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Original Article

The role of gene variants of the inflammatory markers CRP and TNF-α in cardiovascular heart disease: systematic review and meta-analysis

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Abstract: It is widely acknowledged that cardiovascular heart disease (CHD) has a genetic influence. Several studies have investigated the role of inflammatory markers like C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) in the causation of cardiovascular diseases. Although there have been several positive studies associating CRP and TNF-α genes with CHD, the evidence is not entirely consistent. Therefore, we performed a meta-analysis to gain a better understanding into this issue. The meta-analysis was conducted with 22 articles of genetic association studies of CRP (G1059C rs1800947, C1444T rs1130864, C717T rs2794521 and G3872A rs1205) and TNF-α (C857T rs1799724, C863A rs1800630 and T1031C rs1799964) genes. To analyze the association of these variants with CHD we used the following models: allelic, additive, dominant and recessive. In addition, we performed a sub-group analysis by Caucasian population using the same four models. CRP and TNF-α gene polymorphisms showed a positive significant association with CHD. This study provides evidence that rs2794521 of the CRP gene and rs1799724, rs1800630 and rs1799964 of the TNF-α gene polymorphisms may be risk factors to manifest CHD. The analysis of rs1800947 and rs1205 of the CRP gene yielded a protective effect in the pathogenesis of this disease. Only the analysis of the rs1130864 polymorphism showed a lack of association with CHD. To have conclusive outcomes it is necessary to integrate more studies to confirm our findings.

Keywords: Cardiovascular disease, polymorphisms, C-reactive protein, TNF-α, meta-analysis and systematic review

Introduction

The global burden of cardiovascular heart disease (CHD) represents the highest cause of mortality and one of the highest causes of morbidity around the world [1]. Several reports have explored a contribution in the pathogenesis of CHD considering environmental and intrinsic variables such as smoking, infections, age, obesity, lipid levels, blood pressure, among other causes, but nowadays there is growing evidence indicating a substantial genetic component [2, 3]. Several studies have investigated the role of inflammatory markers like C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) in the causation of cardiovascular diseases [4, 5]. The human CRP gene is located on chromosome 1q21-1q23. It spans approximately 1,900 base pairs and contains 2 exons [6, 7]. There are more than 30 single nucleotide polymorphisms (SNPs) of the human CRP gene listed (accessed on September 2014) in the National Center for Biotechnology Information (NCBI) SNP Database (http://www.ncbi.nlm.nih.gov/SNP). The most studied variant of the CRP gene is rs1800947 in which a change of guanine to cytosine at position 1059 has occurred. CRP polymorphisms have been related to sev-

eral diseases [8-11]. The other CRP variant associated with CHD is rs1130864, where the change of cytosine to thymine at position 1444 has taken place [12-14]. With regard to polymorphisms rs2794521 and rs1205, these have been less studied in association studies with CHD, but similarly to the above mentioned polymorphisms they have yielded interesting outcomes [14-16]. The genetic change of rs2794521 occurs at position 717, where a cytosine is replaced by thymine; as for rs1205 a guanine is substituted by adenine at position 3872 [11, 17]. With regard to the gene encoding TNF-α, it is located on chromosome 6p21 [18, 19]. Some studies have reported that rs1799964, a specific TNF-α gene polymorphism, is associated with increased TNF-α secretion (Bennet et al., 2006; Cui et al., 2012; Ghazouani et al., 2009); in this variant T is substituted by C in the promoter region at position 1031. Other studies have shown that the TNF-α gene promoter region bears other polymorphisms, including C857T rs1799724 and C863A rs1800630, which are associated with CAD. Several studies have investigated whether the TNF-α gene polymorphisms that affect TNF-α expression or activity influences the susceptibility of cardiovascular disorders (Asifa et al., 2013; Bennet et al., 2006; Cho et al., 2013; Koch et al., 2001).

Although numerous studies have been conducted, this issue has not been settled conclusively. Some of these studies did not find an association between CRP and TNF-α with CHD, whereas other reports presented some evidence in favor of this hypothesis [20, 21]. It is necessary to conduct larger and more detailed analyses to get more reliable assessment for the possibility of any moderate causal role. For this reason our aim was to perform a meta-analysis and updated systematic review with the following polymorphisms: G1059C rs1800947, C1444T rs1130864, C717T rs2794521 and G3872A rs1205 of the CRP gene, and C857T rs1799724, C863A rs1800630 and T1031C rs1799964 of the TNF-α gene to get a better understanding of the role these polymorphisms play in the pathogenesis of cardiovascular disease.

Materials and methods

The meta-analysis and systematic review were performed by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [22, 23].

Identification and selection of publications

The literature search was conducted using PubMed and EBSCO databases, using the following keywords: “C-reactive protein AND polymorphisms AND cardiovascular heart disease”, “C-reactive protein AND polymorphisms AND coronary heart disease”, “CRP AND polymorphisms AND CVD”, “CRP AND polymorphisms AND CHD (PubMed: 474; EBSCO: 486) and “TNF-α AND polymorphisms AND cardiovascular heart disease”, “TNF-α AND polymorphisms AND coronary heart disease”, “TNF-α AND polymorphisms AND CVD”, “TNF-α AND polymorphisms AND CHD (PubMed: 316; EBSCO: 310). These words were combined to retrieve the summaries. The search also implicated the review of the bibliography cited at the end of the various research articles.

Inclusion criteria

Two researchers (González-Castro and Juárez-Rojop) working independently screened each of the titles, abstracts and full texts to determine inclusion. When the researchers were in disagreement a third researcher (Tovilla-Zárate) was consulted. Eligible studies fulfilled the following criteria: (1) to be published in peer-reviewed journals, (2) to contain independent data, (3) to be association studies in which the frequencies of three genotypes were clearly stated or could be calculated, (3) diagnosis of cardiovascular disease in the patient study group, and (4) the articles had to be written in English. The following polymorphisms were studied: G1059C rs1800947, C1444T rs1130864, C717T rs2794521 and G3872A rs1205 of the CRP gene, and C857T rs1799724, C863A rs1800630 and T1031C rs1799964 of the TNF-α gene

Data extraction

The same authors mentioned previously extracted the information from all the included reports. These researchers worked independently and in agreement with the inclusion criteria listed above. The following data were obtained from each of the studies: authors, year of publication, location, ethnic group, number of cases and/or controls, age, gender, car-

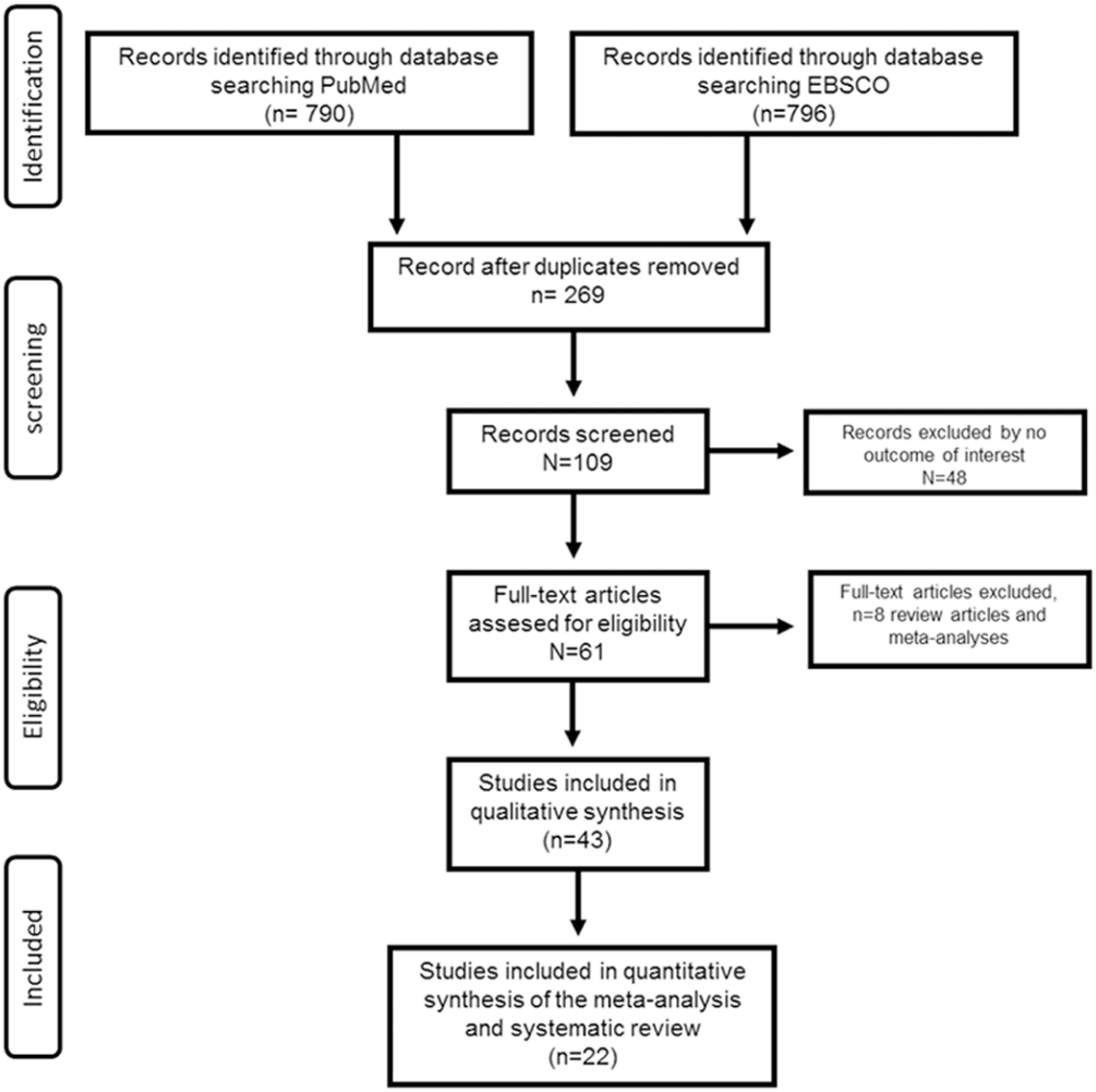

Figure 1. Flow-chart showing the search strategy and inclusion/exclusion criteria used in the meta-analysis and systematic review.

diovascular diagnosis of the participants and CRP serum levels. If these data were not available in the studies, we contacted the respective authors to ask for the lacking information. The outcomes of the meta-analysis were built by taking into consideration the categories reported in previously published studies [25-28].

Statistical analysis

For the meta-analysis the odds ratio (OR) and 95% confidence interval (CI) were estimated and used to evaluate the strength of the association of CRP and TNF-α variants with CHD risk. Pooled ORs were calculated respectively for each of the models used, viz.: allelic (Example: C vs. A), additive (e.g. C/C vs A/A), dominant (e.g. C/C+C/A vs A/A) and recessive (e.g. C/C vs C/A+A/A); OR and 95% CI values were estimated for each study. Also, we analyzed these CRP variants by populations. For all these procedures we used the EPIDAT 3.1 program (http://dxsp.sergas.es). This software is freely available for epidemiologic analysis of tabulated data. Data were analyzed with the random-effects model following the reports in the literature [29-31]. On the other hand, to

Table 1. Genotype and allele distribution in association studies on CRP (rs1800947, rs1130864, rs2794521 and rs1205) and TNF-α (rs1799724, rs1800630 and rs1799964) gene variants with CHD

Reference	Genotype cases			Genotype controls			Allele cases		Allele controls		HWE cases	HWE controls
CRP gene variants												
G1059C rs1800947	GG	GC	CC	GG	GC	CC	G	C	G	C	*p* value	*p* value
Zee R.Y. [8]	142	81	3	638	86	2	1365	87	1362	90	0.614	0.02*
Brull D.J. [9]	163	231	1	209	23	1	349	25	441	25	0.670	0.00*
Miller D.T. [14]	568	75	2	615	79	2	1209	77	1309	83	0.748	0.774
Balistreri C.R. [32]	84	18	4	112	7	1	186	26	231	9	0.03*	0.02*
Dai D.F. [10]	303	55	7	138	29	4	661	69	305	37	0.113	0.02*
Pai J.K. [16]	414	80	5	89	100	4	908	90	1882	108	0.00*	0.607
Grammer T.B. [12]	2238	305	12	620	72	1	4781	329	1312	74	0.463	0.643
Pasalic D. [33]	184	20	2	101	23	1	388	24	225	25	0.803	0.098
Akbarzadeh-Najar R. [11]	845	92	13	834	105	11	1782	118	1773	127	0.00*	0.00*
Ghattas M.H. [34]	128	21	1	121	27	2	277	123	269	3	0.725	0.891
Singh P. [13]	140	37	3	142	31	2	317	43	315	35	0.833	0.759
Total	5209	1015	53	3619	582	31	12223	1011	9424	616	0.155	0.646
C144T rs1130864	CC	CT	TT	CC	CT	TT	C	T	C	T	*p* value	*p* value
Brull D.J. [9]	86	78	22	122	92	13	250	122	336	118	0.42	0.50
Miller D.T. [14]	315	270	58	331	298	67	900	386	960	432	0.99	0.98
Grammer T.B. [12]	1150	1124	281	305	316	76	3424	1686	926	468	0.66	0.78
Singh P. [13]	90	75	15	113	55	7	255	105	281	69	0.92	0.91
Total	1892	1739	418	1344	1144	266	5523	2575	3832	1676	0.32	0.53
C717T rs2794521	CC	CT	TT	CC	CT	TT	C	T	C	T	*p* value	*p* value
Brull D.J. [9]	98	73	14	117	88	17	269	101	322	122	0.93	0.93
Chen J. [17]	452	163	4	439	158	18	1067	179	1067	179	0.41	0.00*
Miller D.T. [14]	352	247	44	361	281	54	951	335	1003	389	0.94	0.94
Grammer T.B. [12]	1395	981	179	351	294	52	3771	1339	996	398	0.37	0.71
Akbarzadeh-Najar R. [11]	683	252	15	648	249	53	1618	282	1545	355	0.00*	0.12
Singh P. [13]	112	60	8	137	35	3	284	76	309	41	0.66	0.99
Total	3092	1776	264	2053	1105	197	7960	2312	5242	1484	0.06	0.66
G3872A rs1205	CC	CT	TT	CC	CT	TT	C	T	C	T	*p* value	*p* value
Miller D.T. [14]	248	303	92	313	308	75	799	487	934	458	0.95	0.97
Mathew J.P. [15]	153	132	10	61	73	14	438	152	195	101	0.23	0.00*
Pai J.K. [16]	218	221	56	447	447	89	657	1333	1341	625	0.12	0.99
Total	619	656	158	821	828	178	1894	1972	2470	1184	0.13	0.42
TNF-α gene variants												
C857T rs1799724	CC	CT	TT	CC	CT	TT	C	T	C	T	*p* value	*p* value
Herrmann, S.M.[35]	153	41	1	125	45	1	348	43	295	47	0.47	0.20
Herrmann, S.M.[35]	302	122	10	340	155	10	726	142	835	175	0.72	0.12
Bennet, A.M. [36]	959	161	16	1265	210	21	2079	193	2740	252	0.00*	0.00*
Cui, G. [37]	907	459	22	700	299	28	2273	503	1699	355	0.00*	0.66
Cui, G. [37]	642	278	41	529	262	30	1562	360	1320	322	0.13	0.82
Cho, H.C. [38]	133	54	10	145	30	53	320	74	672	136	0.16	0.00*
Total	3096	1115	100	3104	1001	143	7308	1315	7561	1287	0.97	0.30
C863A rs1800630	CC	CA	AA	CC	CA	AA	C	A	C	A	*p* value	*p* value
Koch, W. [39]	716	261	21	242	90	8	1693	303	574	106	0.71	1.00
Koch, W. [39]	546	227	20	242	90	8	1319	267	574	106	0.61	1.00

Bennet, A.M. [36]	792	314	37	1011	438	43	1898	388	2460	524	0.40	0.65
Asifa, G.Z. [40]	92	215	3	201	101	8	399	221	503	117	0.00*	0.35
Cho, H.C. [38]	141	54	2	313	51	40	336	58	677	131	0.26	0.00*
Total	2287	1071	83	2009	770	107	5645	1237	4788	984	0.07	0.06
T1031C rs1799964	TT	TC	CC	TT	TC	CC	T	C	T	C	*p* value	*p* value
Bennet, A.M. [36]	726	364	55	889	523	68	1816	474	2301	659	0.00*	0.24
Ghazouani, L. [41]	270	134	14	284	111	11	674	162	679	133	0.00*	1.00
Cui, G. [37]	650	281	30	557	239	25	1581	341	1353	289	0.89	1.00
Asifa, G.Z. [40]	178	106	26	182	210	18	462	158	474	146	0.97	0.98
Total	2696	1360	166	2511	1464	169	6752	1692	6386	1702	0.88	0.99

*p value: statistical significance.

explore the problem of publication bias, the Egger's test and funnel plots were calculated with the same software. This last approach standardizes the effect of each of the published studies on the vertical axis and its correspondent precision on the horizontal axis. Sample heterogeneity was analyzed with the Dersimonian and Laird's Q test. Q test results were complemented with graphs to help the visualization of those studies favoring heterogeneity. Next, a chi-squared (χ^2) analysis was used to calculate the Hardy-Weinberg equilibrium to evaluate genotype distribution.

In order to strengthen the analysis we evaluated publication bias using the GRADE approach and assessed the risk of bias. The Newcastle-Ottawa Assessment Scale (NOS) was used for inclusion in the systematic review by scoring the methodological quality. We established a score of six or more as a cut-off point to distinguish high from low quality studies (see Additional file).

Results

Figure 1 shows the stages of the meta-analysis and systematic review. The combined search included 1586 potentially relevant articles (790 in PubMed and 796 in EBSCO). In the end, 22 articles were obtained after discarding overlapping references that did not agree with the inclusion criteria [8-17, 32-41, 44, 47]. The total data were gathered from 17 521 CHD patients and 13 089 controls with respect to CRP gene variants, and 12 268 CHD patients and 12 162 controls for TNF-α gene variants. We divided the included studies into Caucasian populations and the sample sizes were: 15 077 CHD patients and 10 853 controls for CRP gene variants and 5844 CHD patients and 5824 controls for TNF-α gene variants. Also, we measured the Hardy-Weinberg equilibrium (HWE) in both groups (cases and controls) for all the samples of CRP and TNF-α gene variants and additionally we explored all populations in a combined way (**Table 1**). To develop the analysis further we present descriptive characteristics of the studies in **Table 2**.

PCR gene variants

G1059C rs1800947 polymorphism: In the analysis of rs1800947, we included eleven association studies with CHD. When we explored the role of this variant in all populations in the allelic and recessive models with heterogeneity we found a slight association [fixed: OR 0.86; CI 95%: (0.77-0.96); Q test: <0.0001; Egger's test: 0.12; and fixed: OR 0.85; (CI 95%: 0.75-0.96); Q test: <0.0001; Egger's test: 0.74, respectively (**Figures 2** and **3**)]. With regard to the rest of the models, the analysis of all populations in the study yielded a lack of association. Moreover, we performed a sub-analysis in Caucasian populations to get a more comprehensive understanding of this common variant and we could confirm the association in the same allelic and recessive models with heterogeneity [fixed: OR 0.83; CI 95%: (0.72-0.95); Q test: 0.0007; Egger's test: 0.87 and fixed: OR 0.75; (CI 95%: 0.65-0.87); Q test: <0.0001; Egger's test: 0.72] (see Additional file). The rest of the outcomes as well as the results excluding heterogeneity and bias in the publication are shown in **Table 3**.

C1444T rs1130864 polymorphism: When the whole sample was explored with respect to this variant gene, the analysis revealed no significant association of this polymorphism in relation to CHD using the following models: allelic

Table 2. Descriptive characteristics of the studies about variants of the CRP and TNF-α genes included in the meta-analysis and systematic review

Reference	Date of publication	Cases	Controls	Mean age cases	Mean age controls	Location	Origin	Diagnosis or procedure	CRP serum levels in cases/controls
CRP gene variants									
G1059C rs1800947									
Zee R.Y. [8]	May 2002	726	726	60	60	USA	Caucasians	Arterial thrombosis	1.43 mg/L/1.23 mg/L
Brull D.J. [9]	July 2003	187	233	63	63	UK	Caucasians	Patients with coronary artery bypass	1.39 mg/L/1.19 mg/L
Miller D.T. [14]	Jun 2005	643	696	60	60	USA	Caucasians	Myocardial infarction and ischemic stroke	1.6 mg/L/1.2 mg/L
Balistreri C.R. [32]	May 2006	106	120	41	39	Italy	Caucasians	Acute myocardial infarction	-
Mathew J.P. [15]	Jan 2007	295	148	61	60	USA	Caucasians	Patients with coronary artery bypass	-
Dai D.F. [10]	May 2007	365	171	60	62	China	Asians	Coronary angiography	3.3 mg/L/-
Pai J.K. [16]	Jan 2008	499	995	60	60	USA	Caucasians	Acute myocardial infarction	1.02 mg/L/-
Grammer T.B. [12]	Jan 2009	2555	693	64	58	Germany	Caucasians	Coronary angiography	4.2 mg/L/2.8 mg/L
Pasalic D. [33]	April 2009	206	125	61	58	Croatia	Caucasians	Coronary angiography	2.8 mg/L/2.8 mg/L
Akbarzadeh-Najar R. [11]	April 2012	950	950	53	50	Iran	Asians	Acute myocardial infarction	2.5 mg/L/2.5 mg/L
Ghattas M.H. [34]	Nov 2012	150	150	-	-	Egypt	Africans	Acute myocardial infarction	-
Singh P. [13]	Jun 2014	180	175	55	54	Punyab	Indians	Coronary angiography	2.3 mg/L/1.4 mg/L
C144T rs1130864									
Brull D.J. [9]	July 2003	227	186	63	63	UK	Caucasians	Myocardial infarction and ischemic stroke	1.6 mg/L/1.2 mg/L
Miller D.T. [14]	Jun 2005	643	696	60	60	USA	Caucasians	Myocardial infarction and ischemic stroke	1.6 mg/L/1.2 mg/L
Pai J.K. [16]	Jan 2008	485	959	60	60	USA	Caucasians	Acute myocardial infarction	1.02 mg/L/-
Grammer T.B. [12]	Jan 2009	2555	697	64	58	Germany	Caucasians	Coronary angiography	4.2 mg/L/2.8 mg/L
C717T rs2794521									
Brull D.J. [9]	July 2003	185	222	63	63	UK	Caucasians	Patients with coronary artery bypass	1.39 mg/L/1.19 mg/L
Chen J. [17]	Jan 2005	619	615	53	53	China	Asians	Acute mycocardial infarction	2.38 mg/L-1.82 mg/L
Miller D.T. [14]	Jun 2005	643	696	60	60	USA	Caucasians	Myocardial infarction and ischemic stroke	1.6 mg/L/1.2 mg/L
Grammer T.B. [12]	Jan 2009	2555	697	64	58	Germany	Caucasians	Coronary angiography	4.2 mg/L/2.8 mg/L
Akbarzadeh-Najar R. [11]	April 2012	950	950	53	50	Iran	Asians	Acute myocardial infarction	2.5 mg/L/2.5 mg/L
Singh P. [13]	Jun 2014	180	175	55	54	Punyab	Indians	Coronary angiography	2.3 mg/L/1.4 mg/L
G3872A rs1205									
Miller D.T. [14]	Jun 2005	643	696	60	60	USA	Caucasians	Myocardial infarction and ischemic stroke	1.6 mg/L/1.2 mg/L
Mathew J.P. [15]	Jan 2007	295	148	61	60	USA	Caucasians	Patients with coronary artery bypass	-

Association of CRP and TNF-α genes with CHD

Reference	Date of publication	Cases	Controls	Mean age cases	Mean age controls	Location	Origin	Diagnosis	CRP serum levels in cases/controls
TNF-α gene variants									
C857T rs1799724									
Herrmann, S.M. [35]	Jan 1998	195	171	-	-	UK	Caucasians	Myocardial infarction or angina pectoris	-
Herrmann, S.M. [35]	Jan 1998	434	505	-	-	France	Caucasians	Myocardial infarction or angina pectoris	-
Bennet, A.M. [36]	Jan 2006	1136	1496	61	61	Sweden	Caucasians	Myocardial infarction	1.8 mg/L/1.2 mg/L
Cui, G. [37]	Oct 2012	1338	1027	-	-	China	Asians	Ischemic stroke	-
Cui, G. [37]	Oct 2012	961	821	-	-	China	Asians	Ischemic stroke	-
Cho, H.C. [38]	March 2013	394	808	61	62	Korea	Asians	Myocardial infarction	1.9 mg/L/-
C863A rs1800630									
Koch, W. [39]	Jan 2001	998	340	64	63	Germany	Caucasians	Coronary stenosis	-
Koch, W. [39]	Jan 2001	793	340	63	63	Germany	Caucasians	Myocardial infarction	-
Bennet, A.M. [36]	Jan 2006	1143	1492	61	61	Sweden	Caucasians	Myocardial infarction	1.8 mg/L/1.2 mg/L
Asifa, G.Z. [40]	Sep 2013	310	310	54	53	Pakistan	Oriental	Coronary angiography	-
Cho, H. C. [38]	March 2013	394	808	61	62	Korea	Asians	Myocardial infarction	1.3 mg/L/-
T1031C rs1799964									
Bennet, A.M. [36]	Jan 2006	1145	1480	61	61	Sweden	Caucasians	Myocardial infarction	1.8 mg/L/1.2 mg/L
Ghazouani, L. [41]	July 2009	418	406	58	57	Tunisia	African	Myocardial infarction	-
Cui, G. [37]	Oct 2012	1338	1027	0	0	China	Asians	Ischemic stroke	-
Cui, G. [37]	Oct 2012	961	821	0	0	China	Asians	Ischemic stroke	-
Asifa, G.Z. [40]	Sep 2013	310	310	54	53	Pakistan	Oriental	Ischemic stroke	-

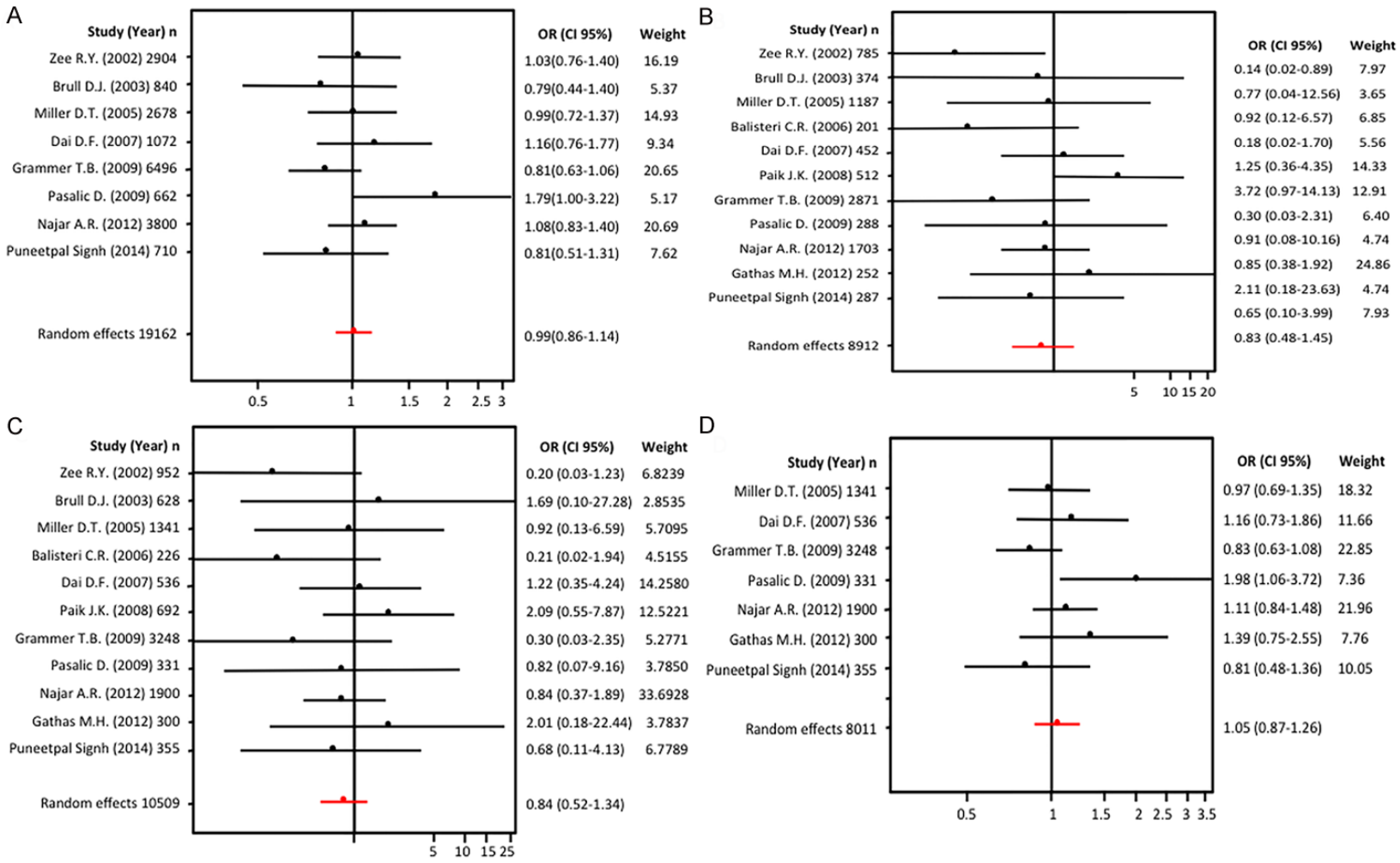

Figure 2. Odds ratios and forest plots of the PCR rs1800947 variant in overall studies, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

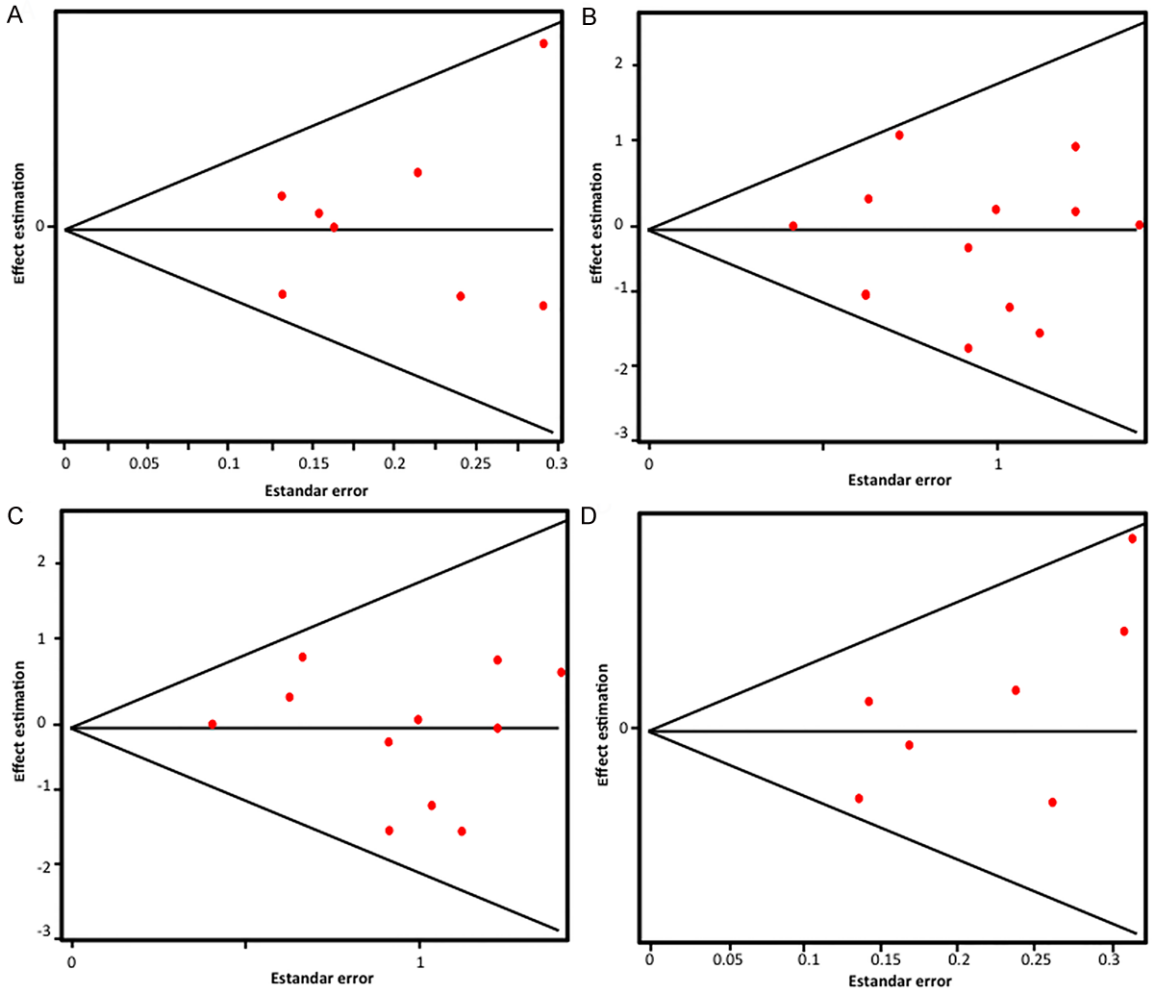

Figure 3. Egger's funnel plots in overall studies indicating publication bias in studies on CHD and PCR rs1800947 variant, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

[random: OR 1.00; CI 95% (0.88-1.14); Q test: 0.09; Egger's test: 0.25], additive [random: OR 1.02; CI 95% (0.76-1.37); Q test: 0.11; Egger's test: 0.28], dominant [random: OR 1.03; CI 95% (0.81-1.30); Q test: 0.23; Egger's test: 0.38], and recessive [random: OR 1.03; CI 95% (0.92-1.16); Q test: 0.35; Egger's test: 0.15] (**Figures 4** and **5**). Due to these results, we explored the role of this variant gene in the Caucasian population only (see Additional file), and even though the results did not reveal heterogeneity we confirmed the same results of the first analysis, using the same models: allelic [random: OR 1.00; CI 95% (0.88-1.14); Q test: 0.09; Egger's test: 0.25], additive [random: OR 0.98; CI 95% (0.71-1.35); Q test: 0.06; Egger's test: 0.30], dominant [random: OR 0.98; CI 95% (0.73-1.30); Q test: 0.09; Egger's test: 0.35], and recessive [random: OR 1.03; CI 95% (0.92-1.16); Q test: 0.35; Egger's test: 0.15]. Additional data can be found in **Table 3**.

C717T rs2794521 polymorphism: The analysis of all the populations as a whole showed that the rs2794521 polymorphism in the four models analyzed yielded a significant relation to present CHD clinically in the following models: allelic [random: OR 1.13; CI 95% (1.04-1.22); Q test: 0.30; Egger's test: 0.47; without heterogeneity], dominant [random: OR 2.04; CI 95% (1.60-2.60); Q test 0.97; Egger's test: 0.53; without heterogeneity] and recessive [random: OR 1.14; CI 95% (1.04-1.26); Q test: 0.92; Egger's test: 0.28; without heterogeneity] (**Figures 6** and **7**). Furthermore, a more careful analysis of this gene variant was performed reporting Caucasian population only and we still observed the same results showing a

Table 3. Analysis of association studies on CRP (rs1800947, rs1130864, rs2794521 and rs1205) and TNF-α (rs1799724, rs1800630 and rs1799964) gene variants with CHD in Caucasians and all populations in the study

Model analysis		Caucasians		*P* value of Q test	*P* value of Egger's test	All populations		*P* value of Q test	P value of Egger's test
		Random effects OR (CI 95%)	Fixed effects OR (CI 95%)			Fixed effects OR (CI 95%)	Fixed effects OR (CI 95%)		
PCR gene variants									
G1059C rs1800947									
Allelic	With heterogeneity	0.82 (0.61-1.10)	0.83 (0.72-0.95)	0.0007	0.87	0.74 (0.55-1.01)	0.86 (0.77-0.96)	<0.0001	0.12
	Without heterogeneity	0.91 (0.78-1.07)	0.91 (0.78-1.07)	0.60	0.90	0.99 (0.86-1.14)	0.99 (0.87-1.12)	0.30	0.50
Additive	With heterogeneity								
	Without heterogeneity	0.62 (0.22-1.74)	0.74 (0.35-1.54)	0.08	0.20	0.83 (0.48-1.45)	0.86 (0.54-1.38)	0.27	0.42
Dominant	With heterogeneity								
	Without heterogeneity	0.68 (0.31-1.48)	0.70 (0.34-1.46)	0.35	0.39	0.84 (0.52-1.34)	0.84 (0.52-1.34)	0.53	0.65
Recessive	With heterogeneity	0.65 (0.23-1.78)	0.75 (0.65-0.87)	<0.0001	0.72	0.79 (0.41-1.50)	0.85 (0.75-0.96)	<0.0001	0.74
	Without heterogeneity	1.06 (0.72-1.57)	0.95 (0.78-1.16)	0.06	0.08	1.05 (0.87-1.26)	1.02 (0.88-1.18)	0.16	0.15
C1444T rs1130864									
Allelic	With heterogeneity					0.92 (0.77-1.09)	0.99 (0.91-1.07)	0.004	0.06
	Without heterogeneity	1.00 (0.88-1.14)	1.02 (0.94-1.11)	0.09	0.25	1.00 (0.88-1.14)	1.02 (0.94-1.11)	0.09	0.25
Additive	With heterogeneity					0.87 (0.61-1.25)	0.99 (0.82-1.20)	0.02	0.08
	Without heterogeneity	0.98 (0.71-1.35)	1.03 (0.85-1.25)	0.06	0.30	1.02 (0.76-1.37)	1.05 (0.87-1.28)	0.11	0.28
Dominant	With heterogeneity					0.91 (0.67-1.23)	0.98 (0.82-1.18)	0.05	0.12
	Without heterogeneity	0.98 (0.73-1.30)	1.01 (0.84-1.22)	0.09	0.35	1.03 (0.81-1.30)	1.04 (0.86-1.25)	0.23	0.38
Recessive	With heterogeneity					0.93 (0.76-1.13)	0.99 (0.89-1.10)	0.02	0.06
	Without heterogeneity	1.03 (0.92-1.16)	1.03 (0.93-1.15)	0.35	0.15	1.03 (0.92-1.16)	1.03 (0.93-1.15)	0.35	0.15
C717T rs2794521									
Allelic	With heterogeneity					1.02 (0.86-1.21)	1.10 (1.01-1.19)	0.001	0.08
	Without heterogeneity	1.10 (1.00-1.21)	1.10 (1.00-1.21)	0.81	0.29	1.13 (1.03-1.23)	1.13 (1.04-1.22)	0.30	0.47
Additive	With heterogeneity					1.47 (0.86-2.54)	1.39 (1.11-1.73)	<0.0001	0.79
	Without heterogeneity	1.15 (0.90-1.47)	1.15 (0.90-1.47)	0.93	0.45	1.08 (0.80-1.45)	1.10 (0.86-1.40)	0.29	0.12
Dominant	With heterogeneity					3.60 (1.83-7.09)	2.79 (2.24-3.47)	<0.0001	0.37
	Without heterogeneity	2.05 (1.61-2.62)	2.05 (1.61-2.62)	0.93	0.98	2.04 (1.60-2.60)	2.04 (1.60-2.60)	0.97	0.53
Recessive	With heterogeneity					1.03 (0.86-1.24)	1.10 (1.00-1.21)	0.009	0.37
	Without heterogeneity	1.14 (1.01-1.29)	1.14 (1.01-1.29)	0.74	0.12	1.14 (1.04-1.26)	1.14 (1.04-1.26)	0.92	0.28
G3872A rs1205									
Allelic	With heterogeneity	0.64 (0.22-1.88)	0.44 (0.40-0.48)	<0.0001	0.45	0.64 (0.22-1.88)	0.44 (0.40-0.48)	<0.0001	0.45
	Without heterogeneity								

Additive	With heterogeneity	1.05 (0.53-2.09)	0.79 (0.62-1.01)	0.001	0.07	1.05 (0.53-2.09)	0.79 (0.62-1.01)	0.001	0.07
	Without heterogeneity	0.70 (0.54-0.90)	0.70 (0.54-0.90)	0.48	1.00	0.70 (0.54-0.90)	0.70 (0.54-0.90)	0.48	1.00
Dominant	With heterogeneity	1.02 (0.58-1.81)	0.83 (0.66-1.04)	0.007	0.07	1.02 (0.58-1.81)	0.83 (0.66-1.04)	0.007	0.07
	Without heterogeneity	0.74 (0.58-0.95)	0.74 (0.58-0.95)	0.7567	1.00	0.74 (0.58-0.95)	0.74 (0.58-0.95)	0.75	1.00
Recessive	With heterogeneity	0.99 (0.71-1.37)	0.91 (0.79-1.06)	0.01	0.29	0.99 (0.71-1.37)	0.91 (0.79-1.06)	0.01	0.29
	Without heterogeneity	0.85 (0.69-1.04)	0.85 (0.73-0.99)	0.19	1.00	0.85 (0.69-1.04)	0.85 (0.73-0.99)	0.19	1.00
TNF-α gene variants									
C857T rs1799724									
Allelic	With heterogeneity								
	Without heterogeneity	1.04 (0.90-1.20)	1.04 (0.90-1.20)	0.65	0.10	1.00 (0.92-1.09)	1.00 (0.92-1.09)	0.65	0.45
Additive	With heterogeneity					1.42 (0.08-2.51)	1.35 (1.03-1.79)	0.003	0.80
	Without heterogeneity	0.96 (0.57-1.61)	0.96 (0.57-1.61)	0.96	0.73	1.08 (0.80-1.46)	1.08 (0.80-1.46)	0.65	0.99
Dominant	With heterogeneity					1.46 (1.07-2.75)	1.38 (1.05-1.82)	0.0006	0.82
	Without heterogeneity	0.95 (0.56-1.59)	0.95 (0.56-1.59)	0.95	0.89	1.07 (0.79-1.45)	1.07 (0.80-1.45)	0.40	0.98
Recessive	With heterogeneity								
	Without heterogeneity	1.06 (1.00-1.24)	1.06 (0.90-1.24)	0.48	0.13	1.02 (1.00-1.14)	1.01 (0.92-1.12)	0.32	0.08
C863A rs1800630									
Allelic	With heterogeneity					1.16 (0.84-1.61)	1.10 (1.00-1.22)	<0.0001	0.58
	Without heterogeneity	0.98 (0.88-1.10)	0.98 (0.88-1.10)	0.64	0.52	0.97 (0.88-1.08)	0.97 (0.88-1.08)	0.75	0.94
Additive	With heterogeneity								
	Without heterogeneity	1.05 (1.04-1.51)	1.05 (1.04-1.51)	0.89	0.60	0.77 (0.42-1.39)	0.92 (0.65-1.28)	0.06	0.19
Dominant	With heterogeneity					1.41 (0.86-2.34)	1.18 (1.06-1.33)	<0.0001	0.26
	Without heterogeneity	0.97 (0.86-1.10)	0.97 (0.86-1.10)	0.54	0.41	1.02 (0.88-1.18)	1.00 (0.89-1.13)	0.28	0.09
Recessive	With heterogeneity					0.64 (0.32-1.28)	0.87 (0.62-1.22)	0.01	0.08
	Without heterogeneity	1.06 (0.75-1.52)	1.06 (0.75-1.52)	0.88	0.44	0.99 (0.70-1.40)	0.99 (0.70-1.40)	0.47	0.14
T1031C rs1799964									
Allelic	With heterogeneity					0.99 (0.70-1.40)	0.99 (0.70-1.40)	0.47	0.14
	Without heterogeneity					0.97 (0.86-1.10)	0.94 (0.87-1.02)	0.06	0.06
Additive	With heterogeneity								
	Without heterogeneity					0.97 (0.71-1.32)	0.93 (0.74-1.17)	0.13	0.32
Dominant	With heterogeneity					0.88 (0.73-1.06)	0.88 (0.80-0.96)	0.003	0.92
	Without heterogeneity					0.94 (0.81-1.11)	0.92 (0.83-1.01)	0.06	0.06
Recessive	With heterogeneity								
	Without heterogeneity					1.05 (1.00-1.51)	1.00 (0.80-1.25)	0.06	0.39

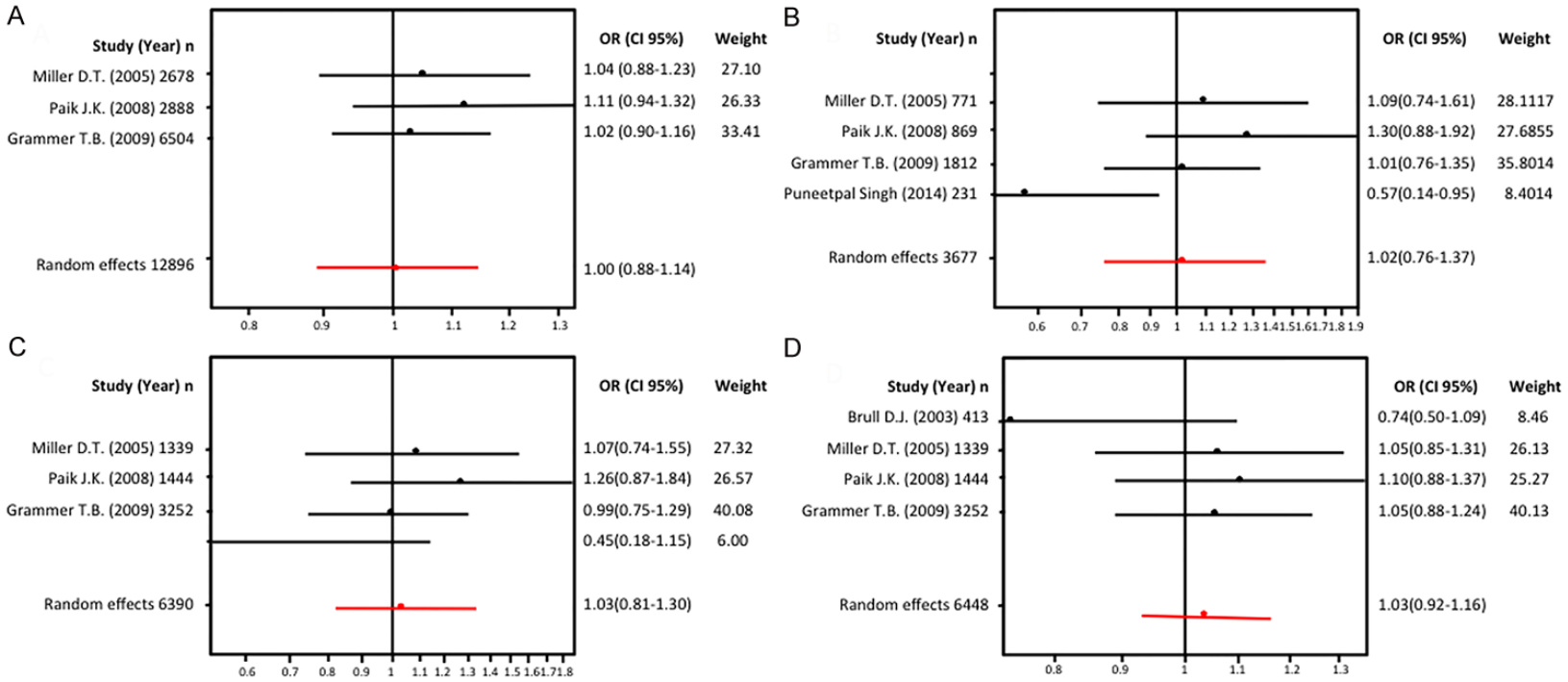

Figure 4. Odds ratios and forest plots of PCR rs1130864 variant in overall studies, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

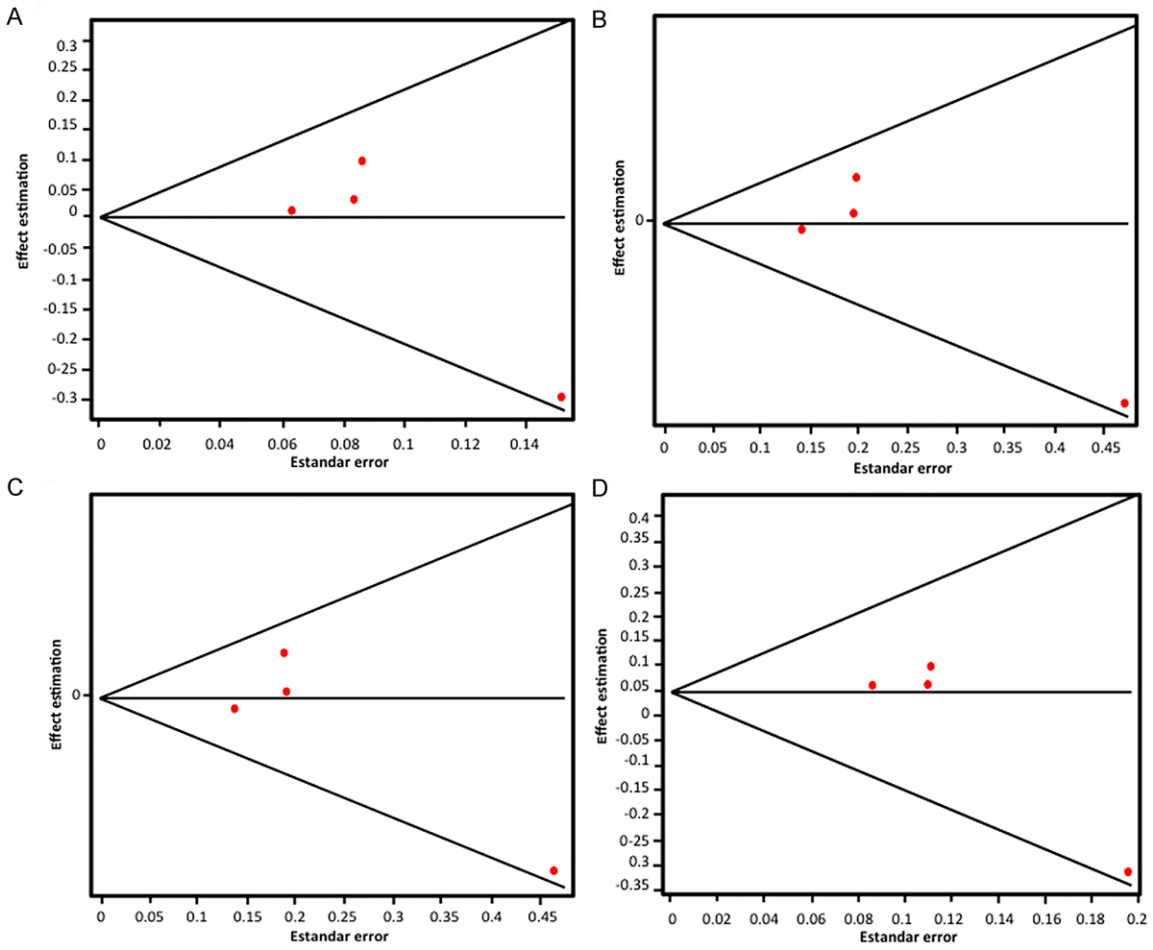

Figure 5. Egger's funnel plots in overall studies indicating publication bias in studies on CHD and PCR rs1130864 variant, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

strong relationship of this polymorphism and CHD: allelic [random: OR 1.10; CI 95% (1.00-1.21); Q test: 0.81; Egger's test: 0.29], dominant [random: OR 2.05; CI 95% (1.61-2.62); Q test: 0.93; Egger's test: 0.98] and recessive [random: OR 1.14; CI 95% (1.01-1.29); Q test: 0.74; Egger's test: 0.12]. These data did not reveal heterogeneity (**Table 3**).

G3872A rs1205 polymorphism: In this gene variant we only included reports with Caucasian populations (see Additional file). We conducted only one analysis taking the whole population as sample and found a significant association of this polymorphism with CHD in the following models: additive [random: OR 0.70; CI 95% (0.54-0.90); Q test: 0.48; Egger's test: 1.00] and dominant [random: OR 0.74; CI 95% (0.58-0.95); Egger's test: 0.75; Egger's test: 1.00] (**Figures 8** and **9**). In the analysis with the allelic model we could not exclude heterogeneity (**Table 3**).

TNF-α gene variants

C857T rs1799724 polymorphism: The analysis of this variant included the same models proposed in the CRP polymorphisms: allelic, additive, dominant and recessive with and without heterogeneity. In this way we could observe in the recessive model without heterogeneity a significant association of allele T of the rs1799724 polymorphism in whole CHD population [random: OR 1.02; CI 95% (1.00-1.14); Q test: 0.32; Egger's test: 0.08] (**Figures 10** and **11**). This result was confirmed when we explored this same variant but only in Caucasians, using the recessive model without heterogeneity [random: OR 1.06; CI 95% (1.00-1.24); Q test: 0.48; Egger's test: 0.13] (see Additional file). In addition, the findings in the

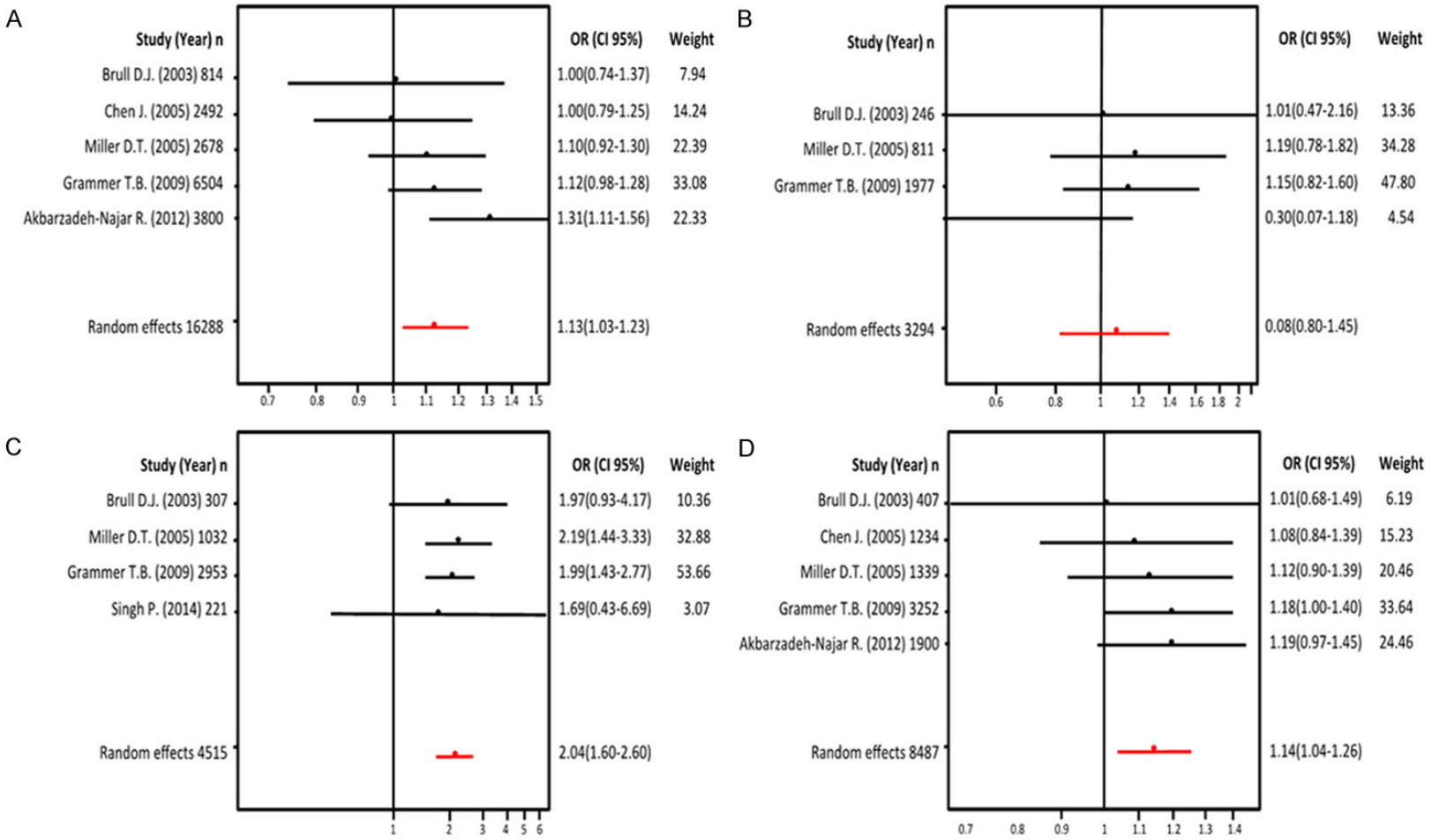

Figure 6. Odds ratios and forest plots of the PCR rs2794521 variant in overall studies, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

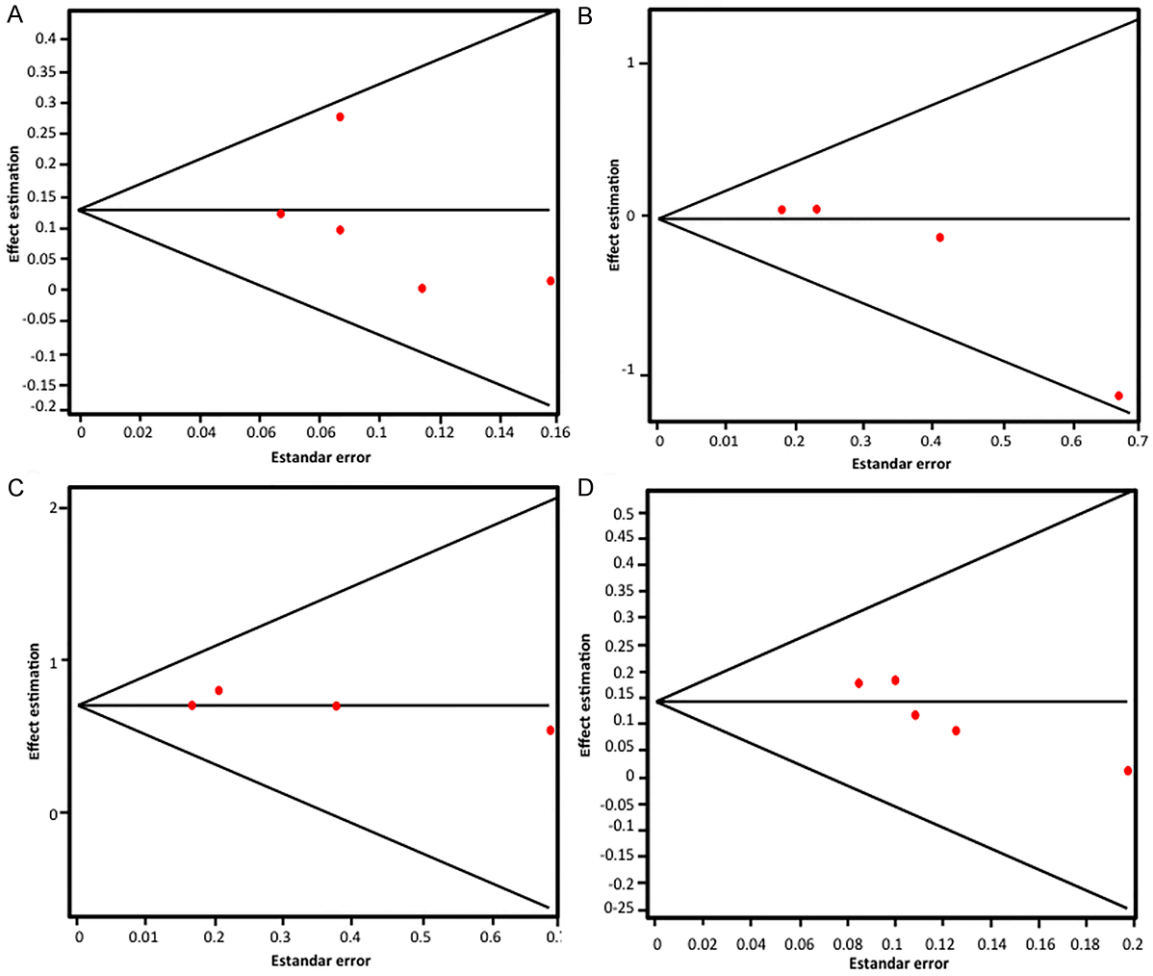

Figure 7. Egger's funnel plots in overall studies indicating publication bias in studies on CHD and PCR rs2794521 variant, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

others models did not show C857T polymorphisms as a predisposing factor in CHD (**Table 3**).

C863A rs1800630 polymorphism: First, the interaction of this variant in CHD was analyzed; the outcomes did not show a significant association in the population when heterogeneity was discarded. Subsequently, we explored this association only in Caucasians (see Additional file) and we could observe in the additive model without heterogeneity a slight 5% increase in the risk to present CHD [random: OR 1.05; CI 95% (1.04-1.51); Q test: 0.89; Egger's test: 0.60] (**Figures 12** and **13**).

T1031C rs1799964 polymorphism: The findings of this variant in the dominant model with heterogeneity revealed a probability that this SNP could have a protective effect in the CHD for allele T [random: OR 0.88; CI 95% (0.80-0.96); Q test: 0.003; Egger's test: 0.92]. Although the outcome in the recessive model without heterogeneity [random: OR 1.05; CI 95% (1.00-1.51); Q test: 0.06; Egger's test: 0.39] showed that allele C of the variant T1031C could be considered a risk factor (**Figures 14** and **15**). An analysis by ethnicity was not performed.

Discussion

It is well known that CHD is a complex disease where multiple genetic markers interact and inflammatory markers play a vital role in its pathogenesis. Due to this, the present study aimed to explore the involvement of TNF-α and CRP genetic variants with CHD in a meta-analysis and systematic review to get a more comprehensive understanding of this pathology. To

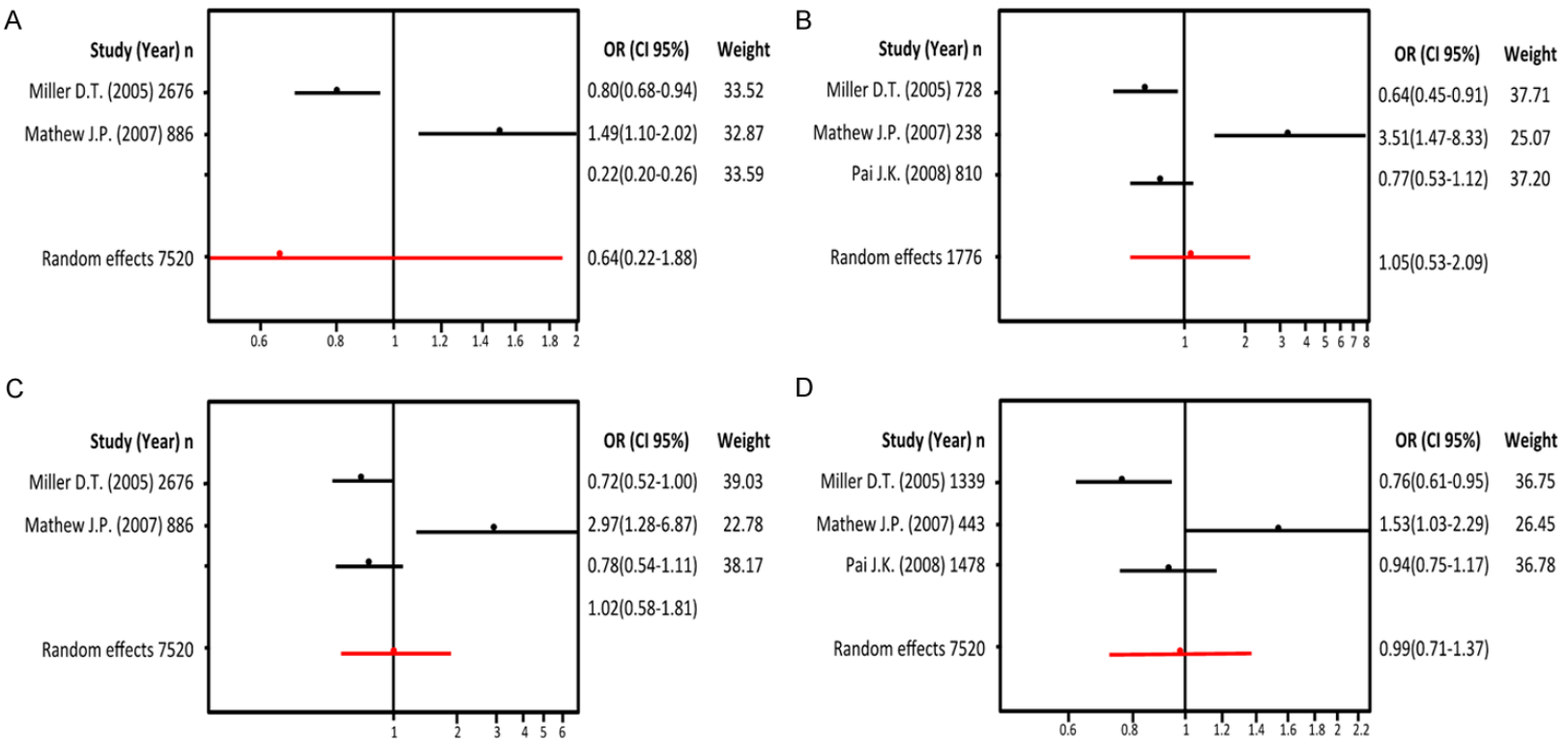

Figure 8. Odds ratios and forest plots of the PCR rs1205 variant in overall studies, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

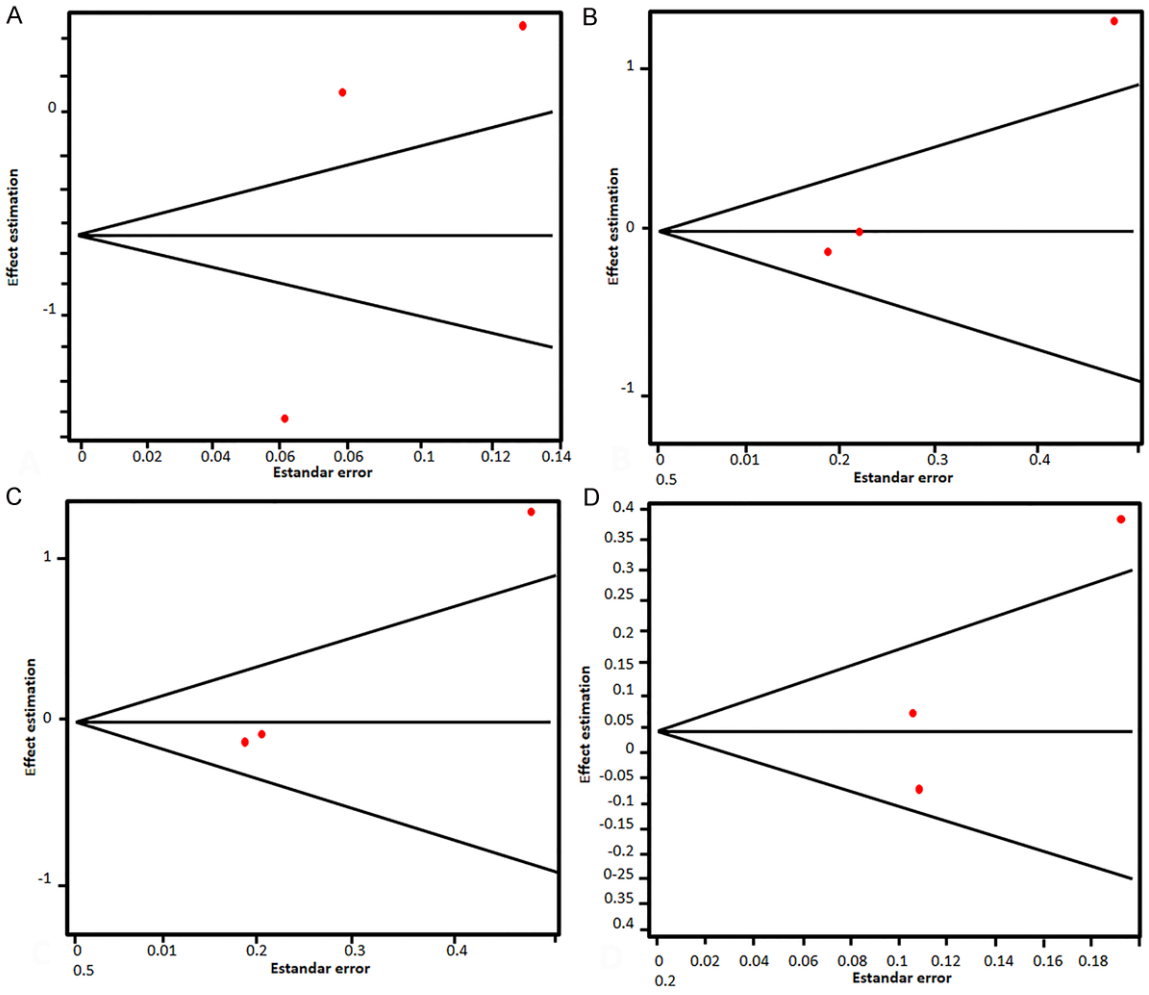

Figure 9. Egger's funnel plots in overall studies indicating publication bias in studies on CHD and PCR rs1205 variant, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

start, we chose the TNF-α and CRP genes because there is strong evidence that they are powerful predictors of incident cardiovascular events. As a result, the most common variants studied in association with CHD were the following polymorphisms: G1059C rs1800947, C1444T rs1130864, C717T rs2794521 and G3872A rs1205 of the CRP gene, and C857T rs1799724, C863A rs1800630 and T1031C rs1799964 of the TNF-α gene with interesting results.

First, we explored the rs1800947 polymorphism and found that in all the studies concerning this variant, the pooled ORs suggested a possible protective role to present CHD clinically. The allelic model was used to analyze all the populations as a whole [fixed: OR 0.86; CI 95% (0.77-0.96)], and also Caucasian populations only [fixed: OR 0.83; CI 95% (0.72-0.95); with heterogeneity] (**Table 3**). This polymorphism is the most studied CRP gene in relation to CHD. We found that our results are in agreement with other reports on the subject [33, 34]. However, there are also reports not showing such association [9, 10, 14]. We encourage researchers to take into consideration that the fixed model is not as conservative as the random model, because the latter assumes the existence of normal distribution effects and parameterizes inter-studies. Therefore, the outcomes from the random effects model are more reliable when heterogeneity is present.

Next, we analyzed the rs1130864 variant in association studies with CHD, but we could not

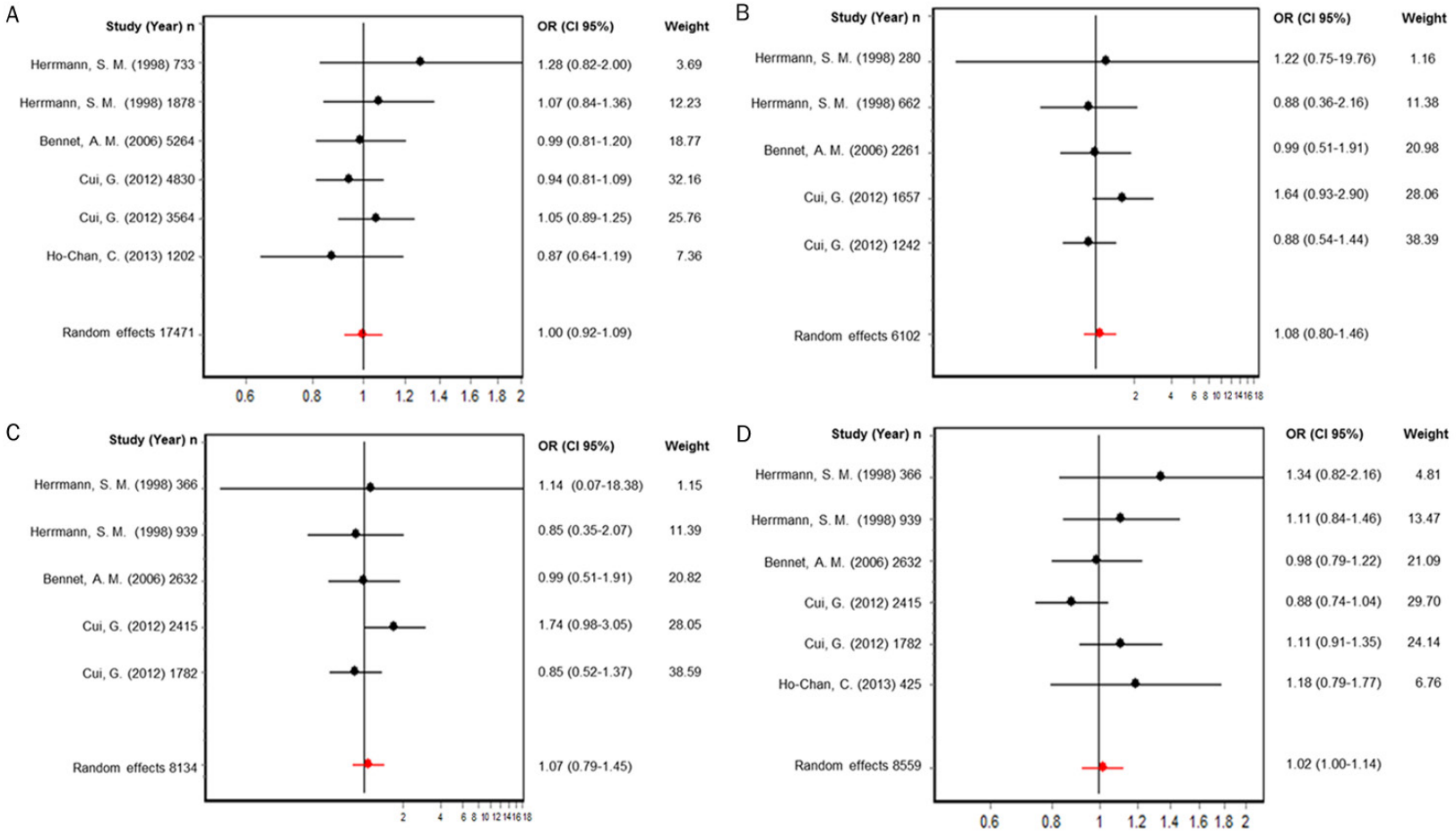

Figure 10. Odds ratios and forest plots of the TNF-α rs1799724 variant in overall studies, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

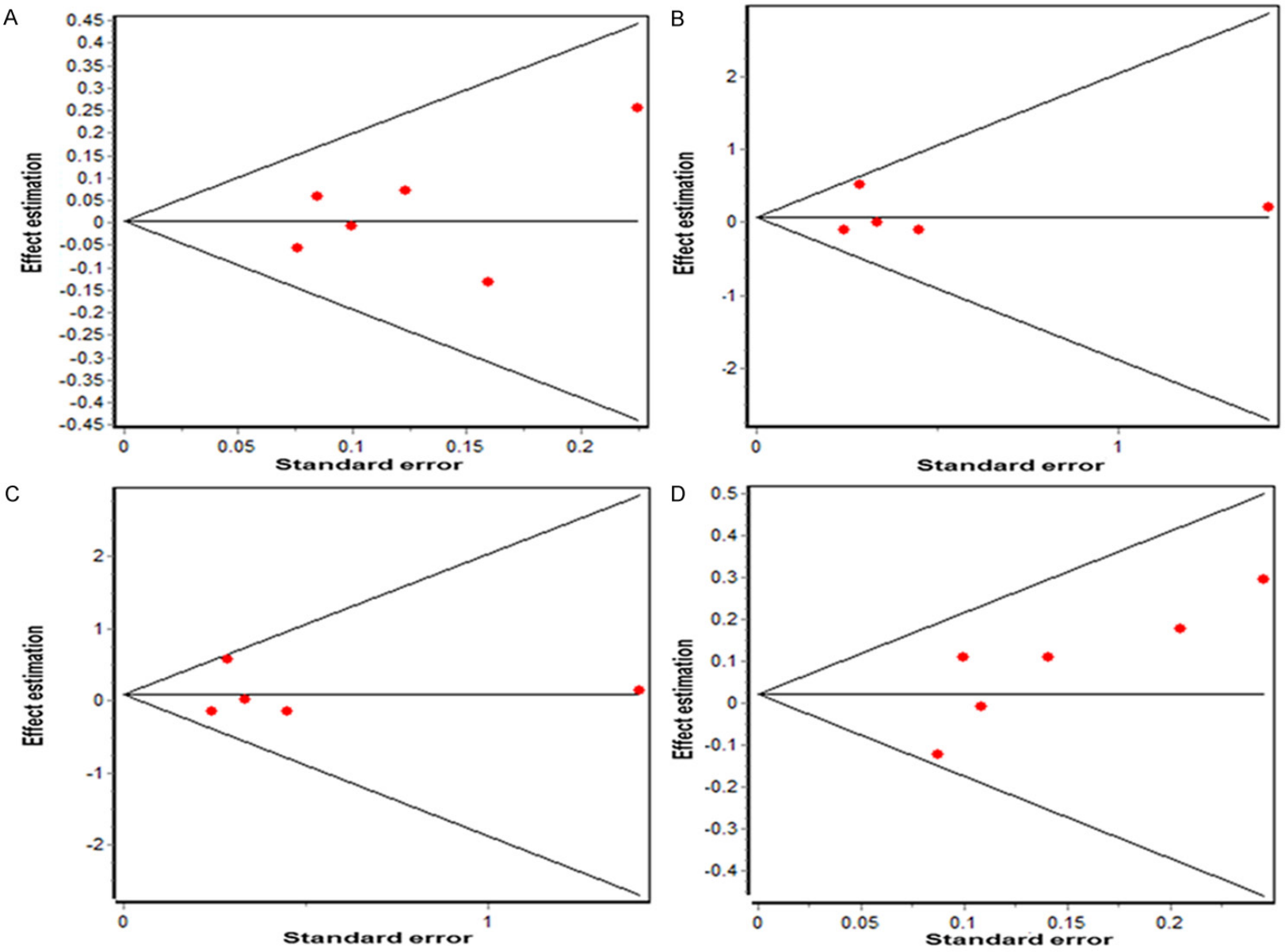

Figure 11. Egger's funnel plots in overall studies indicating publication bias in studies on CHD and TNF-α rs1799724 variant, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

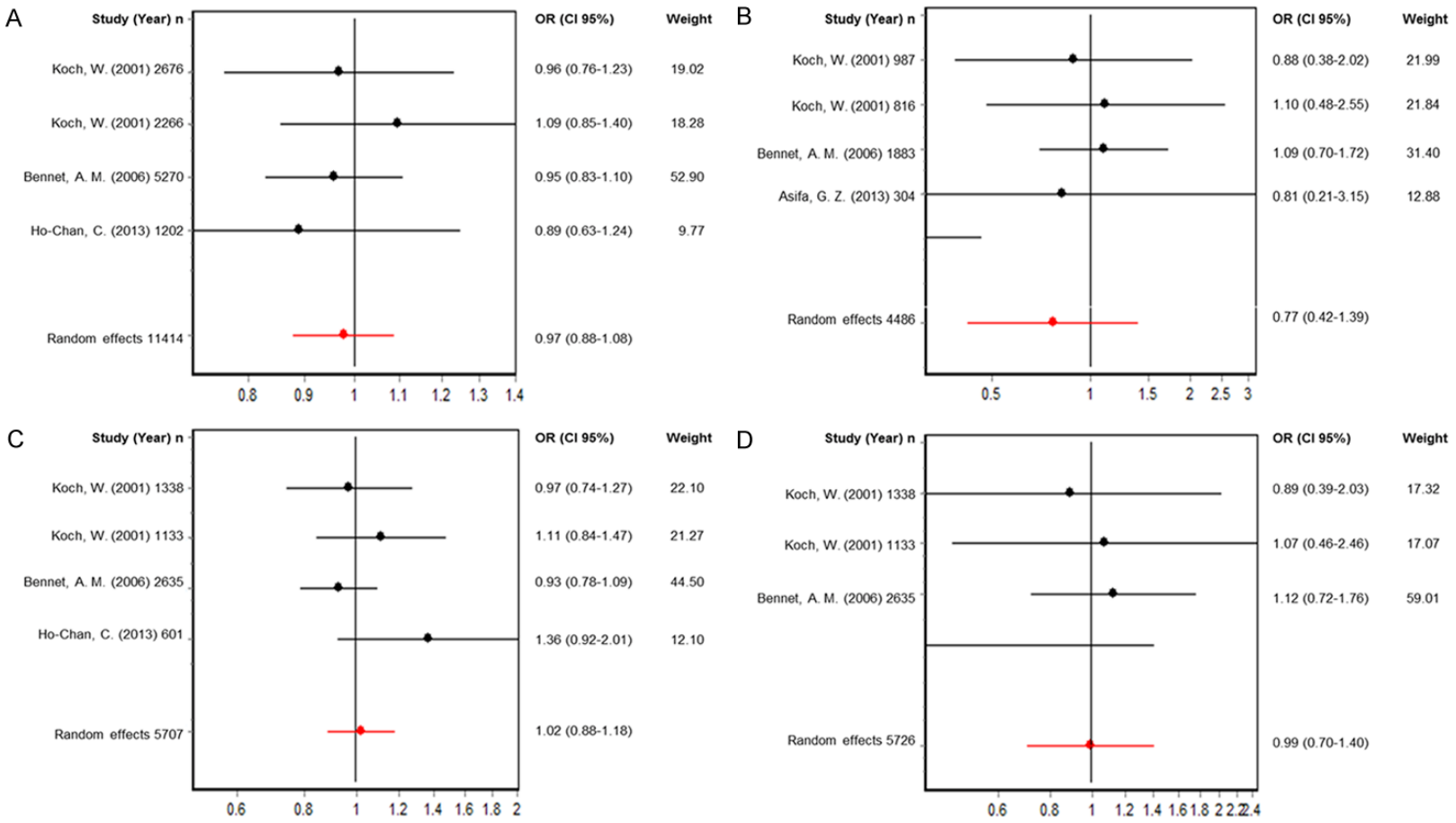

Figure 12. Odds ratios and forest plots of the TNF-α rs1800630 variant in overall studies, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

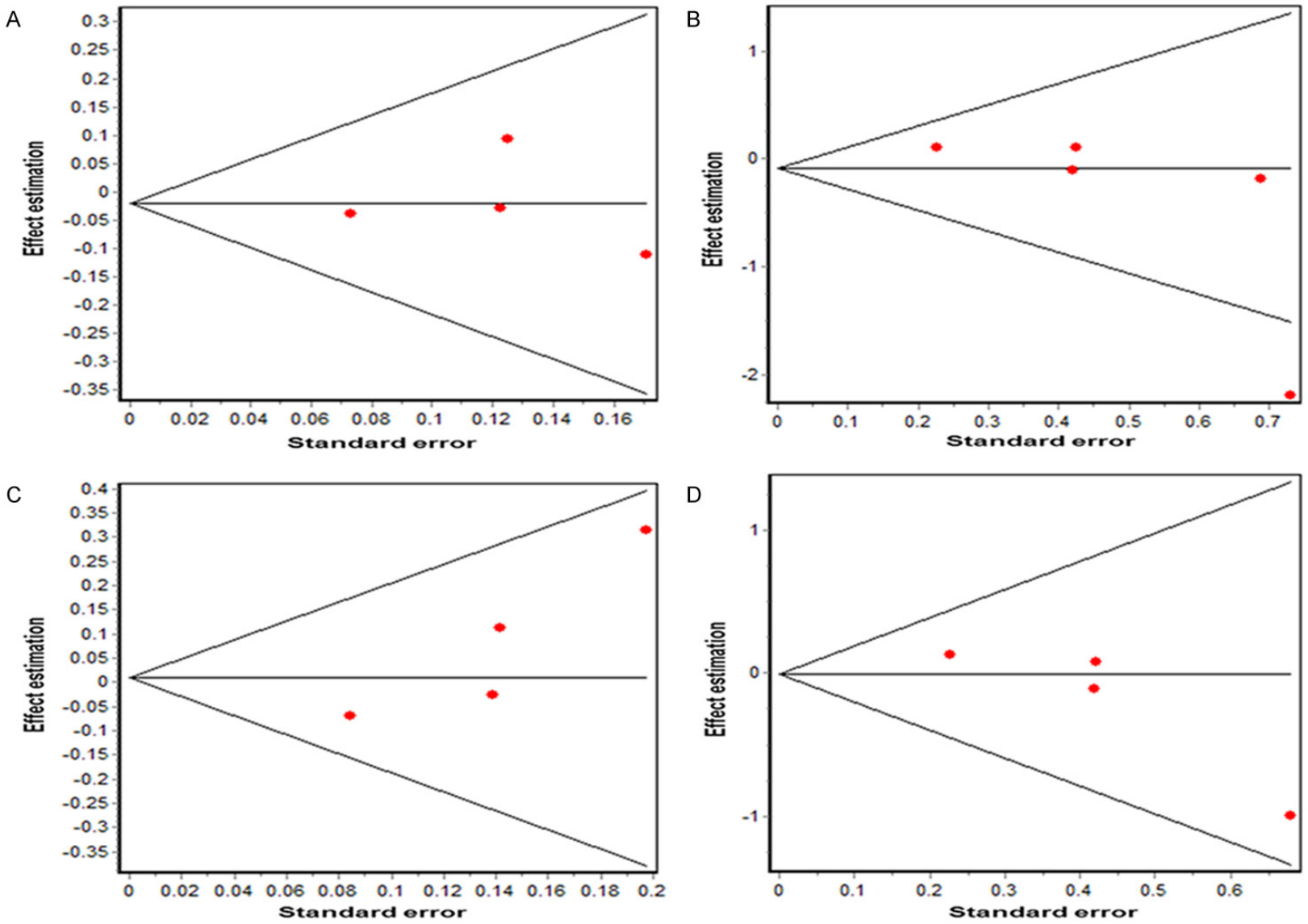

Figure 13. Egger's funnel plots in overall studies indicating publication bias in studies on CHD and TNF-α rs1800630 variant, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

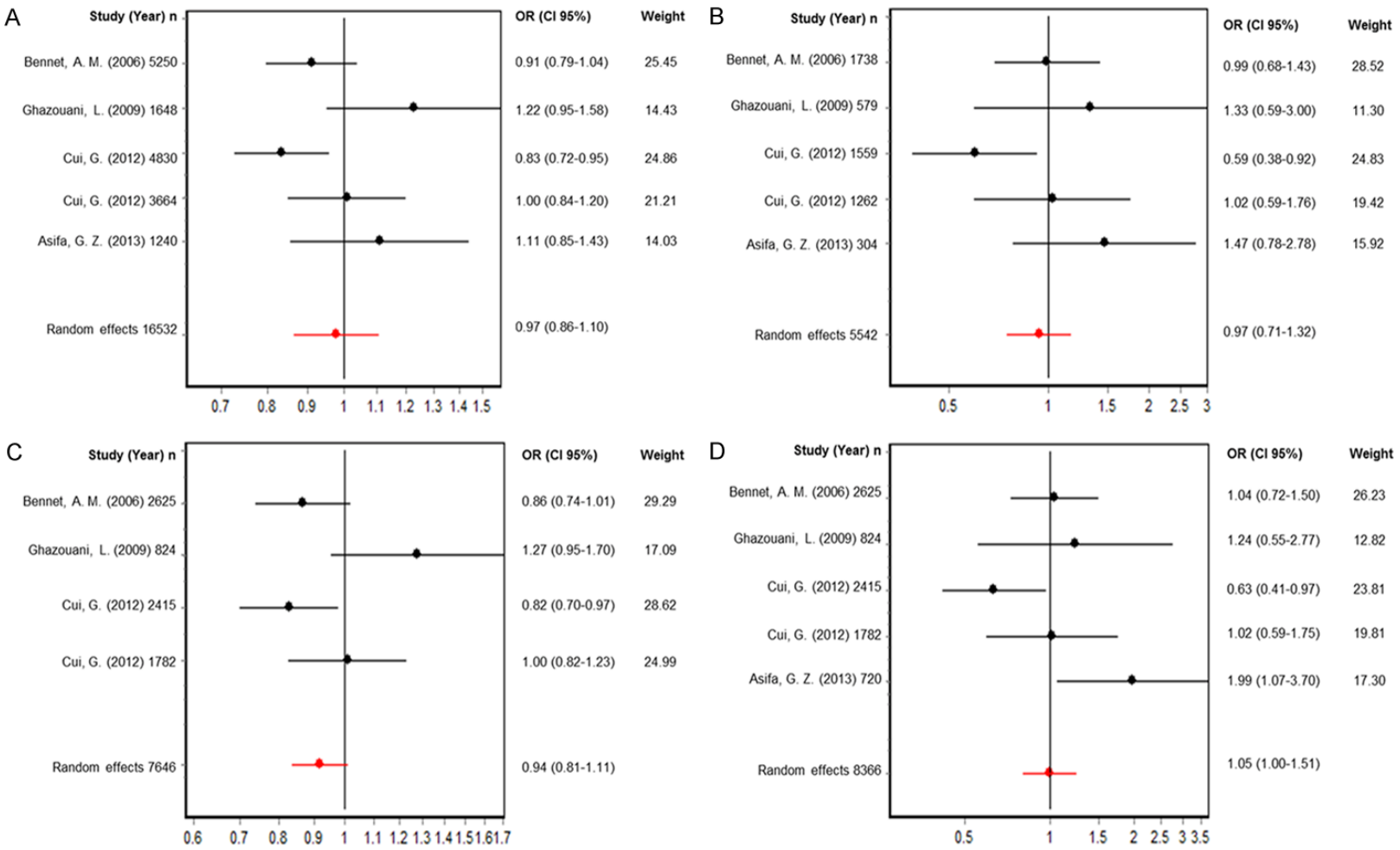

Figure 14. Odds ratios and forest plots of the TNF-α rs1799964 variant in overall studies, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

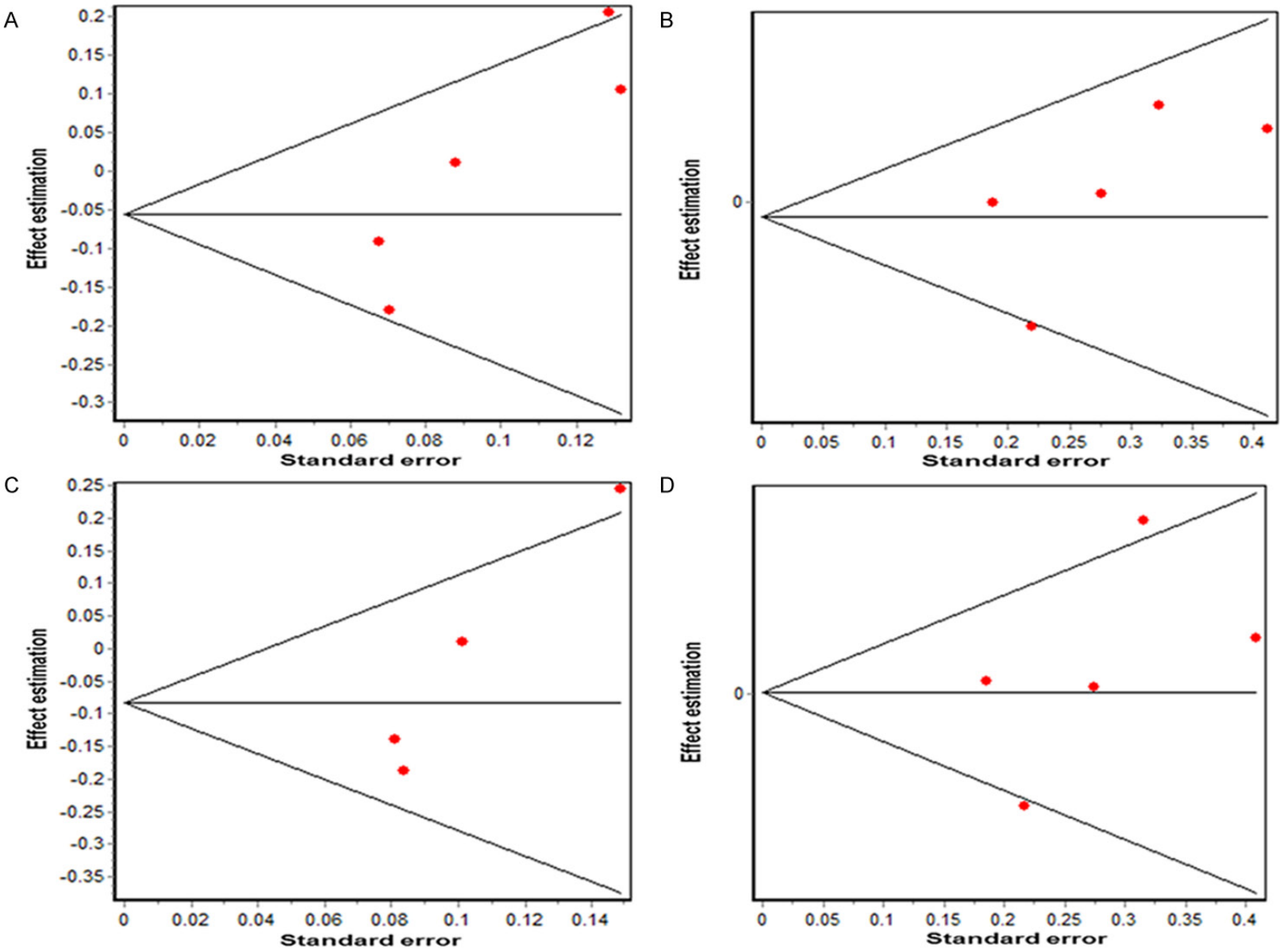

Figure 15. Egger's funnel plots in overall studies indicating publication bias in studies on CHD and TNF-α rs1799964 variant, without heterogeneity, using the following models: A. Allelic; B. Additive; C. Dominant, and D. Recessive.

find any significant association in all the analyses performed (**Table 3**); these outcomes are in agreement with other studies [9, 13]. The lack of association could be explained by the scarce number of studies, fewer than for rs1800947. Hence, it is necessary to increase the number of studies to have a definitive outcome. In the next analysis we studied the role of rs2794521 in CHD and we encountered that pooled ORs in almost all the models used in this variant showed a tendency from 13-260% to be a risk factor to present CHD (**Table 3**). Even though this variant has not been as studied as rs1800947, our data could be helpful in the search for genetic markers in this pathology. Researchers should take this information with caution because the sample size limits the outcomes obtained. Finally, the last CRP variant addressed was rs1205. Even though this polymorphism has been even less studied than the rest, the outcomes showed the same results as for the rs180097 polymorphism (**Table 3**), i.e., this variant may have a protective effect in CHD. However, we cannot take this result as conclusive -even with the agreement encountered with other studies [15]- given that when the meta-analysis was performed we could not exclude heterogeneity in all the models and this may have an effect on population variation and stratification. Moreover, we could not perform an analysis by ethnic group, since we thought useful to explore the interaction of the gene depending on the origin of the subjects.

With regard to the TNF-α gene, we selected polymorphisms C857T rs1799724, C863A rs1800630 and T1031C rs1799964 for this study. The first approach was with the rs1799724 variant where we obtained a probability range of 2-46% for this variant to be a marker of risk in CHD in the general population. But when we analyzed this role in Caucasians we only observed a 6% risk. This same tendency was seen in the analysis of rs1800630 where in the case of Caucasians we got a 5% risk to manifest CHD. Moreover, in the analysis of all populations with the random effects model, no percentage of risk was obtained. This may be so because in some association studies the genotype distribution may depend on the ethnicity of the subjects studied and probably in other populations the interaction of a hypothetical gene is necessary to manifest CHD [36, 40]. In the final variant, rs1799964, the statistical analysis yielded a slight association with CHD in the recessive model (CC+TC vs TT) (**Table 3**). Therefore, there is a remote possibility of a protective effect with allele T when using the dominant form with heterogeneity in the fixed effects model. But as was explained previously, we did not take into consideration these results given the limitations present with the fixed effects model when heterogeneity is present.

To our knowledge the present study is the first meta-analysis and systematic review with several gene variants of inflammatory markers in the analysis. We also used different models for the analyses (allelic, additive, dominant and recessive; Caucasian population only) to gain a better comprehension of CHD. On the other hand, there are some limitations in our study that must be taken into consideration. First, our findings can be ambiguous because the case-control design of the studies can be affected by population stratification, where systematic differences in the ancestry can lead to spurious findings, even though we tried to address this problem by conducting an analysis which only included Caucasians. Second, although we analyzed several TNF-α and CRP gene variants, some of the studies used a small sample size, which may not provide sufficient power to detect small effects of the gene. Alternatively, we did not conduct an analysis of all TNF-α and CRP gene variants in the Asian population or an analysis by gender, because there were not enough studies with available data. In addition, although we evaluated heterogeneity in the studies, we could not exclude it from the sample as a whole.

In conclusion the present investigation demonstrates that polymorphisms rs2794521 of CRP gene, and rs1799724, rs1800630 and rs1799964 of TNF-α gene are possible risk markers to present CHD. Conversely, the analysis of rs1800947 and rs1205 of the CRP gene could exert a protective effect on the pathogenesis of this disease. Only the analysis of polymorphism rs1130864 shows a lack association with CHD, but it is necessary to integrate more studies to obtain more robust conclusions.

Disclosure of conflict of interest

None.

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