

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.

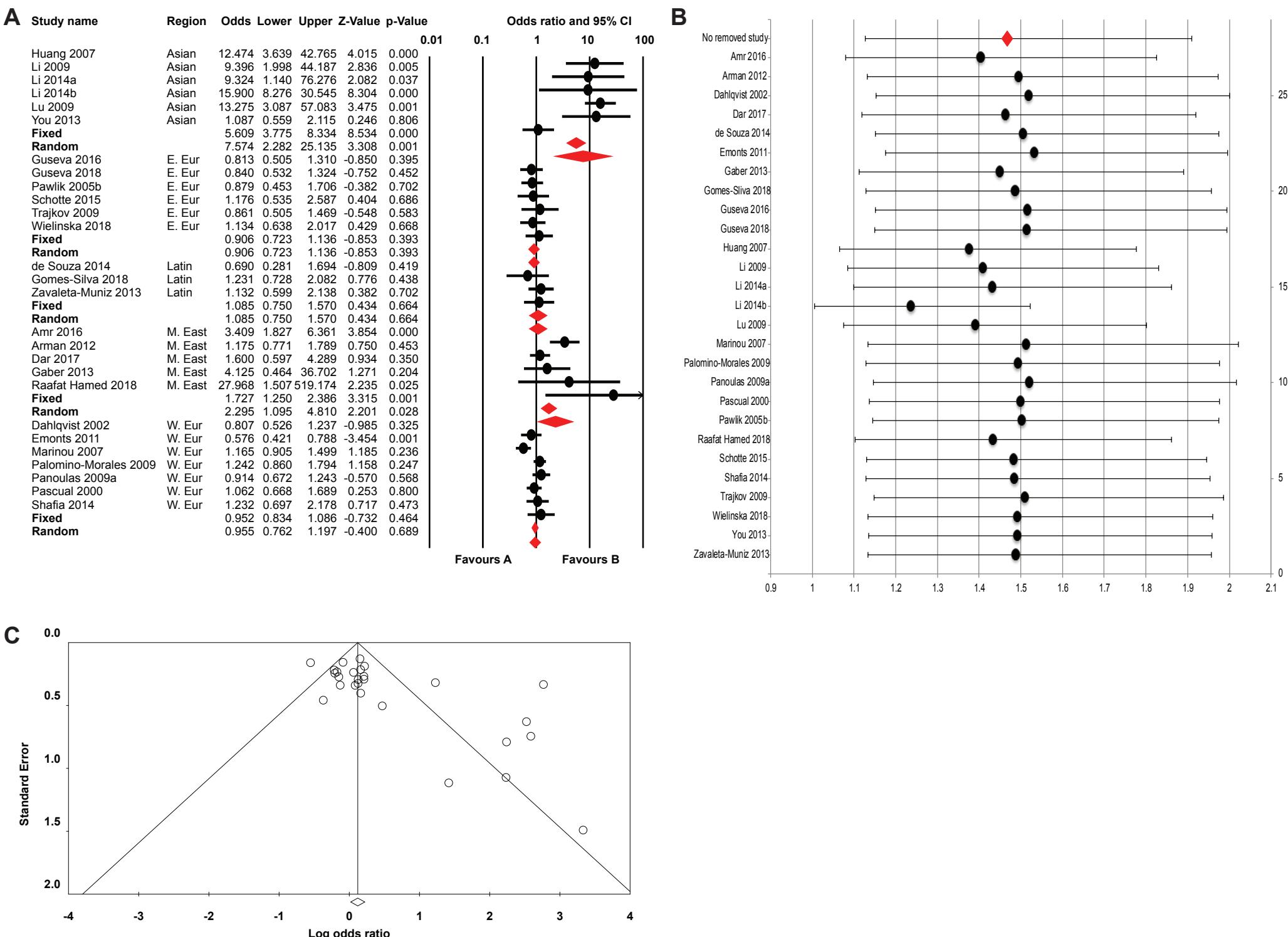
2 Indicates Multicentric Hospital-base study.

C Indicates Community

H Indicates Local Hospital

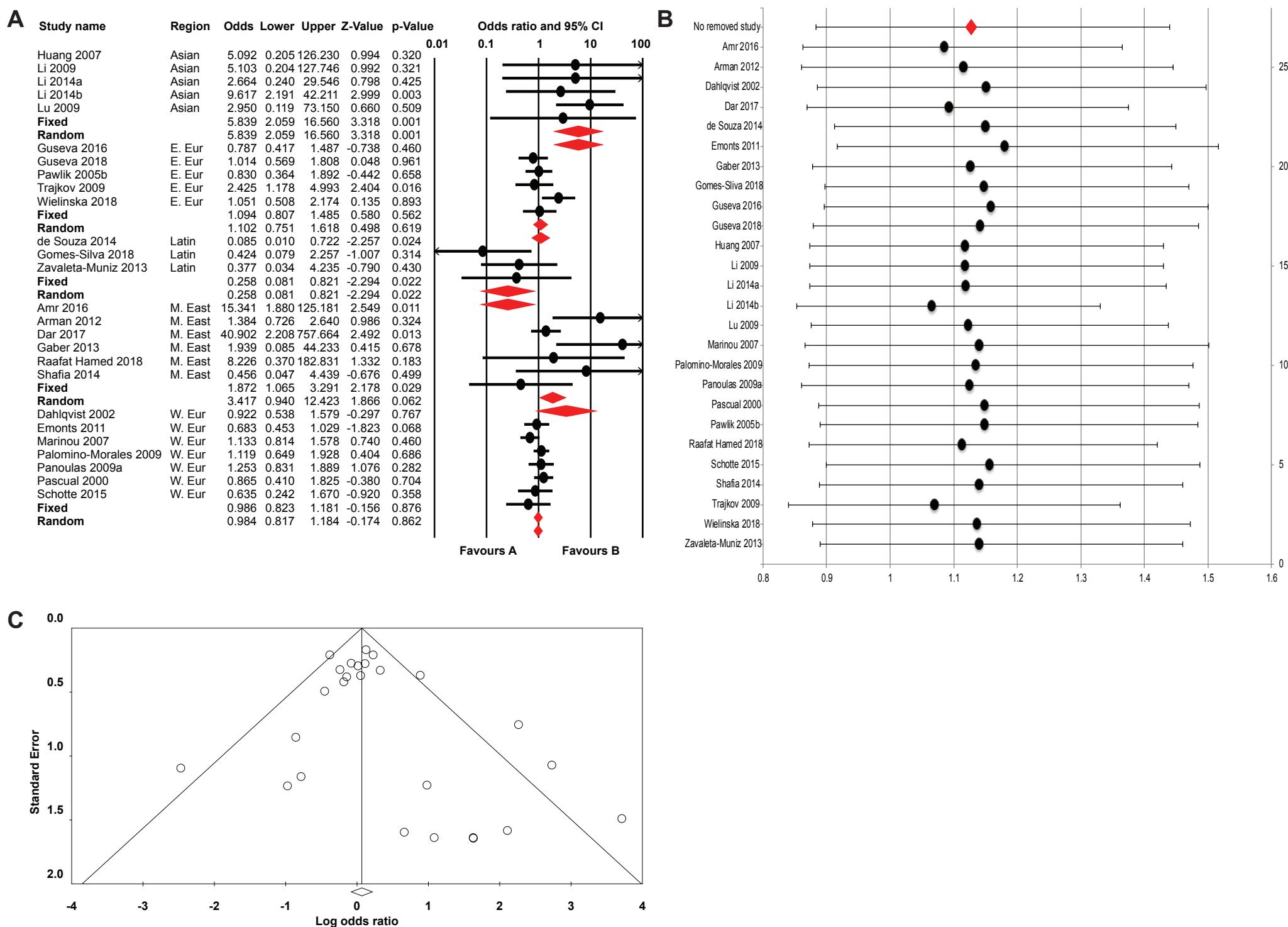
Supplementary Figure 1. Heterozygous model -174 G>C

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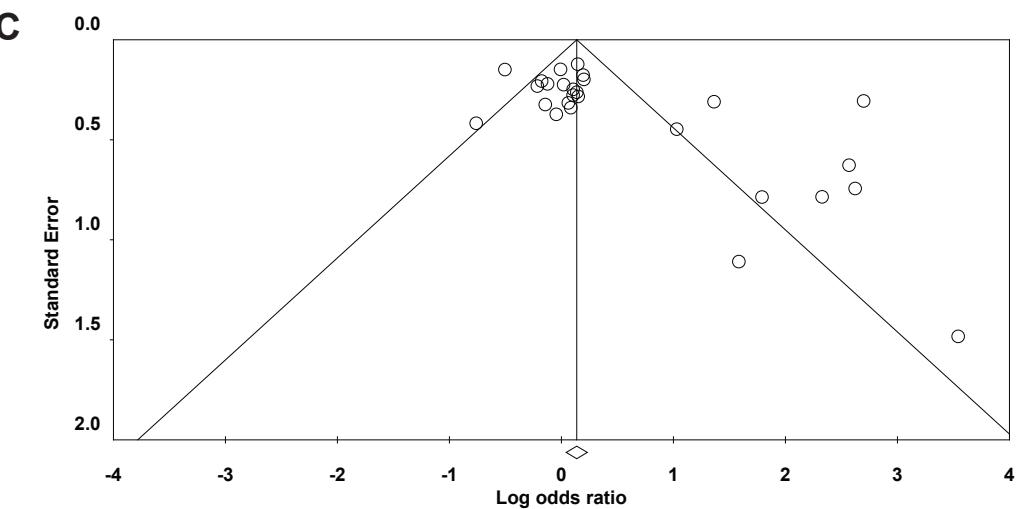
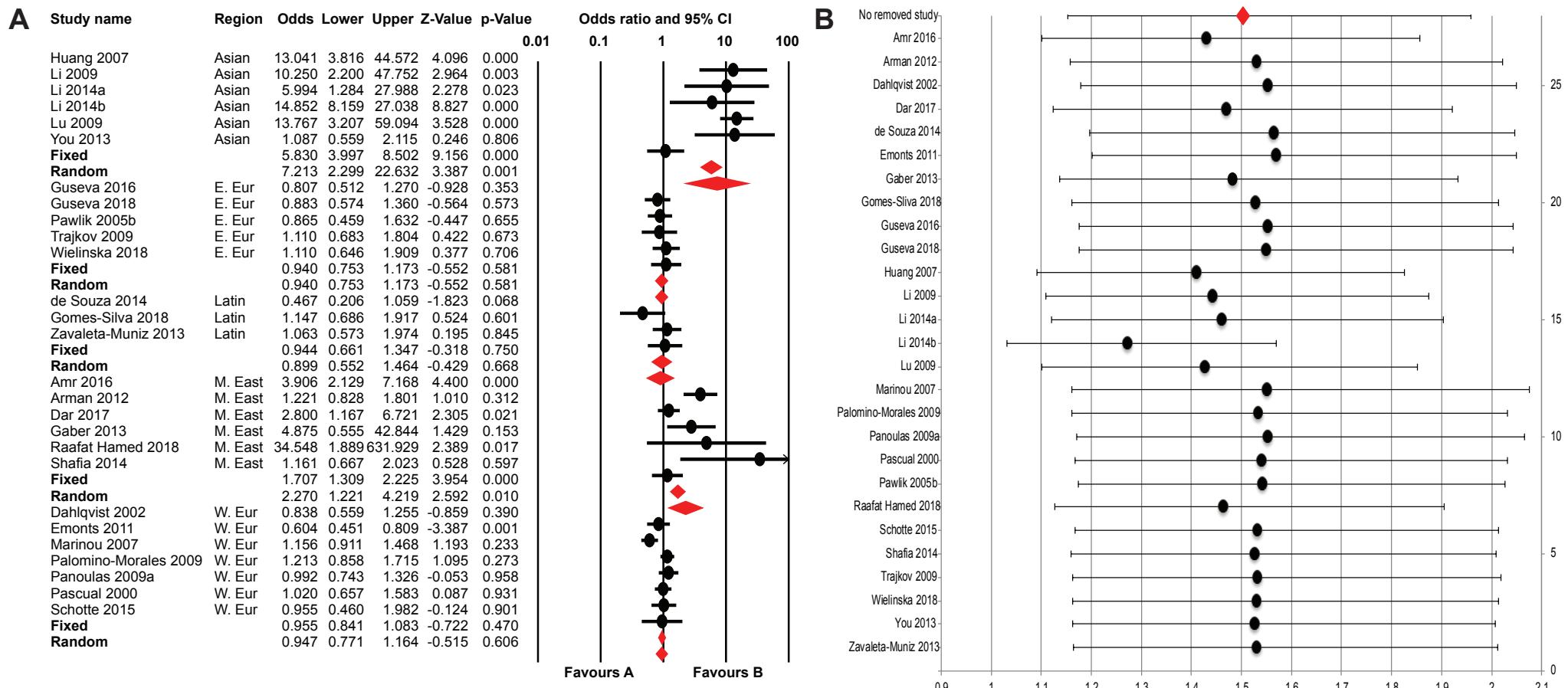
Supplementary Figure 2. Homozygous model -174 G>C

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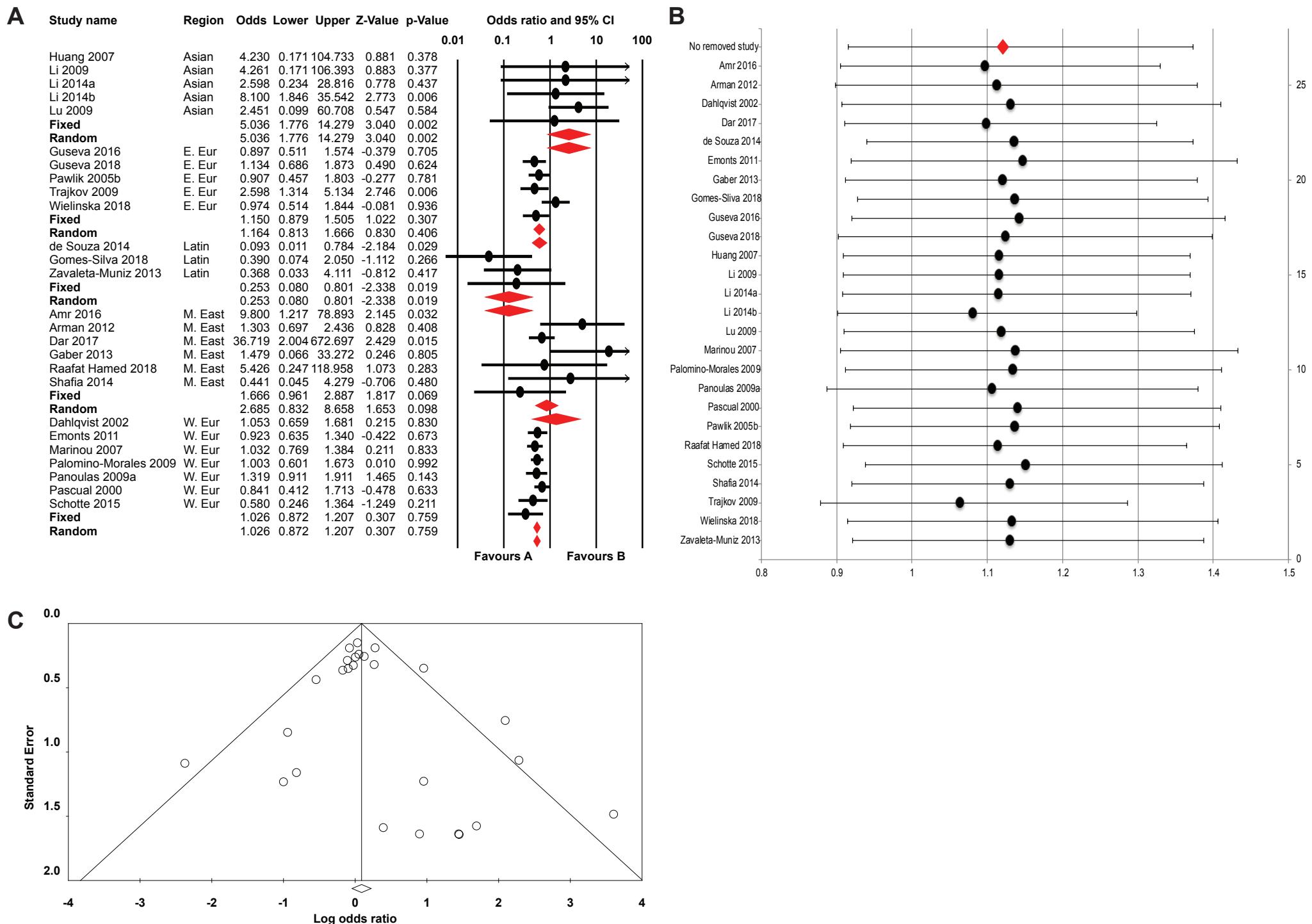


Supplementary Figure 3. Dominant model 174 G>C

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Supplementary Figure 4. Recessive model -174 G>C



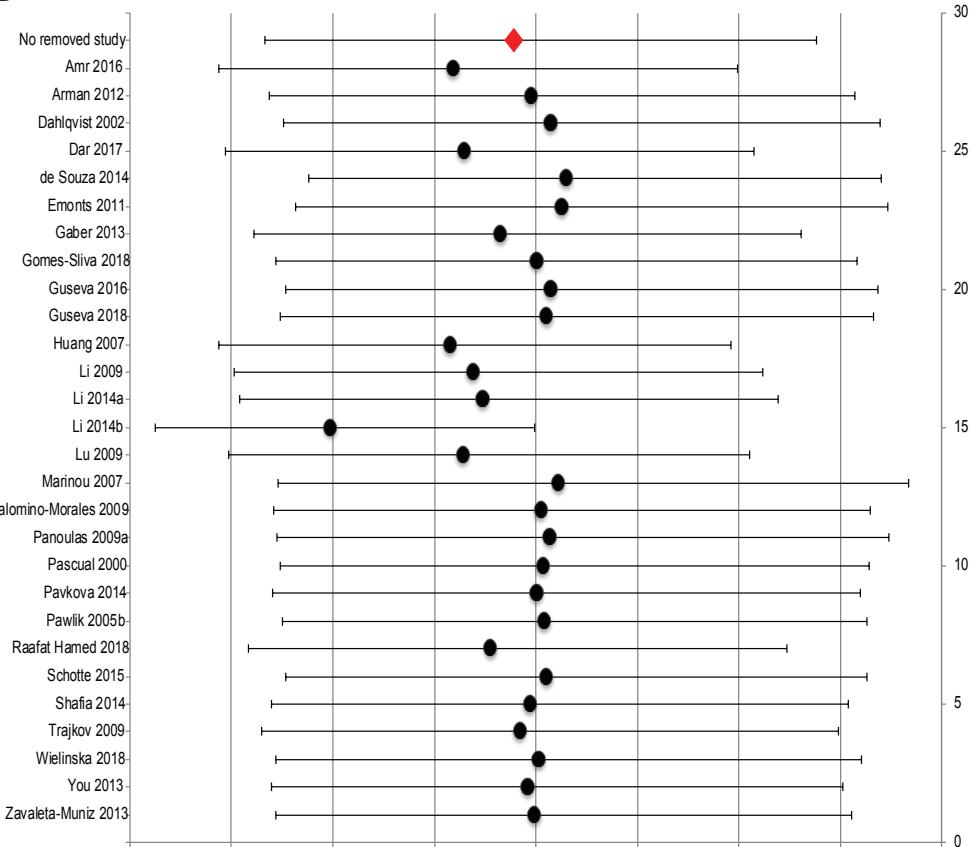
Supplementary Figure 5. Allelic model - 174 G>C

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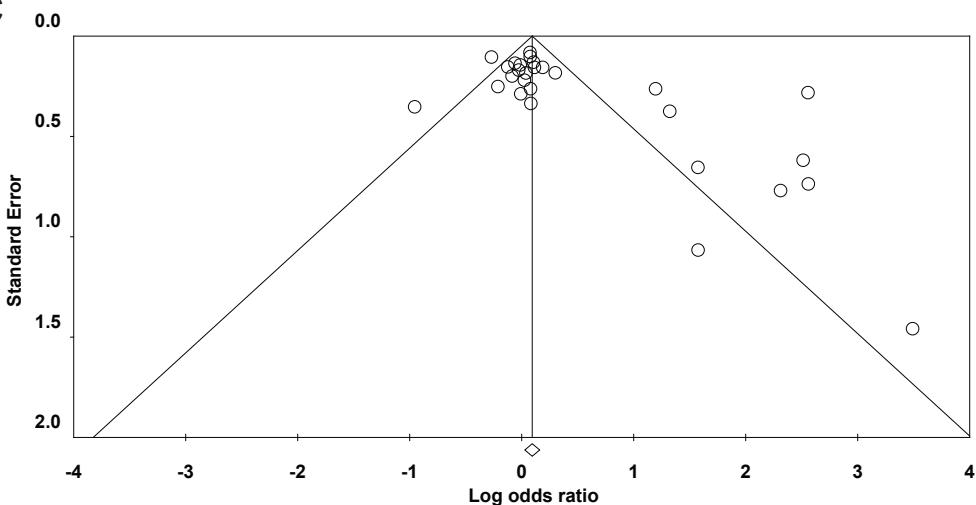
A Study name

	Region	Odds	Lower	Upper	Z-Value	p-Value	0.01	0.1	1	10	100
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					
Pawlak 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

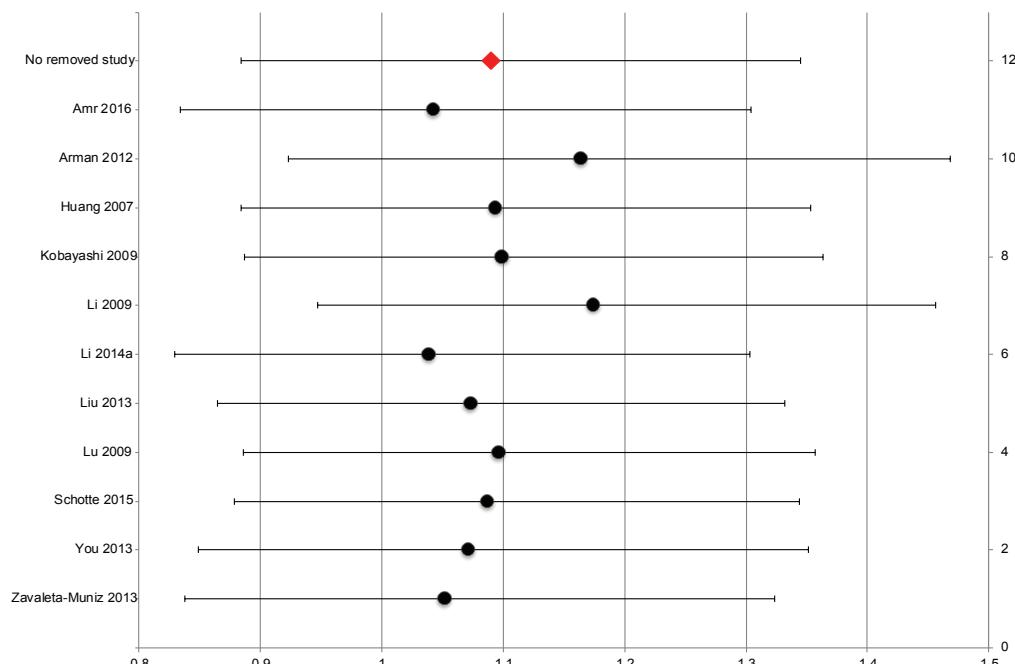
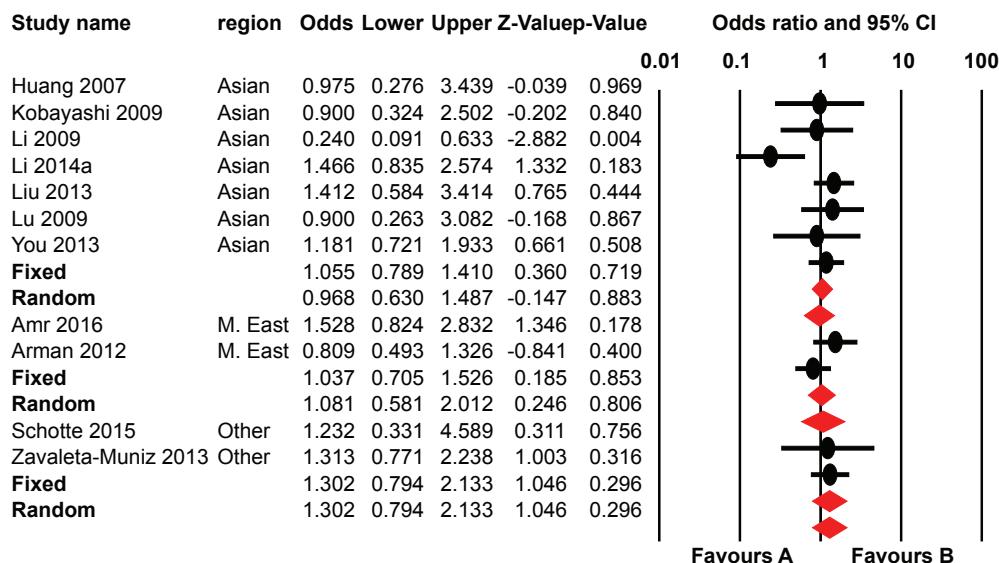


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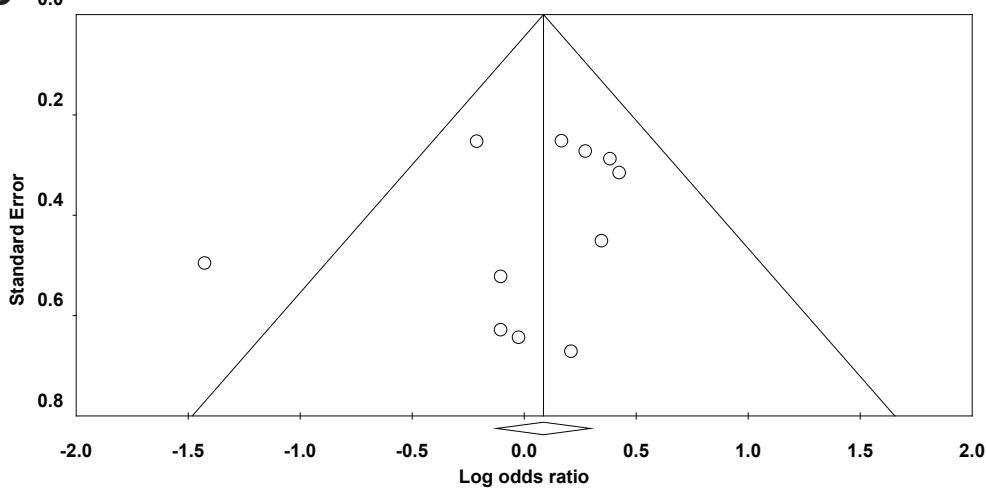


Supplementary Figure 6. Heterozygous model -572 G>C

A

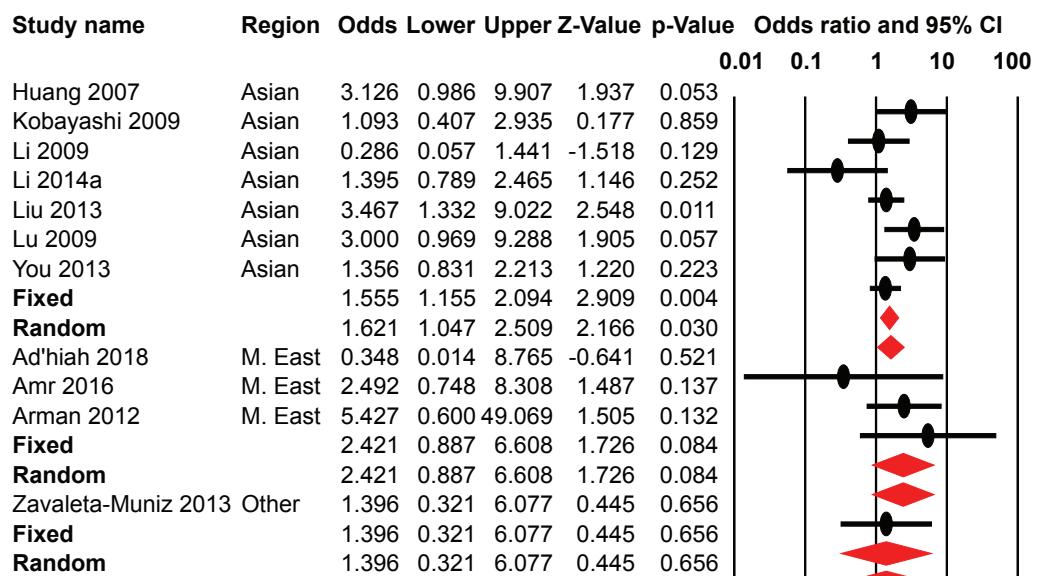


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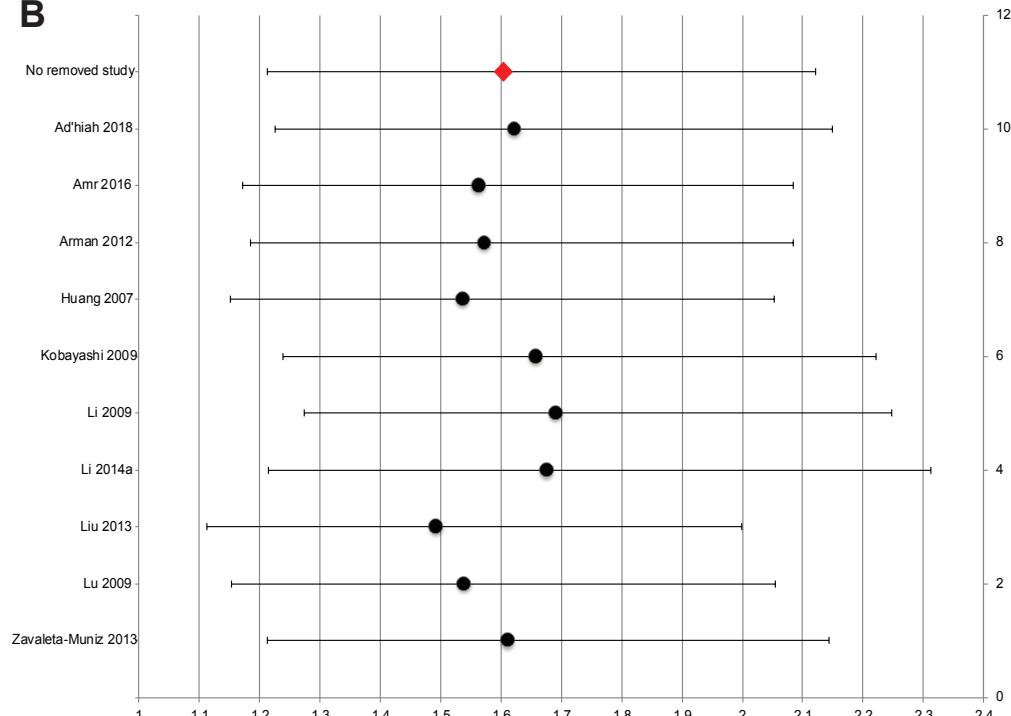


Supplementary Figure 7. Homozygous model -572 G>C

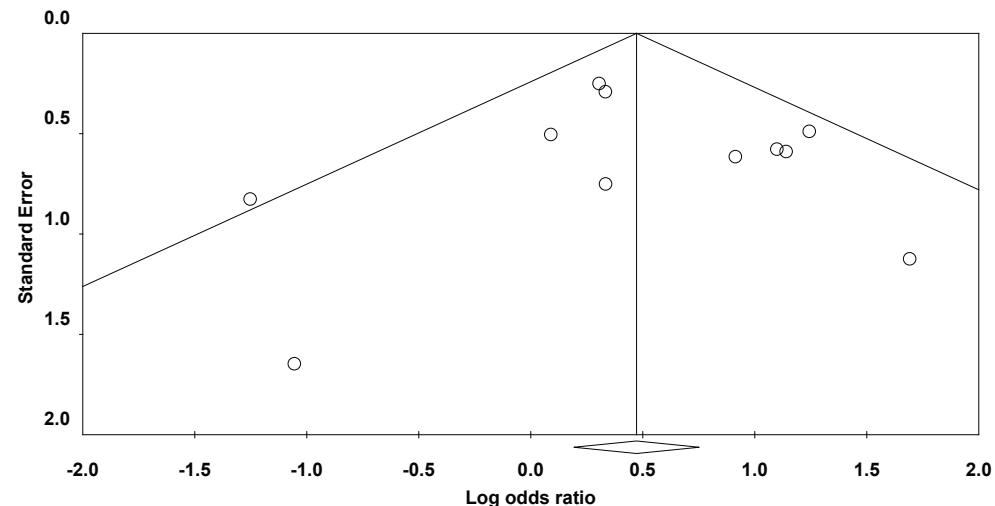
A



B

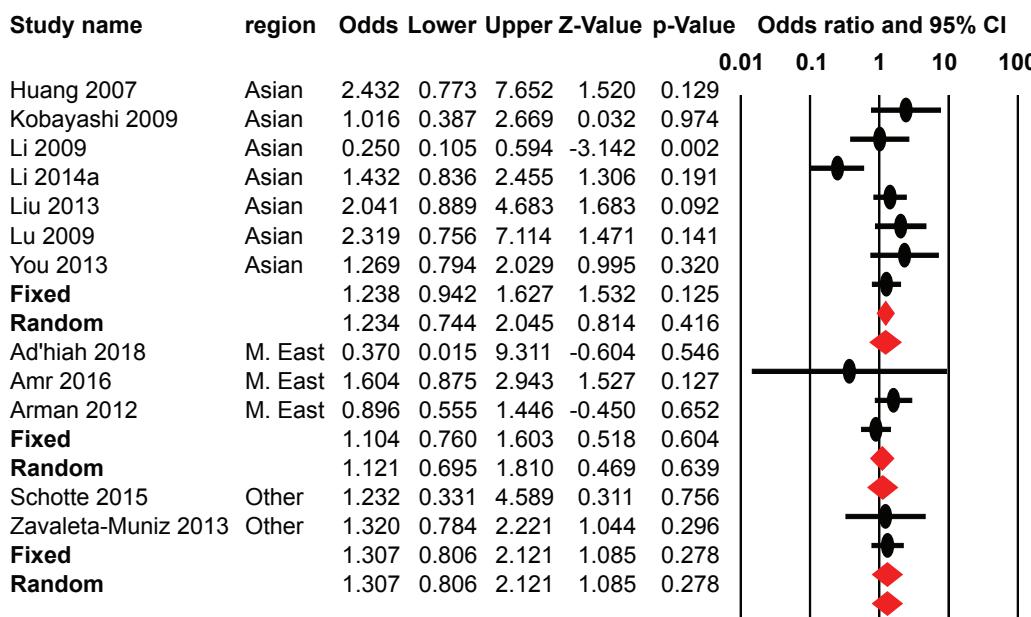


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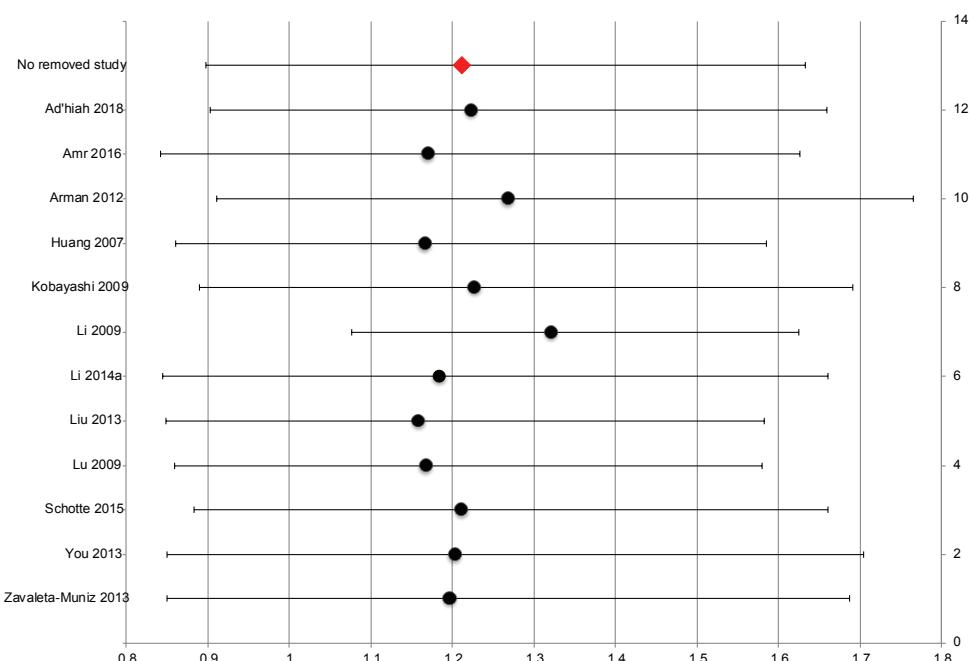


Supplementary Figure 8. Dominant model -572 G>C

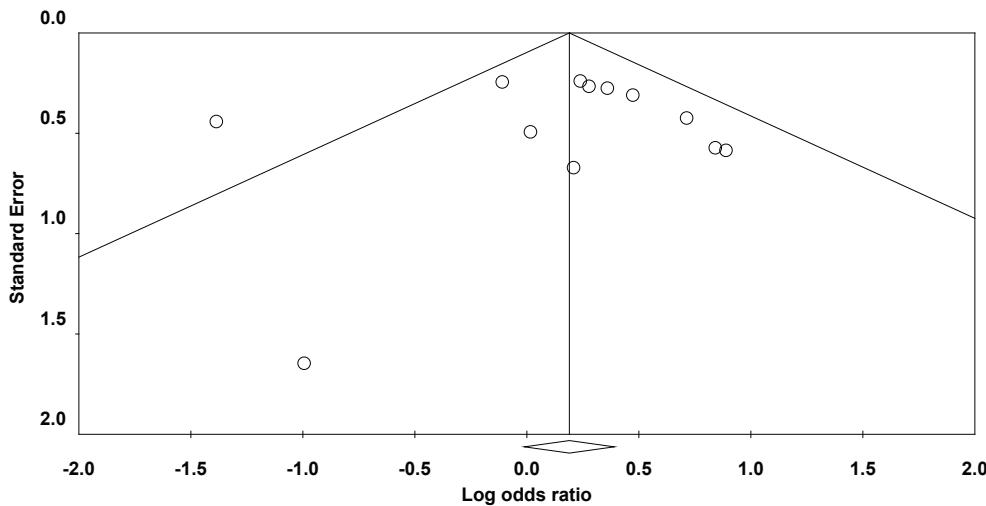
A



B

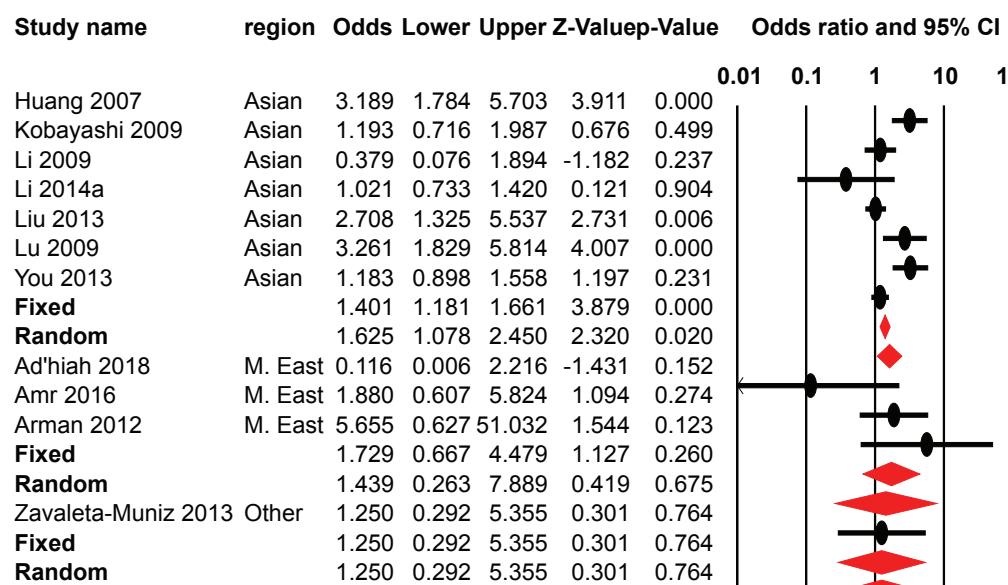


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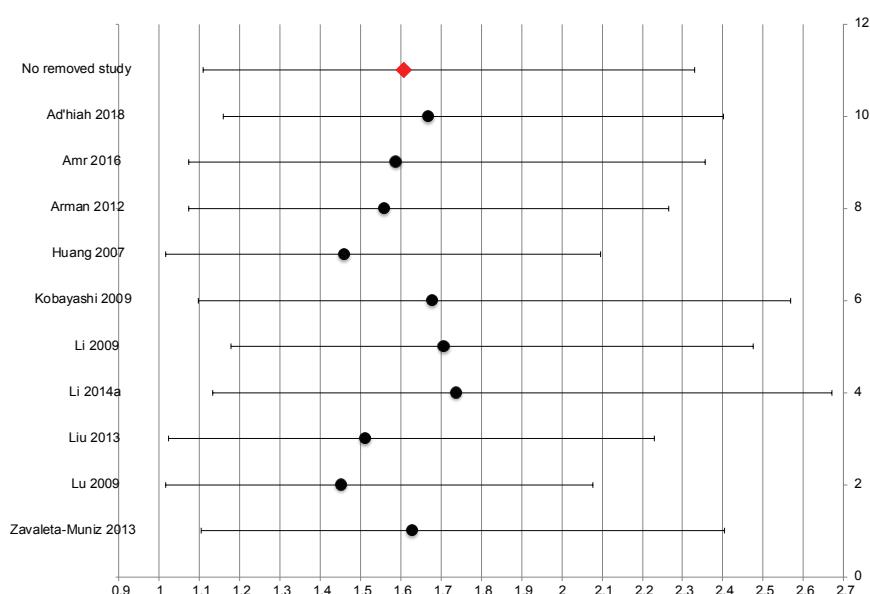


Supplementary Figure 9. Recessive model -572 G>C

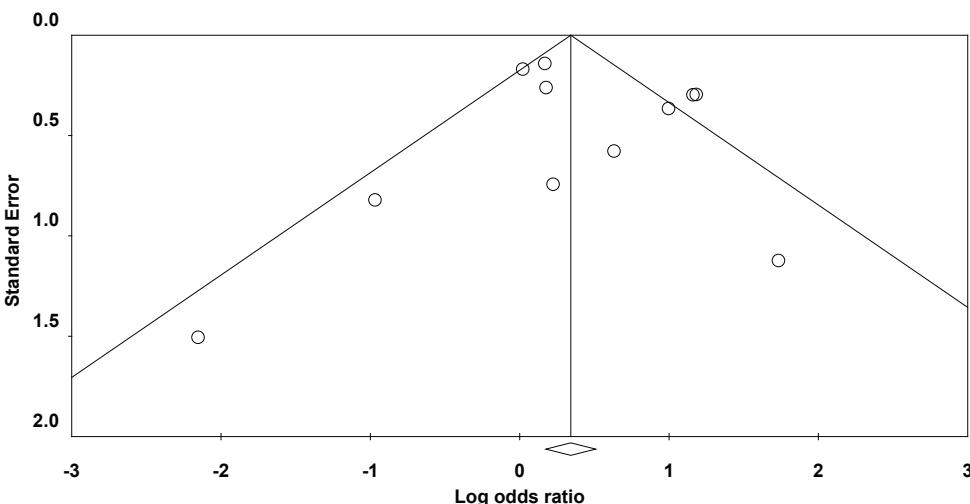
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B

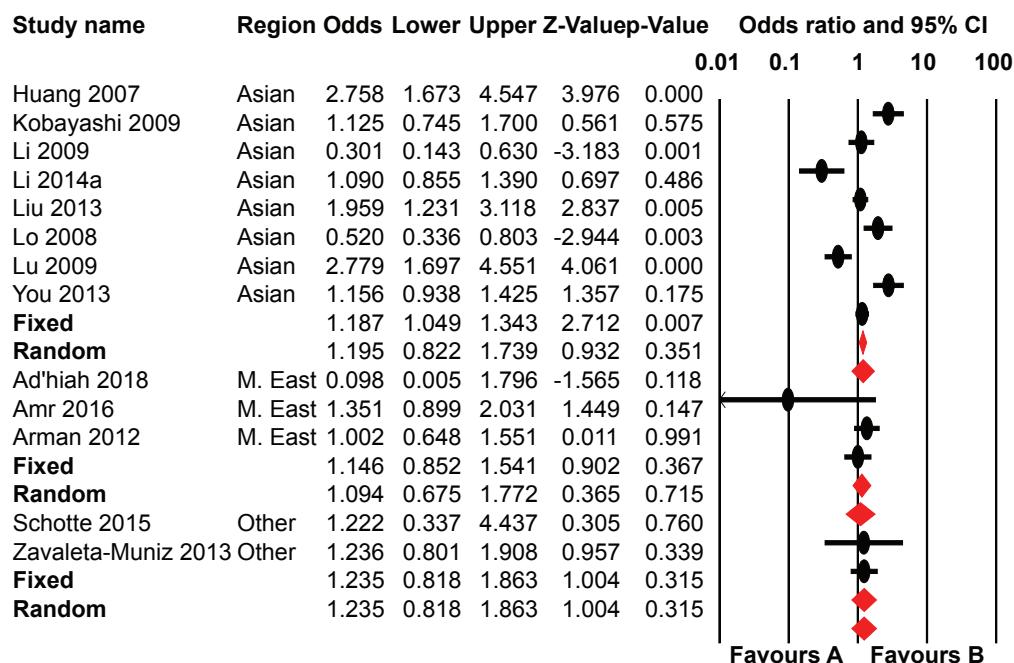


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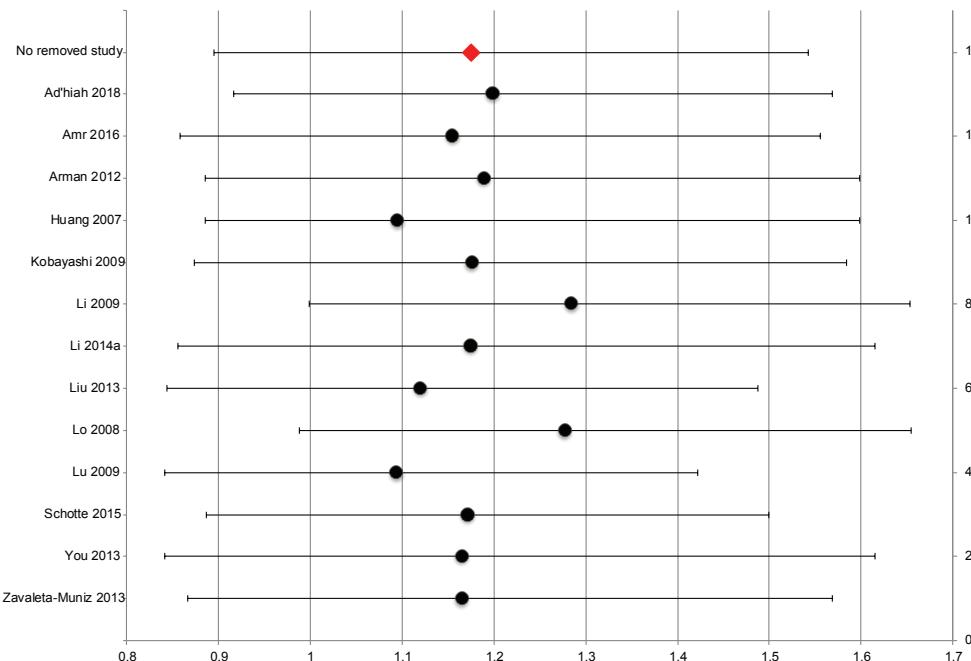


Supplementary Figure 10. Allelic -572 G>C

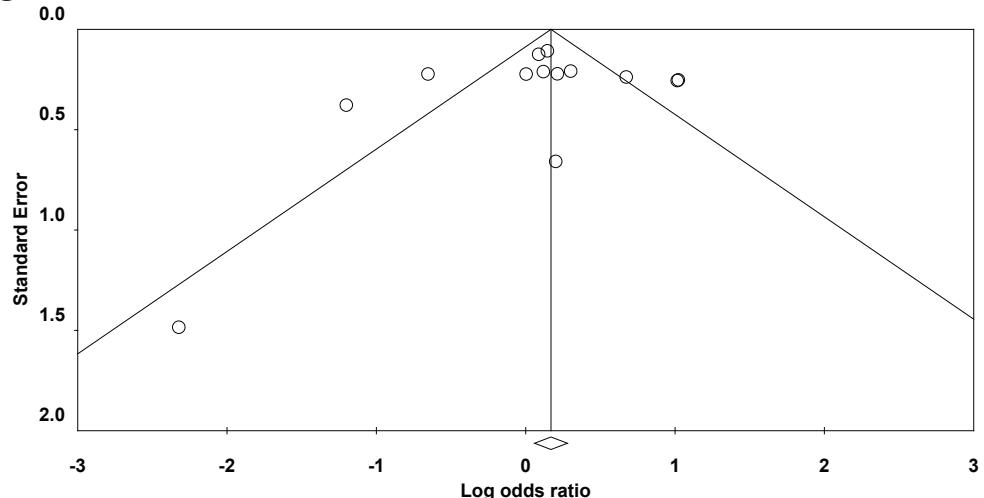
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B

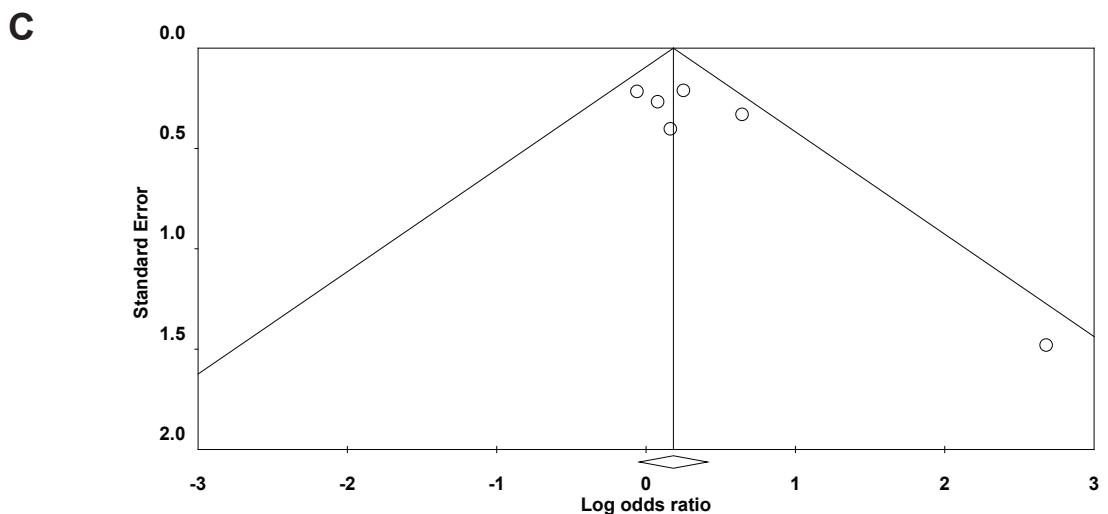
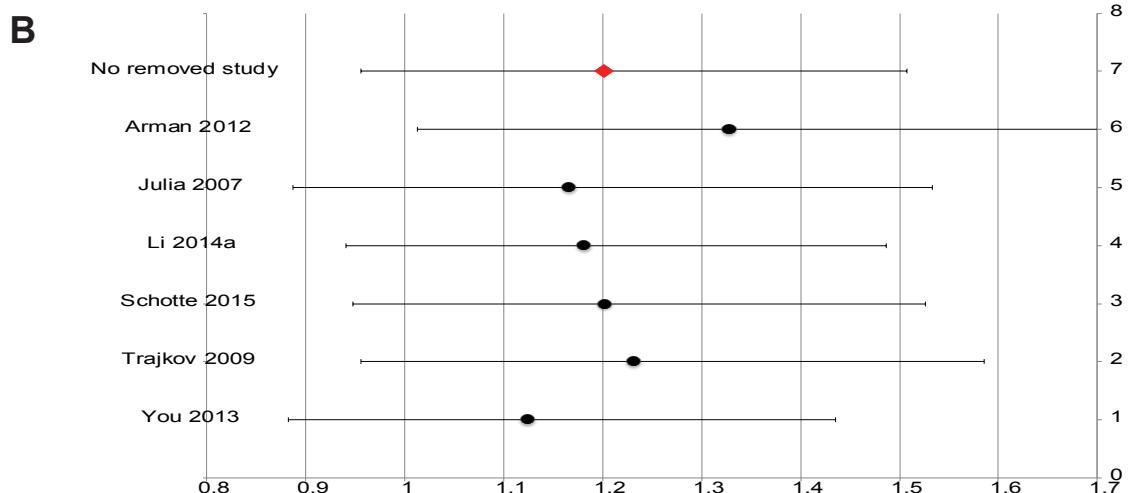
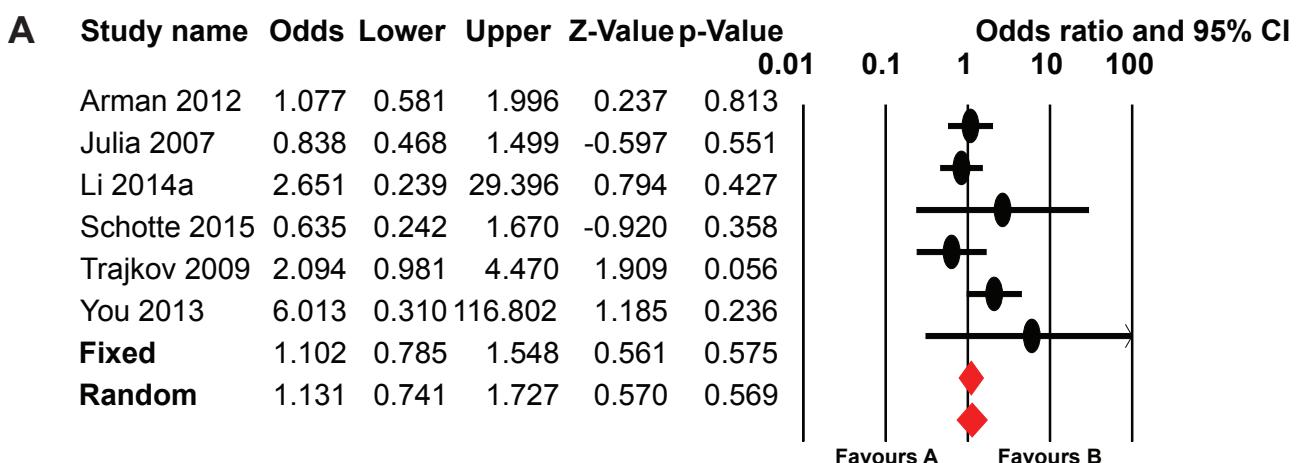


C



Supplementary Figure 11. Heterozygous model -597 G>A

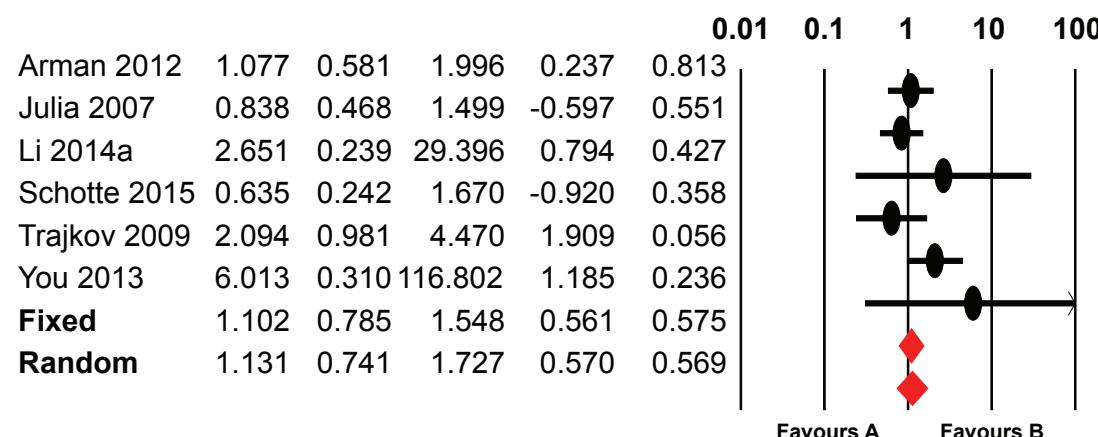
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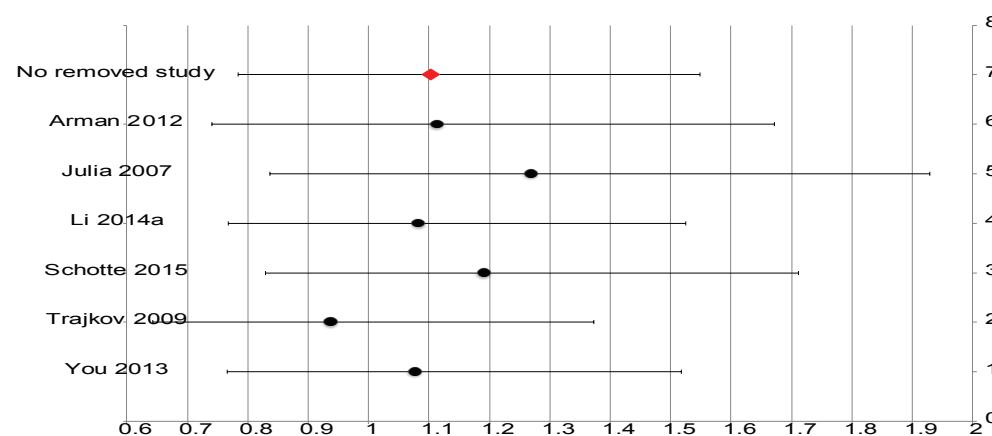
Supplementary Figure 12. Homozygous model -597 G>A

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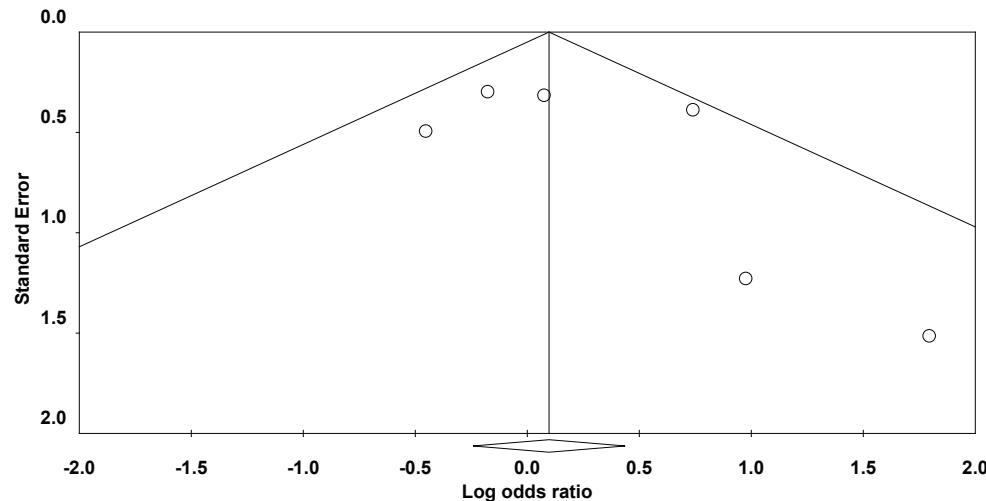
A Study name Odds Lower Upper Z-Value p-Value Odds ratio and 95% CI



B



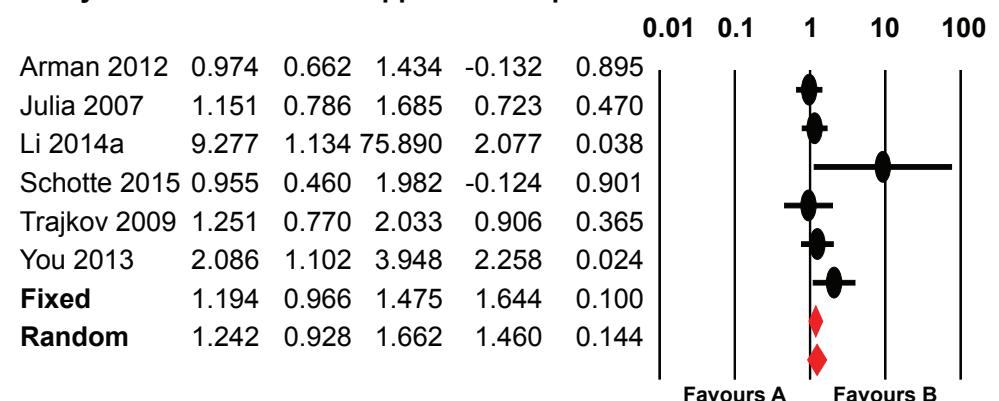
C



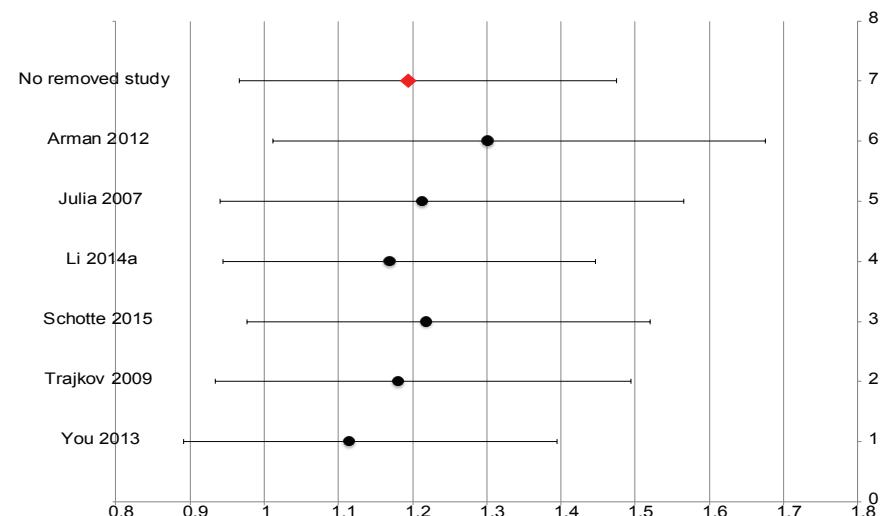
Supplementary Figure 13. Dominat model -597 G>A

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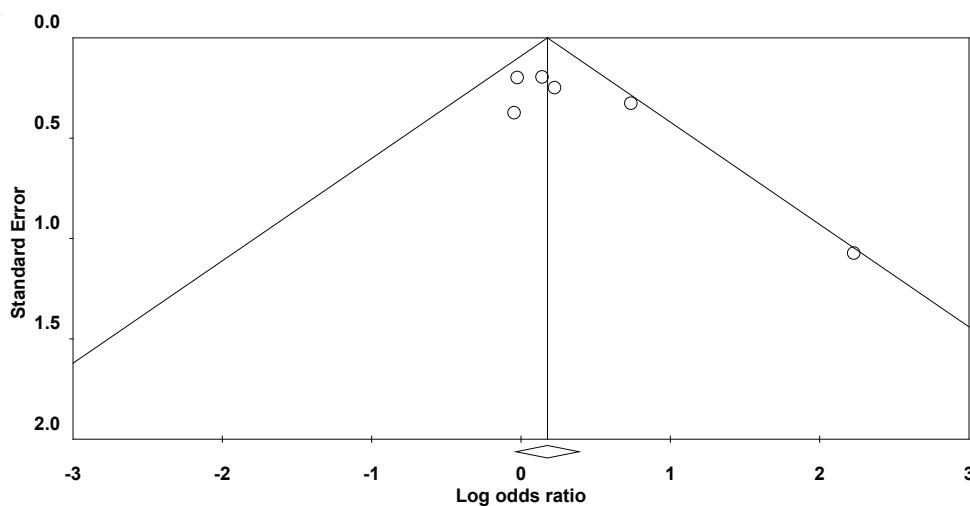
A Study name Odds Lower Upper Z-Value p-Value Odds ratio and 95% CI



B



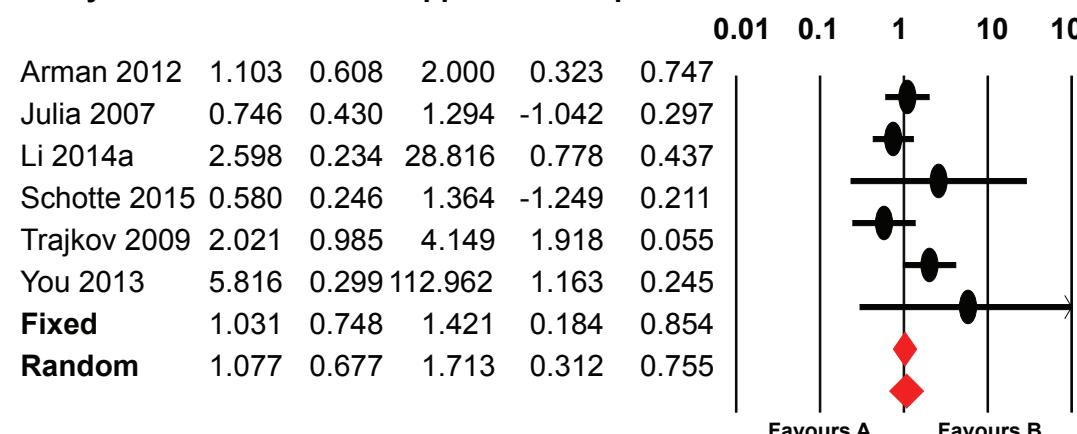
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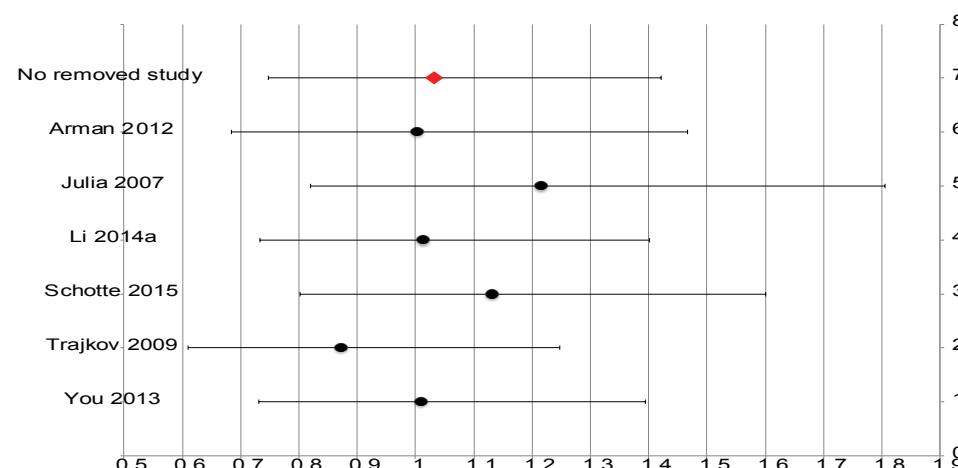
Supplementary Figure 14. Recessive model -597 G>A

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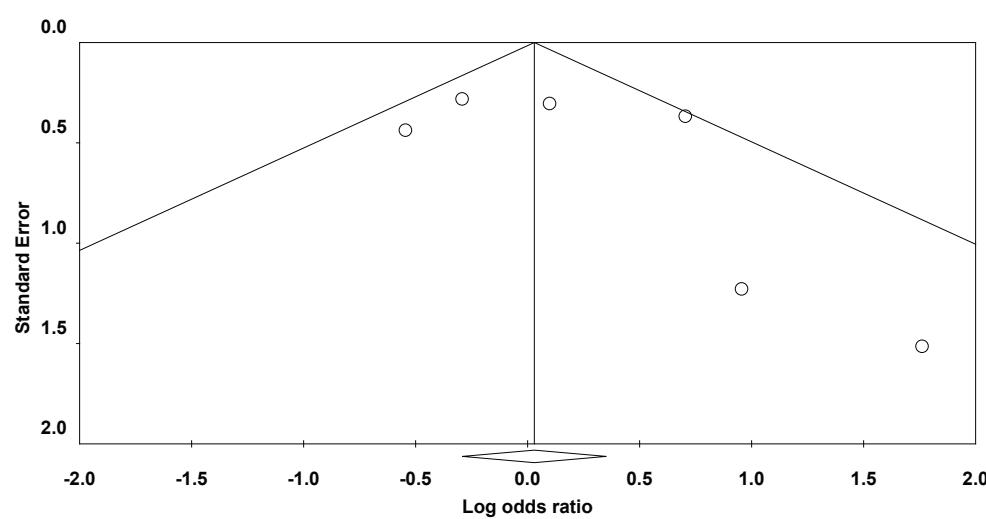
A Study name Odds Lower Upper Z-Value p-Value Odds ratio and 95% CI



B



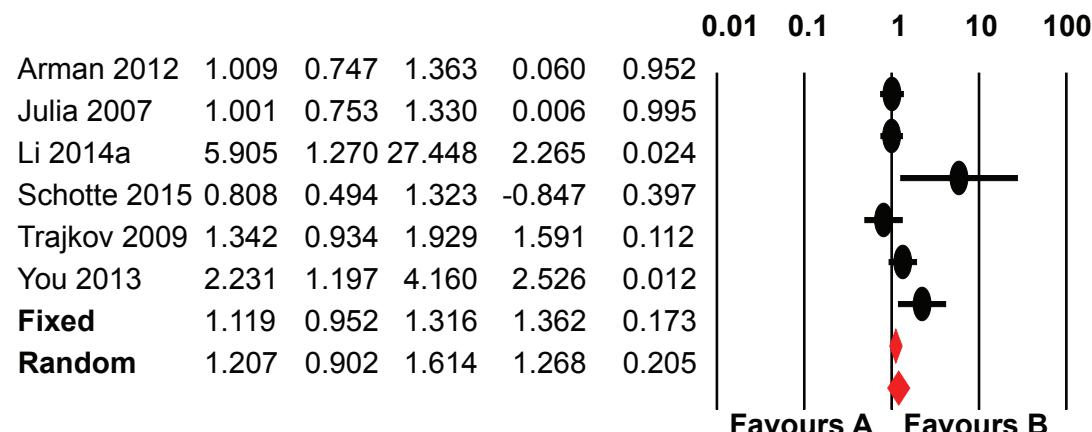
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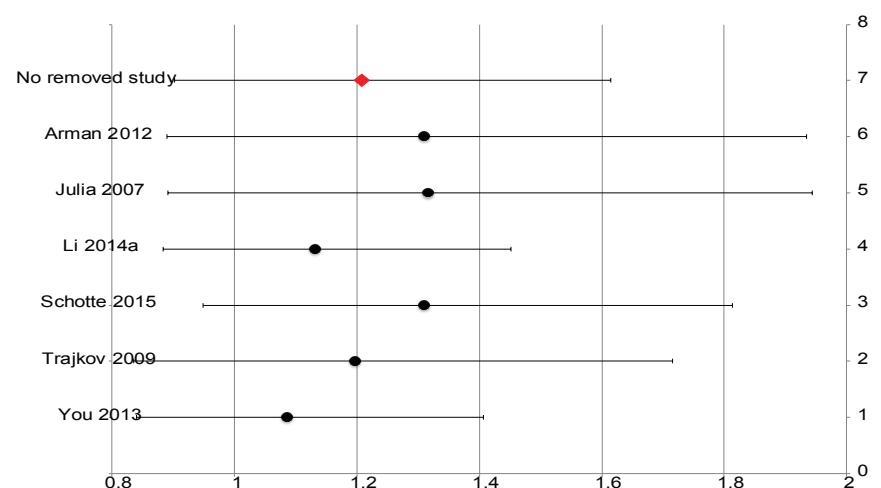
Supplementary Figure 15. Allelic model -597 G>A

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A Study name Odds Lower Upper Z-Value p-Value Odds ratio and 95% CI



B



C

