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A Meta-Analysis for Association of ACE I/D Polymorphism with Susceptibility to Preterm Birth

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ABSTRACT

Background: Preterm birth is one of the main contributors to newborn mortality, morbidity, and hospitalization in the first year of life globally. To date, several numbers of studies have reported that Angiotensin-Converting enzyme Insertion/Deletion polymorphism (ACE I/D) is linked with preterm birth. But those results are conflicting. Thus, we carried out this meta-analysis to summarize the existing data and evaluated the association.

Methods: All eligible studies were collected from PubMed, Scopus, SciELO, MedRxiv, SID, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBLD) up to 01 March 2021. The pooled odds ratios (ORs) and 95% confidence interval (CIs) under all five genetic models were calculated using either random-effects or fixed-effects models dependent on study heterogeneity.

Results: A total of five case-control studies with 480 preterm birth cases and 702 healthy subjects were included. Pooled data showed that the ACE I/D polymorphism was significantly associated with increased risk of preterm birth under the allele model (I vs. D: OR = 1.219, 95% CI 1.023-1.453, P = 0.027), homozygote model (II vs. DD: OR = 0.662, 95% CI 1.149-2.385, P = 0.007), and recessive model (DD vs. DI+II: OR = 0.707, 95% CI 1.082-1.948, P = 0.013). Stratified analysis by ethnicity indicated that the ACE I/D polymorphism was significantly associated with preterm birth in Caucasian descendants.

Conclusion: Our pooled data revealed that ACE I/D polymorphism is associated with the risk of preterm birth. However, larger and more rigorous studies among different populations are needed to evaluate the association with preterm birth.

Introduction

Preterm birth or preterm delivery is described as birth before 37 weeks of gestation, which remains a crucial issue in long-term morbidity and mortality in children less than 5 years of age.[1,2] More than 40% of preterm birth cases are occurred spontaneously rather than medically indicated [3, 4]. Despite advances in medicine, the rate of preterm birth is increasing globally.[5] In the United States and Europe, preterm birth occurs in 12-15% and 5-9% of pregnancies, respectively.[5-7] To date, several risk factors have been identified. However, our knowledge to predict the occurrence of preterm birth is limited.[7,8] The leading risk factor for preterm birth is a personal or family history [9]. Moreover, several lines of evidence have confirmed that genetic susceptibility is a predictor of preterm birth.[9-11] The risk of preterm delivery in mothers who have a mother or a sister with a history of preterm birth is higher than general population.[10,12] According to the previous studies in different populations the role of maternal genetic in preterm birth is between 15-40% for the maternal genetic contribution.[13] Moreover, environmental factors, as well as genetic predictors, contribute to preterm birth. This has led some to look for gene-environment interaction such as associations between candidate genes involved in metabolic detoxification and exposure to pollutants and xenobiotics (such as air pollution, sulfur dioxide, bisphenol A, agricultural pesticides, and herbicides), low choline intake during pregnancy, coffee consumption and maternal smoking.[4, 13-15]

Several molecular studies have been conducted to evaluate the association of genetic variants at progesterone receptor (PGR), Oxytocin (OXT), Oxytocin receptor (OXTR), Relaxin 2 (RLN2), follicle - stimulating hormone receptor (FSHR), insulin-like growth factor receptor (IGF1R) and prostaglandin E receptor 3 (PTGER3) genes with preterm birth.[15] Among them, the role of the angiotensin converting enzyme (ACE) gene has been evaluated by several epidemiological studies. This gene is a member of the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) which is involved in catalyzing the conversion of angiotensin I into physiologically active peptide angiotensin II.[16-18] The Human ACE gene is mapped on chromosomes 17q23.3, contains 26 exons, and spans 21 kb. To date, several polymorphisms at ACE gene such as 240A > T, 2350G > A, 17888C > T and ACE I/D have been identified in association with different diseases.[19] The ACE insertion/deletion (I/D) polymorphism is a nonsense and 287 bp Alu repeat sequence of DNA in the intron 16 of ACE gene.[20-23] Some studies have examined the relation between ACE I/D polymorphism and preterm birth. But, the results are inconsistent and inconclusive that might be due to small sample size of recruited subjects. Thus, we conducted this meta-analysis by including all eligible studies to evaluate the association of ACE I/D polymorphism with preterm birth risk globally.

Materials and Methods

Publication Search: A comprehensive computer- based literature search was performed on PubMed, Web of Knowledge, Web of Science, Scopus, MedRxiv, EMBASE, Scientific Information Database (SID), WanFang, VIP, Chinese Biomedical Database (CBD), Scientific Electronic Library Online (SciELO), VIP, Chinese literature (Wan Fang), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal database and Egyptian Knowledge Bank (EKB) database for finding all relevant studies on ACE I/D polymorphism and preterm birth until 01 March 2021. The following terms and keywords were used in various combinations to search: (‘’Preterm Birth’’ OR ‘’Preterm Delivery’’ OR ‘’ Spontaneous Preterm Birth’’) AND (‘’Angiotensin Converting

Enzyme'' OR ''ACE'' OR ''insertion/deletion'' OR ''I/D'' OR ''rs4646994'') AND (''Gene'' OR ''Genotype'' OR ''Allele'' OR ''Polymorphism'' OR '' Single nucleotide polymorphisms'' OR ''SNPs'' OR ''Variant'' OR ''Variation'' OR ''Mutation''). The search was carried out in English and Chinese. Moreover, the reference lists of the retrieved articles were checked to identify more potential studies missed during the online search.

Inclusion and Exclusion Criteria: The following criteria were applied for study selection: 1) case-control or cohort studies; 2) studies evaluated the association of the ACE I/D polymorphism with preterm birth risk; 3) studies with sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). The studies with the following characteristics were excluded: 1) studies on animals; 2) case only studies; 3) studies with insufficient available data or lacking genotypes distribution data; 4) family based studies and linkage studies; 5) case reports, abstracts, letters to the editor, comments, conference abstracts, editorials, reviews, meta-analysis; and 6) published studies containing duplicate data. If there was overlapping data on the same cases included in more than one publication, only the one with the larger sample size or newly published was included in the pooling data.

Data extraction: Data was carefully extracted from all the eligible studies by two authors independently based on selection criteria. Titles and abstracts of these articles were also screened for relevance by two authors to determine which articles were to undergo full-text review. The following data were collected from each study: first author name, year of publication, country of origin, ethnicity, genotyping methods, numbers of cases and controls, genotype frequency of cases and controls, minor allele frequency (MAF) and Hardy-Weinberg equilibrium (HWE) in controls, and Newcastle-Ottawa Scale (NOS) for quality assessment of the study. If chosen articles did not report necessary data, the corresponding authors were contacted by email to request the missing data.

Assessment of study quality: The quality of the selected studies was determined by the Newcastle-Ottawa Scale (NOS). NOS has consisted of three parts including a selection of participants (four items), comparability of cases, and control groups (two items), and adequacy of Outcome (three items). It evaluated studies with a star-rating system ranging from zero to nine stars, in which the score ≥ 7 were expressed as high quality and ≤ 7 represent low or moderate quality (high or moderate risk of bias).

Statistical Analysis: The association of ACE I/D polymorphism and the preterm birth risk was evaluated by calculating the odds ratio (OR) and 95% confidence interval (95% CI). The significance of the pooled OR was evaluated by the Z-test. The pooled ORs were performed under five genetic models, i.e., allele (D vs. I), homozygote (DI vs. II), heterozygote (DD vs. II), dominant (DD+DI vs. II) and recessive model (DD vs. DI+II), respectively. A Chi-square-based Q-test was performed to evaluate the heterogeneity between these studies. The Chi-square test was used to evaluate the HWE of ACE I/D polymorphism distribution in the healthy subjects. A Cochran's Q-test was carried out to examine between- study heterogeneity and was considered significant when $P < 0.10$. Moreover, I^2 value was used for heterogeneity validation as well. The test of heterogeneity using I^2 statistics was as following: I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2=50-75%, large heterogeneity; I^2 = 75-100%, extreme heterogeneity. The pooled data in the fixed effect model (Mantel-Haenszel method) were selected when no significant between-study heterogeneity existed; otherwise, the random-effects model (DerSimonian-Laird method) was used.[24-27] A sensitivity analysis performed by the leave-one-out method to examine the effect of a single study on pooled ORs. The funnel plot

was used to assess the publication bias. The asymmetry of the funnel plot was evaluated by Egger's test. The HWE was tested by Fisher's exact test. All of the statistical calculations were performed using comprehensive meta-analysis (CMA) software version 2.0 (Biostat, USA). Two-sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of the Studies: As shown in Figure 1, our initial search yielded 205 studies, and 131 were remained after removing duplicates. Following the inclusion- exclusion criteria, 126 studies were excluded. Finally, a total of five case-control studies [28-32] with 480 preterm birth cases and 702 healthy subjects were selected. Table 1 shows a summary of the characteristics of all eligible studies. The selected studies were published between 2004 and 2020.

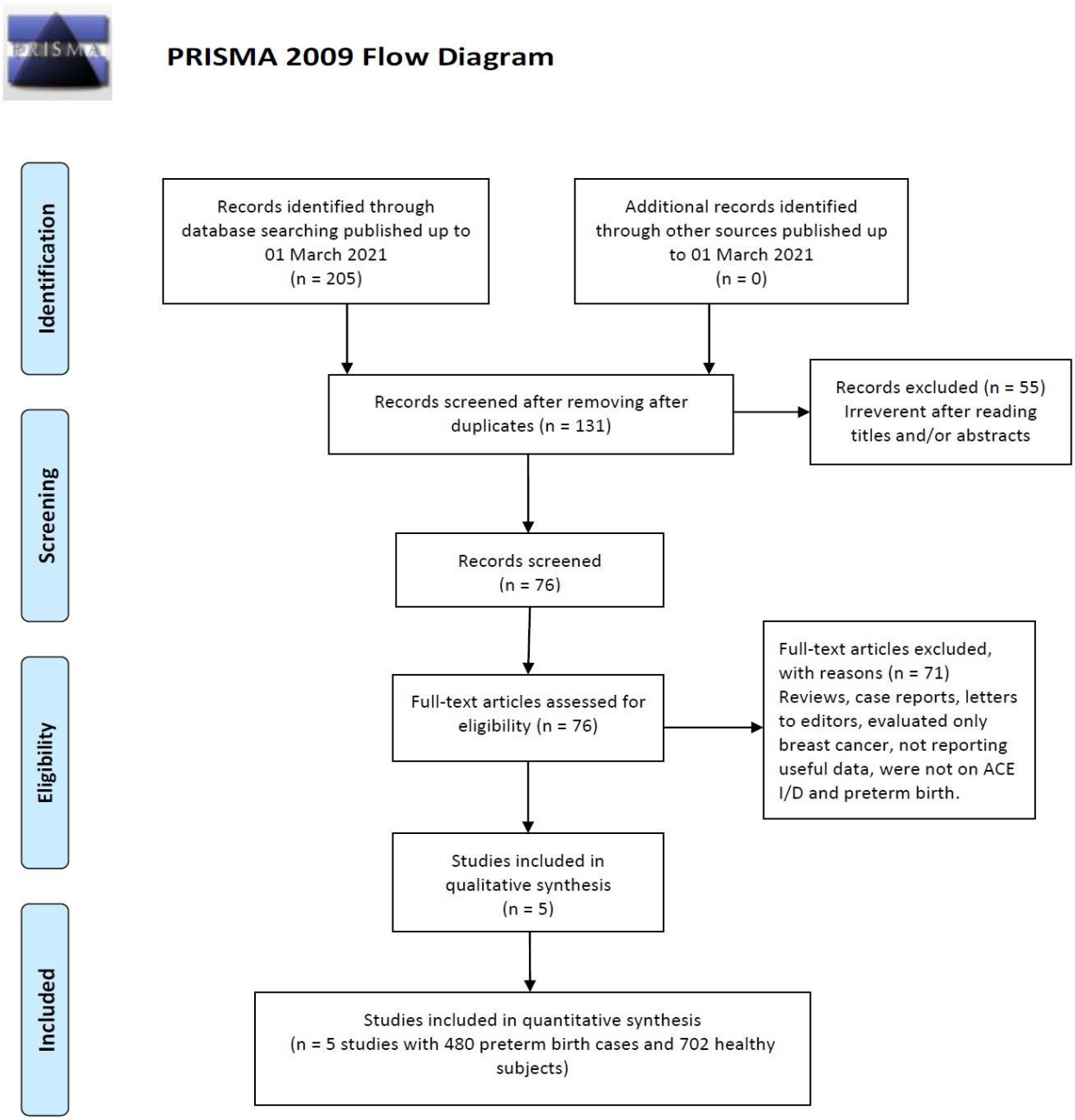

Figure 1. Flow chart for the process of selecting eligible studies

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

First author/Year	Country (Ethnicity)	Genotyping Methods	Case/Control	Preterm-Birth					Controls					MAFs	HWE	NOS
				Genotypes			Alleles		Genotypes			Alleles				
				II	ID	DD	I	D	II	ID	DD	I	D			
Lee 2019	Korea (Asian)	PCR	111/143	50	43	18	143	79	50	75	18	175	111	0.388	0.212	6
Hocevar 2018	Slovenia (Caucasian)	PCR	217/316	34	113	70	181	253	37	78	43	152	164	0.519	0.887	7
Uvuz 2009	Turkey (Caucasian)	PCR	50/50	15	21	14	51	49	19	26	5	64	36	0.360	0.363	6
Uma 2008	UK (Caucasian)	PCR	17/113	4	9	4	17	17	23	64	26	110	116	0.513	0.155	6
Valdez 2004	Mexico (Mixed)	Sequencing	85/238	16	44	25	76	94	66	123	49	255	221	0.464	0.548	6

MAFs: Minor Allele Frequencies; HWE: Hardy-Weinberg Equilibrium; NOS: Newcastle-Ottawa Scale

The studies have been carried out in Korea, Slovenia, turkey, England, and Mexico. In terms of ethnicity, three studies were performed among Caucasian descendants, one study among mixed population, and one study was performed among Arian descendants. Two genotyping methods including PCR and direct sequencing were used to genotype the polymorphism. The genotypes and minor allele frequency (MAF) distributions of ACE I/D polymorphism in cases and controls were presented in Table 1. Hardy-Weinberg equilibrium (HWE) was calculated for all eight publications and $P < 0.05$ was considered as a departure from HWE (Table 1). The NOS score of eligible articles ranged from 6 to 7, which showed that all included studies were of high quality (Table 1).

Quantitative Data Synthesis: The summary for the association of ACE I/D polymorphism with preterm birth risk are shown in Table 2. The combined data showed that the ACE I/D polymorphism was significantly associated with increased risk of preterm birth under the allele model (I vs. D: OR = 1.219, 95% CI 1.023-1.453, $P = 0.027$, Figure 2A), homozygote model (II vs. DD: OR = 0.662, 95% CI 1.149-2.385, $P = 0.007$, Figure 2B), and the recessive model (DD vs. DI+II: OR = 0.707, 95% CI 1.082-1.948, $P = 0.013$, Figure 2C) in overall population. Furthermore, stratified analysis by ethnicity showed that the ACE I/D polymorphism was significantly associated with preterm birth in Caucasian descendants under the allele model (I vs. D: OR = 1.316, 95% CI 1.031-1.680, $P = 0.027$) and the homozygote model (II vs. DD: OR = 1.842, 95% CI 1.109-3.060, $P = 0.018$).

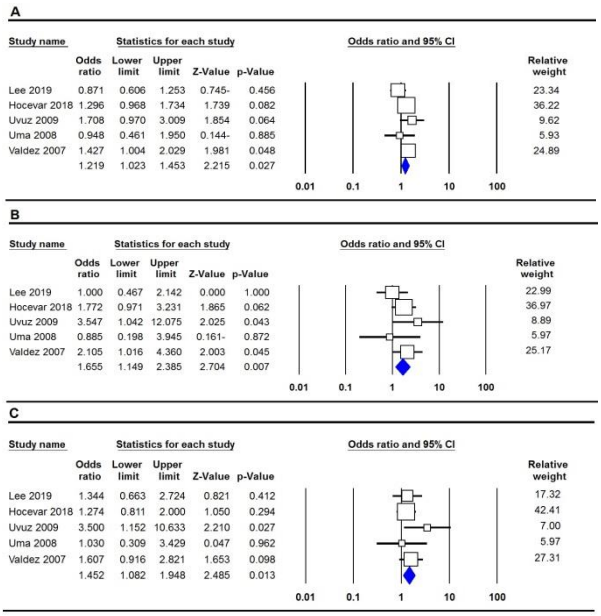

Figure 2: Forest plot for association between ACE I/D polymorphism and preterm birth risk. A: allele model (A vs. T); B: homozygote model (DD vs. II); and C: recessive model (DD vs. DI+II)

Test of heterogeneity: The heterogeneity in overall population and by stratified analyses is presented in Table 2. In this study, there was no significant between-study heterogeneity under all five genetic models in the overall population. Therefore, the fixed effect model (Mantel-Haenszel method) was selected to report the ORs for the association.

Table 2. Summary risk estimates for association of the ACE I/D polymorphism with preterm birth risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio(OR)				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{OR}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	D vs. I	Fixed	33.94	0.196	1.219	1.023-1.453	2.215	0.027	1.000	0.960
	DI vs. II	Fixed	50.77	0.087	1.042	0.771-1.409	0.270	0.787	0.806	0.958
	DD vs. II	Fixed	7.158	0.366	1.655	1.149-2.385	2.704	0.007	1.000	0.971
	DD+DI vs. II	Fixed	52.41	0.078	1.170	0.880-1.555	1.082	0.279	0.806	0.943
	DD vs. DI+II	Fixed	0.00	0.522	1.452	1.082-1.948	2.485	0.013	0.806	0.495
Ethnicity										
Caucasian	D vs. I	Fixed	0.00	0.445	1.316	1.031-1.680	2.205	0.027	1.000	0.928
	DI vs. II	Fixed	0.00	0.524	1.311	0.846-2.031	1.213	0.225	0.296	0.117
	DD vs. II	Fixed	1.920	0.361	1.842	1.109-3.060	2.360	0.018	0.311	0.211
	DD+DI vs. II	Fixed	0.00	0.594	1.467	0.970-2.220	1.816	0.069	0.202	0.296
	DD vs. DI+II	Fixed	33.97	0.220	1.414	0.953-2.099	1.720	0.085	1.000	0.683

NA: Not Applicable

Sensitivity analysis: A sensitivity analysis is necessary to explore the impact of different decisions on pooled ORs. We carried out a sensitivity analysis to assess the effect of individual study by excluding a single study in turn on pooled data. The results showed that no individual study had an influence on the pooled OR for association of ACE I/D polymorphism with preterm birth, suggesting the stability of our conclusions.

Publication bias: Begg's funnel plot and Egger's test were used to assess the potential publication bias for included studies on ACE I/D polymorphism with preterm birth. The Egger's test results under all five genetic models are presented in Table 2. The Egger's test and Begg's funnel did not statistically revealed a significant publication bias in any of the models for ACE I/D polymorphism association with preterm birth (Figure 3).

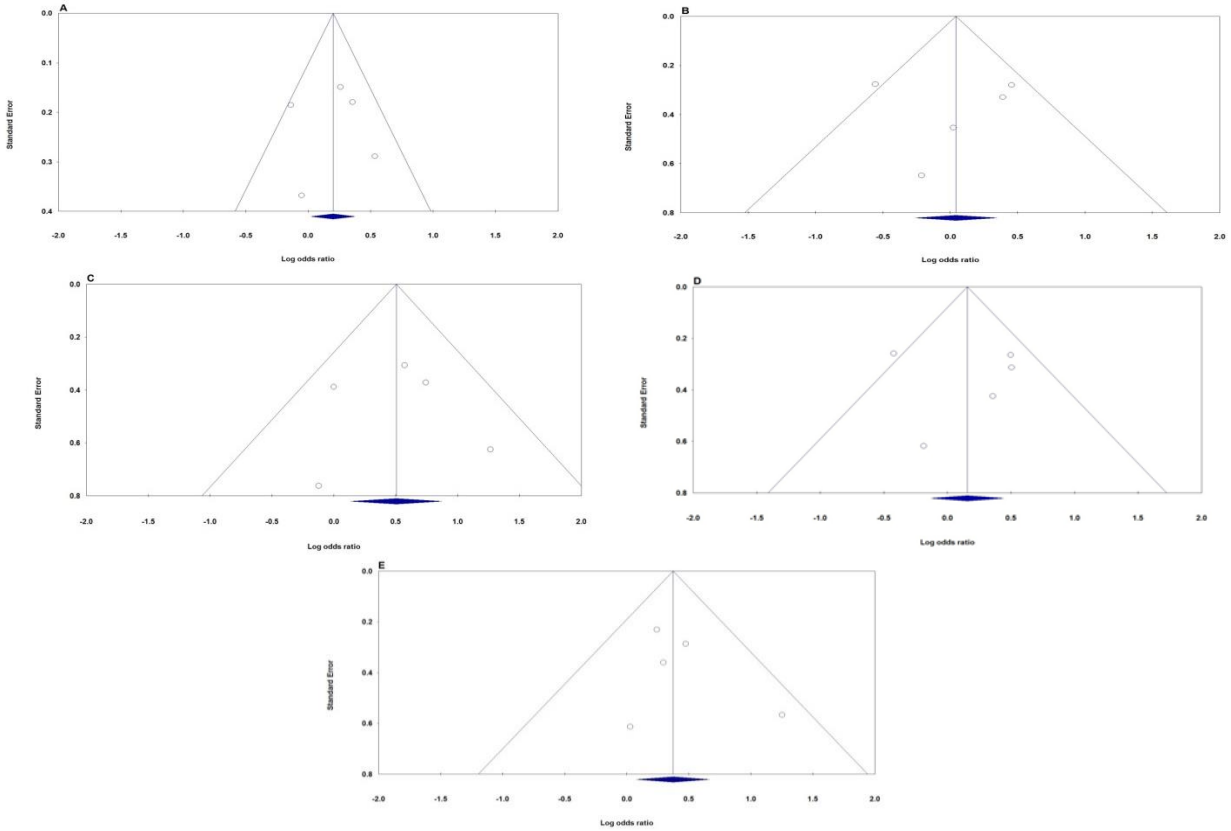

Figure 3: The funnel plots of publication bias for association of ACE I/D polymorphism and preterm birth risk. A: allele (D vs. I); B: homozygote (DI vs. II); C: heterozygote (DD vs. II); D: dominant (DD+DI vs. II) and E: recessive model (DD vs. DI+II)

Discussion

In 2004, Valdez et al., for first time assessed the association of ACE I/D polymorphism with preterm birth risk. They have evaluated the association in 86 women with preterm birth and a control group of adults from Guadalajara, Mexico. The study reported significant differences in the frequency of ACE I/D between women who had a history of preterm birth and healthy subjects.[32] Since then, a few studies evaluated the association of ACE I/D polymorphism with preterm birth risk in limited populations.

Here, we carried out a meta-analysis to assess the association of the ACE I/D polymorphisms with preterm birth risk. In meta-analysis a total of five case-control studies with 480 preterm birth cases and 702 healthy subjects were included. The combined data showed that the ACE I/D polymorphism was significantly associated with increased risk of preterm birth under the allele model (I vs. D: OR = 1.219, 95% CI 1.023-1.453, *P* = 0.027), homozygote model (II vs. DD: OR = 0.662, 95% CI 1.149-2.385, *P* = 0.007), and the heterozygote model (ID vs. DD: OR = 0.707, 95% CI 1.082-1.948, *P* = 0.013) in overall population. Lee et al., in a case-control study and meta-analysis evaluated the association of the ACE I/D polymorphism with preterm birth risk. They evaluated 111 patients with preterm birth and 143 women at ≥ 38 week's gestation as controls in the Korean population. Their case-control study revealed that the ACE I/D polymorphism was significantly associated with preterm birth and that the ID genotype of ACE I/D polymorphism has a protective effect for preterm birth. Similarly, their pooled data revealed that the ACE ID genotype has a significant association with preterm birth and is a protective factor for the disease.[28] Moreover, Hočevar et al., in another case-control study and meta-analysis evaluated the association of the ACE I/D polymorphism with preterm birth risk. Their case-control study included 217 women with a history of preterm birth and 158 women with full-term pregnancy in Serbian population. Their case-control study did not show a significant association of ACE I/D polymorphism with preterm birth. However, their pooled ORs indicated that ACE I/D polymorphism was associated with preterm birth under three genetic models including allele (D vs. I: OR = 1.35, 95% CI = 1.11-1.65, *P* = 0.0033), dominant (DD + ID vs. II: OR = 1.52, 95% CI = 1.08-2.15, *P* = 0.0161) and recessive (DD vs. ID + II: OR = 1.48, 95% CI = 1.07-2.04, *P* = 0.0184).[29]

Some limitations of this meta-analysis should be considered. First, the number of included studies to evaluate the association of ACE I/D polymorphism with risk of preterm birth was not large enough to generate meaningful results, which pooled results based on restricted studies that lack sufficient power to support or deny an association. Second, in this meta-analysis, there were included limited studies by ethnicity. Thus, the discrepancy of the associations in different ethnicities should be interpreted cautiously. Third, the strength of the association was measured by unadjusted ORs for confounding factors such as age, gestational age, and environmental factors due to the lack of primary data, which might have affected our results. Finally, preterm birth is a multifactorial disease and interactions between genetic and environmental factors might affect the development of this disease. In the current meta-analysis, gene-gene and gene-environment interactions were not evaluated due to the limited availability of such data.

Conclusion

Considering all the findings, this meta-analysis indicated that the ACE I/D polymorphism is associated with an increased risk of preterm birth in overall population. Our pooled data may help understand the role and mechanism of the ACE gene in development of preterm birth. However, larger and more rigorous studies among

different ethnicities are needed to evaluate the association of ACE I/D polymorphism with preterm birth.

Conflict of Interests

Authors have no conflict of interests.

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