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Association of TNF- α and IL-1 β gene Polymorphisms with Preterm Birth- Replication Study and Meta Analysis

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Abstract: ***Background: Imbalance between pro-inflammatory and anti –inflammatory cytokine can lead to erratically initiate the labour, leading to PTB. Due to the widespread belief of the role of pro-inflammatory cytokines in preterm birth and limited availability of study data of TNF-α and IL1β gene polymorphisms. Replication and Meta analysis was performed to generate promising evidence in order to elucidate their association with preterm birth. Objectives: The aim of the current work was to systematically review the available literature for the association of TNF-α and IL1β polymorphisms with preterm birth, replicate the association on an Indian population and combine data from the findings using Meta analysis. Methods: TNF-α (-308G/A) and IL-1β (-511C/T) has been involved in the preterm mechanism, 559 cases and 559 controls were genotyped for these SNPs. Our efforts were to replicate and Meta analyze the currently available data linking TNF-α polymorphism and IL-1 β to preterm birth. Data Sources: PubMed and Science Direct (till 2015). Study eligibility criteria: The included studies in this review were a) Association of TNF-α (-308) G/A and IL-1β (-511) C/T with PTB b) case-control design. The following were excluded a)where no allele frequency was given b) with no full text availability c) IL-1 antagonist. Conclusion: Replication analysis reported no association of TNF-α (-308) G/A with preterm birth while meta analysis confirmed the positive associations of TNF-α (-308) G/A and no association of IL1β-511 C/T polymorphisms with preterm birth. In order to arrive at a valid conclusion, more number of studies incorporating large population pools in diverse ethnic groups has to be undertaken.***

Keywords: Inflammation, Preterm Birth, Proinflammation

1. Introduction

Preterm Birth (PTB) is one among the leading causes of neo-natal morbidity and mortality[1]. Every year an estimated 15 million neonates are born preterm and this number is raising at an alarming rate reports WHO [2]. Preterm neonates are highly susceptible to a sequel of repercussions like respiratory distress, cognitive disability, sensory malfunctions and an array of other acute and chronic medical disorders.

The inherent causes of preterm birth are multi-factorial including genetic, environmental, medical, behavioral and socio-economic background. Genetic influences of the mother and the fetus are believed to be the important contributing factors for the early onset of labour leading to birth preterm. It is also surmised that the various components of the immune system play an integral part for the maintenance of safe pregnancy and any imbalance/infection/ inflammation is bound to trigger the immune system to work erratically and initiate labour[3].

Infection and/ or Inflammation are the most studied patho-physiological states which provoke a cascade of biochemical changes terminating in the premature birth [4]. Cytokines, the effector molecules of the host defense mechanism play a pivotal role in regulating inflammatory responses and hence are proved to be a part in initiating preterm births[5,6] .The immune system maintains a delicate balance between the production of pro-inflammatory and anti-inflammatory cytokines and during pregnancy the host normally diminishes the production of pro-inflammatory cytokines to maintain a conducive environment for the fetal growth. But in the case of infection/inflammation there exists disequilibrium in the pro-inflammatory and anti-inflammatory cytokine ratio which leads to earlier parturition and thus preterm -birth.[7, 8, 9]

Earlier reports have convincing results to emphasis the need to study the involvement of up-regulated pro-inflammatory cytokines like IL-1, IL-2, TNF during preterm birth. Among the pro-inflammatory cytokines, Interleukin 1 and TNF-α are the key mediator of inflammation is the most widely studied for their role in a number of diseased conditions. The two distinct Cytokines, TNF-α and IL1-β have been reported to have associations with preterm birth.

TNF-α (-308) G/A and IL1β-511 C/T polymorphisms and their implications on gestational age have been well reported in various populations across the globe. Hence, it becomes necessary to replicate and analyze their relationship in an Indian scenario and pool the world wide results by Meta analysis to arrive at a more meaningful understanding. Therefore, we carried out up to date meta-analysis of TNF-α and IL1β with our replication study to assess the overall effect of these genes with PTB.

Objectives

The aim of the current work was to systematically review the available literature for the association of TNF-α and IL1β polymorphisms with preterm birth, replicate the association on an Indian population and combine data from the findings using Meta analysis.

2. Materials and Methods

Search Strategy: We searched all the relevant studies till date (2015) in Pubmed and Science Direct. Available studies

for TNF-α ,IL-1 and preterm birth were collected by different combinations of key words: , TNF-α ,IL-1, PTB, variant or mutant; preterm birth .An exhaustive search of the databases resulted in a total of 418 articles related to preterm birth, TNF - α and interleukin1 polymorphisms. 25 full text articles were short listed from the initial search and they were scrutinized for their relevance to TNF-α and IL1β polymorphisms with preterm birth. Further evaluation yielded 22 full length articles in case of TNF-α (-308)G/A meta analysis and 3 article -511 C/T polymorphism.
Language restriction was not imported only published literatures with full text available were included in the meta-analysis.

Inclusion and Exclusion Criteria of the study: The included studies in this review were a) Association of TNF-α (-308) G/A and IL-1β(-511)C/T with PTB b)case-control design and cohort design c) presented data for mothers. The following were excluded: a) where no allele frequency was given b) with no full text availability c) IL-1 antagonist d) pregnancy with complications.

Data Extraction: Eligible studies were extracted by 2 reviewers (Pandey & Sundaram) independently based on inclusion and exclusion criteria .Disagreement was resolved by third reviewer (Awasthi).

Study Population: 559 cases with delivery at < 37 weeks and controls with delivery at ≥ 37 weeks were recruited from the King George's Medical University and Hospital, Lucknow, Uttar Pradesh. The study was approved by the Institutional Ethics Committee and the written informed consent was obtained from the patients for their participation in the study. Demographic, environmental, clinical and physical examination findings were recorded for all the cases and controls. Data was collected by trained Medical Scientist .

Ethics approval- This study was ethically approved by KGMU ethical committee.

Genotyping: DNA was extracted from the peripheral blood leucocytes using a phenol-choroform extraction method. Two SNPs rs1800629 and rs16944 of the TNF-α[10] and *IL-1*[11] respectively were selected for screening. Genotyping was done by polymerase chain reaction, restriction fragment length polymorphisms (PCR-RFLP) .PCR amplification was conducted in a total volume of 15 μL with 20 pmol of each primer. PCR conditions were as follows: initial denaturation of 95◦C for 5 min, 40 cycles of 95◦C for 45 s, 60–65◦C for 45 s, and 72◦C for 30 s, followed by a final extension of 72◦C for 30 s. The PCR products were then digested overnight by restriction endonuclease at 37◦C and were thereafter separated by electrophoresis on 10% polyacrylamide gel and stained with ethidium bromide.

Statistical Analysis
Statistical Analysis The association between polymorphisms of the TNF-α, IL1β genes and was tested using binary logistic regression model. Odds ratios (ORs) for this model with the corresponding 95 % confidence intervals (95 % CIs) were computed. Allele frequencies were assessed by counting alleles and calculating sample proportions. The allelic frequency distributions in the case and controls groups were compared by the Pearson chi-squared test. In each group the allele distribution was checked for deviations from Hardy-Weinberg equilibrium using an exact test. The associations between genotypes of TNF-α (-308) G/A and -511C/T polymorphisms with clinical, laboratory characteristics of preterm birth were investigated using one way ANOVA, Pearson chi-squared tests. Revman Version 5.3 software was employed for meta-analysis. Statistical analyses were performed with SPSS software, version 12. Results were considered statistically significant when the probability of findings occurring by chance was less than 5% (P< 0.05).

Systematic Review:
A large scale search of the available literature was done by using a combination of keywords "preterm birth" along with either of "cytokine polymorphism/ interleukin1 polymorphism/ TNF-α polymorphism/ IL-β polymorphism rs1800629 and rs16944" in the databases of Pubmed and Science direct. The collected articles were scrutinized for their relevance to our current hypothesis.

Meta Analysis:
Meta Analysis on the available literature including this study was done using Review Manager software - RevMan version 5.1 from the Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark. The number of cases and controls, genotypic frequencies of the dominant and recessive alleles were extracted from the articles considered for analysis. The studies were assessed for publication bias by forest plot. Inconsistency index I^2 provided data about the degree of heterogeneity among the studies. A fixed effects model was used where there was no heterogeneity and random effects model was used when the articles were heterogeneous from each other.

3. Results

Characteristics of the Eligible Studies. As shown in Figure 1, a total of 418 potentially relevant articles were identified from PubMed and Science Direct, databases using different combinations of key terms. To reduce redundancy 186 studies were excluded from the study. After reading the titles and abstracts, we excluded articles 121 studies that assessed unrelated polymorphisms, pertaining to bacterial vaginosis, were not case-control studies, were conducted in cell lines, and were performed in animal model. After reading the full texts of the remaining 24 articles regarding the association between *IL-1* polymorphisms and preterm birth, 20 articles were excluded. Finally, a total of 25 articles were identified for data extraction and assessment, including 832 cases and 1101 controls for IL-1β -511 C/T and 2253 cases and 5220 controls for TNF-α (-308)G/A.

Quantitative Analysis: A summary description of all studies is included in Table1and Table2. Included studies were comprised of different ethnic groups, seven with 1091 cases and 2503 controls were Caucasians, four with 274 cases and 317 controls were Asians, three with 327 cases and 599 controls were Americans, one with 27 cases and 237 controls were Africans , and six with 534 cases and 1564 controls were mixed .

Replication Analysis: Our current study included 559 cases(born <37 weeks of gestation) and 559 controls(born at ≥37 weeks of gestation).We found no association of **TNF-α -308G/A** {GG [Reference] ,GA,AA :OR=1.9,2.08(95%CI =1.04-5.18, 0.75-5.8)p=0.195, 0.163} and **IL-1β-511C/T**{CC [Reference] CT,TT OR=0.90, 1.30 (95%CI =0.42-1.93, 0.64-2.6),p=0.80, 0.46 with PTB.

Association of TNF-α with PTB

There was significant heterogeneity among all the genetic contrast models TNF-a G308A polymorphism was statistically associated with an increased risk of PTB under both allelic model and genotypic contrast models($OR_{AA+AGVsGG}$=1.52(1.16-2.00,I^2=74%,p=0.005,$OR_{AG\ VS\ GG+AA}$ =13.06(6.94-24.55), I^2 =91%,p<0.0001),while in other contrast models no significant association was found .In subgroup analysis on the basis of ethnicity significant association was found in Asian population $OR_{AA+AG\ VS\ GG}$=1.35(1.10-1.66), I^2=87%,p=0.04, $OR_{AA\ VS\ GG+AG}$ =1.51(1.06-2.17),I^2 =0%,p=0.02, OR_{GG+AG} =0.66(0.46-0.94), I^2 =0%,p=0.02, $OR_{A\ vs\ G}$ =2.54(0.99-6.54), I^2 =89%,p=0.05.) and in American population ($OR_{AG\ VS\ GG+AA\ =}$ 2.36(1.6-3.2), I^2 =93%,p=<0.0001.Therefore, random-effect model was applied to synthesize the data where heterogeneity was found and fixed effect was applied where no heterogeneity occurs. Meta analysis of pooled population data across diverse ethnic groups with our population shows significant association of TNF - with PTB (Fig 2).

Association of IL-1 β with PTB

For IL-1β-511C/T, a total of 832 cases and 1101 controls were included in the study. We found significant heterogeneity under all genetic models. However, we did not found any significant association between *IL1* −511 polymorphism under both the allelic and genetic contrast models($OR_{TT\ Vs\ CC+TT}$ =0.89(0.70-1.12),I^2 =87%, p=0.31, $OR_{CC\ Vs\ TT\ +CT}$ =1.46(0.82-2.60), I^2 =75%,p=0.20,$OR_{CT\ Vs\ CC+TT}$ =1.03(0.63-1.67), I^2 =78%,p=0.91,$OR_{T\ Vs\ C}$ =0.54(0.25-1.13), I^2 =91%, p=0.10)

Sensitivity Analysis. In order to assess the reliability of our results, we performed a sensitivity analysis by sequentially excluding individual study. Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of this meta-analysis.

Publication Analysis.-Publication bias was evaluated by Begg`s funnel plot.

4. Discussions

The arena of genetic predisposition to preterm birth has gained immense interests among the research community. In the present study we reviewed the effect of TNF –α and IL-1 β polymorphisms and found significant association of TNF –α. However, our replication analysis in Indian population did not find any association of TNF –α with PTB.

Many alterations in inflammatory pathway can be triggered by the activities of TNF-a, mainly those leading to the amplification of immunologic and inflammatory processes. Evidences have supported that increased concentration of TNF-α in amniotic fluid has been associated with Preterm birth and preterm premature rupture of membranes[37] .The high level of TNF may alter the delicate balance of anti-inflammatory/ proinflammatory cytokines and induce preterm delivery. G308A polymorphism is a well-characterized variant in the TNF-α, which is located at -308. The allele A is associated with increased transcriptional activity. Therefore, it has been showed that individuals with the -308A allele may hyper respond to infections and these individuals have increased complications from infections such as sepsis, cerebral malaria, and human papilloma virus[38-40]. There are several conflicting results for TNF-a G308A polymorphism and preterm delivery. Meta-analysis of available studies here showed that the presence of TNF-a G308A polymorphism may modify the risk of preterm delivery as the confidence intervals for the cumulative OR included unity.

Statistical heterogeneity was evident in the meta-analysis. Studies recruited in this meta-analysis were different populations of women confirmed with PTB. In order to explore potential sources of heterogeneity, we also conducted subgroup analysis based on ethnicity. The subgroup meta-analysis confirmed that TNF-α G308A polymorphism was statistically associated with increased risk of preterm delivery among Caucasians and Asians. Furthermore, we found no association between the polymorphism and preterm among neither preterm generally nor spontaneous preterm. No publication bias was detected in our meta-analysis.

There are certain limitations to the conclusions made by the current study. Parturition is in itself an intricate phenomenon and there happens a complication to disorient this whole natural process terminating the gestation and delivering the infant preterm. First, PTB is multifactorial and hence a single gene polymorphism cannot stand alone as the underlying etiology. Secondly, in the present study, various interactive contributing factors like environmental in combination with genetic influences, gene-interactions in case of maternal-fetal genotypes and haplotypes have not been considered. Thirdly, the impact of polymorphisms was checked but the functional consequences of the same were not assessed. Finally, there occur significant discrepancies among the studies. This can be attributed to the fact of varying study designs and ethnic differences among population which would vastly affect the outcome of any study.

Nevertheless, we propound that Interleukin1 secretory form β and TNF-α are robust candidates for further research in exploring the molecular basis of PTB and more studies incorporating larger populations in diverse ethnic groups are to be undertaken in order to understand the role of single nucleotide polymorphisms in the early onset of labor and childbirth

Table 1: Characteristics of studies included in the meta-analysis of the link between the TNF-α G308A and IL-1 β C511T gene polymorphism and PTB

Studies	*Publication*		*Ethnicity*	*Case*	*Control*	*Genotype*	*Hardy – Weinberg*

	Year	*Location*										*Equilibrium*
						1	**2**	**3**	**1***	**2****	**3*****	
TNF-α G308A												
Annells[15]	2004	Australian	Caucasian	202	185	27	41	134	21	28	136	Yes
Capasso[16]	2007	Italy	Caucasian	166	164	4	83	79	13	48	77	Yes
Drews[17]	2014	Poland	Caucasian	150	150	103	45	6	103	39	3	Yes
Menon[18]	2006	USA	Caucasian	102	325	1	26	75	7	86	232	Yes
Moore[19]	2004	UK	Caucasian	48	84	14	34	0	67	11	6	Yes
Roberts[20]	1999	USA	Caucasian	55	110	0	24	31	0	33	77	Yes
Stonek[21]	2007	Australian	Caucasian	268	1384	9	55	204	32	338	1014	Yes
Yilmaz[8]	2012	Turkey	Caucasian	100	101	9	7	84	19	10	72	Yes
Chen[22]	2003	China	Asian	54	79	3	31	20	1	9	69	Yes
Current Study	2015	India	Asian	559	559	72	179	307	50	190	318	Yes
Jafarzadzh[23]	2013	Iran	Asian	64	72	0	2	62	0	1	71	Yes
Pu[24]	2007	China	Asian	46	50	3	15	28	3	6	41	Yes
Zhao[25]	2010	China	Asian	110	116	0	17	93	0	18	98	Yes
Menon[26]	2006	USA	American	127	407	3	34	90	6	113	288	Yes
Maura[27]	2009	Brazil	American	113	97	23	90	27	70	20	7	Yes
Maura[27]	2009	Brazil	American	79	104	15	64	30	74	7	23	Yes
Valdez[28]	2004	Mexico	American	86	174	0	9	77	4	27	143	Yes
Macones[29]	2004	USA	Mixed	125	250	7	44	74	4	52	194	Yes
Mattar[30]	2006	Brazil	Mixed	81	48	15	66	14	34	18	6	Yes
Menon[31]	2006	USA	Mixed	49	224	15	29	5	71	104	49	Yes
Nuk[32]	2012	Australia	Mixed	76	197	1	21	54	3	52	142	Yes
O` Callaghan[33]	2013	Australia	Mixed	46	582	0	14	32	16	196	370	Yes
Speer[34]	2006	USA	Mixed	79	80	15	64	19	61	19	0	Yes
												Yes
IL-1 β C511T												
Current	2015	India	Asian	559	559	199	223	137	166	266	127	Yes
Sata[35]	2009	Japan	Asian	73	341	26	27	20	86	162	93	Yes
Schmidt[36]	2012	Austria	Asian	100	100	37	47	16	43	39	18	Yes
Yilmaz[8]	2012	Turkey	Caucasian	100	101	41	52	7	35	36	30	Yes

1=AA or CC, 2=AG or CT, 3=GG or TT

Table 2: Summary of pooled odd ratios and heterogeneity result for the genetic contrasts of TNF-α G308A polymorphism for the risk of PTB

Genetic Model	**Heterogeneity**		*Model*	*Overall effect*	
	I^2 (%)	**p-value**		*O.R.(95%CI)*	*p-value*
AA+AG vs GG	74%	<0.0001	R	1.50(1.13-1.98)	0.005
AA vs AG+GG	88%	<0.0001	R	0.60(0.32-1.13)	0.11
AG vs AA+GG	91%	<0.0001	R	2.40(1.58-3.66)	<0.0001
GG vs AG+AA	77%	<0.0001	R	0.90(0.69-1.18)	0.44
Caucasian					
AA+AG vs GG	69%	<0.0001	R	1.14(0.79-1.66)	0.48
AG vs AA+GG	88%	<0.0001	R	1.70(0.93-3.12)	0.09
AA vs AG+GG	84%	<0.0001	R	0.48(0.19-1.19)	0.11
GG vs AG+AA	88%	<0.0001	R	2.61(0.90-7.53)	0.08
A vs C	76%	<0.0001	R	1.03(0.70-1.50)	0.90
Asian					
AA+AG vs GG	87%	<0.0001	R	1.35(1.10-1.66)	0.04
AA vs AG+GG	0%	0.88	F	1.51(1.06-2.17)	0.02
AG vs AA+GG	88%	<0.0001	R	2.27(0.84-6.17)	0.11
GG+GA vs AA	0%	0.59	F	0.66(0.46-0.94)	0.02
A vs G	89%	<0.0001	R	2.54(0.99-6.54)	0.05
American					
AA vs AG+GG	79%	0.003	R	0.21(0.07-0.65)	0.007
AG +GG vs AA	81%	0.001	R	2.09(0.55-7.81)	0.28
AG vs AA+GG	93%	<0.0001	R	2.36(1.6-3.2)	<0.0001
A vs G	71%	0.06	R	0.74(0.34-1.62)	0.46
Mixed					
AA+AG vs GG	94%	<0.0001	R	1.09(0.83-1.44)	0.52
GG+AG vs AA	95%	<0.0001	R	1.01(0.89-1.14)	0.92
AA vs GG+AG	80%	0.0001	R	0.67(0.32-1.42)	0.30
GG vs AA+AG	79%	0.0003	R	0.98(0.74-1.31)	0.92
A vs G	96%	<0.0001	R	0.75(0.33-1.68)	0.48
IL-1β C511T					
TT vs CC+TT	87%	<0.0001	R	0.89(0.70-1.12)	0.31
CC vs TT +CT	75%	0.008	R	1.46(0.82-2.60)	0.20
CT vs CC +TT	78%	0.003	R	1.03(0.63-1.67)	0.91
T vs C	91%	<0.0001	R	0.54(0.25-1.13)	0.10
C vs T	98%	<0.0001	R	0.16(0.02-1.57)	0.12

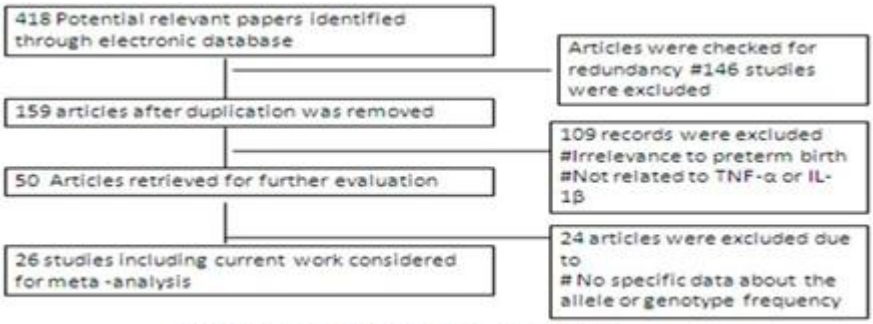

Fig 1.Flow chart for Inclusion procedure

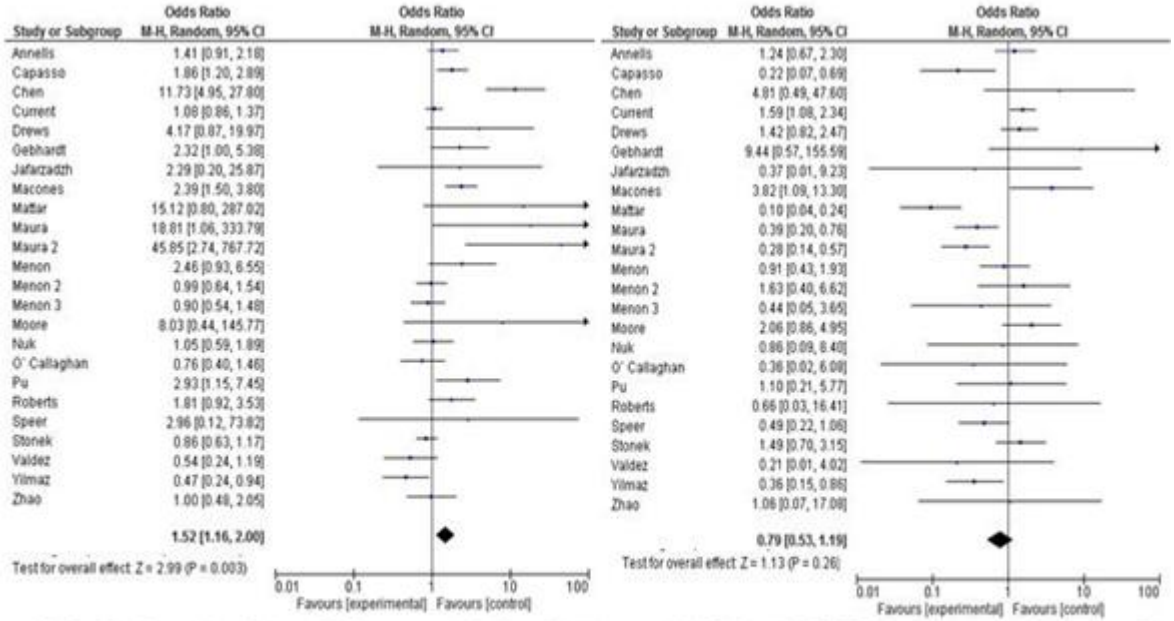

Fig 2. Forest plots of the association between TNF-α G 308A polymorphism and risk of preterm birth for a) AA+AG vs GG b)AA vs AG+GG

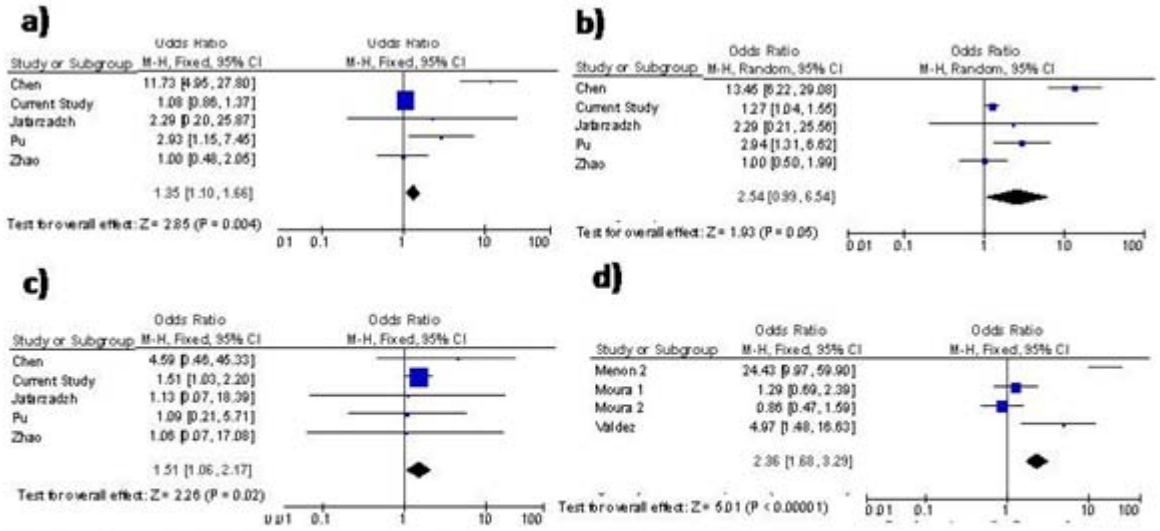

Fig 4. Forest plots of the association between TNF-α G 308A polymorphism and risk of preterm birth for a) AA+AG vs GG b)A vs G allele c) AA vs AG+GG (in Asian population) d)AG vs GG+AA in American population

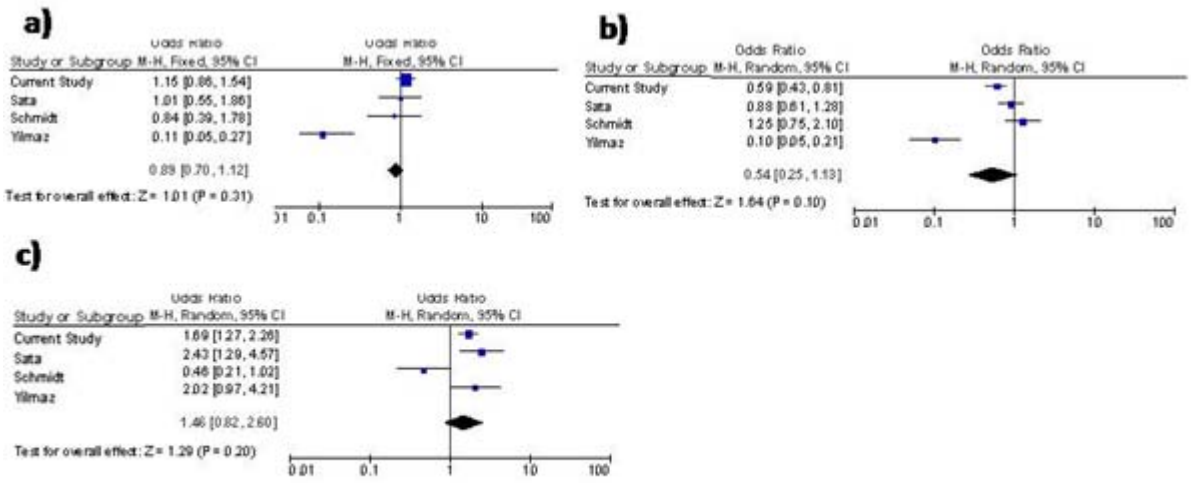

Fig 5. Forest plots of the association between IL-1β C511Tpolymorphism and risk of preterm birth for a) TT vs CC+CT b)T allele Vs C allele c)CC vs CT +TT

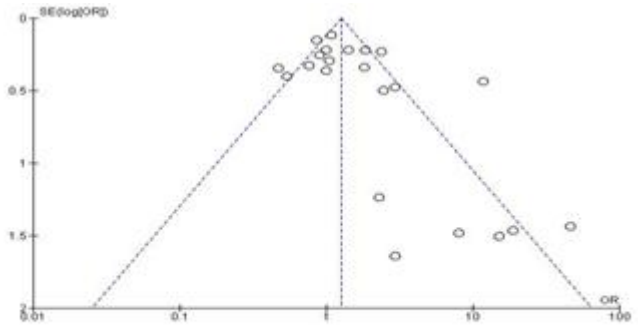

Fig 6. Begg's funnel plot analysis was used to detect publication bias of TNF-G308A polymorphism for AA+AG vs GG .

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