

First Author (Reference number) ¹	Year	Ethnicity - Country	Subject	MTHFR C677T									MTHFR A1298C								Quality score ⁵
				Case, disease type (DT), n (%)				Control, Source of control (SOC), n (%)					Case n (%)			Control n (%)					
				DT ²	CC	CT	TT	SOC ³	CC	CT	TT	HWE ⁴	AA	AC	CC	AA	AC	CC	HWE		
Kuehl [22]	2010	Caucasian - USA	Children	3	12 (21.6)	33 (60.0)	10 (18.2)	2	134 (44.7)	134 (44.7)	32 (10.7)	Yes	NA								21 (4, 10, 7)
Hobbs [23]	2010	Mixed -USA	Mothers	2	285 (51.5)	203 (36.7)	65 (11.8)	3	191 (53.7)	128 (36.0)	37 (10.4)	No	NA								22 (6, 9, 7)
Shaw [24]	2009	Mixed -USA	Children	1	102 (47.7)	89 (41.6)	23 (10.7)	1	101 (46.3)	93 (42.7)	24 (11.0)	Yes	NA								20 (6, 8, 6)
Shaw [25]	2005	Mixed -USA	Children	1	69 (45.1)	68 (44.4)	16 (10.5)	1	180 (41.5)	202 (46.5)	52 (12.0)	Yes	NA								21 (7, 8, 6)
Wenstrom [26]	2001	Mixed -USA	Children	2	17 (65.4)	8 (30.8)	1 (3.8)	1	104 (89.7)	9 (7.8)	3 (2.6)	No	NA								18 (6, 7, 5)
García-Fragoso [27]	2010	Hispanic - Puerto Rico	Mothers	2	10 (37.0)	11 (40.7)	6 (22.2)	7	84 (38.2)	115 (52.3)	21 (9.5)	No	NA								15 (5, 5, 5)
Balderrábano- Saucedo [28]	2013	Hispanic - Mexico	Mothers	1	7 (22.6)	12 (38.7)	12 (38.7)	3	24 (38.7)	31 (50.0)	7 (11.3)	Yes	NA								19 (6, 8, 5)
Sánchez-Urbina [29]	2012	Hispanic - Mexico	Children	2	7 (11.7)	41 (68.3)	12 (20.0)	1	9 (14.5)	46 (74.2)	7 (11.3)	No	NA								17 (3, 8, 6)
			Mothers	2	8 (13.3)	38 (63.3)	14 (23.3)	3	13 (21.0)	37 (59.7)	12 (19.4)	Yes									17 (3, 8, 6)
South America																					
Galdieri [30]	2006	Mixed - Brazil	Children	2	30 (51.7)	21 (36.2)	7 (12.1)	1	18 (47.4)	14 (36.8)	6 (15.8)	Yes	35 (61.4)	21 (36.8)	1 (1.8)	19 (50.0)	16 (42.1)	3 (7.9)	Yes	16 (6, 5, 5)	
			Mothers	2	27 (57.4)	15 (31.9)	5 (10.6)	1	10 (38.5)	15 (57.7)	1 (3.8)	Yes	26 (55.3)	17 (36.2)	4 (8.5)	15 (57.7)	10 (38.5)	1 (3.8)	Yes	16 (7, 4, 5)	
East Asia																					
Chao [31]	2014	East Asian - Taiwan	Children	3	10 (58.8)	5 (29.4)	2 (11.8)	1	19 (55.9)	12 (35.3)	3 (8.8)	Yes	13 (76.5)	2 (11.8)	2 (11.8)	15 (44.1)	19 (55.9)	0 (0)	No	17 (6, 6, 5)	
Lee [32]	2005	East Asian - Taiwan	Children	2	110 (51.6)	89 (41.8)	14 (6.6)	1	114 (58.5)	68 (34.9)	13 (6.7)	Yes	NA								17 (3, 8, 6)
Wang [33]	2016	East Asian - China	Children	2	14 (9.5)	73 (49.7)	60 (40.8)	1	49 (29.2)	84 (50.0)	35 (20.8)	Yes	NA								23 (6, 11, 6)
Shi [34]	2015	East Asian - China	Children	2	37 (26.8)	71 (51.4)	30 (21.7)	1	80 (38.6)	85 (41.1)	42 (20.3)	No	74 (53.6)	57 (41.3)	7 (5.1)	163 (78.7)	36 (17.4)	8 (3.9)	No	20 (2, 11, 7)	
			Mothers	2	55 (35.9)	68 (44.4)	30 (19.6)	3	70 (32.4)	101 (46.8)	45 (20.8)	Yes	95 (62.1)	39 (25.5)	19 (12.4)	157 (72.7)	53 (24.5)	6 (2.8)	Yes	21 (3, 11, 7)	
Li [35]	2015	East Asian - China	Children	2	31 (20.7)	78 (52.0)	41 (27.3)	1	59 (39.3)	66 (44.0)	25 (16.7)	Yes	114 (76.0)	36 (24.0)	0 (0)	131 (87.3)	19 (12.7)	0 (0)	Yes	22 (8, 8, 6)	
Jiang [36]	2015	East Asian - China	Mothers	2	38 (38.0)	46 (46.0)	16 (16.0)	2	41 (41.0)	48 (48.0)	11	Yes	NA								22 (6, 10, 6)

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				Case, disease type (DT), n (%)				Control, Source of control (SOC), n (%)					Case n (%)			Control n (%)					
				DT ²	CC	CT	TT	SOC ³	CC	CT	TT	HWE ⁴	AA	AC	CC	AA	AC	CC	HWE		
Huang [37]	2014	East Asian - China	Children	1	63 (37.5)	45 (26.8)	60 (35.7)	2	84 (41.2)	72 (35.3)	48 (23.5)	No	111 (65.3)	56 (32.9)	3 (1.8)	146 (70.9)	54 (26.2)	6 (2.9)	Yes	21 (6, 9, 6)	
Wang [38]	2013	East Asian - China	Children	2	59 (36.9)	76 (47.5)	25 (15.6)	1	53 (28.2)	100 (53.2)	35 (18.6)	Yes	115 (71.9)	40 (25.0)	5 (3.1)	133 (70.7)	47 (25.0)	8 (4.3)	Yes	21 (4, 11, 6)	
Gong [39]	2012	East Asian - China	Children	1	45 (18.4)	123 (50.4)	76 (31.1)	2	43 (31.6)	72 (52.9)	21 (15.4)	Yes	NA								23 (6, 10, 7)
Xu [40]	2010	East Asian - China	Children	2	162 (32.3)	244 (48.6)	96 (19.1)	2	151 (28.7)	261 (49.5)	115 (21.8)	Yes	316 (62.9)	168 (33.5)	18 (3.6)	326 (61.9)	185 (35.1)	16 (3.0)	Yes	22 (7, 9, 6)	
Li [41]	2009	East Asian - China	Children	2	16 (15.4)	42 (40.4)	46 (44.2)	2	55 (26.4)	114 (54.8)	39 (18.8)	Yes	NA								20 (6, 8, 6)
Liu [42]	2007	East Asian - China	Children	2	30 (22.7)	68 (51.5)	34 (25.8)	1	46 (43.0)	48 (44.9)	13 (12.1)	Yes	NA								17 (6, 5, 6)
Zhong [43]	2006	East Asian - China	Mothers	2	67 (58.3)	33 (28.7)	15 (13.0)	4	76 (66.1)	34 (29.6)	5 (4.3)	Yes	NA								15 (5, 7, 3)
			Fathers	2	67 (58.3)	41 (35.7)	7 (6.1)	6	73 (63.5)	34 (29.6)	8 (7.0)	Yes	NA								15 (5, 7, 3)
Liu [44]	2005	East Asian - China	Children	1	19 (19.6)	54 (55.7)	24 (24.7)	1	33 (28.0)	69 (58.5)	16 (13.6)	No	NA								12 (4, 4, 4)
Yan [45]	2003	East Asian - China	Children	2	32 (17.1)	97 (51.9)	58 (31.0)	1	22 (21.4)	57 (55.3)	24 (23.3)	Yes	NA								12 (4, 3, 5)
Yan [46]	2003	East Asian - China	Mothers	2	32 (17.1)	94 (50.3)	61 (32.6)	4	20 (19.6)	57 (55.9)	25 (24.5)	Yes	NA								11 (4, 2, 5)
			Fathers	2	26 (14.2)	104 (56.8)	53 (29.0)	6	21 (21.0)	57 (57.0)	22 (22.0)	Yes	NA								11 (4, 2, 5)
Liu [47]	2002	East Asian - China	Mothers	2	5 (18.5)	14 (51.9)	8 (29.6)	3	2 (10.0)	15 (75.0)	3 (15.0)	No	NA								14 (6, 5, 3)
South Asia																					
Koshy [48]	2015	South Asian - India	Children	1	95 (99.0)	1 (1.0)	0 (0)	1	83 (92.2)	7 (7.8)	0 (0)	Yes	27 (28.1)	32 (33.3)	37 (38.5)	58 (58.0)	20 (20.0)	22 (22.0)	No	16 (6, 6, 4)	
Middle-East Asia																					
Pishva [49]	2013	M-Eastern- Iran	Children	3	63 (51.2)	60 (48.8)	0 (0)	1	71 (56.8)	54 (43.2)	0 (0)	No	-	-	-	-	-	-	-	20 (5, 10, 5)	
Sahiner [50]	2014	M-Eastern- Turkey	Children	2	69 (50.7)	53 (39.0)	14 (10.3)	1	47 (50.5)	39 (41.9)	7 (7.5)	Yes	45 (32.8)	68 (49.6)	24 (17.5)	31 (33.3)	54 (58.1)	8 (8.6)	No	15 (5, 4, 6)	
Kocakap [51]	2014	M-Eastern - Turkey	Children	1	40 (53.3)	33 (44.0)	2 (2.7)	2	43 (45.3)	44 (46.3)	8 (8.4)	Yes	20 (29.0)	36 (52.2)	13 (18.8)	51 (51.5)	37 (37.4)	11 (11.1)	Yes	14 (5, 4, 5)	
Africa																					

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				Case, disease type (DT), n (%)				Control, Source of control (SOC), n (%)					Case n (%)			Control n (%)					
				DT ²	CC	CT	TT	SOC ³	CC	CT	TT	HWE ⁴	AA	AC	CC	AA	AC	CC	HWE		
Ei-Abd [52]	2014	African -Egypt	Children	2	7	12	7	1	13	5	0	Yes	NA				NA				17
			(26.9)	(46.2)	(26.9)		(72.2)	(27.8)	(0)									(4, 7, 6)			
		African -Egypt	Mothers	2	10	15	1	3	9	9	0	Yes	NA				NA				17
			(38.5)	(57.7)	(0)		(50.0)	(50.0)	(0)									(4, 7, 6)			
Elsayed [53]	2014	African -Egypt	Mothers	3	19	16	0	3	30	24	7	Yes	NA				NA				21
					(54.3)	(45.7)	(0)		(49.2)	(39.3)	(11.5)								(6, 10, 5)		
Zidan [54]	2013	African -Egypt	Children	2	18	21	41	1	32	21	27	No	16	27	37	30	26	24	No	16	
			(22.5)	(26.3)	(51.3)		(40.0)	(26.3)	(33.8)	(20.0)	(33.8)	(46.3)	(37.5)	(32.5)	(30.0)			(5, 5, 6)			
			Mothers	2	21	30	29	3	31	25	24	No	13	32	35	33	25	22	No	16	
			(26.3)	(37.5)	(36.3)		(38.8)	(31.3)	(30.0)	(16.3)	(40.0)	(43.8)	(41.3)	(31.3)	(27.5)			(5, 5, 6)			
Kotby [55]	2012	African -Egypt	Children	1	12	14	4	1	20	8	2	Yes	2	4	24	12	16	2	Yes	19	
			(40.0)	(46.7)	(13.3)		(66.7)	(26.7)	(6.7)	(6.7)	(13.3)	(80.0)	(40.0)	(53.3)	(6.7)			(6, 8, 5)			
			Mothers	1	12	16	2	3	20	10	1	Yes	2	4	24	14	14	2	Yes	18	
			(40.0)	(53.3)	(6.7)		(64.5)	(32.3)	(3.2)	(6.7)	(13.3)	(80.0)	(46.7)	(46.7)	(6.7)			(5, 8, 5)			

¹ Reference numbers refer to the Reference List that follows this table.

² DT: Disease type, 1: cyanotic congenital heart disease (CHD) (n = 12), 2: mixed CHD (n = 42), 3: acyanotic CHD (n = 4).

³ SOC: Sources of control, 1: healthy children (n = 30); 2: children without CHD (n = 7), 3: mother of healthy children (n = 14), 4: mother of children without CHD (n = 2), 5: father of healthy children (n = 2), 6: father of children without CHD (n = 2), 7: healthy volunteer (n = 1).

⁴ HWE: Hardy Weinberg Equilibrium, updated from the original report based on our calculations using the formula available at <http://www.koonec.com/k-blog/2010/06/20/hardy-weinberg-equilibrium-calculator>.

⁵ Quality score ranges: 0 - 28 (External validity, 0 - 9; Internal validity, 0 - 12; Report quality, 0 - 7).

⁶ 5 European Countries: Australia, Belgium, Germany, Netherlands, and United Kingdom.

Reference List of Studies included in the Meta-analysis

Ten meta-analysis papers

1. Xuan, C.; Li, H.; Zhao, J.-X.; Wang, H.-W.; Wang, Y.; Ning, C.P.; Liu, Z.; Zhang, B.B.; He, G.W.; Lun, L.M. Association between mthfr polymorphisms and congenital heart disease: A meta-analysis based on 9,329 cases and 15,076 controls. *Sci Rep* **2014**, *4*, 7311. DOI: 10.1038/srep07311. [[PubMed](#)] [[CrossRef](#)]
2. Zhang, T.; Wu, Q. MTHFR C677T and A1298C polymorphisms are not related to ventricular or atrial septal defect: A meta-analysis of 1272 cases and 1386 controls. *Int J Clin Exp Med* **2016**, *9*, 10673-10683.
3. Chen, K.; Chen, L.; Li, W.; Fang, Y.; Huang, G. Maternal MTHFR C677T polymorphism and congenital heart defect risk in the Chinese Han population: A meta-analysis. *Genet Mol Res* **2013**, *12*, 6212-6219. DOI: 10.4238/2013. [[PubMed](#)] [[CrossRef](#)]
4. Wang, W.; Wang, Y.; Gong, F.; Zhu, W.; Fu, S. MTHFR C677T polymorphism and risk of congenital heart defects: Evidence from 29 case-control and TDT studies. *PLoS One* **2013**, *8*, e58041. DOI: 10.1371/journal.pone.0058041. [[PubMed](#)] [[CrossRef](#)]
5. Yin, M.; Dong, L.; Zheng, J.; Zhang, H.; Liu, J.; Xu, Z. Meta analysis of the association between mthfr c677t polymorphism and the risk of congenital heart defects. *Ann Hum Genet* **2012**, *76*, 9-16. DOI: 10.1111/j.1469-1809.2011.00687.x. [[PubMed](#)] [[CrossRef](#)]
6. Nie, Y.; Gu, H.; Gong, J.; Wang, J.; Gong, D.; Cong, X.; Chen, X.; Hu, S. Methylenetetrahydrofolate reductase C677T polymorphism and congenital heart disease: A meta-analysis. *Clin Chem Lab Med* **2011**, *49*, 2101-2108. DOI: 10.1515/CCLM.2011.673. [[PubMed](#)] [[CrossRef](#)]
7. Li, Z.; Jun, Y.; Zhong-Bao, R.; Jie, L.; Jian-Ming, L. Association between MTHFR C677T polymorphism and congenital heart disease. *Herz* **2015**, *40*, 160-167. DOI: 10.1007/s00059-014-4144-8. [[PubMed](#)] [[CrossRef](#)]
8. Wang, W.; Hou, Z.; Wang, C.; Wei, C.; Li, Y.; Jiang, L. Association between 5, 10-methylenetetrahydrofolate reductase (MTHFR) polymorphisms and congenital heart disease: A meta-analysis. *Meta gene* **2013**, *1*, 109-125. DOI: 10.1016/j.mgene.2013.09.009. [[PubMed](#)]
9. Van Beynum, I.; Den Heijer, M.; Blom, H.; Kapusta, L. The MTHFR 677C→T polymorphism and the risk of congenital heart defects: A literature review and meta-analysis. *QJM* **2007**, *100*, 743-753. DOI: 10.1093/qjmed/hcm094. [[PubMed](#)] [[CrossRef](#)]
10. Verkleij-Hagoort, A.; Blik, J.; Sayed-Tabatabaei, F.; Ursem, N.; Steegers, E.; Steegers-Theunissen, R. Hyperhomocysteinemia and mthfr polymorphisms in association with orofacial clefts and congenital heart defects: A meta-analysis. DOI: 10.1002/ajmg.a.31684. *Am J Med Genet A* **2007**, *143*, 952-960. [[PubMed](#)] [[CrossRef](#)]

Three papers with duplicate use of data on genotype allele counts

11. Obermann-Borst, S.A.; van Driel, L.M.; Helbing, W.A.; de Jonge, R.; Wildhagen, M.F.; Steegers, E.A.; Steegers-Theunissen, R.P. Congenital heart defects and biomarkers of methylation in children: A case - control study. *Eur J Clin Invest* **2011**, *41*, 143-150. DOI: 10.1111/j.1365-2362.2010.02388.x. [[PubMed](#)] [[CrossRef](#)]
12. Zhu, W.L.; Li, Y.; Yan, L.; Dao, J.; Li, S. Maternal and offspring mthfr gene C677T polymorphism as predictors of congenital atrial septal defect and patent ductus arteriosus. *Mol Hum Reprod* **2005**, *12*, 51-54. DOI: 10.1093/molehr/gah252. [[PubMed](#)] [[CrossRef](#)]
13. Li, Y.; Cheng, J.; Zhu, W.; Dao, J.; Yan, L.; Li, M.; Li, S. Study of serum hcy and polymorphisms of hcy metabolic enzymes in 192 families affected by congenital heart disease. *Beijing da xue xue bao. Yi xue ban= Journal of Peking University. Health sci* **2005**, *37*, 75-80. [[PubMed](#)]

Forty-two papers included in meta-analysis

One meta-analysis paper with individual data

14. Mamasoula, C.; Prentice, R.R.; Pierscionek, T.; Pangilinan, F.; Mills, J.L.; Druschel, C.; Pass, K.; Russell, M.W.; Hall, D.; Töpf, A. Association between c677t polymorphism of methylene tetrahydrofolate reductase and congenital heart disease: **meta-analysis** of 7697 cases and 13,125 controls.. *Circ Cardiovasc Genet* **2013**, *6*, 347-353. DOI: 10.1161/CIRCGENETICS.113.000191. [[PubMed](#)] [[CrossRef](#)]

Forty-one individual studies

15. Weiner, A.S.; Gordeeva, L.A.; Voronina, E.N.; Boyarskikh, U.A.; Shabaldin, A.V.; Filipenko, M.L. Polymorphisms in folate-metabolizing genes and risk of having an offspring with congenital anomalies in the west siberian region of Russia: A case-control study. *Prenat Diagn* **2012**, *32*, 1041-1048. DOI: 10.1002/pd.3952. [[PubMed](#)] [[CrossRef](#)]
16. Wintner, S.; Hafner, E.; Stonek, F.; Stuempflen, I.; Metzenbauer, M.; Philipp, K. Association of congenital cardiac defects and the c677t methylenetetrahydrofolate reductase polymorphism. *Prenat Diagn* **2007**, *27*, 704-708. DOI: 10.1002/pd.1761. [[PubMed](#)] [[CrossRef](#)]

17. Junker, R.; Kotthoff, S.; Vielhaber, H.; Halimeh, S.; Kosch, A.; Koch, H.G.; Kassenböhmer, R.; Heineking, B.; Nowak-Göttl, U. Infant methylenetetrahydrofolate reductase 677TT genotype is a risk factor for congenital heart disease. *Cardiovasc Res* **2001**, *51*, 251-254. [[PubMed](#)]
18. Storti, S.; Vittorini, S.; Iascone, M.R.; Sacchelli, M.; Collavoli, A.; Ripoli, A.; Cocchi, G.; Biagini, A.; Clerico, A. Association between 5, 10-methylenetetrahydrofolate reductase c677t and a1298c polymorphisms and conotruncal heart defects. *Clin Chem Lab Med* **2003**, *41*, 276-280. DOI: 10.1515/CCLM.2003.043. [[PubMed](#)] [[CrossRef](#)]
19. van Driel, L.M.; Verkleij-Hagoort, A.C.; de Jonge, R.; Uitterlinden, A.G.; Steegers, E.A.; van Duijn, C.M.; Steegers-Theunissen, R.P. Two MTHFR polymorphisms, maternal B-vitamin intake, and CHDs. *Birth Defects Res A Clin Mol Teratol* **2008**, *82*, 474-481. DOI: 10.1002/bdra.20463. [[PubMed](#)] [[CrossRef](#)]
20. van Beynum, I.M.; Kapusta, L.; den Heijer, M.; Vermeulen, S.H.; Kouwenberg, M.; Daniëls, O.; Blom, H.J. Maternal MTHFR 677C> T is a risk factor for congenital heart defects: Effect modification by periconceptional folate supplementation. *Eur Heart J* **2006**, *27*, 981-987. DOI: 10.1093/eurheartj/ehi815. [[PubMed](#)] [[CrossRef](#)]
21. Marinho, C.; Alho, I.; Guerra, A.; Rego, C.; Areias, J.; Bicho, M. The methylenetetrahydrofolate reductase gene variant (C677T) as a susceptibility gene for Tetralogy of Fallot. *Rev Port Cardiol* **2009**, *28*, 809-812. [[PubMed](#)]
22. Kuehl, K.; Loffredo, C.; Lammer, E.J.; Iovannisci, D.M.; Shaw, G.M. Association of congenital cardiovascular malformations with 33 single nucleotide polymorphisms of selected cardiovascular disease-related genes. *Birth Defects Res A Clin Mol Teratol* **2010**, *88*, 101-110. DOI: 10.1002/bdra.20630. [[PubMed](#)] [[CrossRef](#)]
23. Hobbs, C.A.; Cleves, M.A.; Karim, M.A.; Zhao, W.; MacLeod, S.L. Maternal folate-related gene environment interactions and congenital heart defects. *Obstet Gynecol* **2010**, *116*, 316-322. DOI: 10.1097/AOG.0b013e3181e80979. [[PubMed](#)] [[CrossRef](#)]
24. Shaw, G.M.; Lu, W.; Zhu, H.; Yang, W.; Briggs, F.B.; Carmichael, S.L.; Barcellos, L.F.; Lammer, E.J.; Finnell, R.H. 118 snps of folate-related genes and risks of spina bifida and conotruncal heart defects. *BMC Med Genet* **2009**, *10*, 49-60. DOI: 10.1186/1471-2350-10-49. [[PubMed](#)] [[CrossRef](#)]
25. Shaw, G.M.; Iovannisci, D.M.; Yang, W.; Finnell, R.H.; Carmichael, S.L.; Cheng, S.; Lammer, E.J. Risks of human conotruncal heart defects associated with 32 single nucleotide polymorphisms of selected cardiovascular disease-related genes. *Am J Med Genet A* **2005**, *138*, 21-26. DOI: 10.1002/ajmg.a.30924. [[PubMed](#)]
26. Wenstrom, K.D.; Johanning, G.L.; Johnston, K.E.; DuBard, M. Association of the C677T methylenetetrahydrofolate reductase mutation and elevated homocysteine levels with congenital cardiac malformations. *Am J Obstet Gynecol* **2001**, *184*, 806-817. DOI: 10.1067/mob.2001.113845. [[PubMed](#)] [[CrossRef](#)]
27. García-Fragoso, L.; García-García, I.; Leavitt, G.; Renta, J.; Ayala, M.A.; Cadilla, C.L. MTHFR polymorphisms in puerto rican childrenren with isolated congenital heart disease and their mothers. *Int J Genet Mol Biol* **2010**, *2*, 43-47. [[PubMed](#)]
28. Balderrábano-Saucedo, N.A.; Sánchez-Urbina, R.; Sierra-Ramírez, J.A.; García-Hernández, N.; Sánchez-Boiso, A.; Klunder-Klunder, M.; Arenas-Aranda, D.; Bravo-Hernández, G.; Noriega-Zapata, P.; Vizcaíno-Alarcón, A. Polymorphism 677C→ T MTHFR gene in Mexican mothers of childrenren with complex congenital heart disease. *Pediatr Cardiol* **2013**, *34*, 46-51. DOI: 10.1007/s00246-012-0380-y. [[PubMed](#)] [[CrossRef](#)]
29. Sánchez-Urbina, R.; Galaviz-Hernández, C.; Sierra-Ramírez, J.A.; Rangel-Villalobos, H.; Torres-Saldúa, R.; Alva-Espinoza, C.; de Lourdes Ramírez-Dueñas, M.; García-Cavazos, R.; Arámbula-Meraz, E. Methylenetetrahydrofolate reductase gene 677CT polymorphism and isolated congenital heart disease in a mexican population. *Revista Española de Cardiología (English Edition)* **2012**, *65*, 158-163. DOI: 10.1016/j.recesp.2011.09.022. [[PubMed](#)] [[CrossRef](#)]
30. Galdieri, L.C.; Arrieta, S.R.; Silva, C.M.; Pedra, C.A.; D'Almeida, V. Homocysteine concentrations and molecular analysis in patients with congenital heart defects. *Arch Med Res* **2007**, *38*, 212-218. DOI: 10.1016/j.arcmed.2006.09.012. [[PubMed](#)] [[CrossRef](#)]
31. Chao, C.S.; Wei, J.; Huang, H.W.; Yang, S.C. Correlation between methyltetrahydrofolate reductase (MTHFR) polymorphisms and isolated patent ductus arteriosus in taiwan. *Heart, Lung and Circulation* **2014**, *23*, 655-660. DOI: 10.1016/j.hlc.2014.01.010. [[PubMed](#)]
32. Lee, C.N.; Su, Y.N.; Cheng, W.F.; Lin, M.T.; Wang, J.K.; Wu, M.H.; Hsieh, F.J. Association of the c677t methylenetetrahydrofolate reductase mutation with congenital heart diseases. *Acta Obstet Gynecol Scand* **2005**, *84*, 1134-1140. DOI: 10.1111/j.0001-6349.2005.00611.x. [[PubMed](#)]
33. Wang, Y.; Zhang, H.; Yue, S.; Zhang, K.; Wang, H.; Dong, R.; Yang, X.; Liu, Y.; Ma, Y. Evaluation of high resolution melting for MTHFR C677T genotyping in congenital heart disease. *PloS One* **2016**, *11*, e0151140. DOI: 10.1371/journal.pone.0151140. eCollection 2016. [[PubMed](#)]
34. Shi, H.; Yang, S.; Liu, Y.; Huang, P.; Lin, N.; Sun, X.; Yu, R.; Zhang, Y.; Qin, Y.; Wang, L. Study on environmental causes and SNPs of MTHFR, MS and CBS genes related to congenital heart disease. *PloS One* **2015**, *10*, e0128646. DOI: 10.1371/journal.pone.0128646. eCollection 2015. [[PubMed](#)]
35. Li, D.; Yu, K.; Ma, Y.; Liu, Y.; Ji, L. Correlationship between congenital heart disease and polymorphism of MTHFR gene. *Wei Sheng Yan Jiu* **2015**, *44*, 933-938. [[PubMed](#)]
36. Jiang, Y.; Mei, J.; Zhang, W.; Qian, X.; Zhang, S.; Liu, C.; Yang, H. Correlation between offspring congenital heart disease and mthfr 677 C/T polymorphism and general status of pregnant women. *Zhonghua liu xing bing xue za zhi= Zhonghua Liuxingbingxue Zazhi* **2015**, *36*, 1072-1076. [[PubMed](#)]

37. Huang, J.; Mei, J.; Jiang, L.; Jiang, Z.; Liu, H.; Ding, F. Mthfr rs1801133 C> T polymorphism is associated with an increased risk of tetralogy of Fallot. *Biomed Rep* **2014**, *2*, 172-176. DOI: 10.3892/br.2014.222. [[PubMed](#)]
38. Wang, B.; Liu, M.; Yan, W.; Mao, J.; Jiang, D.; Li, H.; Chen, Y. Association of snps in genes involved in folate metabolism with the risk of congenital heart disease. *J Matern Fetal Neonatal Med* **2013**, *26*, 1768-1777. DOI: 10.3109/14767058.2013.799648. [[PubMed](#)]
39. Gong, D.; Gu, H.; Zhang, Y.J.; Gong, J.; Nie, Y.; Wang, J.; Zhang, H.; Liu, R.; Hu, S.; Zhang, H. Methylenetetrahydrofolate reductase C677T and reduced folate carrier 80 G > A polymorphisms are associated with an increased risk of conotruncal heart defects. *Clin Chem Lab Med* **2012**, *50*, 1455-1461. DOI: 10.1515/cclm-2011-0759. [[PubMed](#)]
40. Xu, J.; Xu, X.; Xue, L.; Liu, X.; Gu, H.; Cao, H.; Qiu, W.; Hu, Z.; Shen, H.; Chen, Y. Mthfr c. 1793 G> A polymorphism is associated with congenital cardiac disease in a chinese population. *Cardiol Young* **2010**, *20*, 318-326. DOI: 10.1017/S1047951110000247. [[PubMed](#)]
41. Li, D.; Jing, X.; Wang, H.; Ye, W.; Fan, H. Study of correlationship between congenital heart disease and 5, 10-methylenetetra hydrofolate reductase gene's polymorphism or folacin intakes. *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]* **2009**, *43*, 700-704. [[PubMed](#)]
42. Liu, Y.; Yin, X.; Wang, J.; Yu, L.; Liu, H.; Meng, F.; Liu, D. Relationship between genetic polymorphism of homocysteine metabolism enzymes and congenital heart disease. *Chinese Journal of Cardiovascular Review* **2007**, *5*, 210-213. [[CrossRef](#)]
43. Zhong, Q.; Qiu, X.; Zeng, X.; Lin, N. Association of congenital heart diseases with MTHFR gene and CBS gene. *Guangxi Medical Journal* **2006**, *8*, 1140-1142.
44. Liu, F.; Bai, P.; Chen, S.; Qiu, W.; Liu, X.; Zhang, Y. Association between 5, 10-methylenetetrahydrofolate reductase c677t polymorphisms and conotruncal heart defects in chinese childrenren. *Chin J Contemp Pediatr* **2005**, *7*, 99-102.
45. Ying, Y.; Li, Y. MTHFR C677T polymorphism and congenital heart disease. *Journal of Peking University (Health Sciences)* **2003**, *35*, 448-402.
46. Yan, L.; Li, S.; Zhao, H.; Zhao, R.; Dao, J.; Zhu, W.; Li, Y. Effect of 5, 10-methylenetetrahydro-folate reductase genotypes in parents on the risk of congenital heart disease in offspring. *Chin J Control Prev* **2003**, *7*, 94-97.
47. Liu, H.; Li, S., L.; Hongmao, M. Y. Maternal homocysteine folic acid, MTHFR gene polymorphism and congenital heart defects in offspring. *Chin J Perinat Med* **2002**, *5*, 102-105. [[CrossRef](#)]
48. Koshy, T.; Venkatesan, V.; Perumal, V.; Hegde, S.; Paul, S.F.D. The A1298C methylenetetrahydrofolate reductase gene variant as a susceptibility gene for non-syndromic conotruncal heart defects in an indian population. *Pediatr Cardiol* **2015**, *36*, 1470-1475. DOI: 10.1007/s00246-015-1188-3. [[PubMed](#)]
49. Pishva, S.R.; Vasudevan, R.; Etemad, A.; Heidari, F.; Komara, M.; Ismail, P.; Othman, F.; Karimi, A.; Sabri, M.R. Analysis of mthfr and mtrr gene polymorphisms in iranian ventricular septal defect subjects. *Int J Mol Sci* **2013**, *14*, 2739-2752. DOI: 10.3390/ijms14022739. [[PubMed](#)]
50. Sahiner, U.M.; Alanay, Y.; Alehan, D.; Tuncbilek, E.; Alikasifoglu, M. Methylene tetrahydrofolate reductase polymorphisms and homocysteine level in heart defects. *Pediatr Int* **2014**, *56*, 167-172. DOI: 10.1111/ped.12222. [[PubMed](#)]
51. Kocakap, B.D.S.; Sanli, C.; Cabuk, F.; Koc, M.; Kutsal, A. Association of MTHFR A1298C polymorphism with conotruncal heart disease. *Cardiol Young* **2015**, *25*, 1326-1331. DOI: 10.1017/S1047951114002467. [[PubMed](#)]
52. El-Abd, D.M.; Said, R.N.; Hanna, B.M.; El-naggar, N.F. Maternal and offspring methylenetetrahydrofolate reductase gene c677t polymorphism: Does it influence the prevalence of congenital heart defects in egyptian neonates? *Comp Clin Path* **2014**, *23*, 317-322. [[CrossRef](#)]
53. Elsayed, G.M.; Elsayed, S.M.; Ezz-Elarab, S.S. Maternal MTHFR C677T genotype and septal defects in offspring with down syndrome: A pilot study. *Egyptian Journal of Medical Human Genetics* **2014**, *15*, 39-44. [[CrossRef](#)]
54. Zidan, H.E.; Rezk, N.A.; Mohammed, D. MTHFR C677T and A1298C gene polymorphisms and their relation to homocysteine level in Egyptian childrenren with congenital heart diseases. *Gene* **2013**, *529*, 119-124. DOI: 10.1016/j.gene.2013. [[PubMed](#)] [[CrossRef](#)]
55. Kotby, A.; Anwar, M.; El-Masry, O.; Awady, M.; El-Nashar, A.; Meguid, N. Genetic variants in the methylenetetrahydrofolate reductase gene in egyptian childrenren with conotruncal heart defects and their mothers. *Maced J Med Sci* **2012**, *5*, 78-84. DOI: 10.3889/MJMS.1857-5773.2012.0222. [[CrossRef](#)]

Supplementary Table 2. Pooled analysis: MTHFR 677 genotype and the risk of congenital heart disease for all study groups (58 studies).

Genotype by ethnicity (number of studies)	Case (N=12,347) n (%)	Control (N=18,106) n (%)	Test of Heterogeneity			Statistical Model	Test of Association		
			Q	p	I ² %		Risk Ratio	(95% CI)	p
TT (58)	1831 (14.8)	2170 (12.0)	113.6	< 0.0001	51.6	Random	1.30	(1.17 - 1.44)	< 0.0001
Caucasian (14)	710 (12.0)	1155 (11.6)	25.3	0.0211	48.6	Random	1.20	(1.01 - 1.42)	0.0417
East Asian (20)	756 (24.1)	548 (17.6)	46.4	0.0004	59	Random	1.41	(1.19 - 1.68)	< 0.0001
South Asian (1)	0 (0.0)	0 (0.0)	-	-	-	-	-	-	-
Mixed (7)	131 (10.3)	155 (9.5)	2.08	0.9119	0	Fixed	1.01	(0.80 - 1.27)	0.9543
Mideast (3)	16 (4.8)	15 (4.8)	2.7	0.0989	63.3	Fixed	0.89	(0.43 - 1.81)	0.7388
Hispanic (5)	120 (19.2)	207 (15.6)	12.2	0.0160	67.2	Random	1.61	(0.98 - 2.65)	0.0598
African (8)	98 (10.2)	90 (5.5)	6.998	0.4290	0	Fixed	1.29	(1.00 - 1.66)	0.0510
CT (58)	5311 (43.0)	7653 (42.3)	76.0	0.0472	25	1.01	1.006	(0.98 - 1.03)	0.6431
Caucasian (14)	2693 (45.5)	4439 (44.4)	17.5	0.1774	25.7	Fixed	1.03	(0.99 - 1.07)	0.1109
East Asian (20)	1465 (46.7)	1454 (46.7)	23.1	0.2312	17.9	Fixed	0.98	(0.93 - 1.04)	0.4982
South Asian (1)	1 (1.0)	7 (7.8)	-	-	-	-	0.13	-	-
Mixed (7)	476 (37.5)	617 (37.8)	15.1	0.0192	60.4	Random	0.98	(0.82 - 1.17)	0.8538
Mideast (3)	146 (43.7)	137 (43.8)	1.04	0.5939	0	Fixed	1.01	(0.85 - 1.21)	0.8916
Hispanic (5)	274 (43.8)	604 (45.6)	1.9	0.7502	0	Fixed	0.93	(0.84 - 1.04)	0.1956
African (8)	256 (26.6)	395 (24.2)	8.5	0.2883	17.9	Fixed	1.03	(0.89 - 1.18)	0.7262
CC (58)	5205 (42.2)	8283 (45.7)	148.4	< 0.0001	61.6	Random	0.91	(0.87 - 0.96)	0.0003
Caucasian (14)	2520 (42.5)	4404 (44.0)	24.3	0.0283	46.6	Random	0.94	(0.87 - 1.01)	0.0813
East Asian (20)	918 (29.2)	1111 (35.7)	56.2	< 0.0001	66.2	Random	0.81	(0.71 - 0.92)	0.0015
South Asian (1)	95 (99.0)	83 (92.2)	-	-	-	-	1.07	-	-
Mixed (7)	661 (52.1)	862 (52.8)	8.4	0.2071	29	Fixed	1.01	(0.94 - 1.09)	0.7709
Mideast (3)	172 (51.5)	161 (51.4)	1.9	0.3910	0	Fixed	1.00	(0.86 - 1.16)	0.9960
Hispanic (5)	232 (37.1)	515 (38.8)	4.4	0.3505	9.8	Fixed	1.01	(0.90 - 1.14)	0.8657
African (8)	607 (63.2)	1147 (70.3)	27.6	0.0003	74.7	Random	0.72	(0.55 - 0.95)	0.0204
TT+CT (58)	7142 (57.8)	9823 (54.3)	137.3	< 0.0001	58.5	Random	1.07	(1.04 - 1.11)	< 0.0001
Caucasian (14)	3403 (57.5)	5594 (56.0)	32.9	0.0018	60.4	Random	1.07	(1.01 - 1.14)	0.0253
East Asian (20)	2221 (70.8)	2002 (64.3)	50.2	0.0001	62.2	Random	1.10	(1.04 - 1.16)	0.0015
South Asian (1)	1 (1.0)	7 (7.8)	-	-	-	-	0.13	-	-
Mixed (7)	607 (47.9)	772 (47.2)	13.9	0.0306	56.9	Random	0.98	(0.86 - 1.13)	0.8135
Mideast (3)	162 (48.5)	152 (48.6)	1.8	0.3990	0	Fixed	1.00	(0.85 - 1.17)	0.9960
Hispanic (5)	394 (62.9)	811 (61.2)	5.4	0.2479	26	Fixed	0.99	(0.92 - 1.07)	0.8668
African (8)	354 (36.8)	485 (29.7)	18.7	0.0093	62.5	Random	1.24	(1.01 - 1.51)	0.0388
Subgroups									
TT risk >1 (11 countries)	5040 (53.4)	6162 (44.2)							
TT (42)	1069 (21.2)	885 (14.4)	75.4	0.0008	45.6	Random	1.43	(1.26 - 1.61)	< 0.0001
CT (42)	2311 (45.9)	2798 (45.4)	46.4	0.2601	11.6	Fixed	1.00	(0.96 - 1.04)	0.9429
CC (42)	1660 (32.9)	2479 (40.2)	84.5	< 0.0001	51.5	Random	0.84	(0.77 - 0.90)	< 0.0001
TT+CT (42)	3380 (67.1)	3683 (59.8)	78.6	0.0004	47.8	Random	1.10	(1.06 - 1.15)	< 0.0001
TT risk <1 (2 countries)	4119 (43.6)	7500 (53.8)							
TT (11)	431 (10.5)	812 (10.8)	6.9	0.7332	0	Fixed	0.97	(0.86 - 1.08)	0.5417
CT (11)	1579 (38.3)	2947 (39.3)	18.0	0.0552	44.4	Fixed	0.98	(0.93 - 1.03)	0.3946
CC (11)	2109 (51.2)	3741 (49.9)	16.3	0.0917	38.6	Fixed	1.02	(0.99 - 1.06)	0.2164
TT+CT (11)	2010 (48.8)	3759 (50.1)	30.9	0.0006	67.7	Random	1.01	(0.93 - 1.10)	0.8322
TT risk vary (3 countries)	281 (3.0)	276 (2.0)							
TT (4)	6 (2.1)	6 (2.2)	0.3	0.5603	0	Fixed	0.99	(0.34 - 2.90)	0.9801
CT (4)	83 (29.5)	92 (33.3)	7.5	0.0586	59.8	Fixed	0.91	(0.72 - 1.13)	0.3828
CC (4)	192 (68.3)	178 (64.5)	4.8	0.1857	37.7	Fixed	1.05	(0.94 - 1.17)	0.3808
TT+CT (4)	89 (31.7)	98 (35.5)	7.6	0.0558	60.4	Fixed	0.91	(0.74 - 1.12)	0.3795

Note. Q= Cochran's Q; CI=confidence interval. TT risk >1 (11 countries): Russia, Germany, Italy, Netherlands (5 studies), Portugal, Puerto Rico, Mexico (3 studies), Brazil (2 studies), Taiwan (2 studies), China (18 studies), and Egypt (7 studies); TT risk <1 (2 countries): US (9 studies), Turkey (2 studies); TT risk vary (3 countries): Austria, India, Iran; One study from 5 European countries.

Supplementary Table 3a Pooled analysis: *MTHFR* 677 genotypes and the risks of congenital heart disease for parents (23 Studies).

Genotypes by race or ethnicity (number of studies)	Case (N = 2596) n (%)	Control (N = 3056) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	P	I ² %		Risk Ratio (95% CI)	P
TT (23)	429 (16.5)	379 (12.4)	27.0	0.21	18.6	Fixed	1.24 (1.09 - 1.41)	0.0014
Caucasian (7)	105 (12.7)	150 (10.9)	8.4	0.2107	28.5	Fixed	1.13 (0.90 - 1.44)	0.2976
East Asian (7)	190 (21.6)	119 (15.5)	6.3	0.3909	4.7	Fixed	1.28 (1.04 - 1.58)	0.0226
Mixed (2)	70 (11.7)	38 (9.9)	0.7	0.4089	0	Fixed	1.18 (0.81 - 1.71)	0.3946
Hispanic (3)	32 (27.1)	40 (11.6)	3.9	0.1443	48.3	Fixed	1.94 (1.26 - 3.00)	0.0027
African (4)	32 (18.7)	32 (16.8)	3.3	0.3544	7.8	Fixed	1.05 (0.69 - 1.61)	0.8071
CT (23)	1131 (43.6)	1342 (43.9)	23.6	0.3667	6.9	Fixed	1.01 (0.95 - 1.07)	0.8559
Caucasian (7)	375 (45.3)	602 (43.9)	7.2	0.2997	17.1	Fixed	1.04 (0.94 - 1.15)	0.4344
East Asian (7)	400 (45.5)	346 (45.1)	4.0	0.6735	0	Fixed	0.96 (0.87 - 1.07)	0.4991
Mixed (2)	218 (36.3)	143 (37.4)	4.6	0.0318	78.3	Random	0.79 (0.44 - 1.43)	0.4418
Hispanic (3)	61 (51.7)	183 (53.2)	2.0	0.3686	0	Fixed	0.90 (0.72 - 1.13)	0.3713
African (4)	77 (45.0)	68 (35.8)	1.0	0.7991	0	Fixed	1.25 (0.97 - 1.62)	0.0830
CC (23)	1036 (39.9)	1335 (43.7)	20.7	0.5377	0	Fixed	0.92 (0.87 - 0.98)	0.0121
Caucasian (7)	347 (42.0)	620 (45.2)	5.8	0.4458	0	Fixed	0.93 (0.84 - 1.03)	0.1455
East Asian (7)	290 (33.0)	303 (39.5)	4.0	0.6764	0	Fixed	0.93 (0.82 - 1.05)	0.2211
Mixed (2)	312 (52.0)	201 (52.6)	2.4	0.1211	58.4	Fixed	0.99 (0.87 - 1.12)	0.8544
Hispanic (3)	25 (21.2)	121 (35.2)	1.6	0.4561	0	Fixed	0.75 (0.51 - 1.09)	0.1296
African (4)	62 (36.3)	90 (47.4)	4.0	0.2570	25.8	Fixed	0.79 (0.62 - 1.00)	0.0543
TT + CT (23)	1560 (60.1)	1721 (56.3)	22.1	0.4546	0.4	Fixed	1.06 (1.01 - 1.11)	0.0116
Caucasian (7)	480 (58.0)	752 (54.8)	6.7	0.3508	10.3	Fixed	1.06 (0.98 - 1.14)	0.1375
East Asian (7)	590 (67.0)	465 (60.5)	4.8	0.5735	0	Fixed	1.04 (0.97 - 1.12)	0.2273
Mixed (2)	288 (48.0)	181 (47.4)	3.0	0.0855	66.2	Fixed	1.01 (0.89 - 1.16)	0.8545
Hispanic (3)	93 (78.8)	223 (64.8)	1.2	0.5577	0	Fixed	1.12 (0.98 - 1.28)	0.1111
African (4)	109 (63.7)	100 (52.6)	3.1	0.3729	4	Fixed	1.19 (1.00 - 1.42)	0.0568
Subgroups								
TT risk >1 (9 countries)								
TT (21)	423 (14.7)	373 (10.9)	26.5	0.1502	24.5	Fixed	1.24 (1.09 - 1.42)	0.0012
CT (21)	1109 (38.2)	1311 (40.0)	20.6	0.4237	2.7	Fixed	1.02 (0.95 - 1.08)	0.6480
CC (21)	1002 (47.1)	1311 (49.1)	15.8	0.7272	0	Fixed	0.91 (0.86 - 0.97)	0.0047
TT+CT (21)	1532 (52.9)	1684 (50.9)	17.5	0.618	0	Fixed	1.07 (1.02 - 1.12)	0.0045
TT risk vary (1 country)						Fixed		
TT (2)	6 (14.7)	6 (10.9)	0.3	0.5603	0	Fixed	0.99 (0.34 - 2.90)	0.9801
CT (2)	22 (38.2)	31 (40.0)	0.1	0.7052	0	Fixed	0.70 (0.46 - 1.06)	0.0919
CC (2)	34 (47.1)	24 (49.1)	0.9	0.3517	0	Fixed	1.39 (0.95 - 2.04)	0.0918
TT+CT (2)	28 (52.9)	37 (50.9)	0.5	0.4947	0	Fixed	0.75 (0.53 - 1.05)	0.0911

Note. Q: Cochran's Q; CI: confidence interval. TT risk >1 for 9 countries: Netherlands (3 studies), Russia, Italy, US, Puerto Rico, Mexico (2 studies), Brazil, China (7 studies), and Egypt (4 studies); TT risk vary: Austria (2 studies)

Supplementary Table 3b. Pooled analysis: *MTHFR* 677 genotype and the risk of congenital heart disease for mothers (19 studies).

Genotype by ethnicity (number of studies)	Case (N=2596) n (%)	Control (N=3056) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
TT (19)	336 (16.5)	328 (12.8)	25.0	0.1240	28.1	Fixed	1.21 (1.04 - 1.39)	0.0106
Caucasian (5)	72 (12.7)	129 (11.8)	5.5	0.2391	27.4	Fixed	1.01 (0.77 - 1.31)	0.9704
East Asian (5)	130 (22.3)	89 (16.1)	5.7	0.2196	30.3	Fixed	1.30 (1.02 - 1.67)	0.0379
Mixed (2)	70 (11.7)	38 (9.9)	0.7	0.4089	0	Fixed	1.18 (0.81 - 1.71)	0.3946
Hispanic (3)	32 (27.1)	40 (11.6)	3.9	0.1443	48.3	Fixed	1.94 (1.26 - 3.00)	0.0027
African (4)	32 (18.7)	32 (16.8)	3.3	0.3544	7.8	Fixed	1.05 (0.69 - 1.61)	0.8071
CT (19)	881 (43.2)	1134 (44.3)	21.9	0.2368	17.8	Fixed	1.00 (0.94 - 1.08)	0.9249
Caucasian (5)	270 (47.6)	485 (44.5)	5.9	0.2048	32.5	Fixed	1.07 (0.95 - 1.20)	0.2689
East Asian (5)	255 (43.8)	255 (46.1)	1.9	0.7596	0	Fixed	0.92 (0.81 - 1.05)	0.2189
Mixed (2)	218 (36.3)	143 (37.4)	4.6	0.0318	78.3	Random	0.79 (0.44 - 1.43)	0.4418
Hispanic (3)	61 (51.7)	183 (53.2)	2.0	0.3686	0	Fixed	0.90 (0.72 - 1.13)	0.3713
African (4)	77 (45.0)	68 (35.8)	1.0	0.7991	0	Fixed	1.25 (0.97 - 1.62)	0.0830
CC (19)	821 (40.3)	1098 (42.9)	18.2	0.4395	1.4	Fixed	0.93 (0.87 - 1.00)	0.0498
Caucasian (5)	225 (39.7)	477 (43.7)	4.8	0.3117	16.1	Fixed	0.93 (0.82 - 1.06)	0.2557
East Asian (5)	197 (33.8)	209 (37.8)	2.6	0.6305	0	Fixed	0.97 (0.83 - 1.12)	0.6421
Mixed (2)	312 (52.0)	201 (52.6)	2.4	0.1211	58.4	Fixed	0.99 (0.87 - 1.12)	0.8544
Hispanic (3)	25 (21.2)	121 (35.2)	1.6	0.4561	0	Fixed	0.75 (0.51 - 1.09)	0.1296
African (4)	62 (36.3)	90 (47.4)	4.0	0.2570	25.8	Fixed	0.79 (0.62 - 1.00)	0.0543
TT+CT (19)	1217 (59.7)	1462 (57.1)	20.4	0.3105	11.8	Fixed	1.05 (1.00 - 1.11)	0.0477
Caucasian (5)	342 (60.3)	614 (56.3)	5.57	0.2335	28.2	Fixed	1.05 (0.97 - 1.15)	0.2431
East Asian (5)	385 (66.2)	344 (62.2)	3.25	0.5160	0	Fixed	1.02 (0.94 - 1.11)	0.6447
Mixed (2)	288 (48.0)	181 (47.4)	3.0	0.0855	66.2	Fixed	1.01 (0.89 - 1.16)	0.8545
Hispanic (3)	93 (78.8)	223 (64.8)	1.2	0.5577	0	Fixed	1.12 (0.98 - 1.26)	0.1111
African (4)	109 (63.7)	100 (52.6)	3.1	0.3729	4	Fixed	1.19 (1.00 - 1.42)	0.0568
Subgroups								
TT risk >1 (8 countries)	1619 (79.4)	2017 (78.8)						
TT (16)	293 (18.1)	265 (13.1)	18.2	0.2545	17.4	Fixed	1.29 (1.10 - 1.51)	0.0014
CT (16)	685 (42.3)	906 (44.9)	14.6	0.4813	0	Fixed	0.97 (0.89 - 1.05)	0.5168
CC (16)	641 (39.6)	846 (41.9)	14.2	0.5091	0	Fixed	0.51 (0.86 - 1.01)	0.0777
TT+CT (16)	978 (60.4)	1171 (58.1)	16.3	0.3636	7.9	Fixed	1.05 (1.00 - 1.11)	0.0752
TT risk <1 (2 countries)	419 (20.6)	543 (21.2)						
TT (3)	43 (10.3)	63 (11.6)	2.9	0.2349	31	Fixed	0.89 (0.60 - 1.25)	0.4417
CT (3)	196 (46.8)	228 (42.0)	4.7	0.0964	57.2	Fixed	1.11 (0.96 - 1.28)	0.1734
CC (3)	180 (43.0)	252 (46.4)	4.0	0.0964	50.4	Fixed	1.11 (0.81 - 1.08)	0.3858
TT+CT (3)	239 (57.0)	291 (53.6)	4.1	0.1276	51.4	Fixed	1.05 (0.94 - 1.18)	0.3802

Note. Q: Cochran's Q; CI: confidence interval. TT risk >1 (8 countries): Russia, Italy, US, Puerto Rico, Mexico (2 studies), Brazil, China (5 studies), and Egypt (4 studies); TT risk <1 (2 countries): Netherlands (2 studies) and Austria.

Supplementary Table 3c. Pooled analysis: *MTHFR* 677 genotype and the risk of congenital heart disease for fathers (4 studies).

Genotype by ethnicity (number of studies)	Case (N=558) n (%)	Control (N=496) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
TT (4)	93 (16.7)	51 (10.3)	1.5	0.6737	0	Fixed	1.39 (1.02 - 1.91)	0.0395
Caucasian (2)	33 (12.7)	21 (7.5)	0.0	0.8484	0	Fixed	1.70 (1.01 - 2.86)	0.0450
East Asian (2)	60 (20.1)	30 (14.0)	0.6	0.4544	0	Fixed	1.22 (0.82 - 1.81)	0.3257
CT (4)	250 (44.8)	208 (41.9)	1.7	0.6316	0	Fixed	1.02 (0.88 - 1.17)	0.8280
Caucasian (2)	105 (40.4)	117 (41.6)	0.7	0.4056	0	Fixed	0.97 (0.79 - 1.19)	0.7675
East Asian (2)	145 (48.7)	91 (42.3)	0.8	0.3748	0	Fixed	1.06 (0.88 - 1.28)	0.5257
CC (4)	215 (38.5)	237 (47.8)	2.3	0.5072	0	Fixed	0.89 (0.78 - 1.02)	0.0893
Caucasian (2)	122 (46.9)	143 (50.9)	1.0	0.3098	3.1	Fixed	0.92 (0.77 - 1.10)	0.3553
East Asian (2)	93 (22.5)	94 (43.7)	1.2	0.0099	19.5	Random	0.86 (0.67 - 1.11)	0.2490
TT+CT (4)	343 (61.5)	259 (52.2)	1.1	0.7813	0	Fixed	1.09 (0.99 - 1.21)	0.0920
Caucasian (2)	138 (53.1)	138 (49.1)	1.0	0.3204	0	Fixed	1.08 (0.92 - 1.28)	0.3530
East Asian (2)	205 (68.8)	121 (56.3)	0.1	0.7383	0	Fixed	1.10 (0.97 - 1.25)	0.1301

Note. Q: Cochran's Q; CI: confidence interval. TT risk >1 for all countries (Austria, China (2 studies), and Netherlands) of fathers. All mixed CHD.

Supplementary Table 4a. Pooled analysis: *MTHFR* C677T polymorphism and the risk of congenital heart disease (CHD) per CHD types for children (35 study groups).

Genotype by disease type and ethnicity (number of studies)	Case (N=9751) n (%)	Control (N=15,050) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
TT (35)	1402 (14.4)	1791 (11.9)	85.2	< 0.0001	62.4	Random	1.30 (1.14 - 1.48)	0.0001
Mixed CHD (23)	1179 (14.0)	1571 (12.1)	62.3	< 0.0001	64.7	Random	1.25 (1.08 - 1.45)	0.0028
Caucasian (5)	589 (11.8)	959 (11.9)	8.8	0.0660	54.6	Fixed	1.01 (0.91 - 1.11)	0.9164
East Asian (9)	404 (23.3)	341 (18.4)	34.7	< 0.0001	76.9	Random	1.37 (1.037 - 1.82)	0.0300
Mixed (3)	22 (7.3)	41 (6.8)	0.3	0.8638	0	Fixed	0.89 (0.54 - 1.47)	0.6451
Mideast (1)	14 (10.3)	7 (7.5)	-	-	-	-	1.37	-
Hispanic (2)	88 (17.3)	167 (17.0)	1.7	0.1923	41.2	Fixed	1.02 (0.81 - 1.30)	0.8420
African (3)	62 (8.2)	56 (4.0)	3.47	0.1764	42.4	Fixed	1.42 (1.02 - 1.96)	0.0371
Cyanotic CHD (9)	211 (18.9)	185 (11.7)	14.7	0.0397	52.5	Random	1.41 (1.03 - 1.94)	0.0311
Caucasian (1)	6 (15.8)	14 (5.6)	-	-	-	-	2.82	-
East Asian (3)	160 (31.4)	85 (18.6)	1.2	0.5620	0	Fixed	1.73 (1.37 - 2.19)	< 0.0001
South Asian (1)	0 (0.0)	0 (0.0)	-	-	-	-	1.00	-
Mixed (2)	39 (10.6)	76 (11.7)	0.1	0.7720	0	Fixed	0.92 (0.63 - 1.34)	0.6700
Mideast (1)	2 (2.7)	8 (8.4)	-	-	-	-	0.32	-
African (1)	4 (13.3)	2 (6.7)	-	-	-	-	1.99	-
Acyanotic CHD (3)	12 (6.2)	35 (7.6)	0.1	0.7900	0	Fixed	1.64 (0.90 - 3.01)	0.1092
Caucasian (1)	10 (18.2)	32 (10.7)	-	-	-	-	1.70	-
East Asian (1)	2 (11.8)	3 (8.8)	-	-	-	-	1.34	-
Mideast (1)	0 (0.0)	0 (0.0)	-	-	-	-	1.00	-
CT (35)	4180 (42.9)	6311 (41.9)	52.3	0.0023	35.0	Random	1.00 (0.96 - 1.05)	0.9822
Mixed CHD (23)	3635 (43.1)	5420 (41.6)	36.1	0.0299	39.0	Random	1.00 (0.95 - 1.05)	0.9984
Caucasian (5)	2265 (45.3)	3579 (44.3)	5.7	0.2212		Fixed	1.02 (0.98 - 1.06)	0.2609
East Asian (9)	838 (48.4)	833 (47.7)	15.2	0.0107	47.7	Fixed	1.01 (0.95 - 1.19)	0.6997
Mixed (3)	101 (33.6)	179 (29.8)	10.1	0.0063	80.3	Random	1.04 (0.85 - 1.27)	0.7397
Mideast (1)	53 (39.0)	39 (41.9)	-	-	-	-	0.93	-
Hispanic (2)	213 (41.9)	421 (42.9)	0.0	0.8641	0	Fixed	0.94 (0.83 - 1.06)	0.3174
African (3)	165 (21.7)	319 (22.6)	1.9	0.3806	0	Fixed	0.93 (0.79 - 1.11)	0.4302
Cyanotic CHD (9)	447 (40.1)	691 (43.8)	8.9	0.3510	10.1	Fixed	0.94 (0.86 - 1.03)	0.1915
Caucasian (1)	20 (52.6)	124 (49.4)	-	-	-	-	1.07	-
East Asian (3)	222 (43.6)	213 (46.5)	1.7	0.4256	0	Fixed	0.90 (0.78 - 1.03)	0.1195
South Asian (1)	1 (1.0)	7 (7.8)	-	-	-	-	0.13	-
Mixed (2)	157 (42.8)	295 (45.2)	0.0	0.8926	0	Fixed	0.96 (0.83 - 1.12)	0.6338
Mideast (1)	33 (44.0)	44 (46.3)	-	-	-	-	0.95	-
African (1)	14 (46.7)	8 (26.7)	-	-	-	-	1.75	-
Acyanotic CHD (3)	98 (50.3)	200 (43.6)	1.7	0.4302	0	Fixed	1.19 (0.99 - 1.43)	0.0586
Caucasian (1)	33 (60.0)	134 (44.7)	-	-	-	-	1.34	-
East Asian (1)	5 (29.4)	12 (35.3)	-	-	-	-	0.83	-
Mideast (1)	60 (48.8)	54 (43.2)	-	-	-	-	1.13	-
CC (35)	4169 (42.8)	6948 (46.2)	124.0	< 0.0001	72.6	Random	0.90 (0.85 - 0.96)	0.0014
Mixed CHD (23)	3627 (43.0)	6024 (46.3)	85.8	< 0.0001	74.4	Random	0.90 (0.83 - 0.97)	0.0165
Caucasian (5)	2149 (43.0)	3537 (43.8)	9.3	0.0549	56.8	Fixed	0.98 (0.94 - 1.02)	0.2329
East Asian (9)	491 (28.3)	629 (33.9)	44.8	< 0.0001	82.2	Random	0.73 (0.57 - 0.93)	0.0125
Mixed (3)	178 (59.1)	380 (63.3)	5.2	0.0742	61.6	Fixed	1.00 (0.89 - 1.12)	0.9443
Mideast (1)	69 (50.7)	47 (50.5)	-	-	-	-	1.00	-
Hispanic (2)	207 (40.7)	394 (40.1)	0.4	0.5497	0	Fixed	1.06 (0.93 - 1.79)	0.1288
African (3)	533 (70.1)	1037 (73.4)	14.7	0.0007	86.4	Random	0.64 (0.34 - 1.22)	0.1729
Cyanotic CHD (9)	457 (41.0)	700 (44.4)	33.9	< 0.0001	76.4	Random	0.90 (0.76 - 1.07)	0.2300
Caucasian (1)	12 (31.6)	113 (45.0)	-	-	-	-	0.70	-
East Asian (3)	127 (25.0)	160 (34.9)	4.1	0.1288	51.2	Fixed	0.76 (0.63 - 0.92)	0.0050
South Asian (1)	95 (99.0)	83 (92.2)	-	-	-	-	1.07	-
Mixed (2)	171 (46.6)	281 (43.1)	0.1	0.7066	0	Fixed	1.06 (0.92 - 1.22)	0.4499
Mideast (1)	40 (53.3)	43 (45.3)	-	-	-	-	1.18	-
African (1)	12 (40.0)	20 (66.7)	-	-	-	-	0.60	-
Acyanotic CHD (3)	85 (43.6)	224 (48.8)	6.1	0.0476	67.2	Random	0.79 (0.53 - 1.20)	0.2716
Caucasian (1)	12 (21.8)	134 (44.7)	-	-	-	-	0.49	-
East Asian (1)	10 (58.8)	19 (55.9)	-	-	-	-	1.05	-

Genotype by disease type and ethnicity (number of studies)	Case (N=9751) n (%)	Control (N=15,050) n (%)	Test of Heterogeneity			Statistical Model	Test of Association		
			Q	p	I ² %		Risk Ratio (95% CI)	p	
Mideast (1)	63 (51.2)	71 (56.8)	-	-	-	-	0.90	-	-
TT + CT (35)	5582 (57.2)	8102 (53.8)	115.6	< 0.0001	70.6	Random	1.09	(1.04 - 1.14)	0.0008
Mixed CHDs (23)	4814 (57.0)	6991 (53.7)	84.7	< 0.0001	74	Random	1.08	(1.02 - 1.14)	0.0077
Caucasian (5)	2854 (57.0)	4538 (56.2)	10.1	0.0380	60.6	Random	1.03	(0.96 - 1.10)	0.4416
East Asian (9)	1242 (71.7)	1224 (66.1)	40.7	< 0.0001	80.3	Random	1.13	(1.02 - 1.25)	0.0159
Mixed (3)	123 (40.9)	220 (36.7)	10.5	0.0054	80.9	Random	1.26	(0.73 - 2.15)	0.4044
Mideast (1)	67 (49.3)	46 (49.5)	-	-	-	-	1.00	-	-
Hispanic (2)	301 (59.3)	588 (59.9)	1.1	0.3013	6.4	Fixed	0.96	(0.88 - 1.05)	0.3953
African (3)	227 (29.9)	375 (26.6)	12.1	0.0024	83.4	Random	1.25	(0.84 - 1.87)	0.2671
Cyanotic CHDs (9)	658 (59.0)	876 (55.6)	17.7	0.0235	54.8	Random	1.07	(0.96 - 1.19)	0.2205
Caucasian (1)	26 (68.4)	138 (55.0)	-	-	-	-	1.24	-	-
East Asian (3)	382 (75.0)	298 (65.1)	1.3	0.5346	0	Fixed	1.13	(1.04 - 1.23)	0.0061
South Asian (1)	1 (1.0)	7 (7.8)	-	-	-	-	0.13	-	-
Mixed (2)	196 (53.4)	371 (56.9)	0.1	0.7534	0	Fixed	0.96	(0.85 - 1.08)	0.4536
Mideast (1)	35 (46.7)	52 (54.7)	-	-	-	-	0.85	-	-
African (1)	18 (60.0)	10 (33.3)	-	-	-	-	1.80	-	-
Acyanotic CHDs (3)	110 (56.4)	235 (51.2)	3.3	0.1887	40	Fixed	1.24	(1.06 - 1.45)	0.0066
Caucasian (1)	43 (78.2)	166 (55.3)	-	-	-	-	1.41	-	-
East Asian (1)	7 (41.2)	15 (44.1)	-	-	-	-	0.93	-	-
Mideast (1)	60 (56.4)	54 (43.2)	-	-	-	-	1.31	-	-

Note. Q: Cochran's Q; CI: confidence interval.

Supplementary Table 4b. Pooled analysis: *MTHFR* C677T polymorphism and the risk of congenital heart disease (CHD) per CHD types for parents (23 studies).

Genotype by disease type and ethnicity (number of studies)	Case (N=2596) n (%)	Control (N=3056) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
TT (23)	429 (16.5)	379 (12.4)	27.0	0.21	18.6	Fixed	1.24 (1.09 - 1.41)	0.0014
Mixed CHDs (19)	392 (16.4)	324 (12.0)	18.2	0.4401	1.3	Fixed	1.23 (1.07 - 1.42)	0.0032
Caucasian (6)	82 (11.3)	110 (9.4)	8.4	0.1364	40.3	Fixed	1.14 (0.86 - 1.50)	0.3539
East Asian (7)	190 (21.6)	119 (15.5)	6.3	0.3909	4.7	Fixed	1.28 (1.04 - 1.58)	0.0226
Mixed (2)	70 (11.7)	38 (9.9)	0.7	0.4089	0	Fixed	1.18 (0.81 - 1.71)	0.3946
Hispanic (2)	20 (23.0)	33 (11.7)	1.5	0.2218	33	Fixed	1.49 (0.90 - 2.56)	0.1159
African (2)	30 (28.3)	24 (24.5)	0.2	0.6435	0	Fixed	1.24 (0.80 - 1.93)	0.3409
Cyanotic CHDs (3)	37 (22.6)	48 (16.4)	5.5	0.0632	63.8	Fixed	1.47 (1.01 - 2.16)	0.0470
Caucasian (1)	23 (22.3)	40 (20.0)	-	-	-	-	1.12	-
Hispanic (1)	12 (38.7)	7 (11.3)	-	-	-	-	3.43	-
African (1)	2 (6.7)	1 (3.2)	-	-	-	-	2.09	-
Acyanotic CHDs (1)	0 (0.0)	7 (11.5)	-	-	-	-	-	-
African (1)								
CT (23)	1131 (43.6)	1342 (43.9)	23.6	0.3667	6.9	Fixed	1.01 (0.95 - 1.07)	0.8559
Mixed CHDs (19)	1034 (43.1)	1169 (43.3)	6.5	0.2597	23.2	Fixed	1.06 (0.95 - 1.18)	0.3077
Caucasian (6)	322 (44.5)	494 (42.2)	19.5	0.3620	7.7	Fixed	1.01 (0.94 - 1.07)	0.8748
East Asian (7)	400 (45.5)	346 (45.1)	4.0	0.6735	0	Fixed	0.96 (0.87 - 1.07)	0.4991
Mixed (2)	218 (36.3)	143 (37.4)	4.6	0.0318	78.3	Random	0.79 (0.44 - 1.43)	0.4418
Hispanic (2)	49 (56.3)	152 (53.9)	1.3	0.2561	22.5	Fixed	0.95 (0.74 - 1.21)	0.6617
African (2)	45 (42.5)	34 (34.7)	0.0	0.9131	0	Fixed	1.19 (0.84 - 1.68)	0.3346
Cyanotic (3)	81 (49.4)	149 (50.9)	3.7	0.1564	46.1	Fixed	0.98 (0.81 - 1.20)	0.8693
Caucasian (1)	53 (51.5)	108 (54.0)	-	-	-	-	0.95	-
Hispanic (1)	12 (38.7)	31 (50.0)	-	-	-	-	0.77	-
African (1)	16 (53.3)	10 (32.3)	-	-	-	-	1.65	-
Acyanotic (1)	16 (45.7)	24 (39.3)	-	-	-	-	1.16	-
African (1)								
CC (23)	1036 (39.9)	1335 (43.7)	20.7	0.5377	0	Fixed	0.92 (0.87 - 0.98)	0.0121
Mixed CHD (19)	971 (40.5)	1209 (44.7)	15.8	0.6036	0	Fixed	0.93 (0.87 - 1.00)	0.0225
Caucasian (6)	320 (44.2)	568 (48.5)	5.6	0.3463	10.8	Fixed	0.92 (0.83 - 1.02)	0.1191
East Asian (7)	290 (33.0)	303 (39.5)	4.0	0.6764	0	Fixed	0.93 (0.82 - 1.05)	0.2211
Mixed (2)	312 (52.0)	201 (52.6)	2.4	0.1211	58.4	Fixed	0.99 (0.87 - 1.12)	0.8544
Hispanic (2)	18 (20.7)	97 (34.4)	0.8	0.3830	0	Fixed	0.83 (0.54 - 1.29)	0.4145
African (2)	31 (29.2)	40 (40.8)	0.1	0.7578	0	Fixed	0.70 (0.48 - 1.03)	0.0675
Cyanotic (3)	46 (28.0)	96 (32.8)	3.0	0.2245	33.1	Fixed	0.81 (0.60 - 1.08)	0.1427
Caucasian (1)	27 (26.2)	52 (26.0)	-	-	-	-	1.01	-
Hispanic (1)	7 (22.6)	24 (38.7)	-	-	-	-	0.58	-
African (1)	12 (40.0)	20 (64.5)	-	-	-	-	0.62	-
Acyanotic (1)	19 (54.3)	30 (49.2)	-	-	-	-	1.10	-
African (1)								
TT + CT (23)	1560 (60.1)	1721 (56.3)	22.1	0.4546	0.4	Fixed	1.06 (1.01 - 1.11)	0.0116
Mixed (19)	1426 (59.5)	1493 (55.3)	16.5	0.5553	0	Fixed	1.06 (1.01 - 1.11)	0.0219
Caucasian (6)	404 (55.8)	604 (51.5)	5.8	0.3224	14.3	Fixed	1.08 (0.98 - 1.17)	0.1107
Mixed (2)	348 (58.6)	232 (53.5)	3.0	0.0855	66.2	Fixed	1.01 (0.89 - 1.16)	0.8545
Hispanic (2)	119 (68.0)	190 (63.8)	0.2	0.6563	0	Fixed	1.07 (0.92 - 1.24)	0.4080
East Asian (7)	590 (67.0)	465 (60.5)	4.8	0.5735	0	Fixed	1.04 (0.97 - 1.12)	0.2273
African (2)	75 (70.8)	58 (59.2)	0.0	0.9419	0	Fixed	1.21 (0.99 - 1.48)	0.0691
Cyanotic (3)	118 (72.0)	197 (67.3)	5.1	0.0769	61	Fixed	1.10 (0.97 - 1.25)	0.1319
Caucasian (1)	76 (73.8)	148 (74.0)	-	-	-	-	1.00	-
Hispanic (1)	24 (77.4)	38 (61.3)	-	-	-	-	1.26	-
African (1)	18 (60.0)	11 (35.5)	-	-	-	-	1.69	-
Acyanotic (1)	16 (45.7)	31 (50.8)	-	-	-	-	0.90	-
African (1)								

Note. Q: Cochran's Q; CI: confidence interval.

Supplementary Table 4c. Pooled analysis: *MTHFR* C677T polymorphism and the risk of congenital heart disease (CHD) per CHD types for mothers (19 studies).

Genotype by disease type and ethnicity (number of studies)	Case (N=2038) n (%)	Control (N=2560) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
TT (19)	336 (16.5)	328 (12.8)	25.0	0.1240	28.1	Fixed	1.21 (1.04 - 1.39)	0.0106
Mixed CHDs (15)	299 (16.3)	273 (12.4)	16.1	0.3101	12.8	Fixed	1.20 (1.02 - 1.40)	0.0242
Caucasian (4)	49 (10.6)	89 (10.0)	5.3	0.1511	43.4	Fixed	0.96 (0.69 - 1.33)	0.7894
East Asian (5)	130 (22.3)	89 (16.1)	5.7	0.2196	30.3	Fixed	1.30 (1.02 - 1.67)	0.0379
Mixed (2)	70 (11.7)	38 (9.9)	0.7	0.4089	0	Fixed	1.18 (0.81 - 1.71)	0.3946
Hispanic (2)	20 (23.0)	33 (11.7)	1.5	0.2218	33	Fixed	1.49 (0.90 - 2.56)	0.1159
African (2)	30 (28.3)	24 (24.5)	0.2	0.6435	0	Fixed	1.24 (0.80 - 1.93)	0.3409
Cyanotic CHDs (3)	37 (22.6)	48 (16.4)	5.5	0.0632	63.8	Fixed	1.47 (1.01 - 2.16)	0.0470
Caucasian (1)	23 (22.3)	40 (20.0)	-	-	-	-	1.12	-
Hispanic (1)	12 (38.7)	7 (11.3)	-	-	-	-	3.43	-
African (1)	2 (6.7)	1 (3.2)	-	-	-	-	2.09	-
Acyanotic CHDs (1)	0 (0.0)	7 (11.5)	-	-	-	-	-	-
African (1)								
CT (19)	881 (43.2)	1134 (44.3)	21.9	0.2368	17.8	Fixed	1.00 (0.94 - 1.08)	0.9249
Mixed CHDs (15)	784 (42.6)	961 (43.6)	17.8	0.2184	21.1	Fixed	1.00 (0.93 - 1.08)	0.9500
Caucasian (4)	217 (46.8)	377 (42.3)	4.7	0.1962	36	Fixed	1.10 (0.97 - 1.26)	0.1468
East Asian (5)	255 (43.8)	255 (46.1)	1.9	0.7596	0	Fixed	0.92 (0.81 - 1.05)	0.2189
Mixed (2)	218 (36.3)	143 (37.4)	4.6	0.0318	78.3	Random	0.79 (0.44 - 1.43)	0.4418
Hispanic (2)	49 (56.3)	152 (53.9)	1.3	0.2561	22.5	Fixed	0.95 (0.74 - 1.21)	0.6617
African (2)	45 (42.5)	34 (34.7)	0.0	0.9131	0	Fixed	1.19 (0.84 - 1.68)	0.3346
Cyanotic (3)	81 (49.4)	149 (50.9)	3.7	0.1564	46.1	Fixed	0.98 (0.81 - 1.20)	0.8693
Caucasian (1)	53 (51.5)	108 (54.0)	-	-	-	-	0.95	-
Hispanic (1)	12 (38.7)	31 (50.0)	-	-	-	-	0.77	-
African (1)	16 (53.3)	10 (32.3)	-	-	-	-	1.65	-
Acyanotic (1)	16 (45.7)	24 (39.3)	-	-	-	-	1.16	-
African (1)								
CC (19)	821 (40.3)	1098 (42.9)	18.2	0.4395	1.4	Fixed	0.93 (0.87 - 1.00)	0.0498
Mixed CHD (15)	756 (41.1)	972 (44.1)	13.3	0.5020	0	Fixed	0.94 (0.87 - 1.01)	0.0918
Caucasian (4)	198 (42.7)	425 (47.7)	4.6	0.2059	34.4	Fixed	0.92 (0.80 - 1.05)	0.2093
East Asian (5)	197 (33.8)	209 (37.8)	2.6	0.6305	0	Fixed	0.97 (0.83 - 1.12)	0.6421
Mixed (2)	312 (52.0)	201 (52.6)	2.4	0.1211	58.4	Fixed	0.99 (0.87 - 1.12)	0.8544
Hispanic (2)	18 (20.7)	97 (34.4)	0.8	0.3830	0	Fixed	0.83 (0.58 - 1.29)	0.4145
African (2)	31 (29.2)	40 (40.8)	0.1	0.7578	0	Fixed	0.70 (0.48 - 1.03)	0.0675
Cyanotic (3)	46 (28.0)	96 (32.8)	3.0	0.2245	33.1	Fixed	0.81 (0.60 - 1.08)	0.1427
Caucasian (1)	27 (26.2)	52 (26.0)	-	-	-	-	1.01	-
Hispanic (1)	7 (22.6)	24 (38.7)	-	-	-	-	0.58	-
African (1)	12 (40.0)	20 (64.5)	-	-	-	-	0.62	-
Acyanotic (1)	19 (54.3)	30 (49.2)	-	-	-	-	1.10	-
African (1)								
TT + CT (19)	1217 (59.7)	1462 (57.1)	20.4	0.3105	11.8	Fixed	1.05 (1.00 - 1.12)	0.0477
Mixed (15)	1083 (58.9)	1234 (56.0)	14.8	0.3917	5.4	Fixed	1.05 (0.99 - 1.11)	0.0891
Caucasian (4)	266 (57.4)	466 (52.3)	4.8	0.1834	38.1	Fixed	1.07 (0.97 - 1.19)	0.1948
Mixed (2)	348 (58.6)	232 (53.5)	3.0	0.0855	66.2	Fixed	1.01 (0.89 - 1.16)	0.8545
Hispanic (2)	119 (68.0)	190 (63.8)	0.198	0.6563	0	Fixed	1.07 (0.92 - 1.24)	0.4080
East Asian (5)	275 (66.8)	288 (57.8)	3.3	0.5160	0	Fixed	1.02 (0.94 - 1.11)	0.6447
African (2)	75 (70.8)	58 (59.2)	0.0	0.9419	0	Fixed	1.21 (0.99 - 1.48)	0.0691
Cyanotic (3)	118 (72.0)	197 (67.3)	5.1	0.0769	61	Fixed	1.10 (0.97 - 1.25)	0.1319
Caucasian (1)	76 (73.8)	148 (74.0)	-	-	-	-	1.00	-
Hispanic (1)	24 (77.4)	38 (61.3)	-	-	-	-	1.26	-
African (1)	18 (60.0)	11 (35.5)	-	-	-	-	1.69	-
Acyanotic (1)	16 (45.7)	31 (50.8)	-	-	-	-	0.90	-
African (1)								

Note. Q: Cochran's Q; CI: confidence interval.

Supplementary Table 5a. Pooled analysis: *MTHFR* 1298 genotype and the risk of congenital heart disease for all study groups (21 studies).

Genotype by ethnicity (number of studies)	Case (N=2754) n (%)	Control (N=3419) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
CC (21)	333 (12.1)	287 (8.4)	55.7	< 0.0001	65.9	Random	1.44 (1.07 - 1.95)	0.0174
Caucasian (5)	80 (9.5)	148 (11.3)	6.1	0.1949	34	Fixed	0.81 (0.62 - 1.07)	0.1345
East Asian (7)	54 (4.2)	44 (2.9)	10.9	0.0532	54.2	Fixed	1.52 (1.03 - 2.22)	0.0330
South Asian (1)	37 (38.5)	22 (22.0)	-	-	-	-	1.75 -	-
Mixed (2)	5 (4.8)	4 (6.3)	2.1	0.1444	53.1	Fixed	0.75 (0.20 - 2.79)	0.6642
Mideast (2)	37 (18.0)	19 (9.9)	0.1	0.7335	0	Fixed	1.87 (1.10 - 3.18)	0.0208
African (4)	120 (54.5)	50 (22.7)	18.8	0.0003	84.1	Random	3.34 (1.40 - 7.94)	0.0064
AC (21)	988 (35.9)	1225 (35.8)	73.7	< 0.0001	72.9	Random	1.02 (0.88 - 1.18)	0.8059
Caucasian (5)	349 (41.6)	594 (45.2)	8.3	0.0821	51.7	Fixed	0.89 (0.80 - 0.99)	0.0320
East Asian (7)	398 (30.9)	413 (27.0)	31.6	< 0.0001	81	Random	1.21 (0.88 - 1.65)	0.2403
South Asian (1)	32 (33.3)	20 (20.0)	-	-	-	-	1.67 -	-
Mixed (2)	38 (36.5)	26 (40.6)	0.03	0.8592	0	Fixed	0.90 (0.61 - 1.33)	0.6019
Mideast (2)	104 (50.5)	91 (47.2)	5.3	0.0208	81.3	Random	1.08 (0.67 - 1.74)	0.7659
African (4)	67 (30.5)	81 (36.8)	15.4	0.0015	80.5	Random	0.64 (0.31 - 1.29)	0.2115
AA (21)	1433 (52.0)	1907 (55.8)	111.2	< 0.0001	82	Random	0.91 (0.81 - 1.024)	0.1172
Caucasian (5)	409 (48.8)	573 (43.6)	12.9	0.0120	68.9	Random	1.19 (1.00 - 1.41)	0.0526
East Asian (7)	838 (65.0)	1071 (70.1)	27.6	0.0001	78.3	Random	0.92 (0.82 - 1.04)	0.1724
South Asian (1)	27 (28.1)	58 (58.0)	-	-	-	-	0.48 -	-
Mixed (2)	61 (58.7)	34 (53.1)	0.74	0.3891	0	Fixed	1.10 (0.84 - 1.46)	0.4867
Mideast (2)	65 (31.6)	82 (42.7)	3.9	0.0495	74.1	Fixed	0.75 (0.43 - 1.30)	0.3053
African (4)	33 (15.0)	89 (40.5)	4.95	0.1755	39.4	Fixed	0.37 (0.26 - 0.53)	< 0.0001
CC + AC (21)	1321 (48.0)	1512 (44.2)	107.3	< 0.0001	81.4	Random	1.16 (1.02 - 1.32)	0.0293
Caucasian (5)	429 (51.2)	742 (56.4)	10.8	0.0295	62.8	Random	0.88 (0.76 - 1.02)	0.0848
East Asian (7)	452 (35.0)	457 (29.9)	31.1	< 0.0001	80.7	Random	1.24 (0.94 - 1.64)	0.1361
South Asian (1)	69 (71.9)	42 (42.0)	-	-	-	-	1.71	-
Mixed (2)	43 (41.3)	30 (46.9)	0.7	0.3899	0	Fixed	0.88 (0.62 - 1.25)	0.4777
Mideast (2)	141 (68.4)	110 (57.3)	5.5	0.0188	81.9	Random	1.20 (0.83 - 1.74)	0.3261
African (4)	187 (85.0)	131 (59.5)	2.7	0.4343	0	Fixed	1.43 (1.26 - 1.61)	< 0.0001
Subgroups								
CC risk >1 (6 countries)	1915 (69.5)	2240 (65.5)						
CC (15)	256 (13.4)	148 (6.6)	29.8	0.0050	56.4	Random	1.85 (1.34 - 2.54)	0.0002
AC (15)	647 (33.8)	691 (30.8)	57.6	< 0.0001	75.7	Random	1.09 (0.89 - 1.33)	0.4025
AA (15)	1012 (52.8)	1401 (62.5)	72.6	< 0.0001	80.7	Random	0.80 (0.70 - 0.92)	0.0014
CC + AC (15)	903 (47.2)	839 (37.5)	54.2	< 0.0001	74.2	Random	1.31 (1.15 - 1.51)	< 0.0001
CC risk <1 (3 countries)	839 (30.5)	1179 (34.5)						
CC (6)	77 (9.2)	139 (11.8)	7.4	0.1904	32.7	Fixed	0.78 (0.59 - 1.03)	0.0780
AC (6)	341 (40.6)	534 (45.3)	7.0	0.2201	28.6	Fixed	0.87 (0.78 - 0.97)	0.0135
AA (6)	421 (50.2)	506 (42.9)	10.2	0.0708	50.8	Fixed	1.20 (1.09 - 1.33)	0.0003
CC + AC (6)	418 (49.8)	673 (57.1)	8.9	0.1147	43.6	Fixed	0.85 (0.78 - 0.93)	0.0004

Note. Q: Cochran's Q; CI: confidence interval. CC risk >1 (6 countries): Italy, Taiwan, China (6 studies), India, Turkey (2 studies), and Egypt (4 studies); CC risk <1 (3 countries): Russian, Netherlands (3 studies), and Brazil (2 studies).

Supplementary Table 5b. Pooled analysis: *MTHFR* 1298 genotype and the risk of congenital heart disease for children (13 studies).

Genotype by ethnicity (number of studies)	Case (N=1835) n (%)	Control (N=2003) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
CC (13)	198 (10.8)	133 (6.6)	19.3	0.0564	42.9	Fixed	1.56 (1.28 - 1.91)	< 0.0001
Caucasian (1)	27 (11.8)	25 (10.0)	-	-	-	-	1.18	-
East Asian (6)	35 (3.1)	38 (2.9)	3.3	0.5135	0	Fixed	1.10 (0.70 - 1.72)	0.6766
South Asian (1)	37 (38.5)	22 (22.0)	-	-	-	-	1.75	-
Mixed (1)	1 (1.8)	3 (3.8)	-	-	-	-	0.47	-
Mideast (2)	37 (18.0)	19 (9.9)	0.1	0.7335	0	Fixed	1.87 (1.10 - 3.18)	0.0208
African (2)	61 (55.5)	26 (23.6)	9.6	0.0019	89.6	Random	3.94 (0.44 - 34.95)	0.2187
AC (13)	637 (34.7)	658 (32.9)	60.6	< 0.0001	80.2	Random	1.07 (0.86 - 1.34)	0.5405
Caucasian (1)	90 (39.3)	129 (51.4)	-	-	-	-	0.77	-
East Asian (6)	359 (31.6)	360 (27.4)	31.3	< 0.0001	84	Random	1.23 (0.85 - 1.79)	0.2783
South Asian (1)	32 (33.3)	20 (20.0)	-	-	-	-	1.67	-
Mixed (1)	21 (36.8)	16 (42.1)	-	-	-	-	0.87	-
Mideast (2)	104 (50.5)	91 (47.4)	5.3	0.0208	81.3	Random	1.08 (0.34 - 1.74)	0.7659
African (2)	31 (28.2)	42 (38.2)	7.01	0.0078	85.9	Random	0.54 (0.13 - 2.24)	0.3990
AA (13)	1000 (54.5)	1212 (60.5)	65.9	< 0.0001	81.8	Random	0.88 (0.77 - 1.02)	0.0852
Caucasian (1)	112 (48.9)	97 (38.6)	-	-	-	-	1.27	-
East Asian (6)	743 (65.3)	914 (69.7)	26.4	< 0.0001	81.1	Random	0.94 (0.82 - 1.07)	0.3424
South Asian (1)	27 (28.1)	58 (58.0)	-	-	-	-	0.48	-
Mixed (1)	35 (61.4)	19 (50.0)	-	-	-	-	1.23	-
Mideast (2)	65 (31.6)	82 (42.7)	3.9	0.0495	74.1	Random	0.75 (0.43 - 1.30)	0.3053
African (2)	18 (16.4)	42 (38.2)	2.4	0.1212	58.4	Fixed	0.43 (0.26 - 0.70)	0.0006
CC + AC (13)	835 (45.5)	791 (39.5)	66.9	< 0.0001	82.1	Random	1.20 (1.01 - 1.43)	0.0398
Caucasian (1)	117 (51.1)	154 (61.4)	-	-	-	-	0.83	-
East Asian (6)	394 (34.7)	398 (30.3)	29.6	< 0.0001	83.1	Random	1.20 (0.86 - 1.68)	0.2719
South Asian (1)	69 (71.9)	42 (42.0)	-	-	-	-	1.71	-
Mixed (1)	22 (38.6)	19 (50.0)	-	-	-	-	0.77	-
Mideast (2)	141 (68.4)	110 (57.3)	5.5	0.0188	81.9	Random	1.20 (0.83 - 1.74)	0.3261
African (2)	92 (83.6)	68 (61.8)	1.1	0.2986	7.5	Fixed	1.35 (1.14 - 1.60)	0.0004
Subgroups								
CC risk >1 (5 countries)	658 (35.9)	687 (34.3)						
CC (7)	164 (24.9)	92 (13.4)	12.0	0.0626	49.9	Fixed	1.82 (1.45 - 2.29)	< 0.0001
AC (7)	259 (39.4)	301 (43.8)	27.0	0.0001	77.8	Random	0.89 (0.64 - 1.23)	0.4711
AA (7)	235 (35.7)	294 (42.8)	45.4	< 0.0001	86.8	Random	0.75 (0.49 - 1.15)	0.1936
CC + AC (7)	423 (64.3)	393 (57.2)	39.5	< 0.0001	84.8	Random	1.19 (0.93 - 1.51)	0.1658
CC risk <1 (1 country)	57 (3.1)	38 (1.9)						
CC (1)	1 (1.8)	3 (7.9)	-	-	-	-	0.23	-
AC (1)	21 (36.8)	16 (42.1)	-	-	-	-	0.87	-
AA (1)	35 (61.4)	19 (50.0)	-	-	-	-	1.23	-
CC+AC (1)	22 (38.6)	19 (50.0)	-	-	-	-	0.77	-
CC risk vary (1 country)	1120 (61.0)	1278 (63.8)						
CC (5)	33 (2.9)	38 (3.0)	1.3	0.7208	0	Fixed	1.02 (0.65 - 1.62)	0.9290
AC (5)	357 (31.9)	341 (26.7)	25.2	< 0.0001	84.1	Random	1.37 (0.96 - 1.95)	0.0844
AA (5)	730 (65.2)	899 (70.3)	19.4	0.0007	79.4	Random	0.90 (0.80 - 1.02)	0.0964
CC + AC (5)	390 (34.8)	379 (29.7)	25.0	< 0.0001	84	Random	1.32 (0.95 - 1.84)	0.0959

Note. Q: Cochran's Q; CI: confidence interval. CC risk >1 (5 countries): Netherlands, Taiwan, India, Turkey (2 studies), and Egypt (2 studies); CC risk <1 (1 country): Brazil; CC risk vary (1 country): China (5 studies).

Supplementary Table 5c. Pooled analysis: *MTHFR* 1298 genotype and the risk of congenital heart disease for parents (8 studies).

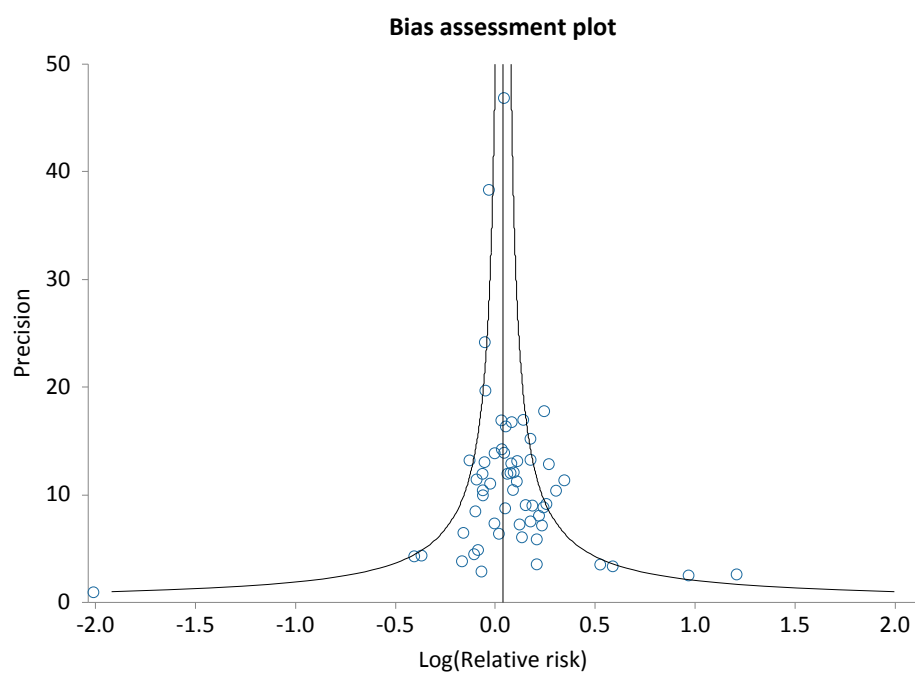
Genotype by ethnicity (number of studies)	Case (N= 919) n (%)	Control (N= 1416) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
CC (8)	135 (14.7)	154 (10.9)	34.4	< 0.0001	79.6	Random	1.44 (0.78 - 2.66)	0.2411
Caucasian (4)	53 (8.7)	123 (11.6)	3.6	0.3112	16.1	Fixed	0.71 (0.51 - 0.98)	0.0350
East Asian (1)	19 (12.4)	6 (2.8)	-	-	-	-	4.43	-
Mixed (1)	4 (8.5)	1 (3.8)	-	-	-	-	2.24	-
African (2)	59 (53.6)	24 (21.8)	9.2	0.0025	89.1	Random	3.99 (0.47 - 33.88)	0.2042
AC (8)	351 (38.2)	567 (40.0)	12.7	0.0807	44.7	Fixed	0.95 (0.85 - 1.06)	0.3684
Caucasian (4)	259 (42.5)	465 (43.7)	4.9	0.1806	38.6	Fixed	0.94 (0.84 - 1.07)	0.3439
East Asian (1)	39 (25.5)	53 (24.5)	-	-	-	-	1.04	-
Mixed (1)	17 (36.2)	10 (38.5)	-	-	-	-	0.94	-
African (2)	36 (32.7)	39 (35.5)	7.7	0.0055	87	Random	0.65 (0.15 - 2.86)	0.5658
AA (8)	433 (47.1)	695 (49.1)	42.8	< 0.0001	83.7	Random	0.93 (0.74 - 1.18)	0.5733
Caucasian (4)	297 (48.8)	476 (44.7)	12.4	0.006	75.9	Random	1.17 (0.93 - 1.45)	0.1756
East Asian (1)	95 (62.1)	157 (72.7)	-	-	-	-	0.84	-
Mixed (1)	26 (55.3)	15 (57.7)	-	-	-	-	0.96	-
African (2)	15 (13.6)	47 (42.7)	1.8	0.1774	45	Fixed	0.32 (0.19 - 0.54)	< 0.0001
CC + AC (8)	486 (52.9)	721 (50.9)	38.7	< 0.0001	81.9	Random	1.09 (0.88 - 1.34)	0.4291
Caucasian (4)	312 (51.2)	588 (55.3)	10.0	0.0185	70	Random	0.89 (0.73 - 1.08)	0.2333
East Asian (1)	58 (37.9)	59 (27.3)	-	-	-	-	1.39	-
Mixed (1)	21 (44.7)	11 (42.3)	-	-	-	-	1.06	-
African (2)	95 (86.4)	63 (57.3)	1.0	0.3211	0	Fixed	1.51 (1.26 - 1.80)	< 0.0001
Subgroups								
CC risk >1 (4 countries)	641 (45.6)	784 (36.7)						
CC (5)	90 (21.8)	44 (8.0)	13.5	0.0092	70.3	Random	2.69 (1.24 - 5.82)	0.0124
AC (5)	138 (33.4)	188 (34.1)	7.6	0.1062	47.6	Fixed	1.00 (0.84 - 1.20)	0.9888
AA (5)	185 (44.8)	320 (58.0)	15.6	0.0036	74.3	Random	0.73 (0.53 - 1.01)	0.0538
CC + AC (5)	228 (55.2)	232 (42.0)	7.4	0.1167	45.9	Fixed	1.29 (1.13 - 1.47)	0.0001
CC risk <1 (2 countries)	764 (54.4)	1353 (63.3)						
CC (3)	45 (8.9)	110 (12.7)	2.0	0.3628	1.4	Fixed	0.65 (0.45 - 0.92)	0.0158
AC (3)	213 (42.1)	379 (43.9)	4.4	0.111	54.5	Fixed	0.92 (0.80 - 1.06)	0.2366
AA (3)	248 (49.0)	375 (43.4)	8.9	0.012	77.4	Random	1.24 (0.97 - 1.60)	0.0920
CC + AC (3)	258 (51.0)	489 (56.6)	7.9	0.0191	74.7	Random	0.83 (0.65 - 1.06)	0.1406

Note. Q: Cochran's Q; CI: confidence interval. CC risk >1 (4 countries): Italy, Brazil, China, Egypt (2 studies); CC risk <1 (2 countries): Russia, Netherlands (2 studies)

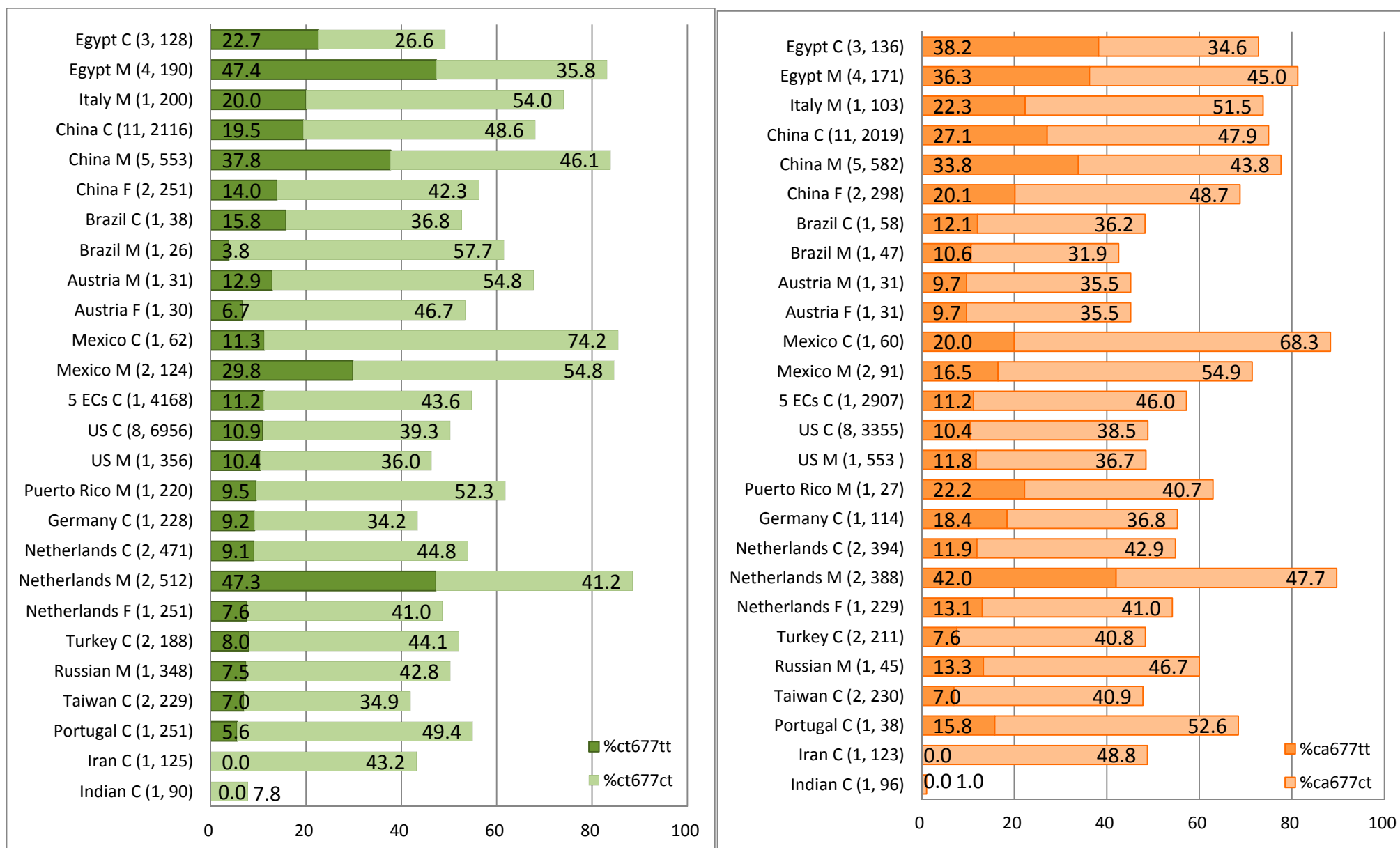
Supplementary Table 5d. Pooled analysis: *MTHFR* 1298 genotype and the risk of congenital heart disease for mothers (7 studies).

Genotype by ethnicity (number of studies)	Case (N = 691) n (%)	Control (N = 1165) n (%)	Test of Heterogeneity			Statistical Model	Test of Association	
			Q	p	I ² %		Risk Ratio (95% CI)	p
CC (7)	116 (16.8)	117 (10.0)	24.7	0.0004	75.7	Random	1.72 (0.89 - 3.31)	0.1042
Caucasian (3)	34 (8.9)	86 (10.6)	2.2	0.3401	7.3	Fixed	0.81 (0.54 - 1.22)	0.3162
East Asian (1)	19 (12.4)	6 (2.8)	-	-	-	-	4.43	-
Mixed (1)	4 (8.5)	1 (3.8)	-	-	-	-	2.24	-
African (2)	59 (53.6)	24 (21.8)	9.2	0.0025	89.1	Random	3.99 (0.47 - 33.9)	0.2042
AC (7)	253 (36.6)	444 (38.1)	11.4	0.0765	47.4	Fixed	0.98 (0.86 - 1.12)	0.7761
Caucasian (3)	161 (42.3)	342 (42.1)	3.8	0.1509	47.1	Fixed	0.98 (0.84 - 1.15)	0.7834
East Asian (1)	39 (25.5)	53 (24.5)	-	-	-	-	1.04	-
Mixed (1)	17 (36.2)	10 (38.5)	-	-	-	-	0.94	-
African (2)	36 (32.7)	39 (35.3)	7.7	0.0055	87	Random	0.65 (0.15 - 2.86)	0.5658
AA (7)	322 (46.6)	604 (51.8)	35.7	< 0.0001	83.2	Random	0.87 (0.67 - 1.13)	0.3053
Caucasian (3)	186 (48.8)	385 (47.4)	10.4	0.0054	80.9	Random	1.11 (0.83 - 1.48)	0.4800
East Asian (1)	95 (62.1)	157 (72.7)	-	-	-	-	0.84	-
Mixed (1)	26 (55.3)	15 (57.7)	-	-	-	-	0.96	-
African (2)	15 (13.6)	47 (42.7)	1.8	0.1774	45	Fixed	0.32 (0.19 - 0.54)	< 0.0001
CC + AC (7)	369 (53.4)	561 (48.2)	24.3	0.0005	75.3	Random	1.15 (0.93 - 1.42)	0.1923
Caucasian (3)	195 (51.2)	428 (52.6)	6.5	0.0385	69.3	Random	0.92 (0.70 - 1.19)	0.5158
East Asian (1)	58 (37.9)	59 (27.3)	-	-	-	-	1.39	-
Mixed (1)	21 (44.7)	11 (42.3)	-	-	-	-	1.06	-
African (2)	95 (86.4)	63 (57.3)	1.0	0.3211	0	Fixed	1.51 (1.26 - 1.80)	< 0.0001
Subgroups								
CC risk >1 (4 countries)								
CC (5)	90 (21.8)	44 (8.0)	13.5	0.0092	70.3	Random	2.69 (1.24 - 5.82)	0.0124
AC (5)	138 (33.4)	188 (34.1)	7.6	0.1062	47.6	Fixed	1.00 (0.84 - 1.20)	0.9888
AA (5)	185 (44.8)	320 (58.0)	15.6	0.0036	74.3	Random	0.73 (0.53 - 1.01)	0.0538
CC + AC (5)	228 (55.2)	232 (42.0)	7.4	0.1167	45.9	Fixed	1.29 (1.13 - 1.47)	0.0001
CC risk <1 (2 countries)								
CC (2)	26 (9.4)	73 (11.9)	1.3	0.2459	25.7	Fixed	0.72 (0.45 - 1.16)	0.1818
AC (2)	115 (41.4)	256 (41.8)	3.7	0.0538	73.1	Fixed	0.96 (0.79 - 1.16)	0.6619
AA (2)	137 (49.3)	284 (46.3)	8.2	0.0042	87.8	Random	1.20 (0.79 - 1.83)	0.3957
CC + AC (2)	141 (50.7)	329 (53.7)	6.0	0.0143	83.3	Random	0.80 (0.46 - 1.40)	0.4290

Note. Q: Cochran's Q; CI: confidence interval. CC risk >1 (4 countries): Italy, Brazil, China, and Egypt (2 studies); CC risk <1 (2 countries): Russia and Netherlands.

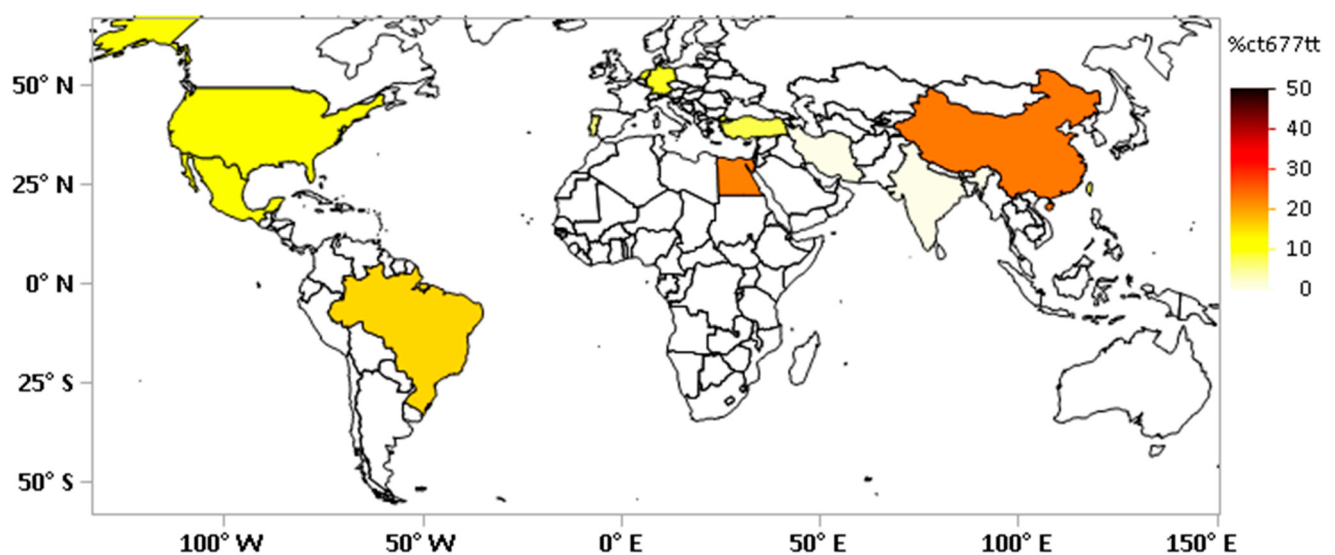


Supplementary Figure 1. The Funnel plot of *MTHFR* 677 TT+CT

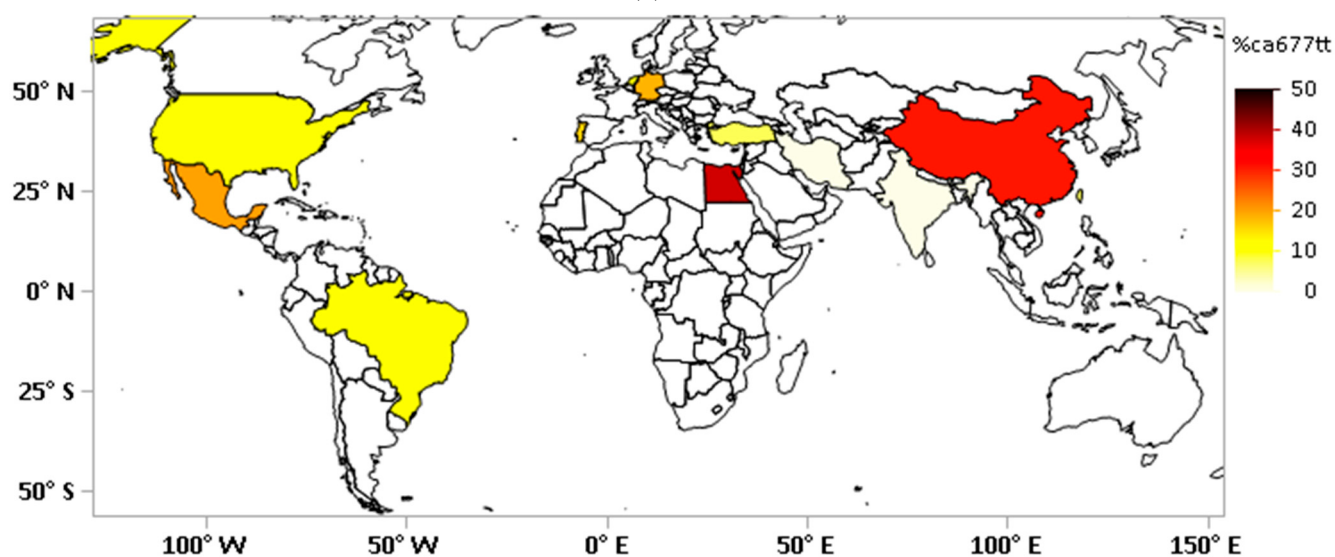


C = children; M = mothers; F = fathers; 5ECs: 5 European Countries: Australia, Belgium, Germany, Netherlands, and United Kingdom.

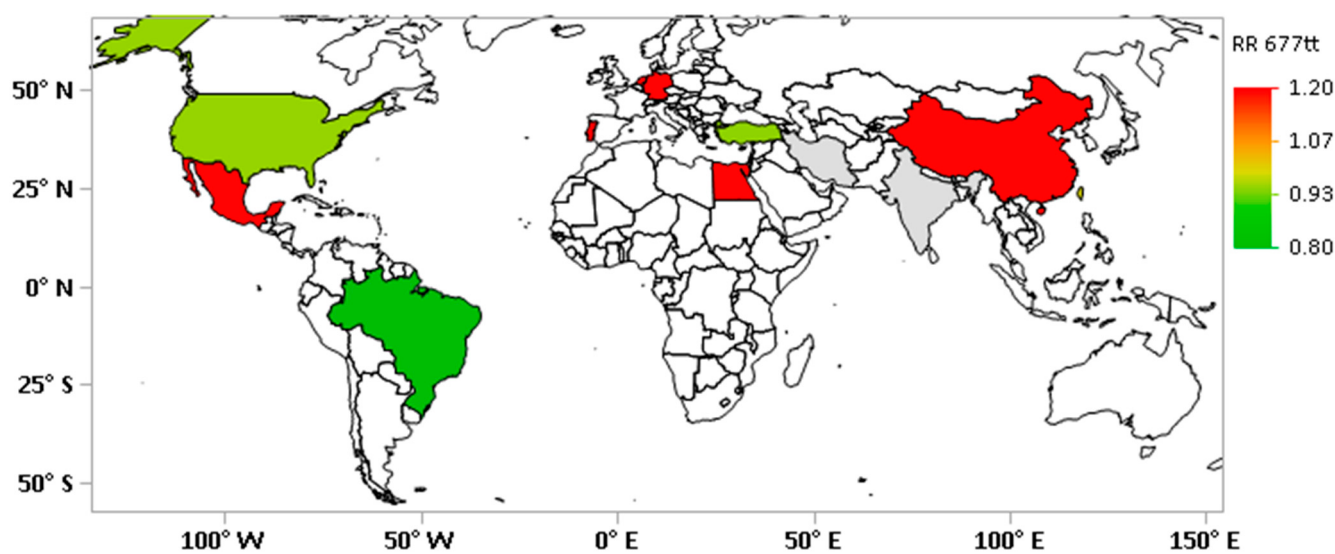
Supplementary Figure 2. The percent of *MTHFR* 677 TT and CT polymorphism per control (left) and congenital heart disease case (right) groups



(a)



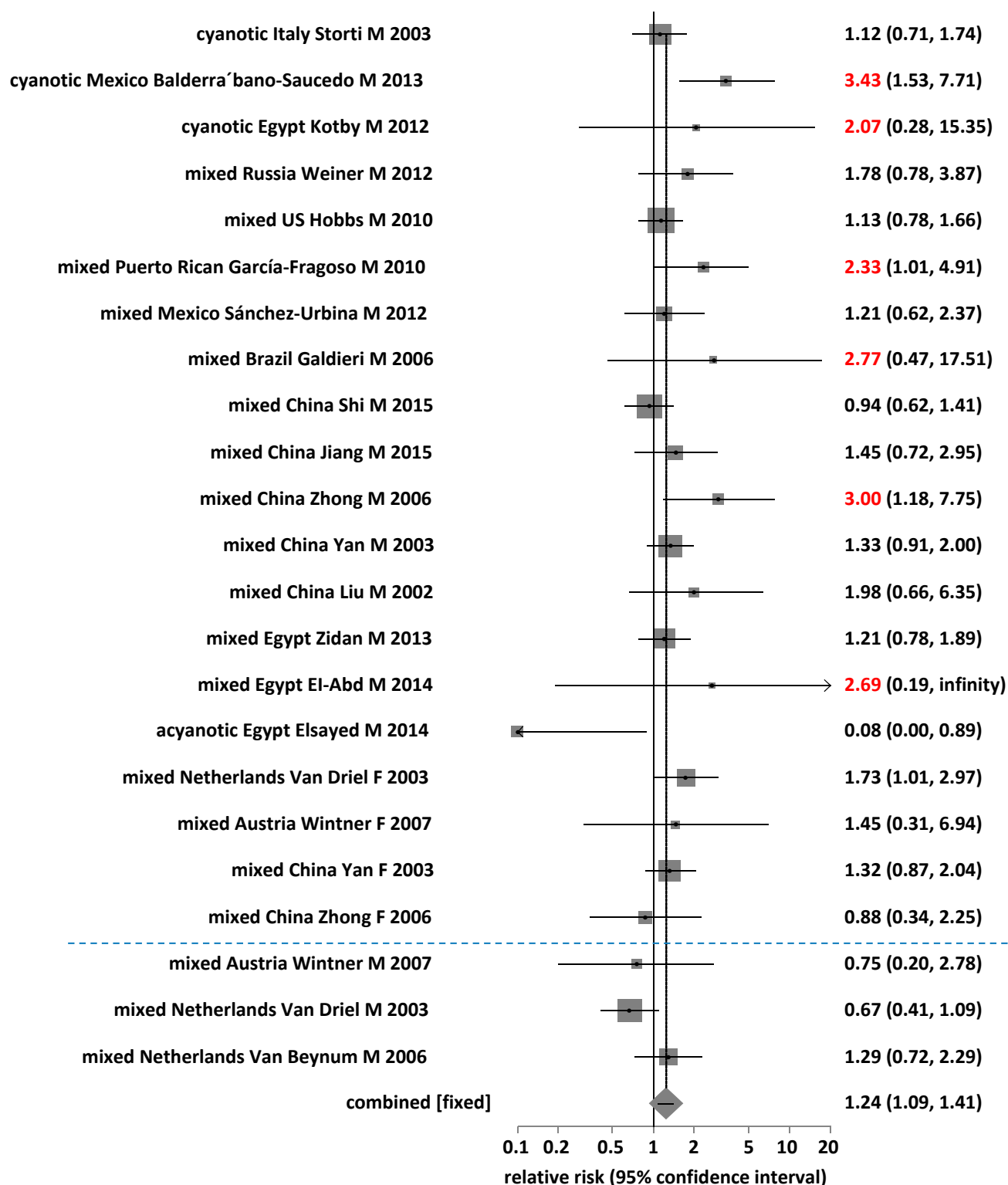
(b)



(c)

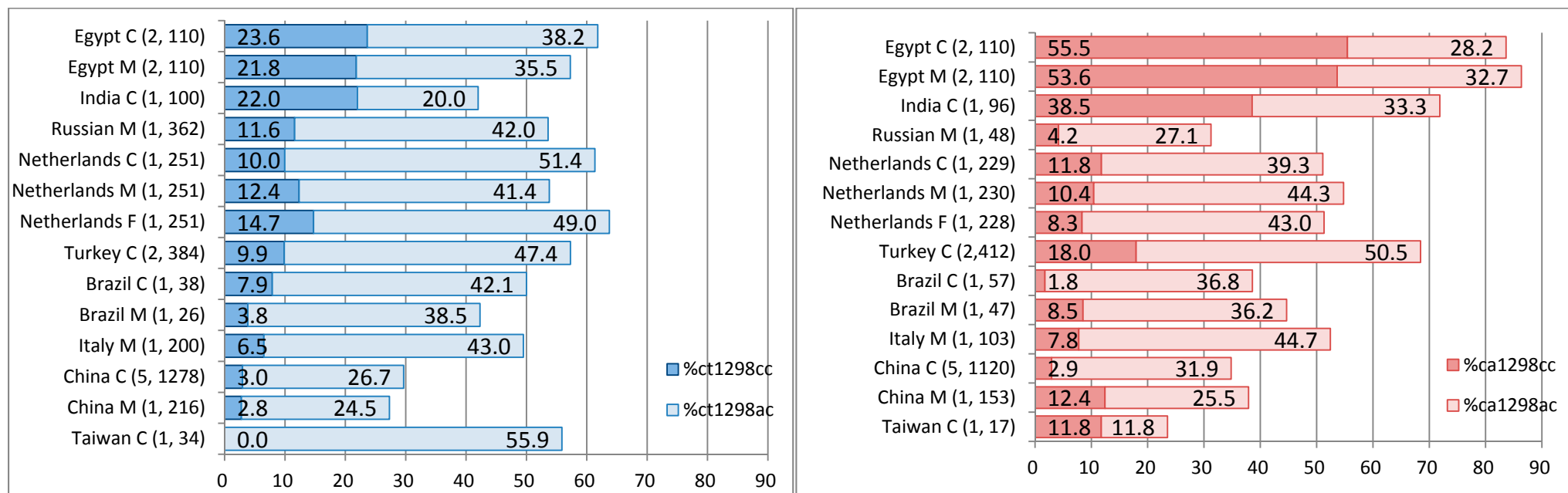
Supplementary Figure 3. Geographic information maps for the percent of *MTHFR* 677 TT polymorphism (a) per control group (ct), (b) per congenital heart disease (CHD) group (ca) and (c) CHD risk for children.

Relative risk meta-analysis plot (fixed effects)



Supplementary Figure 4. Forest plot of risks of congenital heart disease (CHD) by *MTHFR* 677 TT polymorphisms by types of CHD for mothers and fathers.

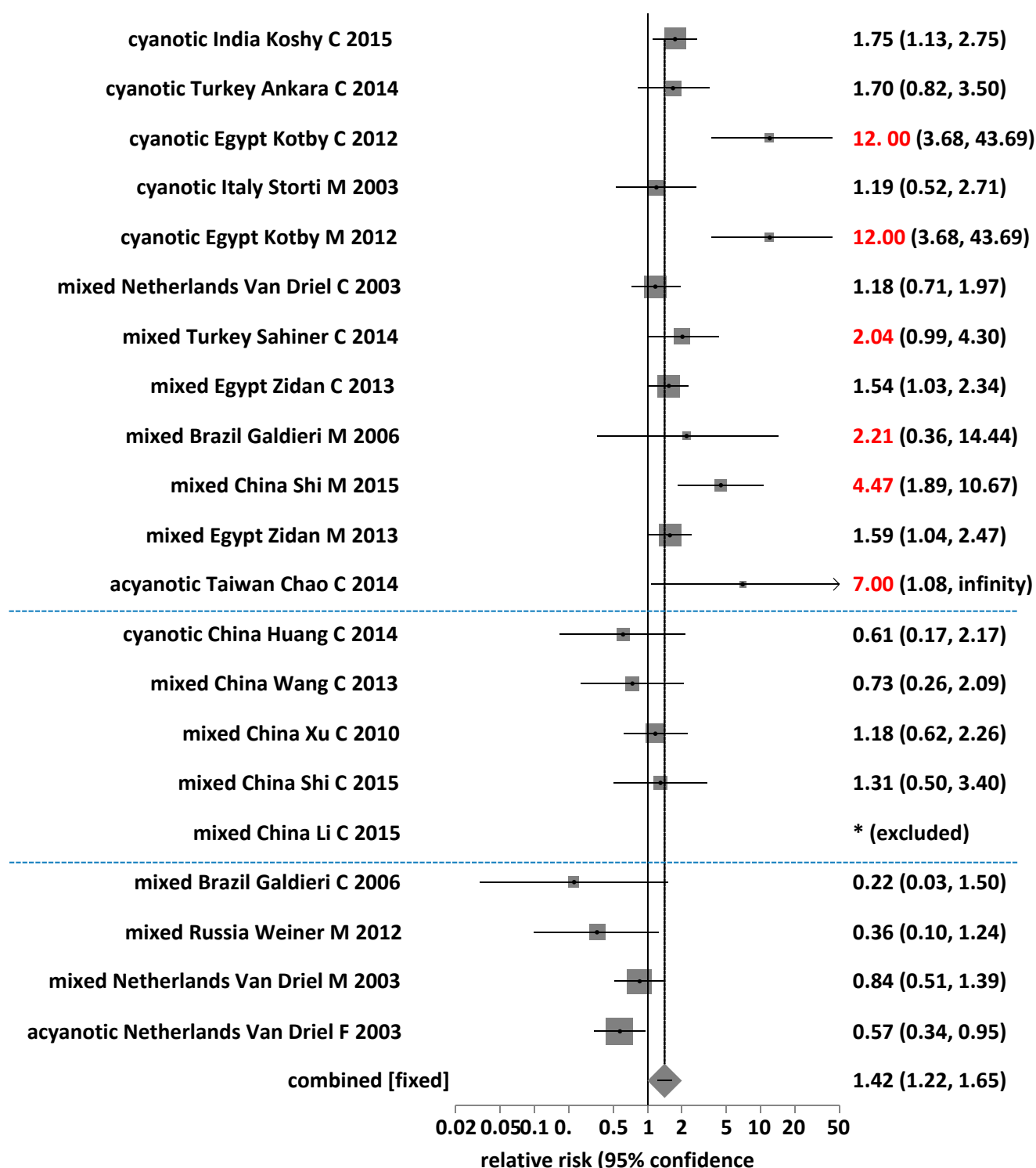
Note. Cyanotic: cyanotic CHDs; mixed: mixed cyanotic and acyanotic CHDs; acyanotic: acyanotic CHDs; M: mothers; F: fathers; studies above dotted line: TT risk >1; studies under dotted line: TT risk <1; red words: relative risk >2.



C = children; M = mothers; F = fathers

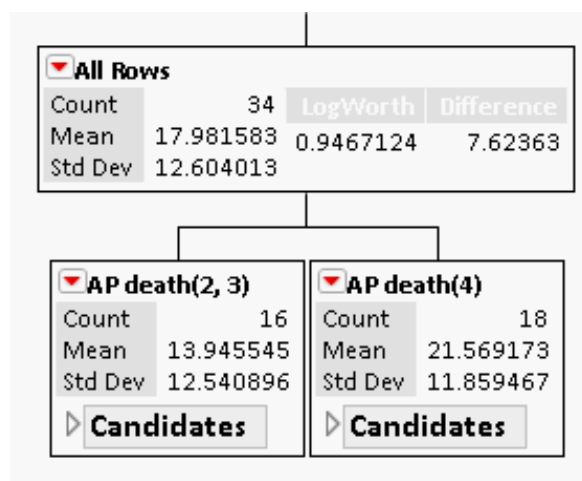
Supplementary Figure 5. The percent of *MTHFR* 1298 CC and AC polymorphism per control (left side) and congenital heart disease case (right side) groups

Relative risk meta-analysis plot (fixed effects)



Supplementary Figure 6. Forest plot of risks of congenital heart disease (CHD) by *MTHFR* 1298 CC polymorphisms per countries for children.

Note. Cyanotic: cyanotic CHDs; mixed: mixed cyanotic and acyanotic CHDs; acyanotic: acyanotic CHDs; C: children; M: mother; F: father; studies above dotted line: CC risk >1; studies between dotted lines: CC risk vary; studies under dotted line: CC risk <1; red words: relative risk >2.



Supplementary Figure 7. Recursive partition tree: the percent of *MTHFR* TT polymorphism by death from air pollution (AP death) for children with congenital heart disease.