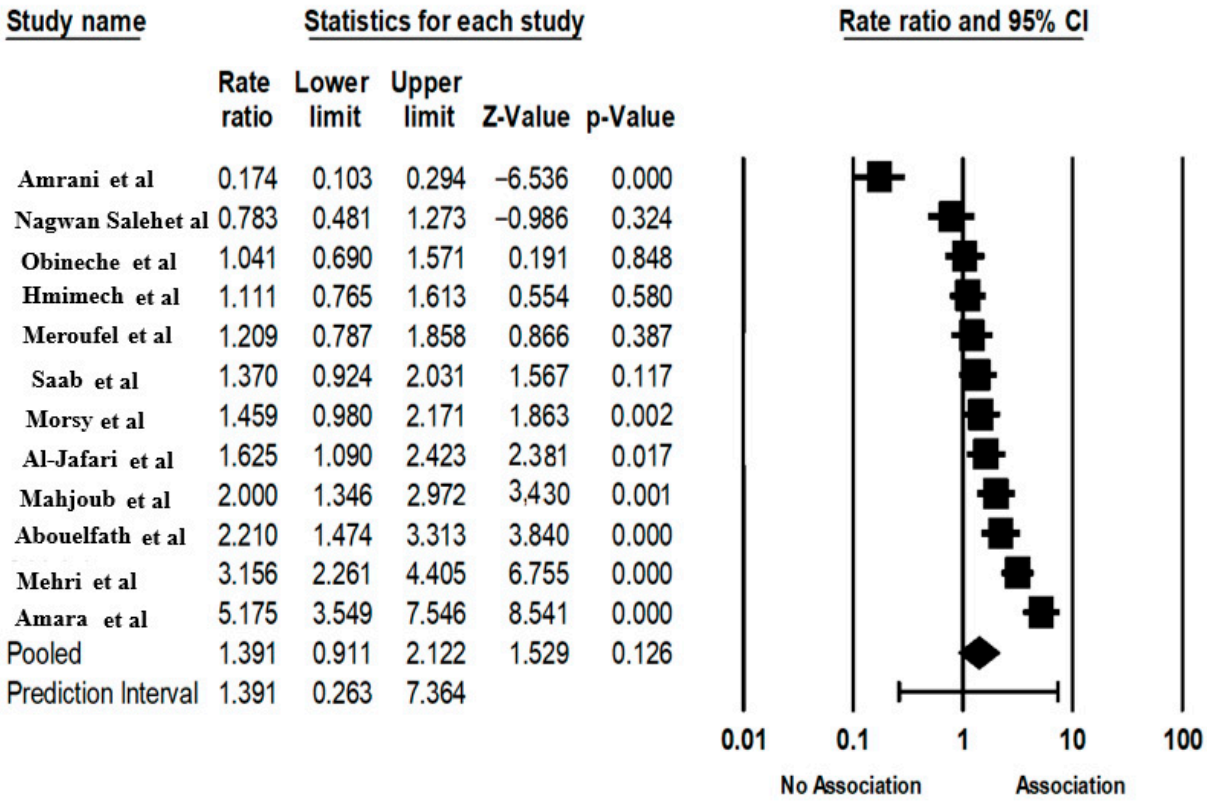

Figure 7. Forest plot of the ACE association [11–22].

People who have the D allele are at a greater risk of developing vascular diseases, including high blood pressure, myocardial infarction, and coronary artery disease [15,26,27]. Research on Tunisian and Moroccan populations have shown that individuals with a heterozygous genotype of the ACE polymorphism are more susceptible to myocardial infarction and coronary artery disease [18]. Furthermore, individuals from Algerian and Moroccan backgrounds who carry the D allele have shown higher rates of hypertension compared to those who do not [28]. In Egyptian populations, the presence of the ACE polymorphism's D allele has been linked to cardiomyopathy and arrhythmias [14] (Table 3).

Table 3. Test of association using random and fixed models.

		Effect Size and 95% Interval			Test of Null (2-Tail)		Prediction Interval		Between Studies		Other Heterogeneity Statistics			
Model	**Number of Studies**	**Point Estimate**	**Lower Limit**	**Upper Limit**	**Z-Value**	***p*-Value**	**Lower Limit**	**Upper Limit**	**Tau**	**Tau Sq**	**Q-Value**	**df (Q)**	***p*-Value**	**I-Squared (%)**
Fixed	7	0.763	0.642	0.906	−3.08231	2.05×10^{-3}	_	_	_	_	1,838,854	6	5.33×10^{-3}	67.370
Random effects	7	0.775	0.559	1.074	−1.5301	0.125993	0.28383	2.117001	0.35362	0.12505	_	_	_	_
Fixed	12	1.567	1.395	1.761	7.576372	3.55×10^{-14}	_	_	_	_	1,440,533	11	0	92.363
Random effects	12	1.390	0.911	2.121	1.529486	0.126144	0.26256	7.364047	0.71640	0.51323	_	_	_	_

4. Discussion

The primary objective of this study was to evaluate the association between the ACE I/D and AGT M235T gene polymorphisms and the risk of cardiovascular disease (CVD) in populations from the Middle East, North Africa (MENA), and the Mediterranean regions. By synthesizing available genetic data and conducting meta-analyses, we aimed to clarify whether these variants contribute to the heightened CVD burden observed in these regions. Our meta-analysis included 12 studies examining the ACE I/D polymorphism and 7 studies focusing on the AGT M235T variant. For the ACE I/D polymorphism, the random-effects model yielded a pooled effect size of 1.39 (95% CI: 0.91–2.12), indicating a potential but not statistically significant association with increased CVD risk (Z = 1.53, $p = 0.126$). The heterogeneity among these studies was substantial ($I^2 = 92.4\%$, Q = 144.05, $p < 0.001$), and the prediction interval (0.26–7.36) suggested considerable variability in effect sizes across different populations. For the AGT M235T variant, the random-effects model estimated an effect size of 0.78 (95% CI: 0.56–1.07), also not reaching statistical significance (Z = −1.53, $p = 0.126$), with moderate heterogeneity ($I^2 = 67.4\%$, Q = 18.39, $p = 0.005$) and a prediction interval of 0.28–2.12. These findings indicate that, while there are trends toward associations between these polymorphisms and CVD, the evidence is inconsistent and highly variable across studies.

The angiotensin-converting enzyme (ACE) plays a central role in the renin–angiotensin system, with the I/D polymorphism in intron 16 influencing plasma enzyme concentrations. Rigat et al. (1990) [27] first reported that individuals with the DD genotype have significantly higher ACE levels, a finding confirmed in large-scale meta-analyses [29]. Our results are consistent with previous reports of an increased risk of CVD among D allele carriers, particularly in North African populations; however, the high heterogeneity and lack of statistical significance in the random-effects model underscore the complexity of this association [30]. Contradictory findings in other MENA populations, such as Saudi Arabia and Egypt, further suggest that environmental factors, population structure, and study design may influence the observed associations [31,32].

Similarly, the AGT M235T polymorphism has been implicated in modulating angiotensinogen levels and vascular risk [33]. While studies in Asian populations have shown a robust association between the T allele and increased CVD risk, our meta-analysis did not find a statistically significant association in the MENA region [34]. The moderate heterogeneity observed may reflect differences in allele frequencies, environmental exposures, or sample sizes across studies. Notably, the distribution of the 235T allele varies widely by ethnicity, and the limited number of studies from the region restricts the generalizability of our findings [35].

The risk of myocardial infarction in Asians was significantly associated with the AGT M235T polymorphism, as reported by Li et al. [36]. However, no significant associations were found in overall populations and Caucasians. Li et al. (2013) conducted meta-analyses

that indicated significant associations between two AGT polymorphisms (M235T, T174M) and the risk of coronary heart disease in the Chinese population [34,36–38]. Additionally, Fajar et al. [37] conducted a meta-analysis exploring the relationship between AGT M235T and AGT T174M polymorphisms and the likelihood of essential hypertension. Their findings revealed that the T allele of AGT M235T and the M allele, as well as the TM genotype of AGT T174M, were associated with an increased risk of essential hypertension [17]. On the other hand, the M allele and MM genotype of AGT M235T, along with the T allele and TT genotype of AGT T174M, were associated with a decreased risk of essential hypertension [22]. The distribution of the 235T allele in white individuals was found to be approximately 21%, while in Africans, it ranged from 74% to 91% [38]. Studies conducted in the Middle East and North Africa have shown an association between polymorphism and an increased risk of cardiovascular disease. However, due to the political conflict in the region, research and development in this area are still underdeveloped [36,37].

Due to a lack of available sources, this study was constrained by examining only two polymorphisms of the renin–angiotensin system. It should be noted that data from Libya and Mauritania in North Africa could not be incorporated for the same reason. The limited accessibility to genetic information and population studies in these regions posed challenges to conducting a more comprehensive analysis. Additionally, our research exclusively focused on the Mediterranean and North African regions, which restricts the generalizability of our findings. Despite attempts to extrapolate results, the inherent limitations of the data available in these areas have influenced our ability to definitively draw conclusions applicable to the entire population.

5. Conclusions

In summary, our study provides a comprehensive assessment of the ACE I/D and AGT M235T polymorphisms in relation to CVD risk in the MENA and Mediterranean regions. While trends toward increased risk were observed for certain genotypes, particularly ACE D allele carriers, the high degree of heterogeneity and lack of statistical significance in pooled analyses call for cautious interpretation. Future research should prioritize large-scale, collaborative studies that address the genetic diversity and environmental complexity of these populations, ultimately supporting the development of precision medicine strategies tailored to the region's needs.

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Abbreviations

The following abbreviations are used in this manuscript:

CVD: cardiovascular disease
AGT: angiotensinogen gene
ACE: angiotensin converter enzyme
CAD: coronary artery disease

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