Supplement legends

Supplementary Table 1. Assessment study quality based of the Newcastle-Ottawa scale.

Supplementary Figure. 1 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -174 G>C polymorphism determined by the heterozygous genetic model (GC v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.
The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 2 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -174 G>C polymorphism determined by the homozygous genetic model (CC v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.
The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 3 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -174 G>C polymorphism determined by the dominant genetic model (CC + GC v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond

represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.

The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 4 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -174 G>C polymorphism determined by the recessive genetic model (CC v GC + GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.

The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 5 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -174 G>C polymorphism determined by the allelic genetic model (C v G). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.

The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 6 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -572 G>C polymorphism determined by the heterozygous genetic model (GC v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95%

confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.

The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 7 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -572 G>C polymorphism determined by the homozygous genetic model (CC v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.

The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 8 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -572 G>C polymorphism determined by the dominant genetic model (CC + GC v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 9 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -572 G>C polymorphism determined by the recessive genetic model (CC v GC + GG). The association was assessed by Forest

Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 10 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -572 G>C polymorphism determined by the allelic genetic model (C v G). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 11 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -597 G>A polymorphism determined by the heterozygous genetic model (GA v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 12 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -597 G>A polymorphism determined by the homozygous genetic model (AA v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond

represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 13 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -597 G>A polymorphism determined by the dominant genetic model (AA + GA v GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 14 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -597 G>A polymorphism determined by the recessive genetic model (AA v GA + GG). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity. The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Figure. 15 The risk associated of developing Rheumatoid Arthritis (RA) with the IL-6 -572 G>A polymorphism determined by the allelic genetic model (C v G). The association was assessed by Forest Plot (A), where the squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI), respectively. The size of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI, determined using either the fixed effects or random effects, depending on the level of heterogeneity.

The sensitivity of the results was determined by removing one study and re-calculating the ORs and 95%CIs (B). Publication bias was determined by assessing the funnel plot (C). Plots were generated using Comprehensive Meta-analysis software V2.

Supplementary Table 1. Assessment study quality based on the Newcastle-Ottawa scale.

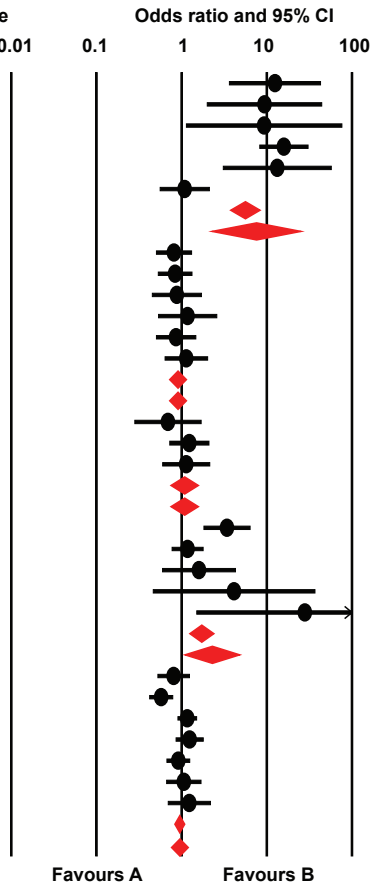
	Author (year)	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total score
1	Ad hiah 2018	★	★	★H	★	★★	★	★	☆	8
2	Amr 2016	★	★	★H	★	☆★	★	★	☆	7
3	Arman 2012	★	★	★H	★	★★	★	★	☆	8
4	Dahlqvist 2002	☆	★	★R	★	★★	★	★	☆	7
5	Dar 2016	★	☆	★M	★	★★	★	★	☆	7
6	de Souza 2014	★	★	★H	★	★★	★	★	☆	8
7	Emonts 2011	★	★	★R	★	☆★	★	★	☆	7
8	Gaber 2013	★	☆	★H	★	★★	★	★	☆	7
9	GomeSilva 2018	★	★	★H	★	★★	★	★	☆	8
10	Guseva 2016	★	★	★R	★	★★	★	★	☆	8
11	Guseva 2018	☆	★	★R	★	☆★	★	★	☆	6
12	Huang 2007	★	★	★H	★	★★	★	★	☆	8
13	Julia 2007	★	★	★R	★	★★	★	★	☆	8
14	Kobayashi 2009	★	★	★H	★	★★	★	★	☆	8
15	Li 2009 C6	★	★	★H	★	★★	★	★	☆	8
16	Li 2014a	★	★	★H	★	★★	★	★	☆	8
17	Li 2014b	★	★	★H	★	★★	★	★	☆	8
18	Liu 2013	★	★	★H	★	★★	★	★	☆	8
19	Lo 2008	★	★	★R	★	★★	★	★	☆	8
20	Lu 2009 C3	★	★	★H	★	★★	★	★	☆	8
21	Marinou 2007	★	★	☆	★	☆★	★	★	☆	6
22	Palomino Morales 2009	★	★	★R	★	★★	★	★	☆	8
23	Panoulas 2009a	★	★	★R	★	☆★	★	★	☆	7
24	Pascual 2000	★	★	★H	★	☆★	★	★	☆	7
25	Pavkova Goldbergova 2014	★	★	★R	★	★★	★	★	☆	8
26	Pawlik 2005b	★	★	★H	★	★★	★	★	☆	8
27	Raafat Hamed 2018	★	☆	★H	★	★★	★	★	☆	7
28	Schotte 2015	★	☆	★M	★	★★	★	★	☆	7
29	Shafia 2014	★	★	★M	★	★★	★	★	☆	8
30	Trajkov 2009	★	★	★R	★	☆★	★	★	☆	7
31	Wielinska 2018	★	★	★H	★	☆★	★	★	☆	7
32	You 2013	★	★	★H	★	★★	★	★	☆	8
33	Zavaleta Muniz 2013	★	★	★H	★	★★	★	★	☆	8

R Indicates Regional Hospital.
2 Indicates Multicentric Hospital-base study.
C Indicates Comunity
H Indicates Local Hospital

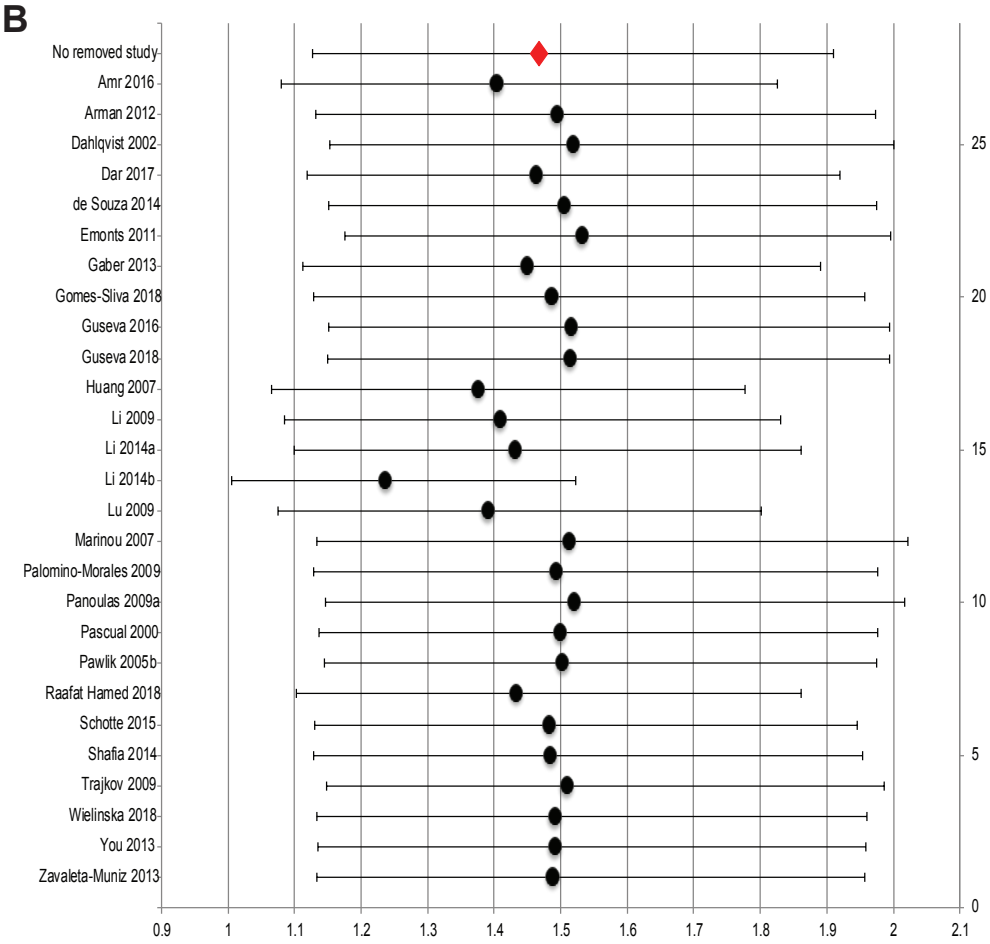
Supplementary Figure 1. Heterozygous model -174 G>C

A

Study name	Region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	12.474	3.639	42.765	4.015	0.000
Li 2009	Asian	9.396	1.998	44.187	2.836	0.005
Li 2014a	Asian	9.324	1.140	76.276	2.082	0.037
Li 2014b	Asian	15.900	8.276	30.545	8.304	0.000
Lu 2009	Asian	13.275	3.087	57.083	3.475	0.001
You 2013	Asian	1.087	0.559	2.115	0.246	0.806
Fixed		5.609	3.775	8.334	8.534	0.000
Random		7.574	2.282	25.135	3.308	0.001
Guseva 2016	E. Eur	0.813	0.505	1.310	-0.850	0.395
Guseva 2018	E. Eur	0.840	0.532	1.324	-0.752	0.452
Pawlik 2005b	E. Eur	0.879	0.453	1.706	-0.382	0.702
Schotte 2015	E. Eur	1.176	0.535	2.587	0.404	0.686
Trajkov 2009	E. Eur	0.861	0.505	1.469	-0.548	0.583
Wielinska 2018	E. Eur	1.134	0.638	2.017	0.429	0.668
Fixed		0.906	0.723	1.136	-0.853	0.393
Random		0.906	0.723	1.136	-0.853	0.393
de Souza 2014	Latin	0.690	0.281	1.694	-0.809	0.419
Gomes-Silva 2018	Latin	1.231	0.728	2.082	0.776	0.438
Zavaleta-Muniz 2013	Latin	1.132	0.599	2.138	0.382	0.702
Fixed		1.085	0.750	1.570	0.434	0.664
Random		1.085	0.750	1.570	0.434	0.664
Amr 2016	M. East	3.409	1.827	6.361	3.854	0.000
Arman 2012	M. East	1.175	0.771	1.789	0.750	0.453
Dar 2017	M. East	1.600	0.597	4.289	0.934	0.350
Gaber 2013	M. East	4.125	0.464	36.702	1.271	0.204
Raafat Hamed 2018	M. East	27.968	1.507	519.174	2.235	0.025
Fixed		1.727	1.250	2.386	3.315	0.001
Random		2.295	1.095	4.810	2.201	0.028
Dahlqvist 2002	W. Eur	0.807	0.526	1.237	-0.985	0.325
Emonts 2011	W. Eur	0.576	0.421	0.788	-3.454	0.001
Marinou 2007	W. Eur	1.165	0.905	1.499	1.185	0.236
Palomino-Morales 2009	W. Eur	1.242	0.860	1.794	1.158	0.247
Panoulas 2009a	W. Eur	0.914	0.672	1.243	-0.570	0.568
Pascual 2000	W. Eur	1.062	0.668	1.689	0.253	0.800
Shafia 2014	W. Eur	1.232	0.697	2.178	0.717	0.473
Fixed		0.952	0.834	1.086	-0.732	0.464
Random		0.955	0.762	1.197	-0.400	0.689



B



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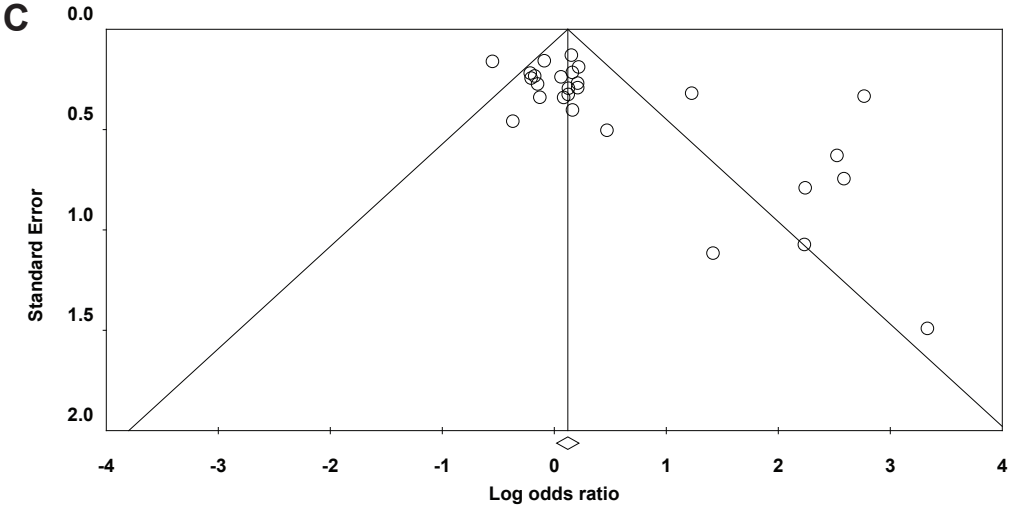
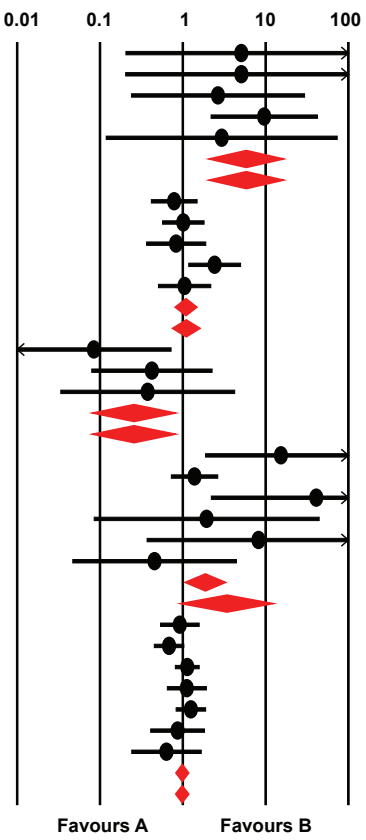


Supplementary Figure 2. Homozygous model -174 G>C

A

Study name	Region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	5.092	0.205	126.230	0.994	0.320
Li 2009	Asian	5.103	0.204	127.746	0.992	0.321
Li 2014a	Asian	2.664	0.240	29.546	0.798	0.425
Li 2014b	Asian	9.617	2.191	42.211	2.999	0.003
Lu 2009	Asian	2.950	0.119	73.150	0.660	0.509
Fixed		5.839	2.059	16.560	3.318	0.001
Random		5.839	2.059	16.560	3.318	0.001
Guseva 2016	E. Eur	0.787	0.417	1.487	-0.738	0.460
Guseva 2018	E. Eur	1.014	0.569	1.808	0.048	0.961
Pawlik 2005b	E. Eur	0.830	0.364	1.892	-0.442	0.658
Trajkov 2009	E. Eur	2.425	1.178	4.993	2.404	0.016
Wielinska 2018	E. Eur	1.051	0.508	2.174	0.135	0.893
Fixed		1.094	0.807	1.485	0.580	0.562
Random		1.102	0.751	1.618	0.498	0.619
de Souza 2014	Latin	0.085	0.010	0.722	-2.257	0.024
Gomes-Silva 2018	Latin	0.424	0.079	2.257	-1.007	0.314
Zavaleta-Muniz 2013	Latin	0.377	0.034	4.235	-0.790	0.430
Fixed		0.258	0.081	0.821	-2.294	0.022
Random		0.258	0.081	0.821	-2.294	0.022
Amr 2016	M. East	15.341	1.880	125.181	2.549	0.011
Arman 2012	M. East	1.384	0.726	2.640	0.986	0.324
Dar 2017	M. East	40.902	2.208	757.664	2.492	0.013
Gaber 2013	M. East	1.939	0.085	44.233	0.415	0.678
Raafat Hamed 2018	M. East	8.226	0.370	182.831	1.332	0.183
Shafia 2014	M. East	0.456	0.047	4.439	-0.676	0.499
Fixed		1.872	1.065	3.291	2.178	0.029
Random		3.417	0.940	12.423	1.866	0.062
Dahlqvist 2002	W. Eur	0.922	0.538	1.579	-0.297	0.767
Emonts 2011	W. Eur	0.683	0.453	1.029	-1.823	0.068
Marinou 2007	W. Eur	1.133	0.814	1.578	0.740	0.460
Palomino-Morales 2009	W. Eur	1.119	0.649	1.928	0.404	0.686
Panoulas 2009a	W. Eur	1.253	0.831	1.889	1.076	0.282
Pascual 2000	W. Eur	0.865	0.410	1.825	-0.380	0.704
Schotte 2015	W. Eur	0.635	0.242	1.670	-0.920	0.358
Fixed		0.986	0.823	1.181	-0.156	0.876
Random		0.984	0.817	1.184	-0.174	0.862



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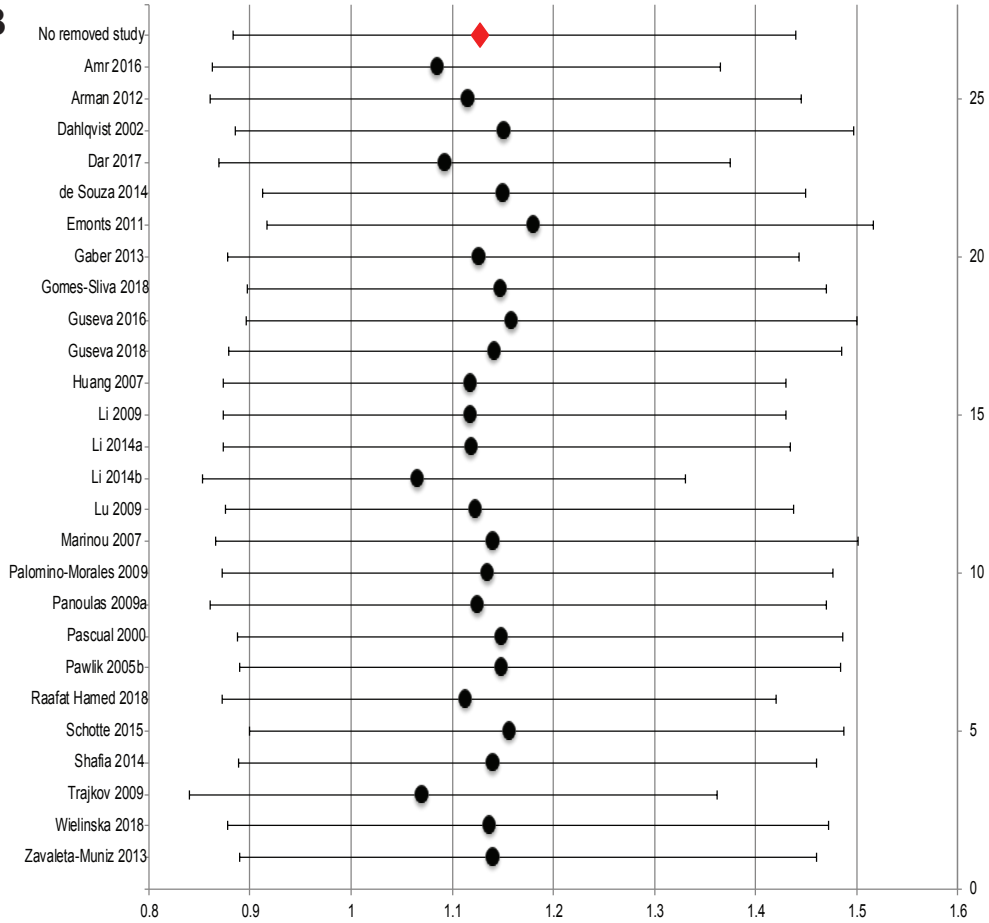

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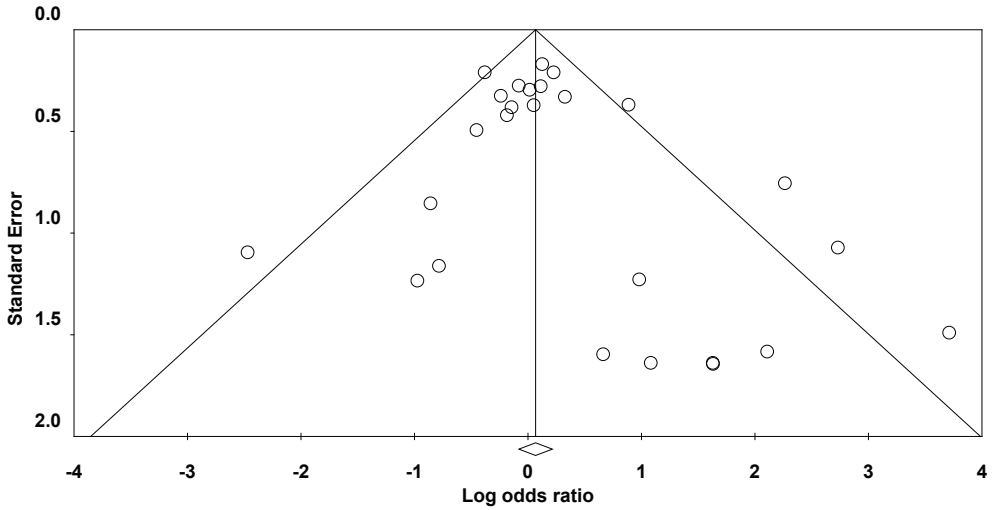
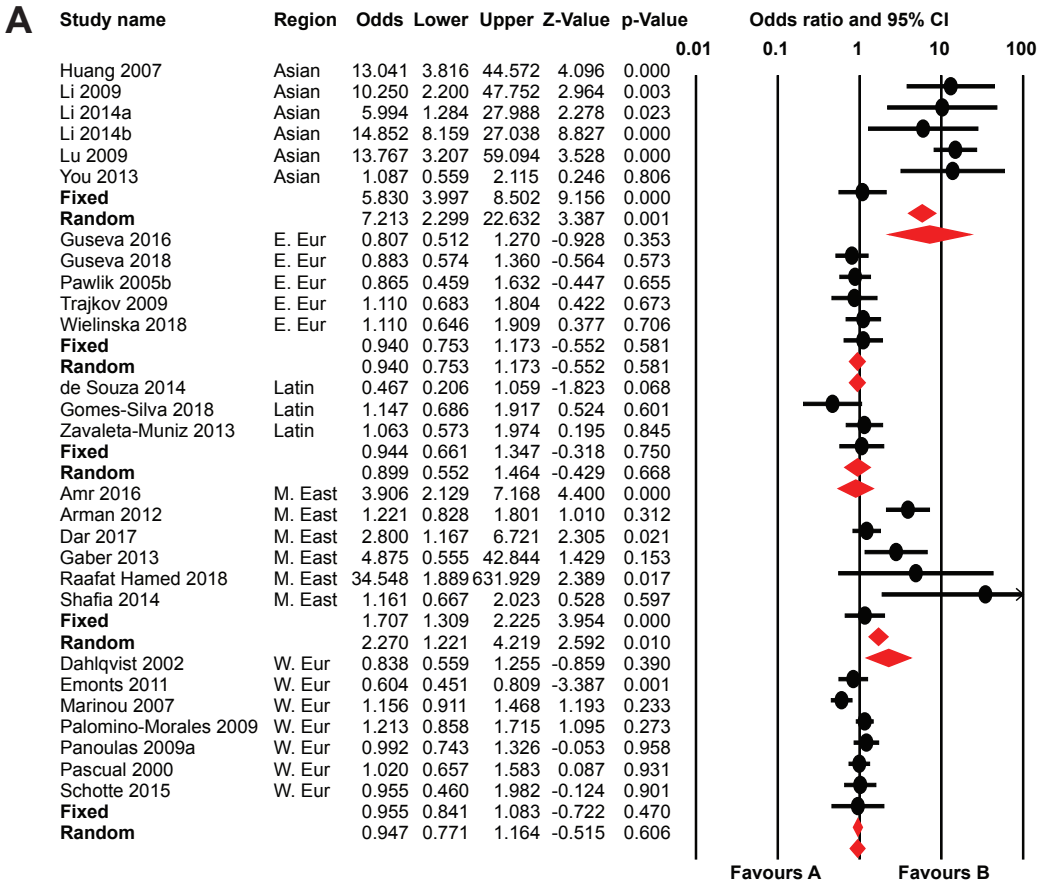
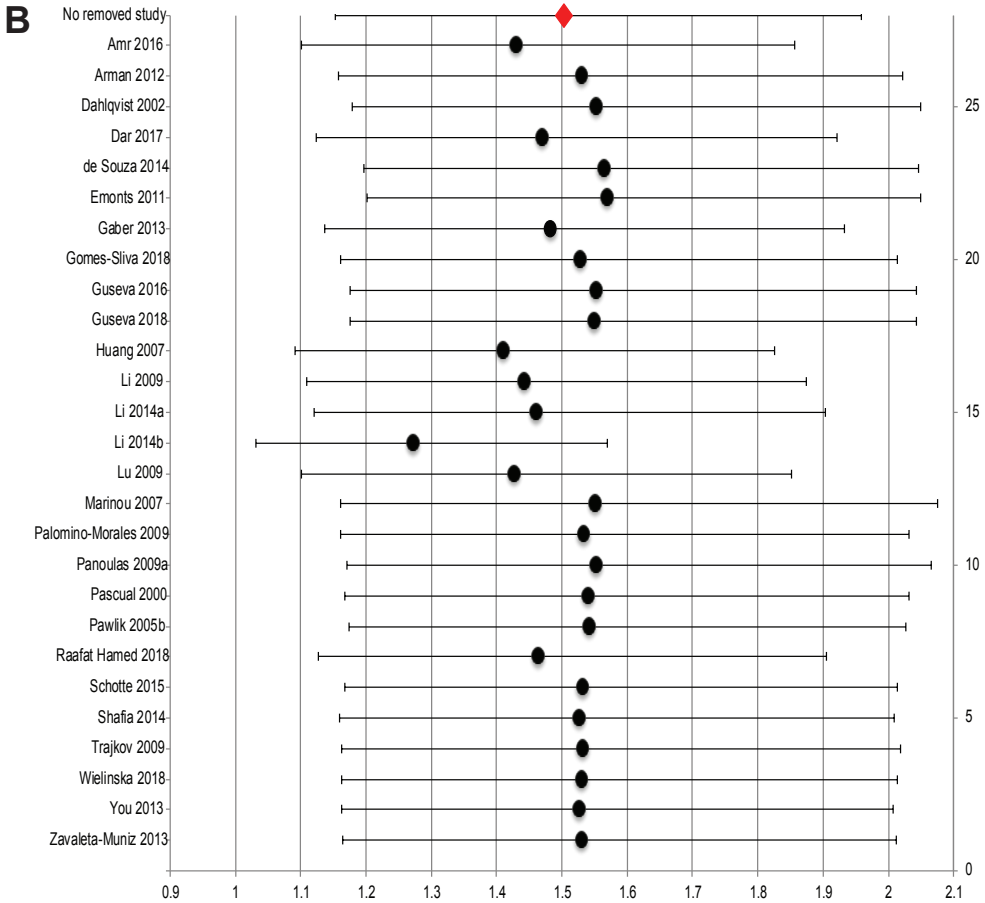
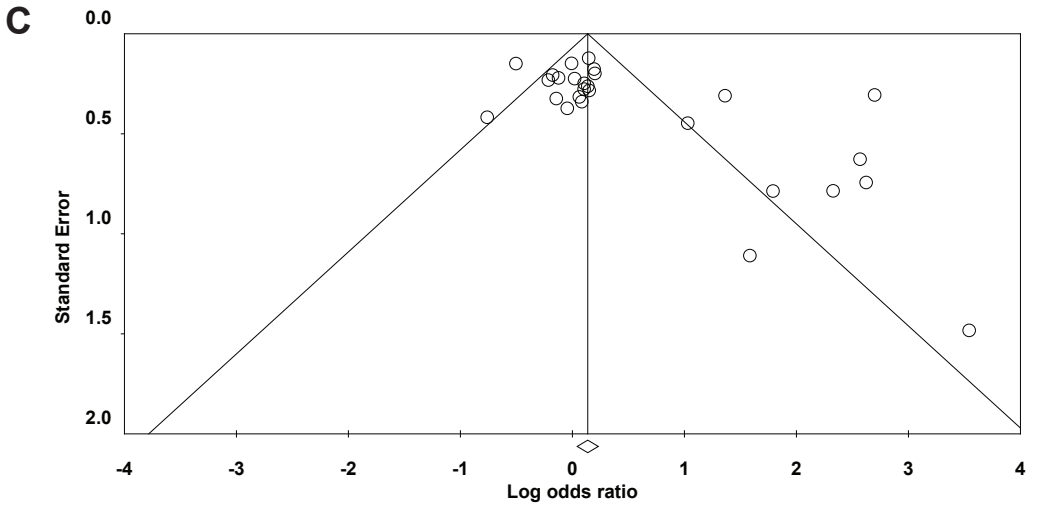


Supplementary Figure 3. Dominant model -174 G>C



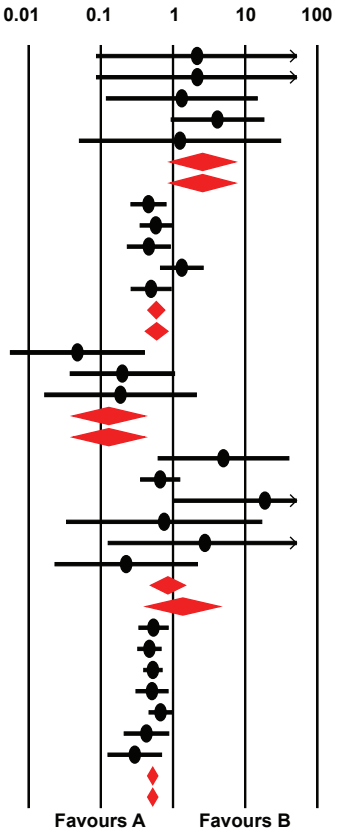




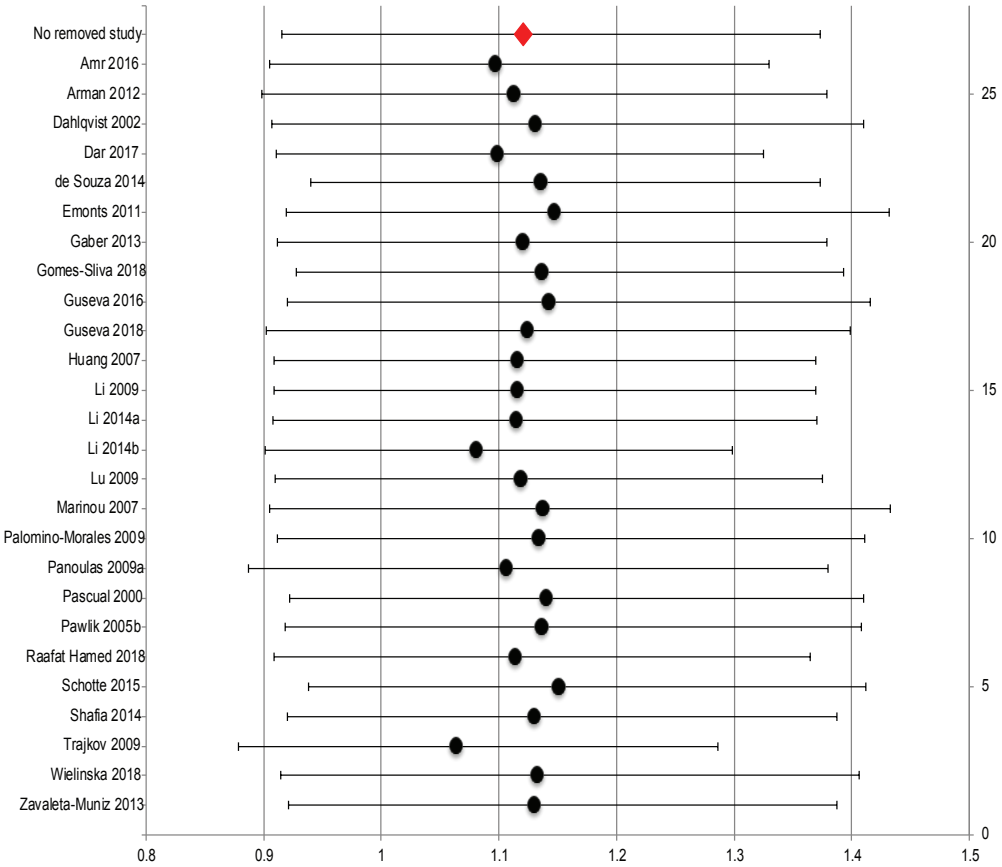
Supplementary Figure 4. Recessive model -174 G>C

A

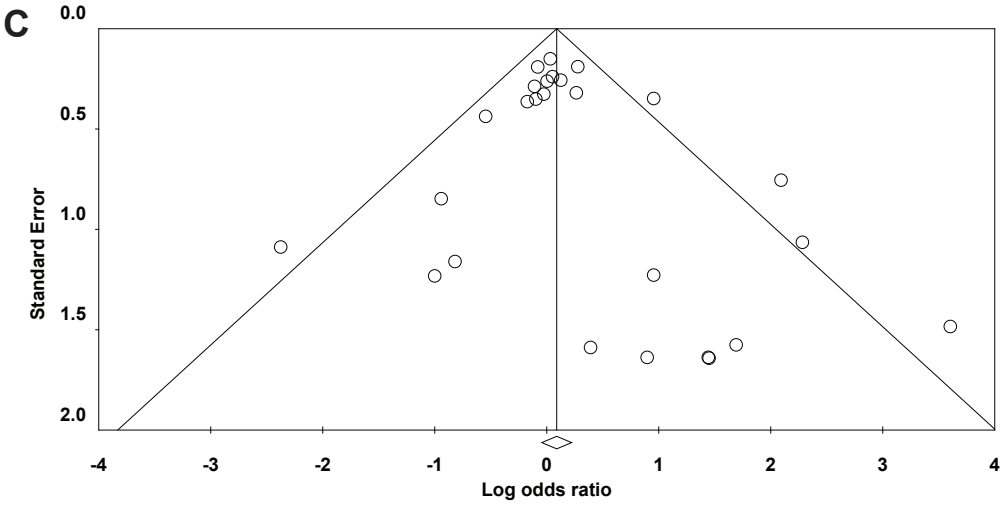
Study name	Region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	4.230	0.171	104.733	0.881	0.378
Li 2009	Asian	4.261	0.171	106.393	0.883	0.377
Li 2014a	Asian	2.598	0.234	28.816	0.778	0.437
Li 2014b	Asian	8.100	1.846	35.542	2.773	0.006
Lu 2009	Asian	2.451	0.099	60.708	0.547	0.584
Fixed		5.036	1.776	14.279	3.040	0.002
Random		5.036	1.776	14.279	3.040	0.002
Guseva 2016	E. Eur	0.897	0.511	1.574	-0.379	0.705
Guseva 2018	E. Eur	1.134	0.686	1.873	0.490	0.624
Pawlik 2005b	E. Eur	0.907	0.457	1.803	-0.277	0.781
Trajkov 2009	E. Eur	2.598	1.314	5.134	2.746	0.006
Wielinska 2018	E. Eur	0.974	0.514	1.844	-0.081	0.936
Fixed		1.150	0.879	1.505	1.022	0.307
Random		1.164	0.813	1.666	0.830	0.406
de Souza 2014	Latin	0.093	0.011	0.784	-2.184	0.029
Gomes-Silva 2018	Latin	0.390	0.074	2.050	-1.112	0.266
Zavaleta-Muniz 2013	Latin	0.368	0.033	4.111	-0.812	0.417
Fixed		0.253	0.080	0.801	-2.338	0.019
Random		0.253	0.080	0.801	-2.338	0.019
Amr 2016	M. East	9.800	1.217	78.893	2.145	0.032
Arman 2012	M. East	1.303	0.697	2.436	0.828	0.408
Dar 2017	M. East	36.719	2.004	672.697	2.429	0.015
Gaber 2013	M. East	1.479	0.066	33.272	0.246	0.805
Raafat Hamed 2018	M. East	5.426	0.247	118.958	1.073	0.283
Shafia 2014	M. East	0.441	0.045	4.279	-0.706	0.480
Fixed		1.666	0.961	2.887	1.817	0.069
Random		2.685	0.832	8.658	1.653	0.098
Dahlqvist 2002	W. Eur	1.053	0.659	1.681	0.215	0.830
Emonts 2011	W. Eur	0.923	0.635	1.340	-0.422	0.673
Marinou 2007	W. Eur	1.032	0.769	1.384	0.211	0.833
Palomino-Morales 2009	W. Eur	1.003	0.601	1.673	0.010	0.992
Panoulas 2009a	W. Eur	1.319	0.911	1.911	1.465	0.143
Pascual 2000	W. Eur	0.841	0.412	1.713	-0.478	0.633
Schotte 2015	W. Eur	0.580	0.246	1.364	-1.249	0.211
Fixed		1.026	0.872	1.207	0.307	0.759
Random		1.026	0.872	1.207	0.307	0.759



B



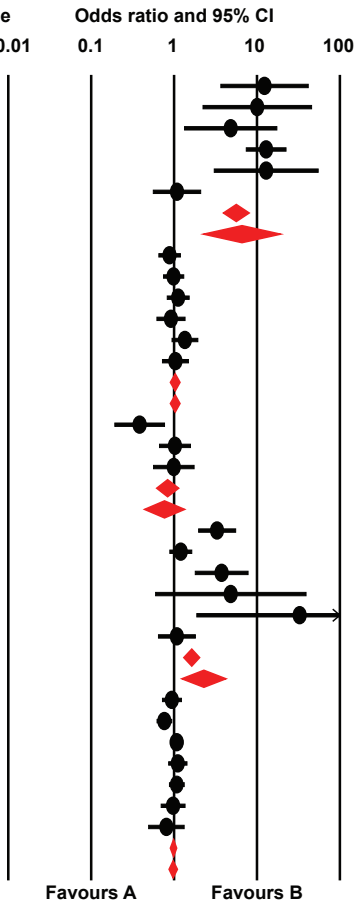
C



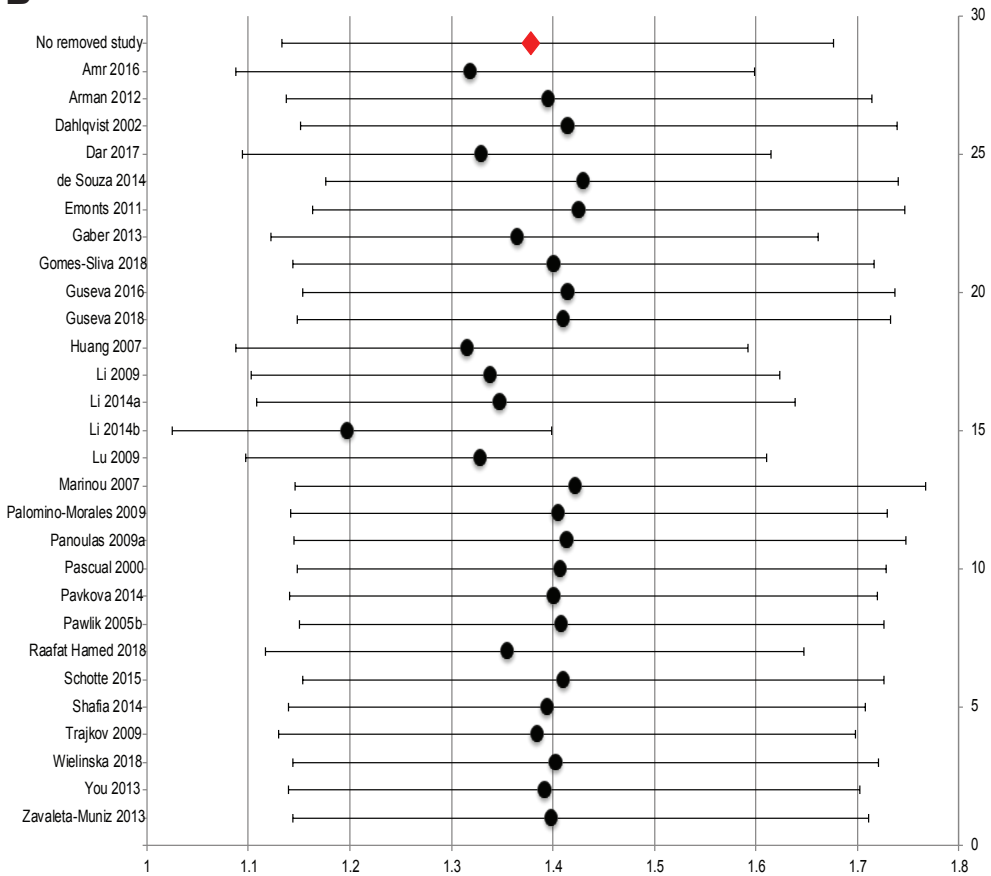
Supplementary Figure 5. Allelic model -174 G>C

A

Study name	Region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	12.333	3.669	41.458	4.061	0.000
Li 2009	Asian	10.084	2.231	45.575	3.003	0.003
Li 2014a	Asian	4.823	1.338	17.379	2.406	0.016
Li 2014b	Asian	12.890	7.423	22.385	9.079	0.000
Lu 2009	Asian	12.925	3.052	54.745	3.475	0.001
You 2013	Asian	1.085	0.562	2.095	0.243	0.808
Fixed		5.636	3.940	8.062	9.467	0.000
Random		6.604	2.263	19.276	3.454	0.001
Guseva 2016	E. Eur	0.883	0.654	1.193	-0.809	0.419
Guseva 2018	E. Eur	0.987	0.745	1.307	-0.093	0.926
Pavkova 2014	E. Eur	1.120	0.825	1.521	0.729	0.466
Pawlik 2005b	E. Eur	0.918	0.621	1.355	-0.432	0.666
Trajkov 2009	E. Eur	1.350	0.943	1.932	1.640	0.101
Wielinska 2018	E. Eur	1.038	0.724	1.489	0.205	0.838
Fixed		1.031	0.903	1.178	0.453	0.650
Random		1.031	0.903	1.178	0.453	0.650
de Souza 2014	Latin	0.385	0.193	0.767	-2.712	0.007
Gomes-Silva 2018	Latin	1.024	0.666	1.575	0.110	0.913
Zavaleta-Muniz 2013	Latin	0.992	0.565	1.742	-0.029	0.977
Fixed		0.837	0.616	1.137	-1.140	0.254
Random		0.768	0.440	1.341	-0.929	0.353
Amr 2016	M. East	3.305	1.976	5.528	4.555	0.000
Arman 2012	M. East	1.205	0.888	1.635	1.200	0.230
Dar 2017	M. East	3.750	1.800	7.813	3.529	0.000
Gaber 2013	M. East	4.831	0.598	39.024	1.478	0.140
Raafat Hamed 2018	M. East	32.792	1.882	571.250	2.394	0.017
Shafia 2014	M. East	1.082	0.647	1.809	0.301	0.764
Fixed		1.633	1.310	2.037	4.355	0.000
Random		2.292	1.242	4.231	2.653	0.008
Dahlqvist 2002	W. Eur	0.942	0.723	1.227	-0.444	0.657
Emonts 2011	W. Eur	0.763	0.622	0.936	-2.590	0.010
Marinou 2007	W. Eur	1.077	0.918	1.263	0.905	0.365
Palomino-Morales 2009	W. Eur	1.111	0.861	1.433	0.809	0.419
Panoulas 2009a	W. Eur	1.079	0.885	1.317	0.753	0.452
Pascual 2000	W. Eur	0.974	0.699	1.357	-0.158	0.875
Schotte 2015	W. Eur	0.808	0.494	1.323	-0.847	0.397
Fixed		0.985	0.903	1.075	-0.342	0.732
Random		0.977	0.870	1.097	-0.400	0.689



B



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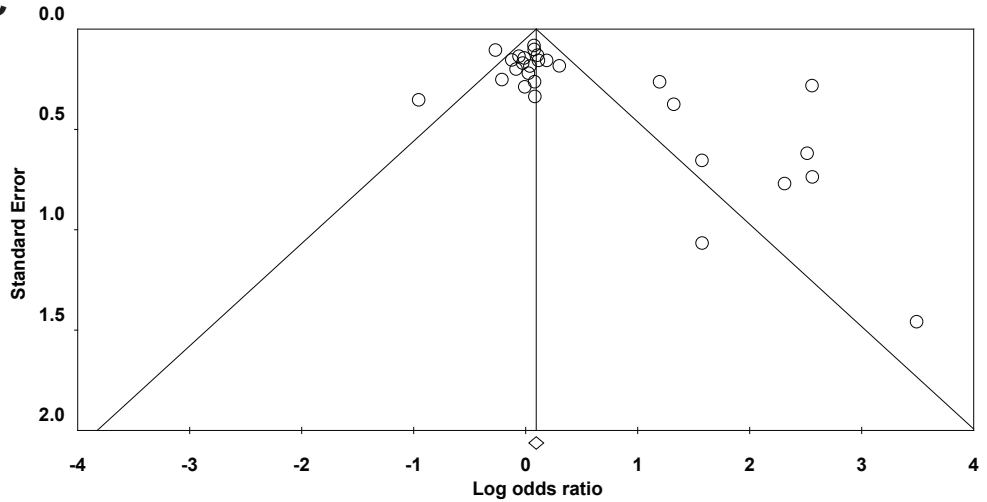
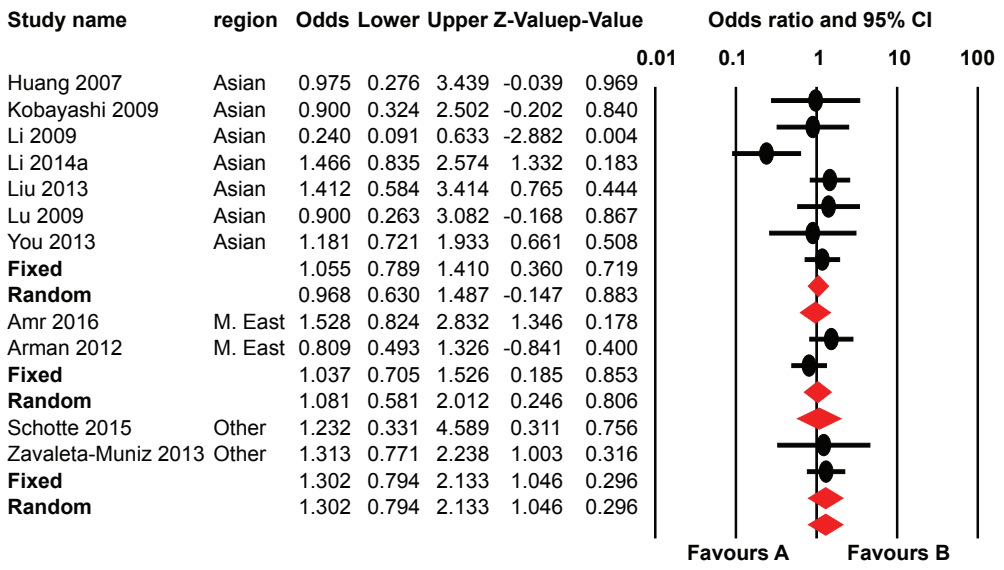
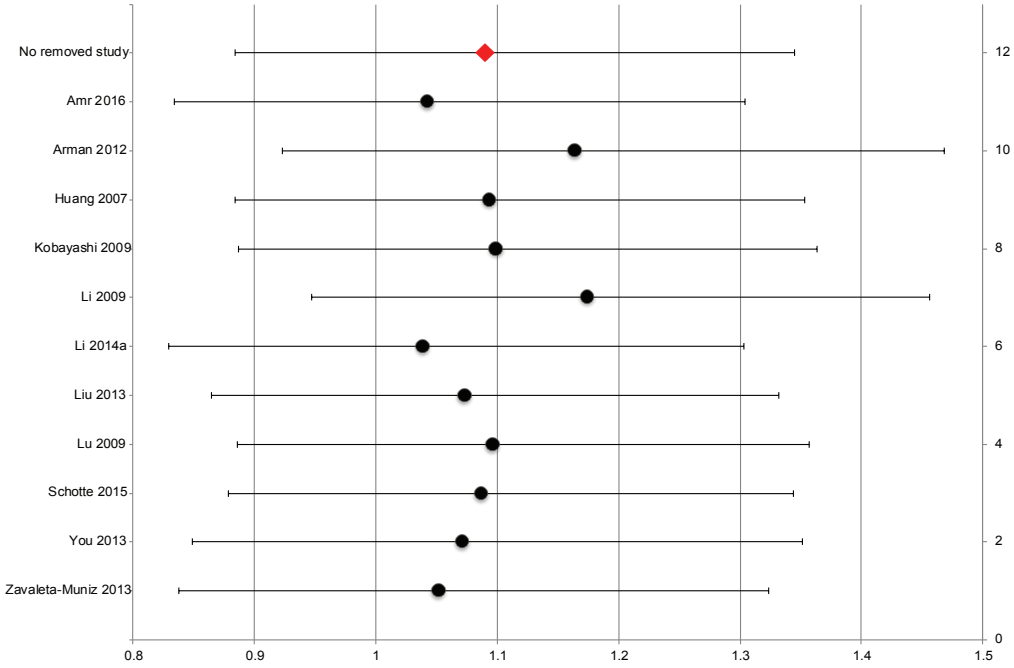


Supplementary Figure 6. Heterozygous model -572 G>C

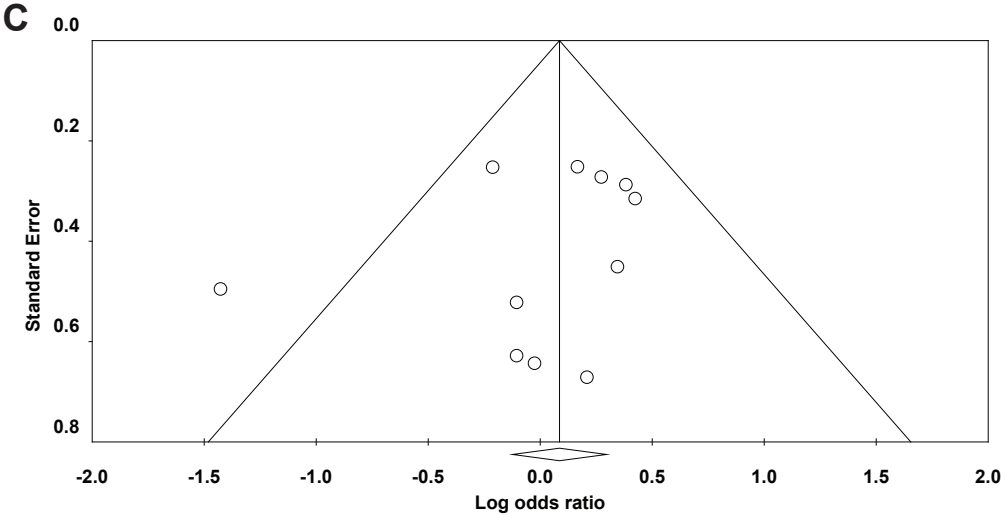
A



Study name	region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	0.975	0.276	3.439	-0.039	0.969
Kobayashi 2009	Asian	0.900	0.324	2.502	-0.202	0.840
Li 2009	Asian	0.240	0.091	0.633	-2.882	0.004
Li 2014a	Asian	1.466	0.835	2.574	1.332	0.183
Liu 2013	Asian	1.412	0.584	3.414	0.765	0.444
Lu 2009	Asian	0.900	0.263	3.082	-0.168	0.867
You 2013	Asian	1.181	0.721	1.933	0.661	0.508
Fixed		1.055	0.789	1.410	0.360	0.719
Random		0.968	0.630	1.487	-0.147	0.883
Amr 2016	M. East	1.528	0.824	2.832	1.346	0.178
Arman 2012	M. East	0.809	0.493	1.326	-0.841	0.400
Fixed		1.037	0.705	1.526	0.185	0.853
Random		1.081	0.581	2.012	0.246	0.806
Schotte 2015	Other	1.232	0.331	4.589	0.311	0.756
Zavaleta-Muniz 2013	Other	1.313	0.771	2.238	1.003	0.316
Fixed		1.302	0.794	2.133	1.046	0.296
Random		1.302	0.794	2.133	1.046	0.296



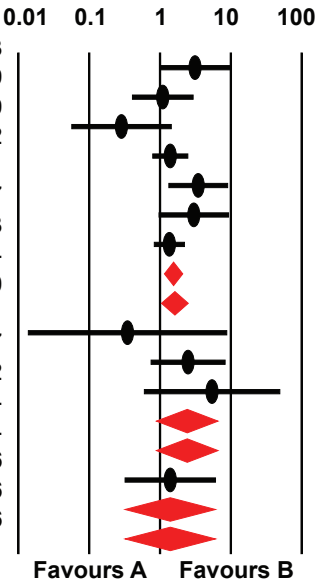
C



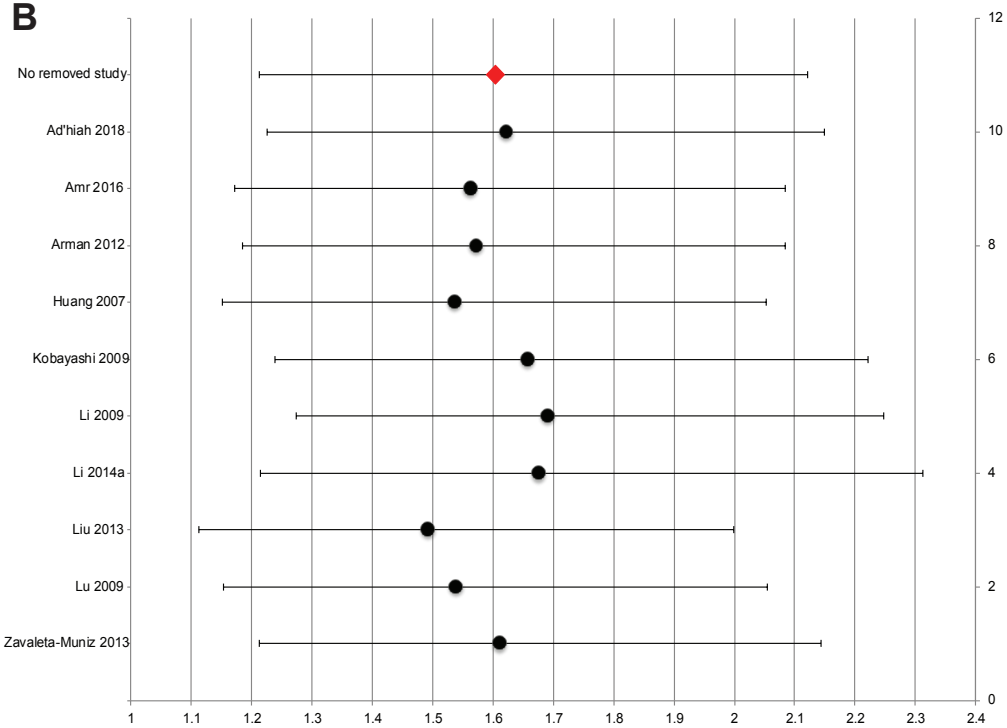
Supplementary Figure 7. Homozygous model -572 G>C

A

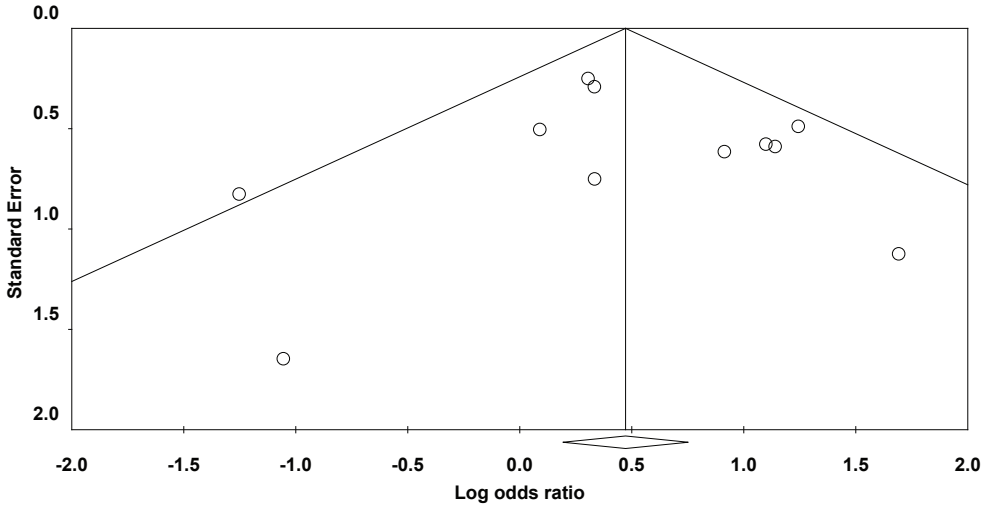
Study name	Region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	3.126	0.986	9.907	1.937	0.053
Kobayashi 2009	Asian	1.093	0.407	2.935	0.177	0.859
Li 2009	Asian	0.286	0.057	1.441	-1.518	0.129
Li 2014a	Asian	1.395	0.789	2.465	1.146	0.252
Liu 2013	Asian	3.467	1.332	9.022	2.548	0.011
Lu 2009	Asian	3.000	0.969	9.288	1.905	0.057
You 2013	Asian	1.356	0.831	2.213	1.220	0.223
Fixed		1.555	1.155	2.094	2.909	0.004
Random		1.621	1.047	2.509	2.166	0.030
Ad'hiah 2018	M. East	0.348	0.014	8.765	-0.641	0.521
Amr 2016	M. East	2.492	0.748	8.308	1.487	0.137
Arman 2012	M. East	5.427	0.600	49.069	1.505	0.132
Fixed		2.421	0.887	6.608	1.726	0.084
Random		2.421	0.887	6.608	1.726	0.084
Zavaleta-Muniz 2013	Other	1.396	0.321	6.077	0.445	0.656
Fixed		1.396	0.321	6.077	0.445	0.656
Random		1.396	0.321	6.077	0.445	0.656



B



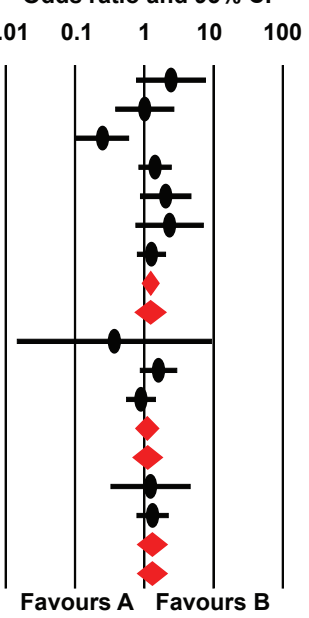
C



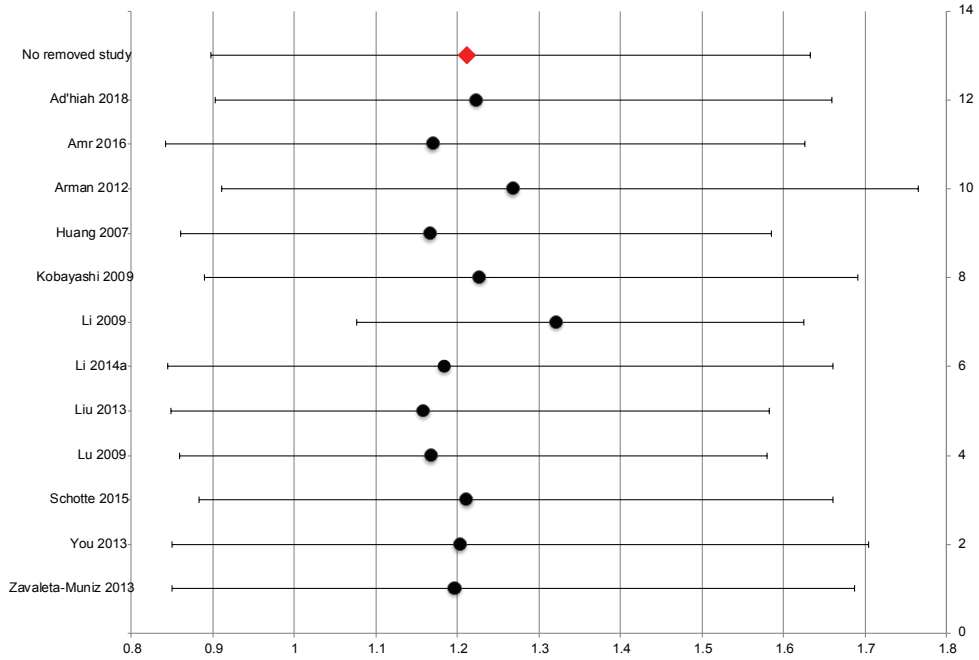
Supplementary Figure 8. Dominant model -572 G>C

A

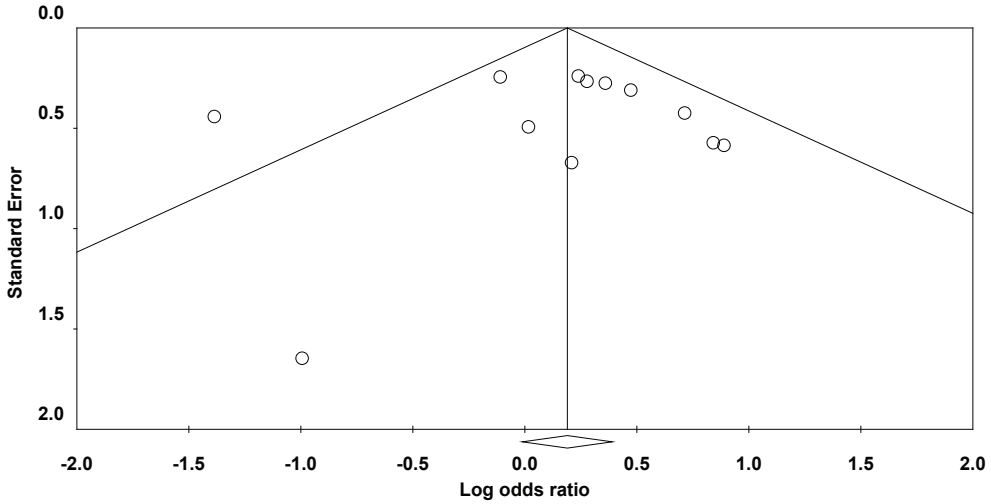
Study name	region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	2.432	0.773	7.652	1.520	0.129
Kobayashi 2009	Asian	1.016	0.387	2.669	0.032	0.974
Li 2009	Asian	0.250	0.105	0.594	-3.142	0.002
Li 2014a	Asian	1.432	0.836	2.455	1.306	0.191
Liu 2013	Asian	2.041	0.889	4.683	1.683	0.092
Lu 2009	Asian	2.319	0.756	7.114	1.471	0.141
You 2013	Asian	1.269	0.794	2.029	0.995	0.320
Fixed		1.238	0.942	1.627	1.532	0.125
Random		1.234	0.744	2.045	0.814	0.416
Ad'hiah 2018	M. East	0.370	0.015	9.311	-0.604	0.546
Amr 2016	M. East	1.604	0.875	2.943	1.527	0.127
Arman 2012	M. East	0.896	0.555	1.446	-0.450	0.652
Fixed		1.104	0.760	1.603	0.518	0.604
Random		1.121	0.695	1.810	0.469	0.639
Schotte 2015	Other	1.232	0.331	4.589	0.311	0.756
Zavaleta-Muniz 2013	Other	1.320	0.784	2.221	1.044	0.296
Fixed		1.307	0.806	2.121	1.085	0.278
Random		1.307	0.806	2.121	1.085	0.278



B



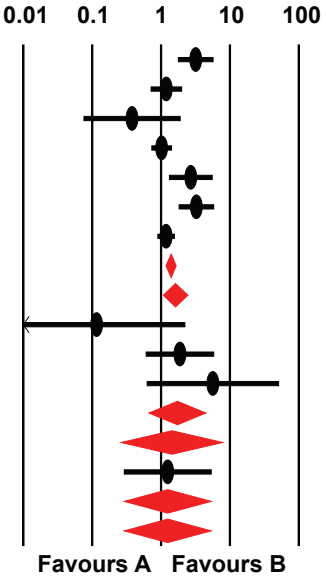
C



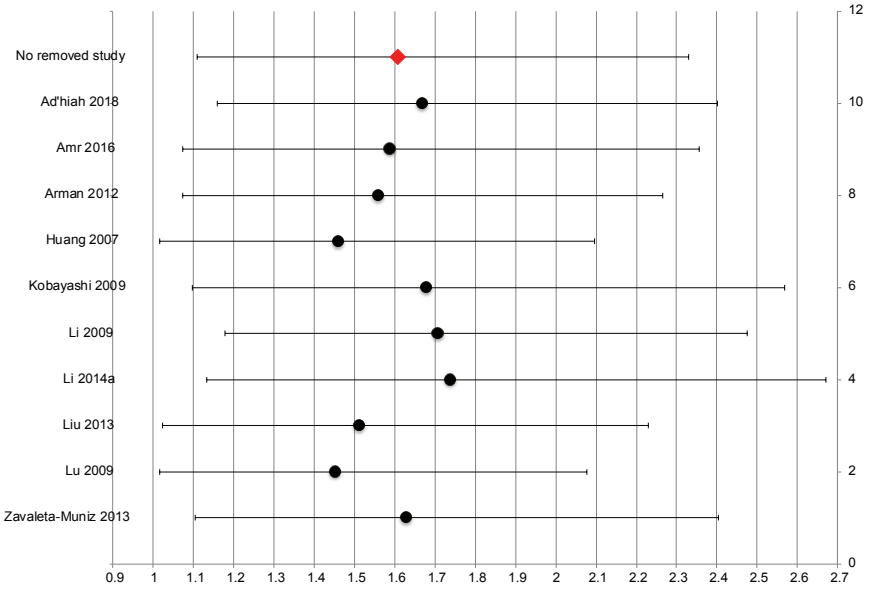
Supplementary Figure 9. Recessive model -572 G>C

A

Study name	region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	3.189	1.784	5.703	3.911	0.000
Kobayashi 2009	Asian	1.193	0.716	1.987	0.676	0.499
Li 2009	Asian	0.379	0.076	1.894	-1.182	0.237
Li 2014a	Asian	1.021	0.733	1.420	0.121	0.904
Liu 2013	Asian	2.708	1.325	5.537	2.731	0.006
Lu 2009	Asian	3.261	1.829	5.814	4.007	0.000
You 2013	Asian	1.183	0.898	1.558	1.197	0.231
Fixed		1.401	1.181	1.661	3.879	0.000
Random		1.625	1.078	2.450	2.320	0.020
Ad'hiah 2018	M. East	0.116	0.006	2.216	-1.431	0.152
Amr 2016	M. East	1.880	0.607	5.824	1.094	0.274
Arman 2012	M. East	5.655	0.627	51.032	1.544	0.123
Fixed		1.729	0.667	4.479	1.127	0.260
Random		1.439	0.263	7.889	0.419	0.675
Zavaleta-Muniz 2013	Other	1.250	0.292	5.355	0.301	0.764
Fixed		1.250	0.292	5.355	0.301	0.764
Random		1.250	0.292	5.355	0.301	0.764



B



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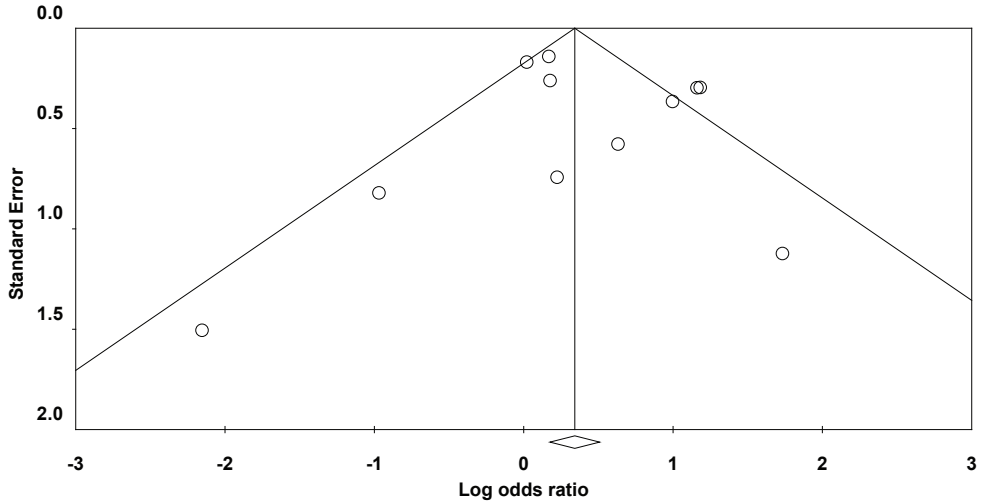
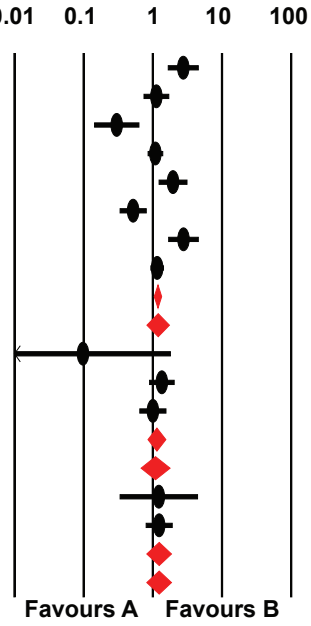


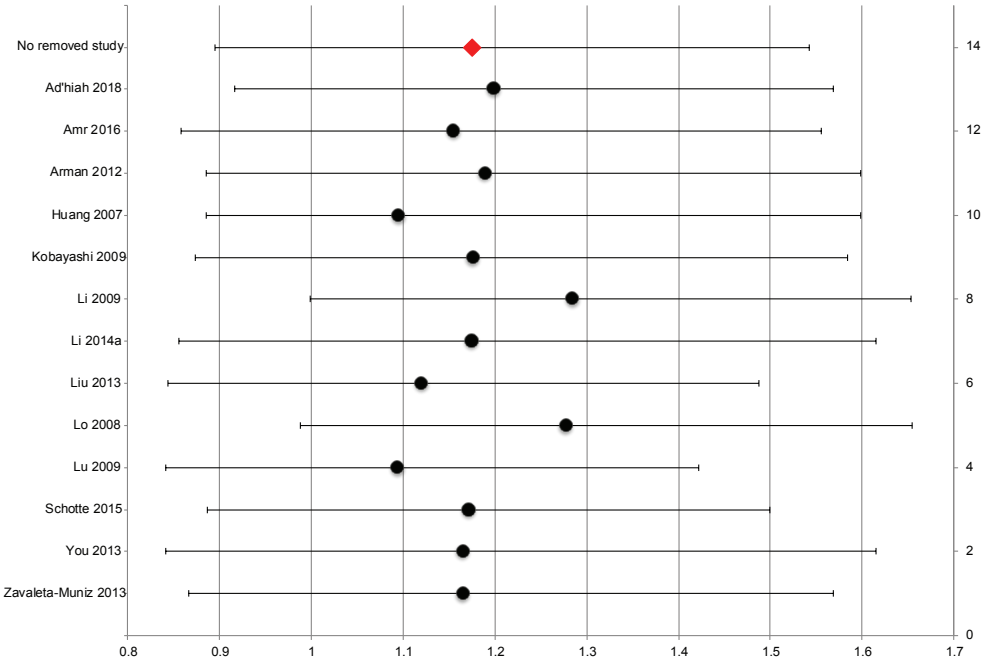
Supplementary Figure 10. Allelic -572 G>C

A

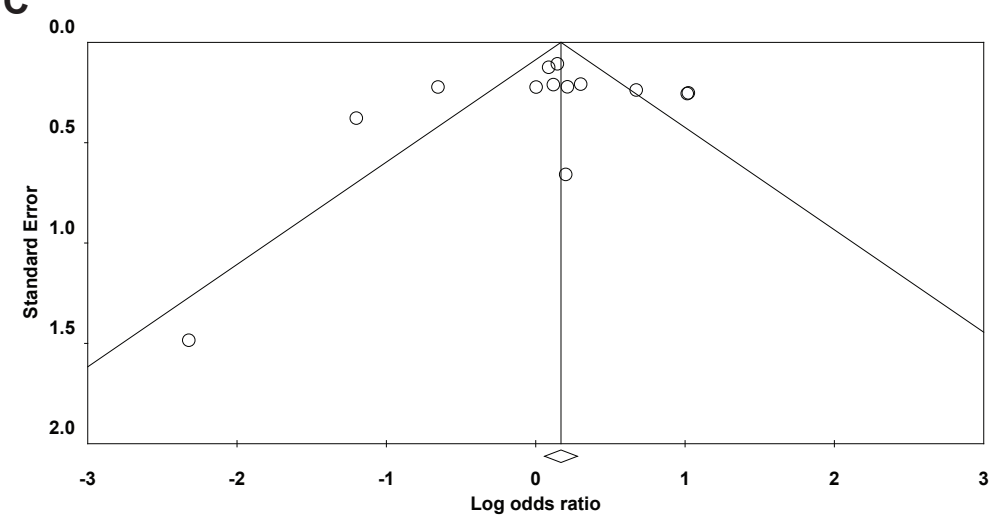
Study name	Region	Odds	Lower	Upper	Z-Value	p-Value
Huang 2007	Asian	2.758	1.673	4.547	3.976	0.000
Kobayashi 2009	Asian	1.125	0.745	1.700	0.561	0.575
Li 2009	Asian	0.301	0.143	0.630	-3.183	0.001
Li 2014a	Asian	1.090	0.855	1.390	0.697	0.486
Liu 2013	Asian	1.959	1.231	3.118	2.837	0.005
Lo 2008	Asian	0.520	0.336	0.803	-2.944	0.003
Lu 2009	Asian	2.779	1.697	4.551	4.061	0.000
You 2013	Asian	1.156	0.938	1.425	1.357	0.175
Fixed		1.187	1.049	1.343	2.712	0.007
Random		1.195	0.822	1.739	0.932	0.351
Ad'hiah 2018	M. East	0.098	0.005	1.796	-1.565	0.118
Amr 2016	M. East	1.351	0.899	2.031	1.449	0.147
Arman 2012	M. East	1.002	0.648	1.551	0.011	0.991
Fixed		1.146	0.852	1.541	0.902	0.367
Random		1.094	0.675	1.772	0.365	0.715
Schotte 2015	Other	1.222	0.337	4.437	0.305	0.760
Zavaleta-Muniz 2013	Other	1.236	0.801	1.908	0.957	0.339
Fixed		1.235	0.818	1.863	1.004	0.315
Random		1.235	0.818	1.863	1.004	0.315



B



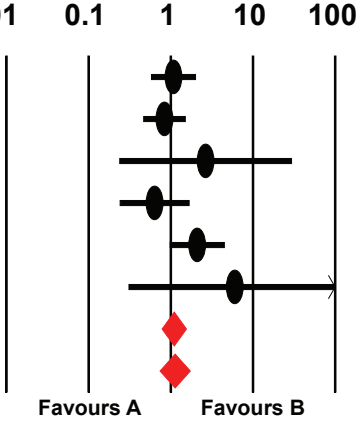
C



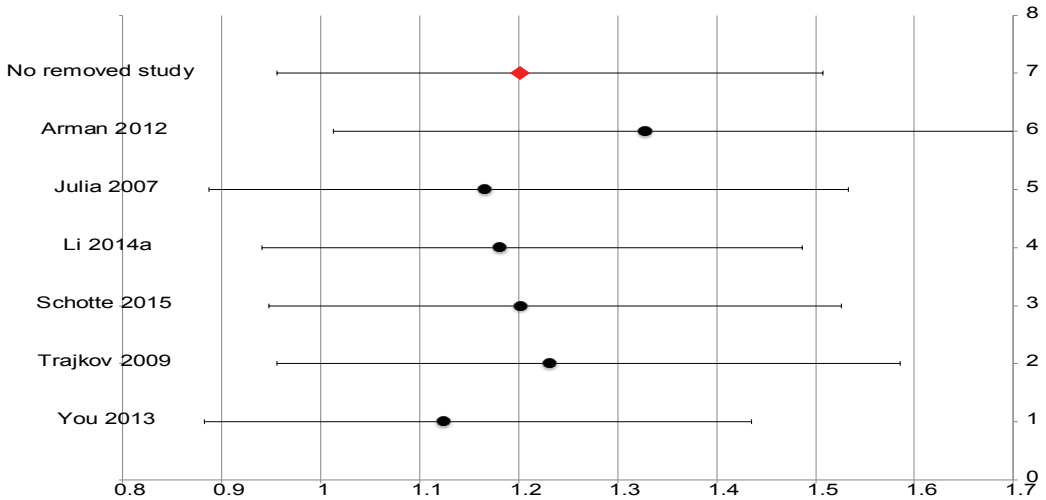
Supplementary Figure 11. Heterozygous model -597 G>A

A

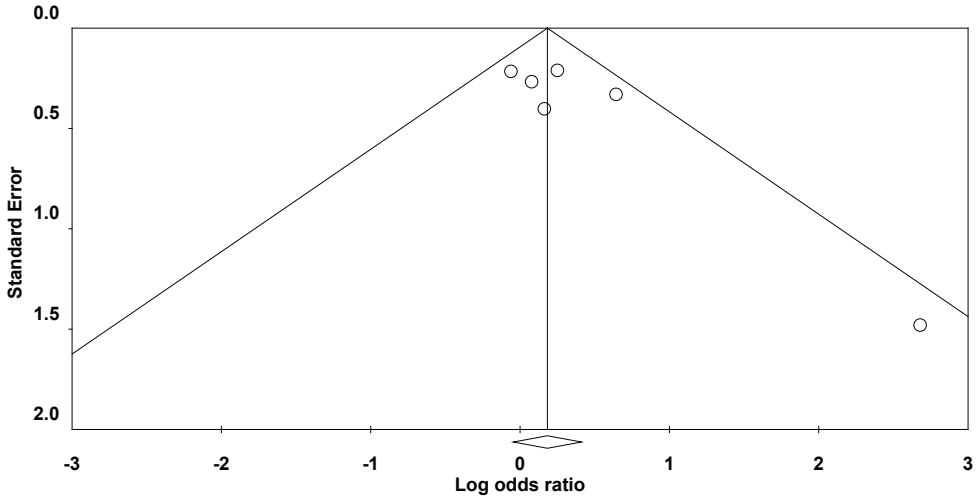
Study name	Odds	Lower	Upper	Z-Value	p-Value
Arman 2012	1.077	0.581	1.996	0.237	0.813
Julia 2007	0.838	0.468	1.499	-0.597	0.551
Li 2014a	2.651	0.239	29.396	0.794	0.427
Schotte 2015	0.635	0.242	1.670	-0.920	0.358
Trajkov 2009	2.094	0.981	4.470	1.909	0.056
You 2013	6.013	0.310	116.802	1.185	0.236
Fixed	1.102	0.785	1.548	0.561	0.575
Random	1.131	0.741	1.727	0.570	0.569



B



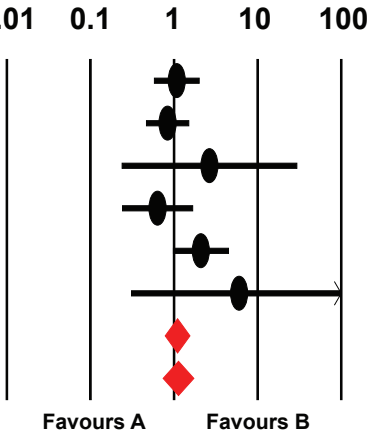
C



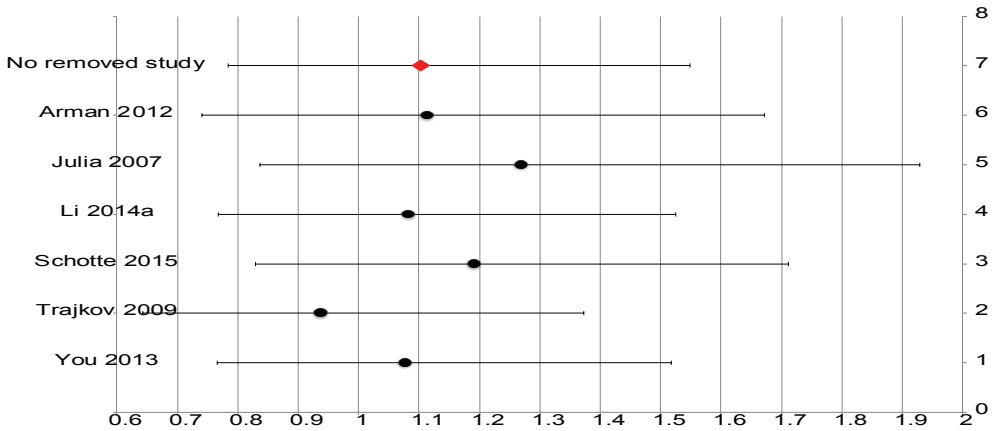
Supplementary Figure 12. Homozygous model -597 G>A

A

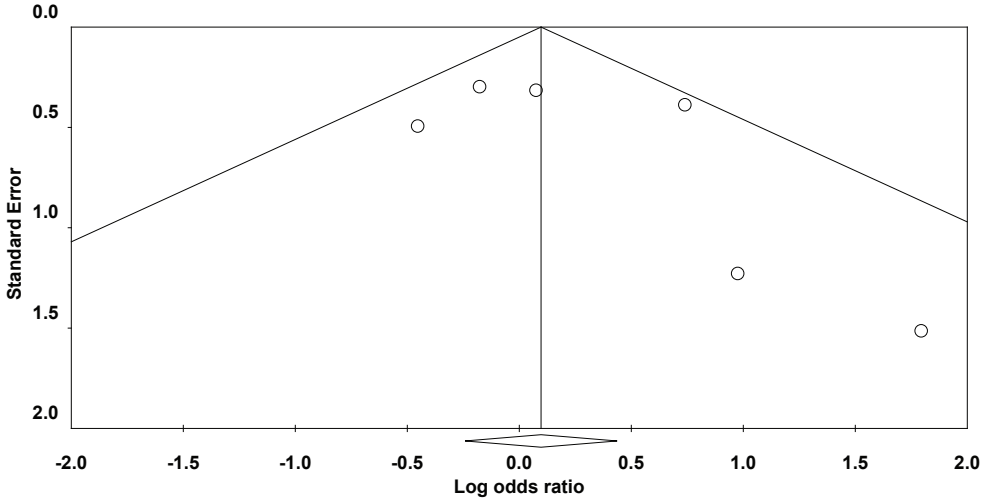
Study name	Odds	Lower	Upper	Z-Value	p-Value
Arman 2012	1.077	0.581	1.996	0.237	0.813
Julia 2007	0.838	0.468	1.499	-0.597	0.551
Li 2014a	2.651	0.239	29.396	0.794	0.427
Schotte 2015	0.635	0.242	1.670	-0.920	0.358
Trajkov 2009	2.094	0.981	4.470	1.909	0.056
You 2013	6.013	0.310	116.802	1.185	0.236
Fixed	1.102	0.785	1.548	0.561	0.575
Random	1.131	0.741	1.727	0.570	0.569



B



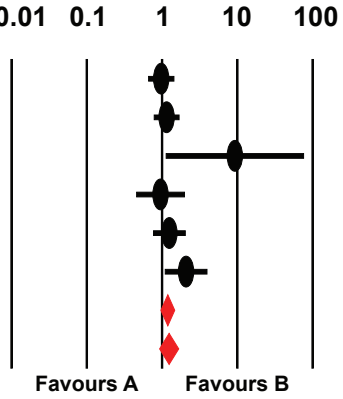
C



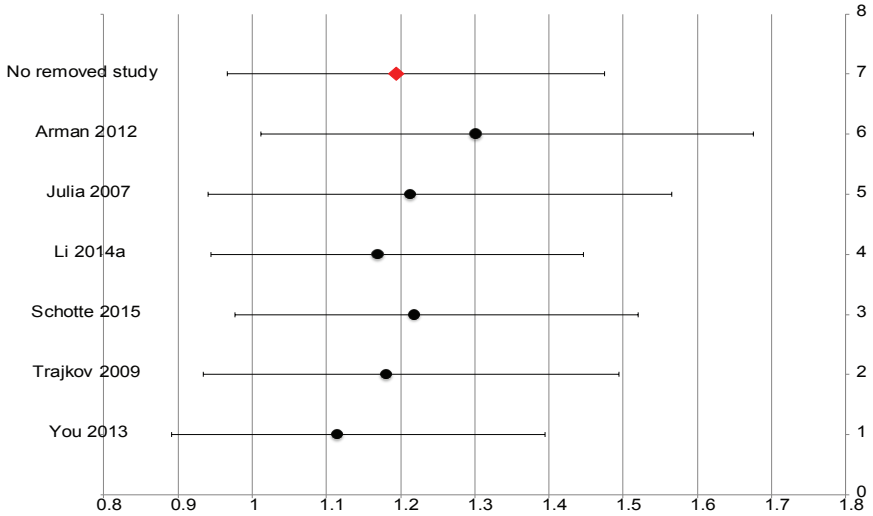
Supplementary Figure 13. Dominat model -597 G>A

A

Study name	Odds	Lower	Upper	Z-Value	p-Value
Arman 2012	0.974	0.662	1.434	-0.132	0.895
Julia 2007	1.151	0.786	1.685	0.723	0.470
Li 2014a	9.277	1.134	75.890	2.077	0.038
Schotte 2015	0.955	0.460	1.982	-0.124	0.901
Trajkov 2009	1.251	0.770	2.033	0.906	0.365
You 2013	2.086	1.102	3.948	2.258	0.024
Fixed	1.194	0.966	1.475	1.644	0.100
Random	1.242	0.928	1.662	1.460	0.144



B



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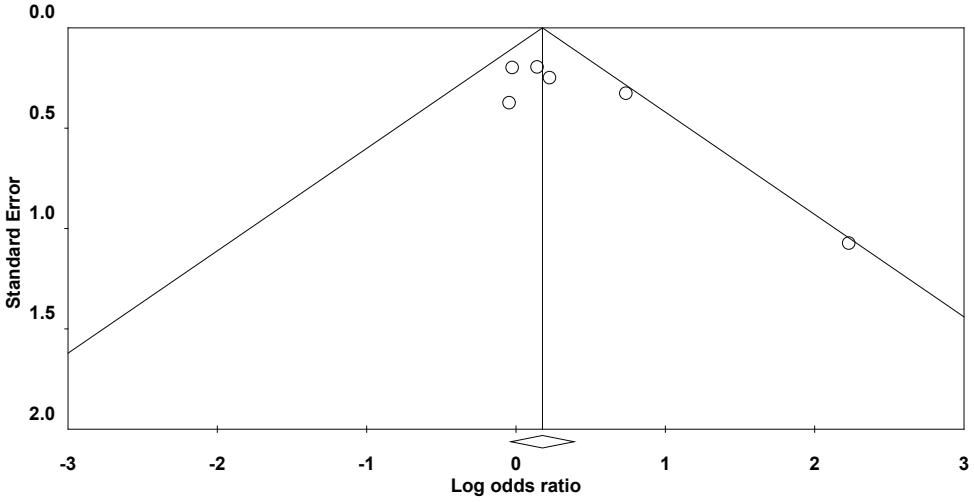
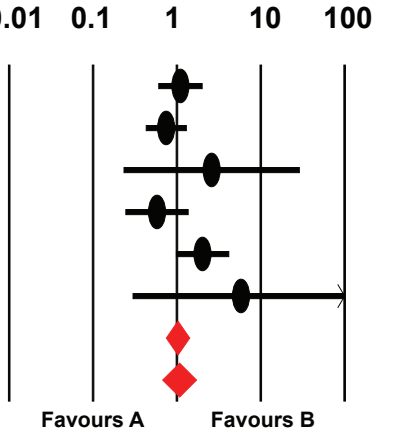


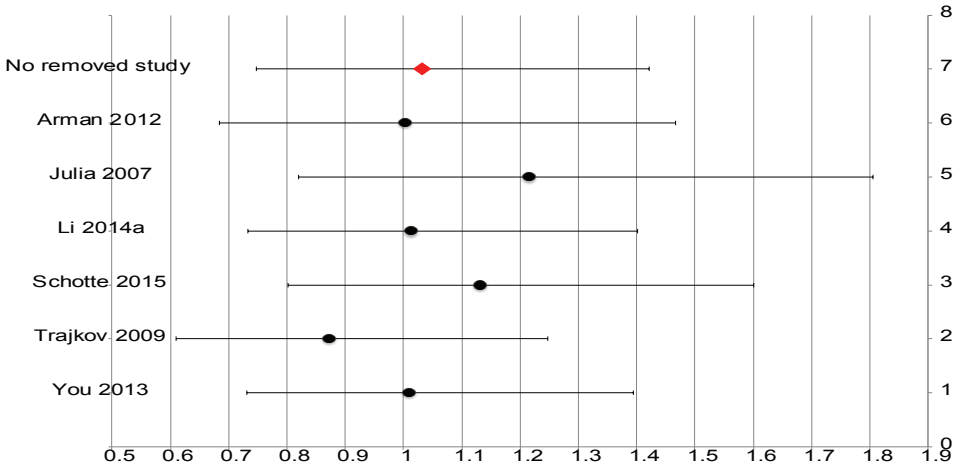
Supplementary Figure 14. Recessive model -597 G>A

A

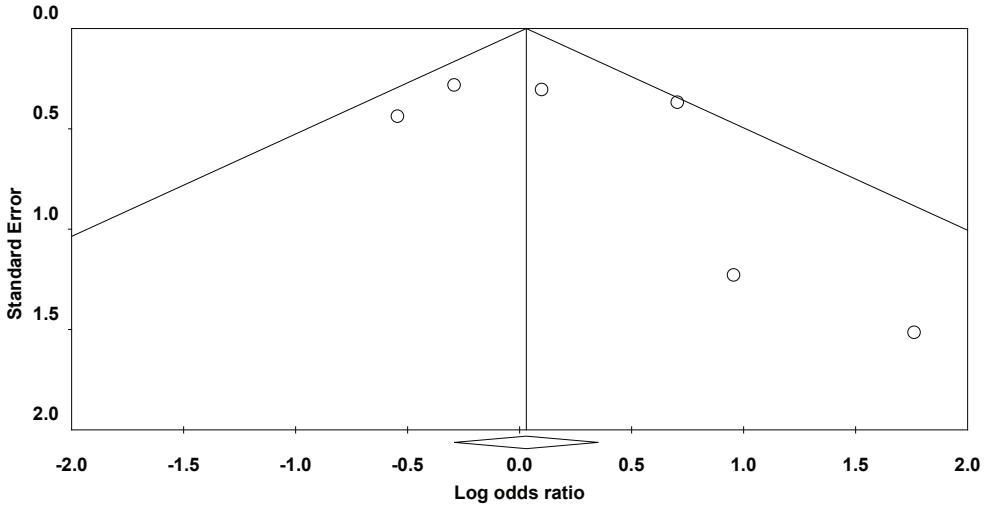
Study name	Odds	Lower	Upper	Z-Value	p-Value
Arman 2012	1.103	0.608	2.000	0.323	0.747
Julia 2007	0.746	0.430	1.294	-1.042	0.297
Li 2014a	2.598	0.234	28.816	0.778	0.437
Schotte 2015	0.580	0.246	1.364	-1.249	0.211
Trajkov 2009	2.021	0.985	4.149	1.918	0.055
You 2013	5.816	0.299	112.962	1.163	0.245
Fixed	1.031	0.748	1.421	0.184	0.854
Random	1.077	0.677	1.713	0.312	0.755



B

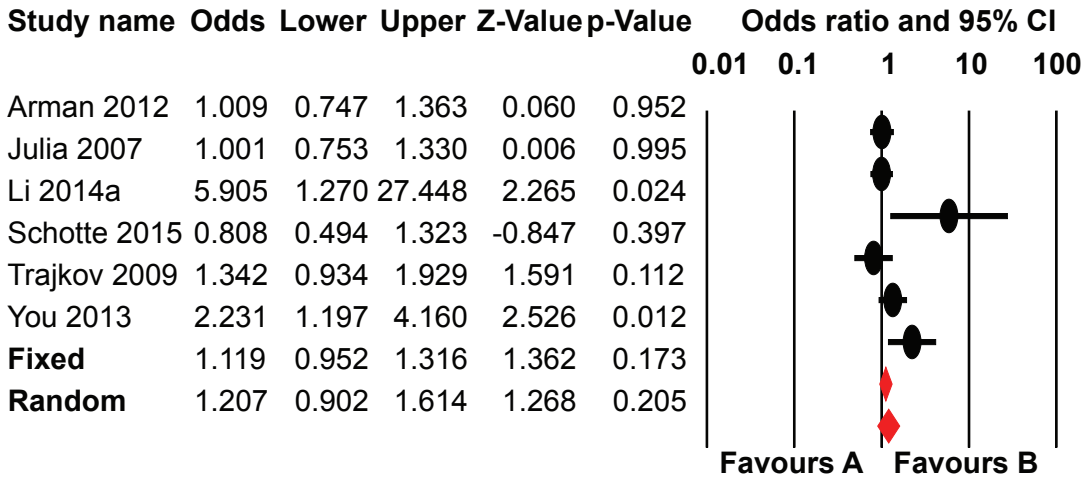


C



Supplementary Figure 15. Allelic model -597 G>A

A



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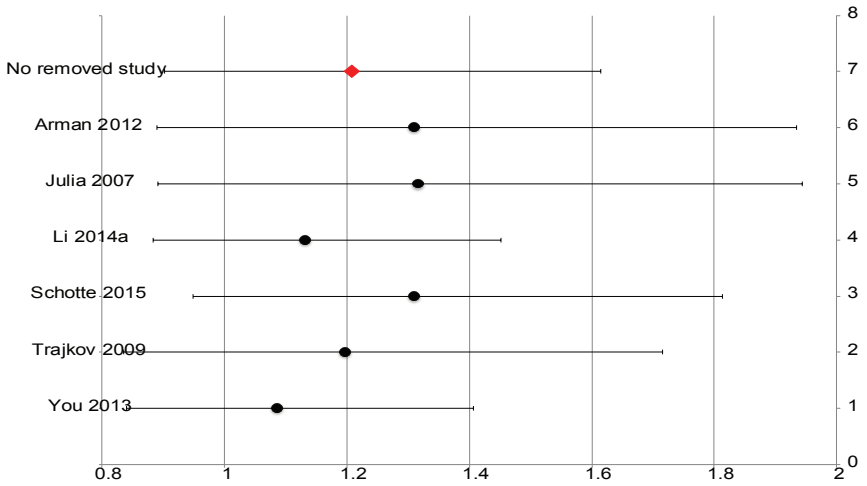

C