DOI: 10.4274/MMJ.galenos.2025.72273
Medeni Med J 2025;40:80-92

Original Article

Large-Scale Meta-Analysis of TNF-α rs1800629 Polymorphism in Schizophrenia: Evidence from 7,624 Cases and 8,933 Controls

Şizofrenide TNF-α rs1800629 Polimorfizminin Geniş Ölçekli Meta-Analizi: 7.624 Olgu ve 8.933 Kontrolden Elde Edilen Kanıtlar

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ABSTRACT

Objective: Schizophrenia is a multifaceted psychiatric disorder that affects about 1% of the world's population and arises from a combination of genetic, environmental, and neurodevelopmental influences. Recent studies highlight the role of immune system disturbances and neuroinflammation in its development, with tumor necrosis factor-alpha (TNF-α) identified as a pivotal cytokine. This meta-analysis aims to clarify the relationship between the TNF-α rs1800629 genetic variant and the risk of schizophrenia by synthesizing data from published research.

Methods: Two independent reviewers systematically searched PubMed, Web of Science, Embase, Cochrane Library, and Chinese National Knowledge Infrastructure for studies published up to January 19, 2024. Odds ratios and 95% confidence intervals were computed using a fixed-effects model, taking into account the absence of significant heterogeneity.

Results: A total of 33 case-control studies were included, encompassing 7,624 individuals with schizophrenia and 8,933 healthy controls from diverse backgrounds (21 studies on Asian populations, 11 on Caucasian, and one on a mixed group) conducted between 2001 and 2020. The pooled analysis did not reveal a significant link between the TNF-α rs1800629 polymorphism and susceptibility to schizophrenia under any genetic model. Further subgroup analyses by ethnicity (Asian, Caucasian), country (China, Poland), genotyping technique, and publication year also yielded no notable associations.

Conclusions: This comprehensive meta-analysis offers strong evidence that the TNF-α rs1800629 variant is not significantly associated with

ÖZ

Amaç: Şizofreni, dünya nüfusunun yaklaşık %1'ini etkileyen ve genetik, çevresel ve nörogelişimsel etkilerin bir kombinasyonundan kaynaklanan çok yönlü bir psikiyatrik bozukluktur. Son çalışmalar, bağışıklık sistemi bozukluklarının ve nöroinflamasyonun gelişimindeki rolünü vurgulamakta ve tümör nekroz faktörü-alfa (TNF-α) önemli bir sitokin olarak tanımlanmaktadır. Bu meta-analiz, yayınlanmış araştırmalardan elde edilen verileri sentezleyerek TNF-α rs1800629 genetik varyantı ile şizofreni riski arasındaki ilişkiyi netleştirmeyi amaçlamaktadır.

Yöntemler: İki bağımsız hakem PubMed, Web of Science, Embase, Cochrane Library ve Çin Ulusal Bilgi Altyapısı'nda 19 Ocak 2024 tarihine kadar yayınlanmış çalışmaları sistematik olarak taramıştır. Odds oranları ve %95 güven aralıkları, anlamlı derecedeki heterojenlik eksikliği dikkate alınarak sabit etkiler modeli kullanılarak hesaplanmıştır.

Bulgular: 2001-2020 yılları arasında yürütülen ve farklı geçmişlere sahip 7.624 şizofreni hastasını ve 8.933 sağlıklı kontrolü (21'i Asyalı, 11'i Kafkasyalı ve biri karma bir grup ile) kapsayan toplam 33 olgu kontrol çalışması çalışmaya dahil edildi. Karma analiz, TNF-α rs1800629 polimorfizmi ile şizofreniye yatkınlık arasında herhangi bir genetik model altında anlamlı bir bağlantı ortaya koymadı. Etnik köken (Asyalı, Kafkasyalı), ülke (Çin, Polonya), genotipleme tekniği ve yayın yılına göre yapılan diğer alt grup analizleri de anlamlı bir ilişki göstermedi.

Sonuçlar: Bu kapsamlı meta-analiz, TNF-α rs1800629 varyantının ne küresel olarak ne de belirli etnik gruplar içinde şizofreni riski ile

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Received: 03 May 2025
Accepted: 10 June 2025
Published: 26 June 2025

Cite as: Dastjerdi G, Fallahpour B, Dastgheib SA et al. Large-scale meta-analysis of TNF-α rs1800629 polymorphism in schizophrenia: evidence from 7,624 cases and 8,933 controls. Medeni Med J. 2025;40:80-92

schizophrenia risk, either globally or within specific ethnic groups. These findings indicate that this polymorphism likely does not play a major role in schizophrenia susceptibility, underscoring the importance of future investigations into other TNF-α variants, gene-gene interactions, or alternative inflammatory mechanisms.

Keywords: Schizophrenia, tumor necrosis factor-alpha, rs1800629, polymorphism, meta-analysis, genetics

anlamlı bir ilişkisi olduğuna dair güçlü kanıtlar sunmaktadır. Bu bulgular, bu polimorfizmin şizofreniye yatkınlıkta muhtemelen önemli bir rol oynamadığını göstermekte ve diğer TNF-α varyantları, gen-gen etkileşimleri veya alternatif enflamatuvar mekanizmalarla ilgili gelecekteki araştırmaların önemini vurgulamaktadır.

Anahtar kelimeler: Şizofreni, tümör nekroz faktörü-alfa, rs1800629, polimorfizm, meta-analiz, genetik

INTRODUCTION

Schizophrenia is a chronic and multifaceted psychiatric illness that affects about 1% of people worldwide. It is marked by a combination of positive symptoms (such as hallucinations and delusions), negative symptoms (including social withdrawal and anhedonia), and cognitive deficits, all of which substantially diminish patients' quality of life and daily functioning[1,2]. The underlying causes of schizophrenia are complex, involving genetic predispositions, environmental exposures, and neurodevelopmental disturbances. Recent research increasingly points to the role of immune system dysfunction and neuroinflammatory processes in the development and progression of the disorder[3,4]. Among the inflammatory molecules implicated in schizophrenia, tumor necrosis factor-alpha (TNF-α) stands out as a key cytokine. Elevated TNF-α levels have been repeatedly documented in individuals with chronic schizophrenia and have been linked to greater severity of negative symptoms[5,6].

TNF-α acts as a pro-inflammatory cytokine, playing a pivotal role in immune regulation and, more recently, has been recognized for its influence on brain development, synaptic remodeling, and neuron survival[7,8]. Evidence suggests that both TNF-α and interleukin-6 are closely associated with the deficit syndrome subtype of schizophrenia, which is characterized by persistent and primary negative symptoms. This observation supports the idea that deficit schizophrenia may involve distinct immune-related pathophysiology[9]. Moreover, higher TNF-α concentrations have been shown to predict the intensity of specific negative symptoms, such as blunted affect and alogia, as well as overall negative symptom scores, indicating a direct contribution of inflammatory processes to clinical manifestations[10,11]. The hypothesis that inflammation plays a central role in schizophrenia is further reinforced by findings that immune-targeted therapies could offer new avenues for treating negative symptoms in individuals with this condition[12].

The TNF-α gene, situated on chromosome 6p21.3, harbors several functional variants that modulate cytokine expression and immune response mechanisms[13,14]. One notable variant is the rs1800629 single nucleotide polymorphism (SNP), also known as -308G>A, located in the gene's promoter region. This SNP has been widely investigated across various inflammatory and autoimmune diseases due to its regulatory effect on TNF-α production. Specifically, the substitution of guanine (G) with adenine (A) at position -308 is associated with increased TNF-α expression in individuals carrying the A allele compared to those with the G allele[15]. Research indicates that carriers of the A allele exhibit significantly reduced fractional anisotropy in broad brain regions, alongside more pronounced deficits in both immediate and delayed verbal memory recall and recognition, relative to individuals with the GG genotype[16]. These observations imply that the A allele, which drives higher TNF-α levels, may be linked to diminished fronto-temporal white matter connectivity and subsequent memory impairments in patients with schizophrenia[16,17].

Previous case-control studies investigating the association between TNF-α rs1800629 polymorphism and schizophrenia susceptibility have yielded inconsistent and sometimes contradictory results, likely due to differences in study populations, sample sizes, ethnic backgrounds, and methodological approaches[6]. While some studies have reported significant associations between specific genotypes and schizophrenia risk, others have found no significant relationship between the polymorphism and disease susceptibility[18]. Additionally, research has indicated that this polymorphism may act as a modulator for disease onset age and cognitive function rather than directly influencing susceptibility, as demonstrated in studies examining the related rs1800629 polymorphism, which showed associations with earlier onset age and cognitive deficits but not with overall disease risk[19]. The heterogeneity in study findings underscores the need for a comprehensive meta-analytical approach to synthesize existing evidence and provide more definitive conclusions about the role of rs1800629 in schizophrenia susceptibility.

Understanding genetic variants in inflammatory pathways has significant clinical and therapeutic implications. Given the influence of TNF-α

polymorphisms on treatment responses in conditions like autoimmune disorders[20], determining if the rs1800629 polymorphism is associated with schizophrenia could inform personalized medicine, guide treatment selection, and aid in developing targeted immunomodulatory interventions. This meta-analysis systematically evaluates case-control studies to determine if the TNF-α rs1800629 polymorphism is associated with increased schizophrenia susceptibility. It also assesses the magnitude of associations across populations and study designs, identifies sources of heterogeneity explaining inconsistencies in prior research, and provides recommendations for future genetic association studies in schizophrenia research.

MATERIALS and METHODS

Search Strategy

Since this meta-analysis did not involve the use of personal data or the recruitment of participants, ethical approval was unnecessary, and patient consent was not applicable. We performed an extensive literature search across a variety of electronic databases to identify publications examining the association between the TNF-α rs1800629 polymorphism and schizophrenia risk, with studies limited to those considered up to January 19, 2024. The databases searched included PubMed, EMBASE, Web of Science, Elsevier, Google Scholar, ScienceDirect, SciELO, Europe PMC, ResearchGate, Circumpolar Health Bibliographic Database, Cochrane Library, Current Contents, Linguamatics, Eye Health Organizations Database, WanFang, China Science and Technology Journal Database, VIP, Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Scientific Information Database, PsycINFO, and ClinicalTrials.gov. To refine our search, we used combinations of keywords such as "schizophrenia", "TNF-α", "rs1800629", "polymorphism", "genetic susceptibility" and "association study", as well as related terms including "gene", "polymorphism", "DNA sequence", "single-nucleotide polymorphism", "SNPs", "genotype", "frequency", "mutation", "mutant", "allele", "variation", "variant" and "genetic predisposition". Additionally, we manually reviewed the reference lists of all relevant articles to ensure no pertinent studies were missed. There was no limitation regarding language or publication year; non-English articles were translated when necessary. Our review prioritized human studies published in English or Chinese, and in cases where multiple articles covered the same subjects, the most recent or those with larger sample sizes were selected.

Inclusion and Exclusion Criteria

We established clear criteria for study selection. The inclusion criteria were: (1) Only case-control or cohort studies that investigated the relationship between the TNF-α rs1800629 polymorphism and schizophrenia risk; (2) schizophrenia diagnosis had to be based on recognized clinical standards; (3) studies needed to provide genotype frequencies for both cases and controls to enable calculation of odds ratios (ORs) and 95% confidence intervals (CIs); (4) studies had to provide sufficient demographic information about participants; and (5) only studies published up to January 2024 were considered for relevance. Exclusion criteria were as follows: (1) Reviews, meta-analyses, abstracts, conference proceedings, case reports, letters to the editor, comments, and duplicate publications; (2) studies without a control group or with inappropriate selection criteria; (3) articles with duplicated data from the same author; (4) studies lacking gene frequency data that could not be supplemented; and (5) animal or *in vitro* research. If multiple publications reported on the same dataset, the study with the largest sample size or the most recent publication was included in the analysis.

Data Extraction

Two independent reviewers assessed the titles, abstracts, and search terms of identified studies to determine eligibility based on the established criteria regarding the TNF-α rs1800629 polymorphism and schizophrenia risk. Any disagreements were resolved through discussion or by consulting a third reviewer, and if needed, the original study authors were contacted for clarification. The screening process began with the evaluation of titles and abstracts to exclude irrelevant studies, followed by a detailed full-text review for final selection. From each eligible study, we extracted the following data: First author's name, participant ethnicity (categorized as Asian, Caucasian, African, Hispanic, or Mixed), publication year, genotyping method, country of study, total number of schizophrenia cases and controls, genotype frequencies of the TNF-α rs1800629 polymorphism in both groups, Hardy-Weinberg equilibrium (HWE) results, and minor allele frequencies (MAFs) among controls. When research groups published multiple related studies, we included the most recent, or the one with the largest sample size.

Statistical Analysis

To evaluate the association between the TNF-α rs1800629 polymorphism and the risk of developing schizophrenia, ORs with corresponding 95% CIs were

calculated. The statistical significance of the overall effect size was determined using the Z-test, with a p-value below 0.05 considered significant. Five genetic models were analyzed: allele comparison (B vs. A), homozygote comparison (BB vs. AA), heterozygote comparison (BA vs. AA), dominant model (BB+BA vs. AA), and recessive model (BB vs. BA+AA). Here, "A" represented the major allele, while "B" denoted the minor allele. To assess heterogeneity among studies, the Cochran Q-test was applied, with a significance threshold set at p≤0.10. The I^2 statistic was also used to quantify heterogeneity, with values ranging from 0% (no heterogeneity) to 100% (extreme heterogeneity): 0-25% indicated none, 25-50%, moderate, 50-75%, high, and 75-100%, very high heterogeneity[22,23]. Depending on the degree of heterogeneity, either the DerSimonian and Laird random-effects model or the Mantel-Haenszel fixed-effects model was used for pooling effect sizes. HWE in the control groups was checked using the chi-square test, and a p-value less than 0.05 indicated a significant deviation from equilibrium[24,25]. Subgroup analyses were performed based on ethnicity and schizophrenia subtype to explore sources of heterogeneity. Sensitivity analyses were conducted by sequentially removing individual studies to test the robustness of the results[26,27]. Potential publication bias was assessed through Begg's and Egger's tests, along with visual inspection of funnel plots for asymmetry. If bias was detected, the Duval and Tweedie "trim-and-fill" method was employed to adjust the results. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). A two-sided p-value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of Selected Studies

A summary of the literature review and study selection process is depicted in Figure 1. The initial search identified 741 articles. After screening titles and abstracts, 312 duplicates and 218 articles related to cell or animal studies, reviews, case reports, and other non-eligible formats were excluded. The full texts of the remaining 211 articles were reviewed in detail, leading to the exclusion of 178 studies based on the set inclusion and exclusion criteria. Ultimately, 33 studies comprising 7,624 schizophrenia cases and 8,933 controls were included in the meta-analysis. Of these, 21 studies focused on Asian populations, 11 on Caucasian populations, and one on a mixed ethnic group. The studies were published between 2001 and 2020 and represented research from various countries, including Italy, Germany, Korea, Singapore, China, Finland, the United States, Canada, Japan, Poland, Pakistan, Saudi Arabia, and Türkiye. With the exception of three studies, the genotype distributions in the control groups conformed to HWE, as outlined in the study protocols. Detailed genotypic frequency data for all included studies are provided in Table 1.

Quantitative Synthesis

Overall Analysis

In the present meta-analysis, no statistically significant relationship was found between the TNF-α rs1800629 polymorphism and the risk of schizophrenia. This conclusion is based on the quantitative synthesis summarized in Table 2 and depicted in the forest plot (Figure 2), which presents results across multiple genetic models (allelic, homozygous, heterozygous, dominant, and recessive). For example, the pooled OR for the allelic comparison (A vs. G) was 1,148 (95% CI: 0.947-1.391, p=0.161), indicating only a slight, nonsignificant increase in risk. Similarly, the homozygous (AA vs. GG: OR=1,332, 95% CI: 0.785-2,260, p=0.289) and heterozygous (AG vs. GG: OR=1,081, 95% CI: 0.905-1,291, p=0.390) comparisons did not reveal significant associations. This lack of significant association was consistent across subgroup analyses stratified by ethnicity (such as Asian, Caucasian, and East Asian populations), country (e.g., China, Poland), HWE status, genotyping technique [polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP), ankle-brachial index (ABI)], and publication period (before and after 2010). For instance, among Asian populations, the OR for A vs. G was 1,198 (95% CI: 0.892-1,595, p=0.235), and for Caucasian populations, it was 1,043 (95% CI: 0.853-1,275, p=0.689), neither reaching statistical significance. However, a notable exception emerged in the subgroup analysis of studies published after 2010, where the combined AA+AG versus GG genotype model showed a significant association with schizophrenia risk, (OR=1,700, 95% CI: 1,073–2.693, p=0.024). When considering both AA and AG genotypes together, more recent research found a statistically significant increase in schizophrenia risk linked to the TNF-α rs1800629 polymorphism.

Heterogeneity Testing and Sensitivity Analysis

The heterogeneity analysis, as indicated by I2 values, reveals substantial variability across the different subgroups and genetic models. Specifically, the overall analysis shows high heterogeneity (I2=74.19% to 86.33%, p≤0.001). Similar trends are observed within ethnicity-based subgroups, with Asians, (I2=89.69% to 80.50%, p≤0.001), Caucasians, (I2=65.40% to 48.83%), and East Asians (I2=89.48% to 81.84%, p≤0.001) all exhibiting considerable heterogeneity. Country-based analyses in

countries, such as China (I2=90.62% to 53.49%, p≤0.011) and Poland (I2=97.01% to 83.22%, p=0.001 to 0.009), also demonstrate significant heterogeneity. Subgroups based on HWE and genotyping methods (PCR-RFLP and ABI) also show high levels of heterogeneity. Finally, stratification by publication year (before and after 2010) reveals high heterogeneity in both periods, suggesting that the observed associations are influenced by various confounding factors. These findings suggest that the overall effect estimates should be interpreted with caution, as the true effect may vary across different populations and study designs.

Publication Bias

The evaluation of publication bias related to the TNF-α rs1800629 polymorphism and its association with schizophrenia involved analyzing various genetic models and subgroups using Begg's and Egger's tests. The results indicated differing levels of publication bias across models (Figure 3). Specifically, Figure 3 (Begg's funnel plot) visually represents the publication bias test for the correlation between TNF-α rs1800629 polymorphism and schizophrenia development. For the A vs. G allele comparison, Begg's test returned a p-value of 0.675, and Egger's test yielded 0.288, both suggesting no significant bias.

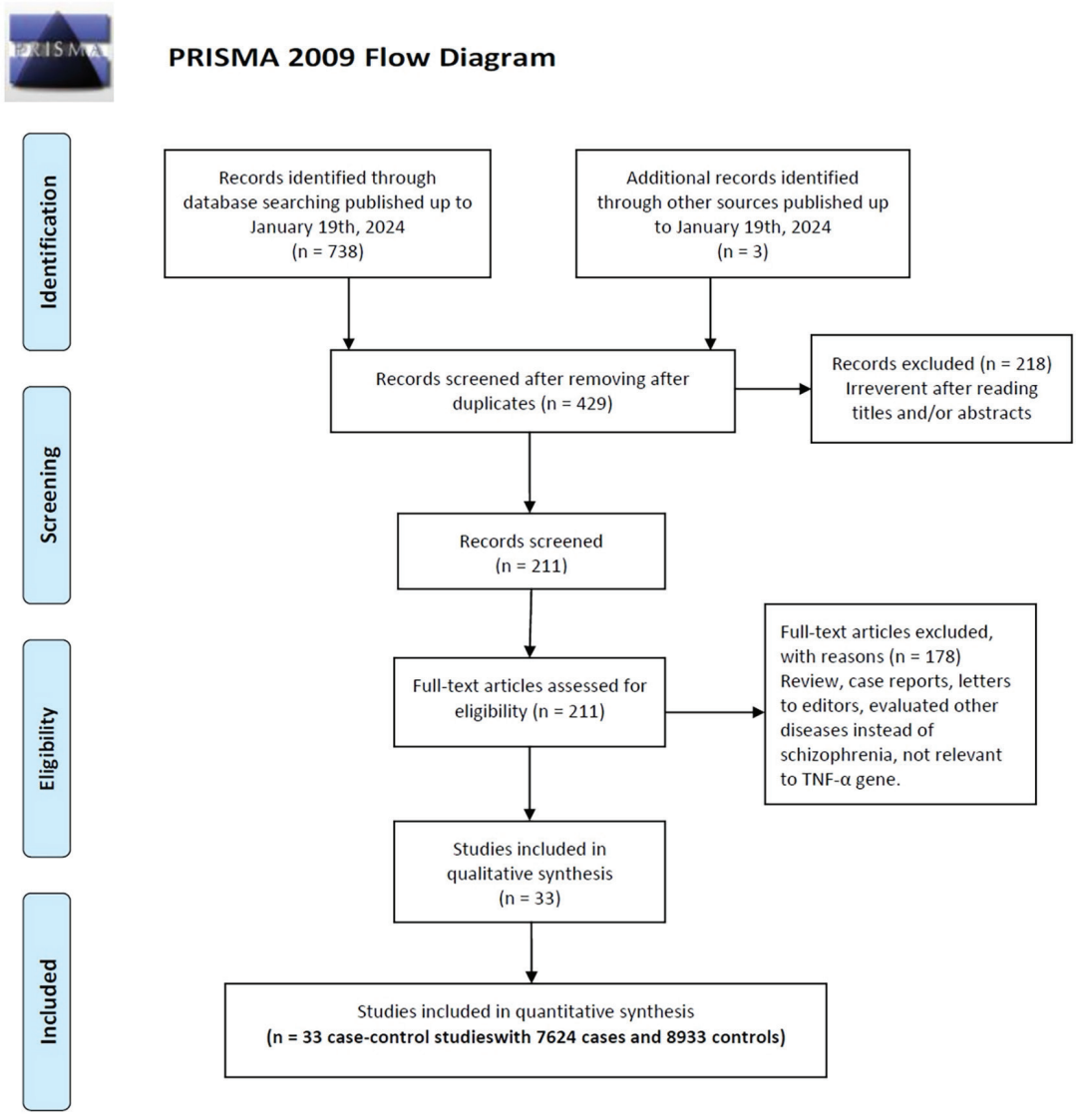

Figure 1. Diagram illustrating the process of study identification, screening, eligibility assessment, and final inclusion for this meta-analysis.

Table 1. Characteristics of studies included in this meta-analysis.

First author/year	Country (Ethnicity)	Genotyping method	SOC	Case/ control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
					GG	GA	AA	G	A	GG	GA	AA	G	A		
Boin 2001	Italy (Caucasian)	PCR-RFLP	HVS	84/138	55	23	6	133	35	109	29	0	247	29	0.105	0.167
Riedel 2002	Germany (Caucasian)	FRET	HVS	157/186	116	39	2	271	43	128	53	5	309	63	0.169	0.861
Meira-Lima 2003	Brazil (Mixed)	PCR-RFLP	HV	186/657	134	44	8	312	60	512	140	5	1164	150	0.114	0.169
Pae 2003	Korea (Asian)	PCR-RFLP	HVS	241/125	212	27	2	451	31	107	18	0	232	18	0.072	0.385
Tan 2003	Singapore (Asian)	PCR-RFLP	HVS	302/152	236	62	4	534	70	90	57	5	237	67	0.220	0.260
Tsai 2003	China (Asian)	PCR-RFLP	HVS	205/192	158	44	3	360	50	161	30	1	352	32	0.083	0.752
Yang 2003	China (Asian)	PCR-RFLP	HP	141/282	50	69	22	169	113	72	159	51	303	261	0.463	0.024
Duan 2004	China (Asian)	ABI 3100	HVS	314/340	269	44	1	582	46	295	42	3	632	48	0.071	0.280
Hashimoto 2004	Japan (Asian)	ABI 7000	HVS	297/458	288	9	0	585	9	451	7	0	909	7	0.008	0.869
Hanninen 2005	Finland (Caucasian)	ABI 7000	HBD	149/393	122	24	3	268	30	292	95	6	679	107	0.136	0.582
Kampman 2005	Finland (Caucasian)	ABI 7000	HBD	94/98	76	14	4	166	22	74	23	1	171	25	0.128	0.589
Duan 2006	China (Asian)	PCR-RFLP	HP	172/344	127	44	1	298	46	262	80	2	604	84	0.122	0.115
Pae 2006	Korea (Asian)	PCR-RFLP	HV	152/152	130	21	1	281	23	129	20	3	278	26	0.086	0.050
Shirts 2006	USA (Caucasian)	ABI 3700	NCB	244/276	173	64	7	410	78	195	73	8	463	89	0.161	0.713
Song 2006	China (Asian)	PCR-RFLP	HV	161/135	86	70	5	242	80	61	66	8	188	82	0.304	0.070
Zai 2006	Canada (Caucasian)	PCR-RFLP	HV	149/149	105	41	3	251	47	108	39	2	255	43	0.144	0.464
Sacchetti 2007	Italy (Caucasian)	PCR-RFLP	HVS	323/346	239	75	9	553	93	272	68	6	612	80	0.116	0.469
Watanabe 2007	Japan (Asian)	ABI 7900	HV	265/424	258	7	0	523	7	409	15	0	833	15	0.018	0.710
Czerski 2008	Poland (Caucasian)	PCR-RFLP	HV	348/351	267	78	3	612	84	242	98	11	582	120	0.171	0.779
Dai 2008	China (Asian)	PCR-RFLP	HP	155/310	113	42	0	268	42	262	48	0	572	48	0.077	0.139
Weidong 2008	China (Asian)	PCR-RFLP	HV	172/344	127	44	1	298	46	262	80	2	604	84	0.122	0.115
Hui 2010	China (Asian)	PCR-RFLP	HVS	253/319	221	32	0	474	32	279	40	0	598	40	0.063	0.232
Naz 2011	Pakistan (Asian)	PCR-RFLP	HVS	100/70	53	29	18	135	65	49	18	3	116	24	0.171	0.427
Jun 2011	China (Asian)	PCR-RFLP	HVS	57/30	38	17	2	93	21	25	4	1	54	6	0.100	0.155
Huijun 2011	China (Asian)	PCR-RFLP	HVS	346/323	315	31	0	661	31	283	40	0	606	40	0.062	0.235
Paul-Samojedny 2013	Poland (Caucasian)	PCR-RFLP	HBD	115/135	25	68	22	118	112	44	79	12	167	103	0.381	0.005
Wei 2013	China (Asian)	PCR-RFLP	HVS	161/135	86	70	5	242	80	61	66	8	188	82	0.304	0.070
Srinivas 2016	India (Asian)	KASPar Assay	NA	246/244	202	39	5	443	49	192	51	1	435	53	0.109	0.214
Kadasah 2017	KSA (Asian)	PCR	HV	180/200	4	176	0	184	176	110	76	14	296	104	0.260	0.859
Suchanek-Raif 2018	Poland (Caucasian)	PCR-ASA	HBD	401/606	273	123	5	669	133	445	144	17	1034	178	0.147	0.202
Feikang 2018	China (Asian)	PCR-RFLP	HVS	254/339	221	30	3	472	36	310	27	2	647	31	0.046	0.107
Lang 2019	China (Asian)	MALDI-TOF	HV	1087/576	762	105	220	1629	545	498	66	12	1062	90	0.078	0.001
Aytac 2020	Türkiye (Caucasian)	PCR-RFLP	HV	113/104	97	14	2	208	18	87	15	2	189	19	0.091	0.181

SOC: Source of controls; HV: Healthy volunteers; HVS: healthy volunteers screened fo rmental illnesses; HP: Health parents; HBD: Healthy blood donors; NCB: Neonatal cord blood; FRET: Fluorescence resonance energy transfer method; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; ABI: ABI Sequence Detection System, HWE: Hardy-Weinberg equilibrium; MAF: Minor allele frequency

Table 2. Summary risk estimates for association of TNF-α rs1800629 polymorphism with risk of schizophrenia.

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	A vs. G	Random	86.33	≤0.001	1.148	0.947-1.391	1.403	0.161	0.675	0.288
	AA vs. GG	Random	74.77	≤0.001	1.332	0.785-2.260	1.061	0.289	0.417	0.333
	AG vs. GG	Random	75.70	≤0.001	1.081	0.905-1.291	0.860	0.390	0.232	0.148
	AA+AG vs. GG	Random	82.51	≤0.001	1.157	0.947-1.413	1.425	0.154	0.187	0.711
	AA vs. AG+GG	Random	74.19	≤0.001	1.261	0.757-2.101	0.890	0.374	0.678	0.223
Ethnicity										
Asians	A vs. G	Random	89.69	≤0.001	1.198	0.892-1.595	1.188	0.235	0.319	0.223
	AA vs. GG	Random	80.63	≤0.001	1.247	0.542-2.866	0.519	0.604	0.558	0.329
	AG vs. GG	Random	81.87	≤0.001	1.162	0.884-1.527	1.078	0.281	0.037	0.033
	AA+AG vs. GG	Random	87.06	≤0.001	1.253	0.919-1.707	1.428	0.153	0.123	0.721
	AA vs. AG+GG	Random	80.50	≤0.001	1.129	0.503-2.532	0.294	0.768	0.821	0.225
Caucasians	A vs. G	Random	65.40	0.001	1.043	0.853-1.275	0.407	0.689	1.000	0.898
	AA vs. GG	Random	51.79	0.023	0.997	0.812-1.223	0.032	0.974	0.533	0.764
	AG vs. GG	Random	52.39	0.021	1.025	0.844-1.246	0.253	0.801	0.876	0.477
	AA+AG vs. GG	Random	59.30	0.006	1.022	0.825-1.267	0.200	0.842	0.755	0.955
	AA vs. AG+GG	Random	48.83	0.034	1.131	0.639-2.003	0.424	0.672	0.436	0.772
East Asian	A vs. G	Random	89.48	≤0.001	1.110	0.809-1.523	0.646	0.518	0.363	0.289
	AA vs. GG	Random	83.55	≤0.001	1.011	0.389-2.630	0.023	0.981	0.160	0.275
	AG vs. GG	Random	62.30	≤0.001	0.997	0.817-1.218	-0.026	0.979	0.225	0.371
	AA+AG vs. GG	Random	82.22	≤0.001	1.071	0.811-1.416	0.484	0.628	0.448	0.307
	AA vs. AG+GG	Random	81.84	≤0.001	1.070	0.439-2.608	0.149	0.882	0.099	0.278
Country										
China	A vs. G	Random	90.62	≤0.001	1.220	0.851-1.748	1.083	0.279	0.200	0.246
	AA vs. GG	Random	86.06	≤0.001	1.196	0.399-3.585	0.319	0.749	0.371	0.398
	AG vs. GG	Random	53.49	0.011	1.069	0.879-1.299	1.299	0.668	0.299	0.317
	AA+AG vs. GG	Random	81.89	≤0.001	1.177	0.872-1.588	1.066	0.286	0.582	0.195
	AA vs. AG+GG	Random	84.74	≤0.001	1.245	0.447-3.463	0.419	0.675	0.283	0.414
Poland	A vs. G	Random	85.48	0.001	1.052	0.669-1.653	0.219	0.826	1.000	0.908
	AA vs. GG	Random	85.42	0.001	0.763	0.159-3.669	-0.338	0.735	0.296	0.283
	AG vs. GG	Random	97.01	0.009	1.126	0.693-1.830	0.480	0.631	1.000	0.957
	AA+AG vs. GG	Random	83.22	0.003	1.117	0.659-1.893	0.410	0.682	1.000	0.840
	AA vs. AG+GG	Random	83.22	0.003	0.702	0.172-2.865	-0.493	0.622	0.296	0.198
HWE	A vs. G	Random	75.69	≤0.001	1.094	0.932-1.284	1.095	0.274	0.784	0.983
	AA vs. GG	Random	74.57	≤0.001	1.347	0.739-2.453	973	0.331	0.381	0.450
	AG vs. GG	Random	76.83	≤0.001	1.100	0.911-1.327	988	0.323	0.535	0.236
	AA+AG vs. GG	Random	83.23	≤0.001	1.179	0.953-1.457	1.519	0.129	0.358	0.145
	AA vs. AG+GG	Random	47.62	0.005	1.066	0.678-1.675	0.276	0.782	0.673	0.774
Gentyping methods										
PCR-RFLP	A vs. G	Random	74.48	≤0.001	1.095	0.916-1.311	0.996	0.319	0.283	0.137
	AA vs. GG	Random	74.48	≤0.001	1.095	0.916-1.311	0.996	0.319	0.283	0.137
	AG vs. GG	Random	69.94	≤0.001	1.068	0.881-1.293	0.668	0.504	0.101	0.151
	AA+AG vs. GG	Random	69.94	≤0.001	1.068	0.881-1.293	0.668	0.504	0.101	0.151
	AA vs. AG+GG	Random	50.63	0.006	1.253	0.786-1.998	0.949	0.343	0.779	0.633

Table 2. Continued

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
ABI	A vs. G	Random	65.23	0.015	0.952	0.750-1.205	-0.721	0.471	0.529	0.385
	AA vs. GG	Random	58.71	0.032	1.158	0.620-2.164	0.563	0.573	0.214	0.896
	AG vs. GG	Random	72.15	≤0.001	1.023	0.835-1.254	0.195	0.845	0.912	0.452
	AA+AG vs. GG	Random	61.98	0.008	0.987	0.799-1.220	-0.105	0.916	0.647	0.719
	AA vs. AG+GG	Random	49.36	0.045	1.311	0.701-2.451	0.992	0.321	0.488	0.555
Publication year										
Before 2010	A vs. G	Random	67.15	≤0.001	1.007	0.858-1.180	0.082	0.935	0.446	0.312
	AA vs. GG	Random	75.22	0.002	1.15	0.65 - 2.03	0.457	0.656	0.558	0.756
	AG vs. GG	Random	68.55	0.015	0.95	0.78 - 1.16	-0.828	0.413	0.924	0.235
	AA+AG vs. GG	Random	64.40	≤0.001	0.979	0.824-1.163	-0.240	0.810	0.843	0.611
	AA vs. AG+GG	Random	39.59	0.043	1.050	0.668-1.650	0.209	0.834	0.306	0.452
After 2010	A vs. G	Random	91.23	≤0.001	1.457	0.984-2.158	1.879	0.060	1.000	0.278
	AA vs. GG	Random	82.11	0.001	1.628	0.88 - 2.97	1.227	0.228	0.339	0.816
	AG vs. GG	Random	79.44	0.005	1.283	0.91 - 1.79	0.956	0.347	0.763	0.498
	AA+AG vs. GG	Random	89.68	≤0.001	1.700	1.073-2.693	2.262	0.024	0.275	0.693
	AA vs. AG+GG	Random	84.23	≤0.001	1.505	0.552-4.101	0.798	0.425	0.591	0.088

Similarly, the AA vs. GG model had p-values of 0.417 (Begg's) and 0.333 (Egger's), indicating an absence of substantial bias. The AG vs. GG comparison also showed no evidence of bias, with p-values of 0.232 and 0.148, respectively. However, subgroup analyses based on ethnicity revealed more complex results: in the Asian subgroup, the AG vs. GG model indicated significant publication bias with p-values of 0.037 (Begg's) and 0.033 (Egger's), suggesting a potential influence of publication bias for this genetic model within this specific ethnic group. Although no significant bias was found in other comparisons within this group, further investigation is required. For Caucasians and East Asians, results generally showed no significant publication bias, with p-values consistently above 0.05. When analyzing by country, Poland showed potential bias with A vs. G model p-values of 1.000 (Begg's) and 0.908 (Egger's), which may indicate a lack of studies showing a significant association in the Polish population for this specific allele comparison. In contrast, analyses for China revealed no publication bias in the assessed models. Examining the HWE subgroup, it was found that no significant publication bias was evident. Similarly, analyses based on genotyping methods (PCR-RFLP and ABI) and publication year (before and after 2010) generally indicated no substantial publication bias.

Minor Allele Frequencies

MAFs ranged from 0.008 to 0.463, demonstrating considerable geographical and ethnic variation. Asian populations exhibited lower MAFs in Japan (0.008) and China (0.071, 0.077) compared to Singapore (0.220) and healthy Chinese parents (0.463). Chinese studies showed diverse MAFs, some exceeding 0.300. Caucasian populations generally had higher MAFs, as seen in Germany (0.169) and Poland (0.171), while Finnish studies reported 0.136 and 0.128. These MAF differences are attributable to nationality, study design, and methodologies, underscoring the importance of population-specific genetic factors in genetic epidemiology. The results indicate a complex interaction of genetic and environmental influences on MAF distribution.

DISCUSSION

The association between the TNF-α rs1800629 polymorphism and schizophrenia susceptibility remains a complex and controversial topic, as evidenced by conflicting findings across various studies. While our CMA, encompassing 33 investigations with 7624 cases and 8933 controls, revealed no significant correlation between this polymorphism and schizophrenia risk across five

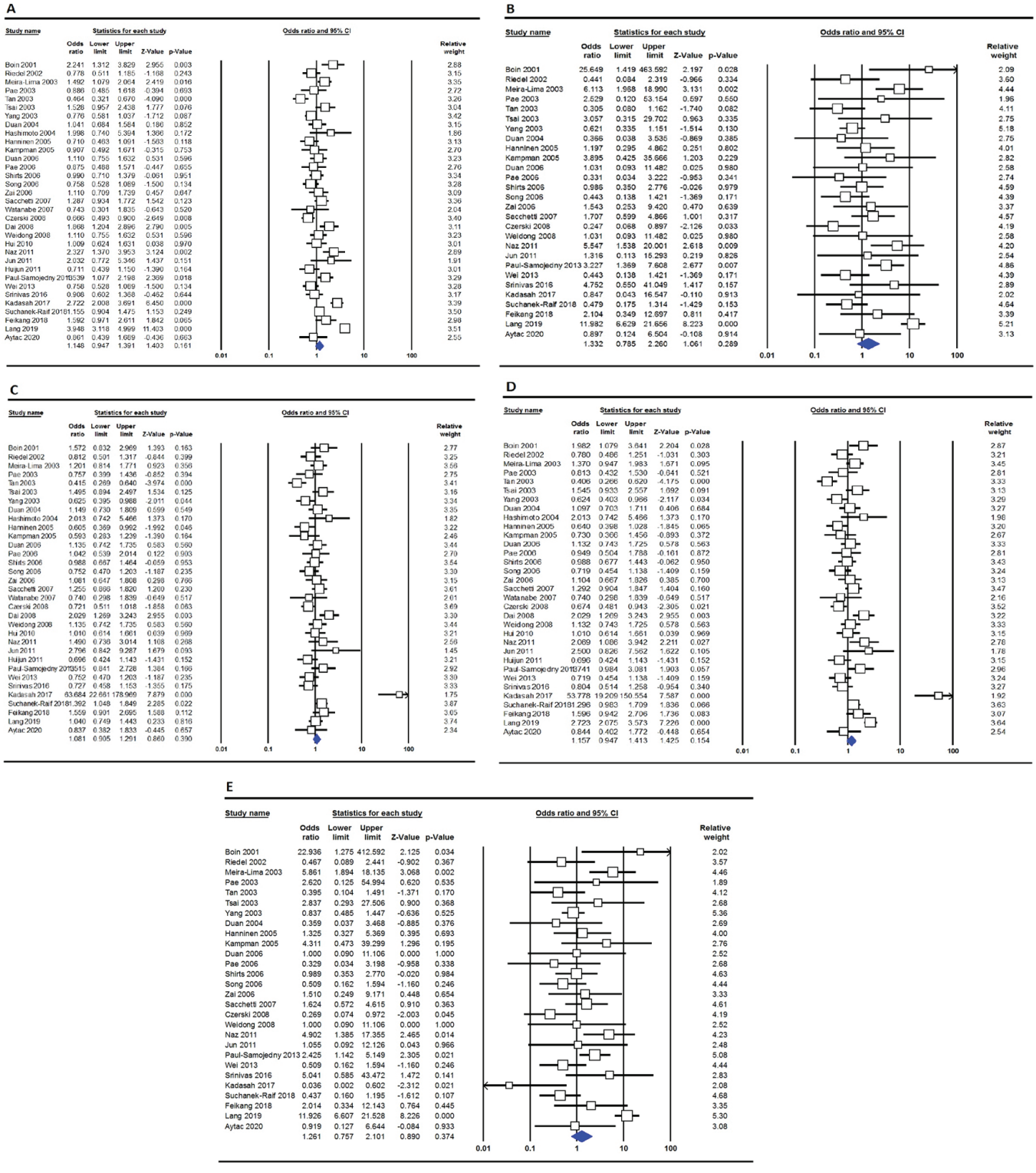

Figure 2. Forest plots depicting the association between the TNF-α rs1800629 genetic variant and schizophrenia risk across all included studies. Results are presented for five genetic models: A) Allelic comparison (A vs. G); B) Homozygote comparison (AA vs. GG); C) Heterozygote comparison (AG vs. GG); D) Dominant model (AA+AG vs. GG); and E) Recessive model (AA vs. AG+GG).

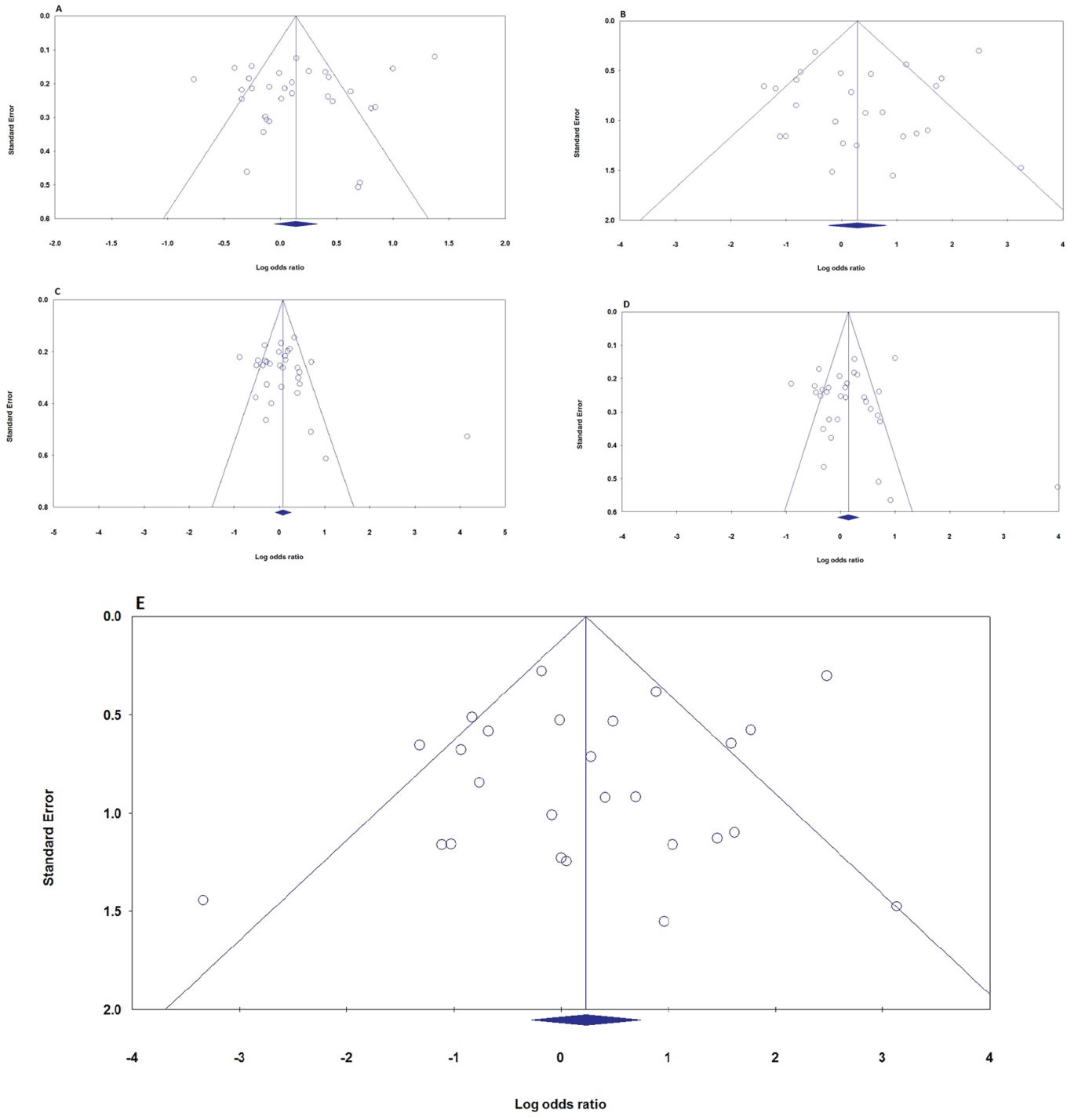

Figure 3. Begg's funnel plots evaluating potential publication bias in the analysis of the TNF-α rs1800629 polymorphism and schizophrenia risk. The plots correspond to: A) Allelic model (A vs. G); B) Homozygote model (AA vs. GG); C) Heterozygote model (AG vs. GG); D) Dominant model (AA+AG vs. GG); and E) Recessive model (AA vs. AG+GG).

genetic models, this contrasts with some prior research. For instance, Sacchetti et al.[28] (2007) reported a weak association between the AA genotype and schizophrenia susceptibility in Caucasoids, further supported by a replication case-control study indicating an association between the A allele and increased schizophrenia susceptibility, particularly in males, with correlations to a later schizophrenia onset at age. However, these initial observations have not been consistently replicated.

More recent meta-analyses, including those by Qin et al.[18] (2013) and He et al.[6] (2022), have found no substantial correlation between the TNF-α rs1800629 polymorphism and schizophrenia susceptibility. Qin et al.[16] analysis of 21 studies showed a lack of association among Caucasian and Asian subgroups, as well as between males and females. Similarly, He et al.[6] pooled analysis of 24 studies found no significant association. Further complicating the picture, studies have explored the influence of specific populations or other factors. Alfimova et al. found that childhood adversity influences the relationship between schizophrenia development and the TNF-α promoter polymorphism rs1800629, while Kang et al.[16] discovered that the A-allele at TNF-α rs1800629 is associated with reduced white matter connectivity in the fronto-temporal region in Korean patients; While Kang et al.[16] discovered that the A-allele at TNF-α rs1800629 is associated with reduced white matter connectivity in the fronto-temporal region in Korean patients[26]. Conversely, Aytec et al.[29] (2022) found no significant difference in the prevalence of TNF-α rs1800629 between Turkish individuals with schizophrenia and healthy controls, and Lang et al.[19] (2020) found no significant relationship between rs1800629 and schizophrenia or suicide. These discrepancies highlight the need for further research to clarify the role of this polymorphism in schizophrenia susceptibility, considering potential influences from ethnicity, environmental exposures, and interactions with other genes.

Clinical Implication

The meta-analysis suggests that the TNF-α rs1800629 polymorphism, on its own, is unlikely to be a strong predictor of schizophrenia risk across diverse populations. Clinically, this implies that routine screening for this specific polymorphism in individuals to assess their risk of developing schizophrenia is not currently warranted. However, clinicians should be aware of the potential for gene-environment interactions and the influence of ethnicity on genetic associations. Further research exploring these factors may refine risk prediction models in the future. It is important to consider other established risk factors and diagnostic criteria when assessing individuals for schizophrenia.

Study Limitations

The study entailed a thorough analysis of the network database. However, there are limitations to this meta-analysis. The primary constraint is that most studies focused on Asian and Caucasian populations, making it challenging to evaluate the impact of TNF-α rs1800629 polymorphism on other groups. This limitation could impact the true association between the polymorphism and schizophrenia. Due to limited data, the relationship between TNF-α rs1800629 polymorphism and the clinical features of schizophrenia could not be fully explored. The analysis was unadjusted; however, an analysis that considered factors like gender, family history of schizophrenia, pregnancy complications, and exposure to toxins or viruses could have been more beneficial. Genetic and environmental interactions were not examined due to insufficient original data. Therefore, further validation with a larger, diverse sample is necessary to confirm the study's findings. Future research should also account for the potential influence of other genetic polymorphisms and lifestyle factors on schizophrenia development. Additionally, exploring the role of epigenetic modifications in conjunction with TNF-α rs1800629 polymorphism could offer a more comprehensive understanding of the underlying mechanisms involved in schizophrenia susceptibility. Collaborative efforts among researchers from diverse ethnic backgrounds and regions could help overcome current limitations and provide a more nuanced perspective on the relationship between TNF-α rs1800629 polymorphism and schizophrenia. Ultimately, a multidisciplinary approach encompassing genetics, epigenetics, environmental factors, and clinical characteristics is crucial for advancing our understanding of the complex etiology of schizophrenia.

CONCLUSION

In summary, our comprehensive analysis does not support a consistent link between the TNF-α rs1800629 polymorphism and increased susceptibility to schizophrenia. However, these findings should be interpreted with caution due to considerable heterogeneity among studies and the limited representation of ethnic groups, as the current meta-analysis primarily included Asian and Caucasian populations. To better understand the potential involvement of TNF-α rs1800629 in schizophrenia, future research should incorporate larger and more ethnically diverse cohorts. Additionally, exploring gene-gene and gene-environment interactions

will be essential for a more complete understanding of the genetic and environmental factors that contribute to schizophrenia risk.

Ethics

Ethics Committee Approval: Since this study is a meta-analysis study, ethical approval is not required.

Informed Consent: Since this study is a meta-analysis study, patient consent is not required.

Footnotes

Author Contributions

Concept: G.D., H.N., Design: B.F., A.G.T., F.N., Data Collection and/or Processing: A.S., M.B., F.N., Analysis and/or Interpretation: H.N., Literature Search: G.D., A.S., M.B., Writing: F.N., H.N.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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