Impact of the *CYP4F2* gene polymorphisms on the warfarin maintenance dose: A systematic review and meta-analysis

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Received December 1, 2015; Accepted January 28, 2016

DOI: 10.3892/br.2016.599

Abstract. Warfarin is an oral anticoagulant with significant interpatient variability in dosage. A large number of studies have confirmed that the individual warfarin dose is mainly affected by the cytochrome P450 complex subunit 2C9 and vitamin K epoxide reductase complex subunit 1. However, the association between cytochrome P450 4F2 (CYP4F2) gene polymorphisms and warfarin dosage in the Asian population remains controversial. To investigate the impact of the CYP4F2 polymorphism rs2108622 (p.V433M) on warfarin dose requirement, a systematic review and meta-analysis were conducted. According to the strict inclusion and exclusion criteria set, a comprehensive literature search was performed, and the studies published before August 5, 2015 were searched for in PubMed, EMBASE and the China National Knowledge Infrastructure databases. The references were checked by two independent reviewers. The association between the warfarin maintenance dose and CYP4F2 polymorphism was analyzed. Twenty-two studies were included in the meta-analysis. Compared with the CYP4F2 genotype CC, carriers of the CT and TT genotypes required a 9 [95% confidence interval (CI): 6.0-13.0] and 20% (95% CI, 13.0-27.0) higher warfarin dose, respectively. In the combined analysis, T carriers (CT+TT) required an 11% (95% CI, 8.0-14.0) higher warfarin dose compared to the CC genotype. In addition, there was a 10% (95% CI, 5.0-15.0) higher warfarin dose in TT carriers compared to the CT genotype (all P<0.05). The results of the meta-analysis suggest that the effects of the CYP4F2 polymorphism on individual warfarin dose have a statistically significant difference, and the effect degree is variable in the subgroups. Further studies are expected to explore whether the pharmacogenetics model

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Key words: warfarin, dose, thrombosis, CYP4F2, polymorphism

including the *CYP4F2* polymorphism can strengthen the prediction of warfarin dose.

Introduction

Warfarin is a commonly oral anticoagulant, mainly used clinically in the treatment of thromboembolic diseases, such as atrial fibrillation (AF) and deep venous thrombosis (DVT); however, the existence of high interpatient variability in drug dosage may increase the risk of bleeding or thrombosis. Studies indicated that individual warfarin dose was influenced by a host of factors, including genetic and environmental factors. Genetic factors are one of the main reasons for the individual difference in warfarin maintenance dosage. Previous studies have also suggested that cytochrome P450 complex subunit 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) polymorphisms, age, weight and body surface area can explain ~50% of the influence on warfarin dose requirement (1-6). Therefore, there remains a 50% uncertainty of the other factors to be further explored.

The cytochrome P450 4F2 (*CYP4F2*) gene, consisting of 13 exons and 12 introns and encoding 520 amino acid residues, is located on chromosome 19p13.12 in humans. Studies have shown that there are numerous single-nucleotide polymorphisms (SNPs) in the *CYP4F2* gene open reading frame, such as rs2108622, rs2074901 and rs2189784. Genome-wide association studies identified that the SNP associated with warfarin dose is *CYP4F2* p.V433M (rs2108622) in exon 11 (7). VKOR is mainly encoded by *CYP4F2*, which reduces VK1 by metabolizing VK1 to hydroxy VK1. Studies have also demonstrated that carriers of the *CYP4F2* p.V433M variant allele have a reduced capacity to metabolize VK1, and therefore, a higher warfarin dose was required to elicit the same anticoagulant response (8).

Since Caldwell *et al* (9) reported for the first time in 2008 that *CYP4F2* gene variants would change the warfarin maintenance dose in patients, an increasing number of research results regarding the correlation between the *CYP4F2* gene polymorphism and warfarin dose have been published. However, the findings are inconsistent, particularly for Asian patients (10-15). In 2012, two results of meta-analyses showed that the *CYP4F2* gene polymorphism was associated with the

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warfarin maintenance dosage (16,17). However, as they all focused on the studies of European and American populations, the impact of the *CYP4F2* genotype on warfarin dose in the Asian population has not been investigated adequately. Furthermore, following the publication of these 2 meta-analyses, new research results regarding the association between the *CYP4F2* polymorphism and warfarin maintenance dose in Asian patients remains inconsistent. Thus, the aim of the present study was to investigate the effect of the *CYP4F2* genotype on warfarin maintenance dose in the Asian population by a meta-analysis.

Materials and methods

Search strategy of the literature. The literature search was conducted in PubMed, EMBASE and China National Knowledge Infrastructure databases (until August 5, 2015). There was no limitation in the date of publication or language. The search keywords were (warfarin* OR coumarin) AND (gene OR genotype OR genetics OR allele* OR polymorphism* OR variant* OR pharmacogenetics) AND (*CYP4F2*). Under the circumstances of missing data or ambiguity, the authors were contacted for additional information.

Study selection. The original studies published in full text were included. Reviews, case reports and editorials were excluded. In addition, the studies that were not of an Asian population, that did not include genotype frequencies or warfarin maintenance dose, and that did not include the indispensable information from the authors contacted were excluded. The following criteria were used to select the appropriate studies: i) Studies on Asian patients >18 years treated with warfarin; ii) *CYP4F2* genotyping performed in all patients or in a random selection of patients; and iii) warfarin maintenance dose (mean and standard deviation) available separately for CC, CT and TT genotypes or for the dominant model. There were no restrictions in the inclusion criteria with respect to patient demographic information.

Data extraction. Data of all the eligible studies were extracted and summarized independently by two reviewers. The recorded original information included the first author, the year of publication, country, the total sample size (the percentage of males), mean age, indication of warfarin, target international normalized ratio range, allele frequencies of *CYP4F2* and warfarin maintenance dose.

Quality score assessment. Two reviewers assessed the quality of the selected studies independently according to the Cochrane handbook and the criteria predefined by Little *et al* (18). The quality criteria were: i) Purpose of the study; ii) analytic validity of genotyping (types of samples used, timing of sample collection and analysis, genotyping method and quality control measures); iii) selection of the study subjects (geographic area, recruitment period, exclusion criteria, mean age and standard deviation or age range of study subjects, and the distribution by gender); and iv) statistical issues (methods of analysis used in reference and software used in the analysis). A study was graded as '++', '+' or '-' according to the satisfaction degree of the aforementioned criteria.



Figure 1. Flow diagram of the study selection procedure.

Statistical analysis. In order to eliminate any heterogeneity among different study populations, the maintenance dose of warfarin was normalized for each *CYP4F2* genotype group using the *CYP4F2* CC genotype as a reference. The normalization process was conducted by dividing the mean dose and associated standard deviations in each group by the mean maintenance dose in the *CYP4F2* CC group according to Lindh *et al* (19). Carriers of the CT or TT genotype were defined as 'T carriers'.

The association between the mean daily warfarin dose (MDWD) and CYP4F2 gene polymorphisms was analyzed using the Review Manager 5.3 software (2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The normalized doses in the three genotype groups (CT, TT and T carriers) were compared with the CC genotype (reference group) by 3 meta-analyses. The TT genotype was compared with the CT genotype. The studies were weighted by the inverse variance method, and the effect of each CYP4F2 genotype on the warfarin dose was defined as the mean difference (MD). The calculated MDs represent the relative differences in the maintenance dose due to the normalization procedure. The total weighted MD (WMD) is the sum of the WMD for each study. Z-test was employed to examine the effect of the CYP4F2 SNP on MDWD, and P<0.05 was considered to indicate a statistically significant difference.

Heterogeneity among studies was estimated by the Cochran's Q-statistic and I² tests. In the case of studies with statistical heterogeneity (P<0.1 or I² >50%), the random-effect model was selected. Otherwise, the fixed-effect model was used.

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First author (year)	Ethnicities	lotal, no. (% male)	Age, years	Indication I for warfarin	NK target range	CC	CT	TT	CC	CT	TT	CT+TT	Quality score	(Refs.)
Lee (2009)	Chinese	235 (56.2)	63.0±12.8	AF, CVR, stroke, DVT, PE	1.7-3.0	58.3	36.2	5.5	2.90±1.35	2.98±1.49	2.63±0.77		+	(10)
Liang (2012)	Chinese	115 (61.7)	64.9±3.0	AF, HVR, DVT, PE	2.0-3.0	41.7	47.8	10.4	2.77±0.99	3.22±1.15	4.0±0.79		+++++++++++++++++++++++++++++++++++++++	(11)
Li (2012)	Chinese	352 (34.9)	45.4 ± 9.29	HVR	1.8-2.5	64.8	29.5	5.7	3.1 ± 0.8	3.4 ± 0.8	3.6 ± 0.9		+ +	(12)
Liang (2013)	Chinese	300 (46.0)	47.9 ± 12.5	NA	1.5 - 3.0	57.3	40.0	2.7	3.26 ± 1.16	3.31 ± 1.31	3.66 ± 1.28		+++	(13)
Li (2015)	Chinese	158 (28.5)	47.65±11.20	CVR	1.5-2.5	63.3	34.2	2.5	[9.87±7.39ª	22.21 ± 6.40^{a}	22.42±7.66 ^a		++++	(14)
Zhuang (2015)	Chinese	211 (46.9)	66.0 ± 10.7	Stroke, other	1.5 - 3.0	57.3	42.	7	2.71 ± 0.80			2.82±0.72	+	(15)
Krishna (2014)	Indian	240 (36.7)	43.3±11.2	PVR, AF, DVT, stroke	2.0-3.5	38.3	48.8	12.9	4.0 ± 1.5	4.9±2.3	6.3±2.5		+++++	(26)
Özer (2013)	Turkish	107 (49.5)	53.89±13.55	HVR, VT, AF, other	2.0-3.0	37.4	45.8	16.8	4.53±1.73	5.58±2.24	5.42±1.10		+++++++++++++++++++++++++++++++++++++++	(27)
Hirai (2015)	Japanese	217 (65.9)	69	AF, HVR, DVT, PE, AFL	NA	53.0	36.9	10.1	2.94±1.19	2.90 ± 1.10	3.46±1.42		+++++	(28)
Nakamura (2012)) Japanese	126 (51.6)	62.7	NA	NA	46.0	46.8	7.1	2.88 ± 1.00			3.55±1.69	+	(29)
Lee (2012)	Korean	188 (33.0)	57.8 ± 10.1	HVR	2.0-3.0	43.6	45.2	11.2	5.34 ± 2.04	5.33 ± 1.64	6.55 ± 2.12		+ +	(30)
Singh (2011)	Asian	124 (56.5)	61	AF, DVT, PVR, PE, other	2.0-3.0	6.99	31.5	1.2	3.0±1.82			3.75±1.82	+	(31)
Cen (2010)	Chinese	222 (46.8)	45 ± 12	HVR	1.5 - 3.0	51.8	41.4	6.8	2.9 ± 1.1			3.2 ± 1.1	+	(20)
Lou (2014)	Chinese	488 (44.7)	56.7±12.3	HVR, AF, PE	1.5 - 3.0	49.8	41.0	9.2	3.39 ± 1.28	3.63 ± 1.53	3.85 ± 1.61		+++	(21)
Zhang (2013)	Chinese	85 (63.5)	64.49±11.77	AF, PE, HVR_other	NA	49.1	43.5	7.4	2.63 ± 0.72	2.81 ± 0.87	3.10 ± 1.35		+++++	(Unpublished)
Fang (2014)	Chinese	104 (NA)	56.8±12.4	AF, HVR, other	1.5-3.0	9.09	35.6	3.8	2.74 ± 0.91	3.16 ± 0.92	3.75 ± 1.06		+++++++++++++++++++++++++++++++++++++++	(Unpublished)
Tan (2012)	Chinese	317 (30.0)	45.2 ± 10.5	HVR	1.7 - 3.0	63.4	33.8	2.8	3.04 ± 1.00	3.48 ± 1.06	3.54 ± 0.84	3.49 ± 1.04	+++	(Unpublished)
Zhang (2012)	Chinese	197 (41.6)	52.92±11.76	HVR	1.5-2.8	58.4	37.1	4.6	2.51 ± 0.82	2.74 ± 0.96	3.20 ± 1.22		+++++	(22)
Zhu (2012)	Chinese	260 (48.5)	67.2 ± 13.1	AF	1.5 - 3.0	56.2	33.1	10.8	2.60 ± 0.84	2.66 ± 1.02	3.04 ± 0.98		+ +	(23)
Yu (2014)	Chinese	100 (43.0)	46.69±9.73	HVR	1.5-2.5	59.0	33.0	8.0	3.01 ± 0.78	3.66 ± 0.99	3.87 ± 1.26		+++++	(Unpublished)
Wang (2011)	Chinese	196 (40.8)	61.89±12.35	HVR, AF, DVT, PE, ACI	1.8-3.0	50.5	42.9	6.6	3.07±1.21	3.66±1.33	3.73±1.55		+++++++++++++++++++++++++++++++++++++++	(24)
Zhang (2014)	Chinese	207 (51.21)	62.8±14.4	HVR, other	2.0-3.0	59.9	35.8	4.4	2.55 ± 0.91	2.60±1.07	2.86 ± 0.90		‡	(25)
"Unit is mg/week. I deep vein thrombos	NR, internatio sis; VT, vein th	mal normalized nrombosis; AC	d ratio; CVR, car I, acute cerebral	diac valve replacemen infarction; AFL, atria	at; HVR, he: I flutter; NA	art valve	replace1 ailable; S	ment; A SD, stan	F, atrial fibrills idard deviatior	ation; PE, pulm 1.	onary embolisn	ı; PVR, prost	netic valv	e replace; DVT,

Table I. Characteristics of the included studies.

А			ст			сс			Mean Difference	Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95% CI	IV. Random. 95% Cl
	Fang SJ 2014	1.15	0.34	37	1	0.33	63	4.2%	0.15 [0.01, 0.29]	
	Krishna Kumar D 2014	1.23	0.58	117	1	0.38	92	4.5%	0.23 [0.10, 0.36]	
	Lee KE 2012	1	0.31	85	1	0.38	82	5.9%	0.00 [-0.11, 0.11]	_
	Li JH 2012	1.1	0.26	104	1	0.26	228	9.6%	0.10 [0.04, 0.16]	-
	Li S 2015	1.12	0.32	54	1	0.37	100	5.5%	0.12 [0.01, 0.23]	
	Liang K 2012 Liang Y 2013	1.16	0.42	120	1	0.36	48 172	3.7%	0.16 [0.01, 0.31]	
	Lou Y 2014	1.07	0.45	200	1	0.38	243	7.9%	0.07 [-0.01, 0.15]	
	MT Lee 2009	1.03	0.51	85	1	0.47	137	4.3%	0.03 [-0.10, 0.16]	_ _
	Tan SL 2012	1.14	0.35	107	1	0.33	201	7.7%	0.14 [0.06, 0.22]	
	Wang Z 2011	1.19	0.43	84	1	0.39	- 69 60	5.0%	0.19 [0.07, 0.31]	
	Zhang HY 2012	1.09	0.33	73	1	0.33	115	5.8%	0.09 [-0.02, 0.20]	
	Zhang T 2013	1.07	0.33	37	1	0.27	42	4.3%	0.07 [-0.06, 0.20]	
	Zhang YT 2014	1.02	0.42	74	1	0.36	124	5.3%	0.02 [-0.09, 0.13]	<u> </u>
	Zhu JR 2012	1.02	0.39	86	1	0.32	146	6.4%	0.02 [-0.08, 0.12]	
	Ozer M 2013	1.23	0.49	49		0.30	40	2.0%	0.23 [0.05, 0.41]	
	Total (95% CI)			1480			2106	100.0%	0.09 [0.06, 0.13]	•
	Heterogeneity: Tau ² = 0.0	00; Chi²	= 29.5	1, df =	17 (P =	0.03);	l ² = 429	6		-0.5 -0.25 0 0.25 0.5
	Test for overall effect: Z =	= 5.45 (F	P < 0.0	0001)						Favours [experimental] Favours [control]
в		с	т+тт			сс			Mean Difference	Mean Difference
<i>р</i> .	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV, Random, 95% Cl
	Cen HJ 2010	1.1	0.38	107	1	0.38	115	5.0%	0.10 [-0.00, 0.20]	
	Fang SJ 2014	1.18	0.34	41	1	0.33	63	3.7%	0.18 [0.05, 0.31]	
	Krishna Kumar D 2014	1.03	0.4	102	1	0.38	92	4.7%	0.03 [-0.08, 0.14]	
	Lee KE 2012	1.04	0.34	106	1	0.38	82	4.8%	0.04 [-0.06, 0.14]	-
	Li JH 2012	1.1	0.26	124	1	0.26	228	7.5%	0.10 [0.04, 0.16]	-
	Li S 2015	1.12	0.32	58	1	0.37	100	4.6%	0.12 [0.01, 0.23]	
	Liang R 2012 Liang Y 2013	1.21	0.41	67 128	1	0.36	48 172	3.4% 5.7%	0.21 [0.07, 0.35]	
	Lou Y 2014	1.02	0.48	245	1	0.38	243	6.3%	0.08 [0.00, 0.16]	
	MT Lee 2009	1.01	0.49	98	1	0.47	137	3.9%	0.01 [-0.11, 0.13]	-
	Nakamura K 2012	1.23	0.59	68	1	0.35	58	2.7%	0.23 [0.06, 0.40]	
	Singh O 2011	1.25	0.61	41	1	0.61	83	1.6%	0.25 [0.02, 0.48]	
	Wang Z 2012	1.15	0.34	97	1	0.33	201	4.3%	0.15 [0.07, 0.23]	———
	Yu SH 2014	1.23	0.34	41	1	0.26	59	4.0%	0.23 [0.11, 0.35]	
	Zhang HY 2012	1.11	0.39	82	1	0.33	115	4.8%	0.11 [0.01, 0.21]	
	Zhang T 2013	1.08	0.36	43	1	0.27	42	3.6%	0.08 [-0.06, 0.22]	
	Zhang YT 2014 Zhu JR 2012	1.03	0.41	83 114	1	0.36	124	4.6%	0.03 [-0.08, 0.14]	
	Zhuang WF 2015	1.00	0.27	90	1	0.3	121	6.2%	0.04 [-0.04, 0.12]	
	Özer M 2013	1.22	0.44	67	1	0.38	40	2.9%	0.22 [0.06, 0.38]	· · · · ·
	Tetel (05% CI)			2066			2402	400.0%	0.44 [0.09.0.44]	
	Heterogeneity: Tau ² = 0.0	00 Chil	= 41.9	2066	21 (P =	0 004)	2483	100.0%	0.11 [0.08, 0.14]	· _ · · · · · · · · · · · · · · ·
	Heterogeneity. Tau - 0.	00, 011	- 41.0	2, ui –	e i (r	0.004)	, 1 - 50	//0		-0.5 -0.25 0 0.25 0.5
	Test for overall effect: Z =	= 6.90 (F	° < 0.0	0001)						
	Test for overall effect: Z =	= 6.90 (F	° < 0.0	0001)						Favours [experimental] Favours [control]
С	Test for overall effect: Z =	= 6.90 (F	 < 0.0 тт сп 	0001)		cc	Tetel	18/-1	Mean Difference	Favours [experimental] Favours [control] Mean Difference
С	Study or Subgroup	= 6.90 (F <u>Mean</u> 1.37	<pre>> < 0.0 TT SD 0.39</pre>	0001) <u>Total</u>	Mean 1	CC SD	Total 63	Weight	Mean Difference <u>IV. Random. 95% CI</u> 0.37 [-0.02_0.76]	Favours [experimental] Favours [control] Mean Difference IV. Random. <u>95% Cl</u>
С	Test for overall effect: Z = <u>Study or Subgroup</u> Fang SJ 2014 Hirai K 2015	= 6.90 (F <u>Mean</u> 1.37 1.18	P < 0.0 TT SD 0.39 0.48	0001) <u>Total</u> 4 22	Mean 1 1	CC SD 0.33 0.4	Total 63 115	<u>Weight</u> 2.5% 5.9%	Mean Difference <u>IV. Random, 95% CI</u> 0.37 [-0.02, 0.76] 0.18 [-0.03, 0.39]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
С	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014	= 6.90 (F <u>Mean</u> 1.37 1.18 1.58	P < 0.0 TT SD 0.39 0.48 0.63	0001) Total 4 22 31	<u>Mean</u> 1 1	CC SD 0.33 0.4 0.38	Total 63 115 92	Weight 2.5% 5.9% 5.2%	Mean Difference IV. Random. 95% CI 0.37 [-0.02, 0.76] 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
С	Test for overall effect: 2 = <u>Study or Subgroup</u> Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012	= 6.90 (F <u>Mean</u> 1.37 1.18 1.58 1.23	> < 0.0 TT SD 0.39 0.48 0.63 0.4	0001) <u>Total</u> 4 22 31 21	<u>Mean</u> 1 1 1	CC SD 0.33 0.4 0.38 0.38	Total 63 115 92 82	Weight 2.5% 5.9% 5.2% 6.6%	Mean Difference IV. Random. 95% CI. 0.37 [-0.02, 0.76] 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
C	Test for overall effect: 2 = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015	= 6.90 (F <u>Mean</u> 1.37 1.18 1.58 1.23 1.16 1.13	> < 0.0 TT SD 0.39 0.48 0.63 0.4 0.29 0.38	0001) <u>Total</u> 4 22 31 21 20	<u>Mean</u> 1 1 1 1	CC SD 0.33 0.4 0.38 0.38 0.26 0.37	Total 63 115 92 82 228 100	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6%	Mean Difference IV. Random. 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.16 (0.03, 0.29) 0.13 (-0.25, 0.51)	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
С	Test for overall effect: 2 = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li JH 2012 Li ang R 2012	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44	> < 0.0 TT SD 0.39 0.48 0.63 0.4 0.29 0.38 0.29	00001) <u>Total</u> 4 22 31 21 20 4 12	<u>Mean</u> 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36	Total 63 115 92 82 228 100 48	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5%	Mean Difference IV. Random. 95% CI 0.37 [-0.02, 0.76] 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 [-0.25, 0.51] 0.44 [0.25, 0.651]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
C	Test for overall effect: 2 = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li SJ 2015 Liang R 2012 Liang Y 2013	= 6.90 (F <u>Mean</u> 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12	> < 0.0 TT SD 0.39 0.48 0.63 0.48 0.29 0.38 0.29 0.39	00001) <u>Total</u> 4 22 31 21 20 4 12 8	<u>Mean</u> 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36	Total 63 115 92 82 228 100 48 172	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3%	Mean Difference IV. Random, 95% CL 0.37 [-0.02, 0.76] 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.13 [-0.25, 0.51] 0.44 [0.25, 0.63] 0.12 [-0.16, 0.40]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
C_	Test for overall effect: 2 = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14	 > < 0.0 TT SD 0.39 0.48 0.63 0.4 0.29 0.38 0.29 0.39 0.39 0.47 	00001) <u>Total</u> 4 22 31 21 20 4 12 8 45	<u>Mean</u> 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36 0.38	Total 63 115 92 82 228 100 48 172 243	Weight 2.5% 5.9% 6.6% 9.0% 2.6% 6.5% 4.3% 8.4%	Mean Difference IV. Random, 95% CI 0.37 [-0.02, 0.76] 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 [-0.25, 0.51] 0.44 [0.25, 0.63] 0.12 [-0.16, 0.40] 0.14 [-0.01, 0.29]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
C	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Ture Of 2019	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91	 > < 0.0 TT SD 0.39 0.48 0.63 0.4 0.29 0.38 0.29 0.38 0.29 0.39 0.47 0.27 227 	00001) Total 4 22 31 21 20 4 12 8 45 13 0	Mean 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36 0.36 0.38 0.47 0.22	Total 63 115 92 228 100 48 172 243 137	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 8.4% 7.5%	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.13 (-0.25, 0.51) 0.44 (0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.40 (-0.20, 0.02)	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Test for overall effect: 2 : Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.21	> < 0.0 TT SD 0.39 0.48 0.63 0.47 0.39 0.47 0.27 0.28 0.5	00001) Total 4 22 31 21 20 4 12 8 45 13 9 13	<u>Mean</u> 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36 0.36 0.38 0.47 0.33 0.39	Total 63 115 92 228 100 48 172 243 137 201 99	Weight 2.5% 5.9% 5.2% 6.6% 2.6% 6.5% 4.3% 8.4% 7.5% 6.7% 4.1%	Mean Difference IV. Random. 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.16 (0.03, 0.29) 0.13 (-0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49)	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
С	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.16 1.21 1.29	> < 0.0 TT SD 0.39 0.48 0.63 0.47 0.29 0.47 0.27 0.28 0.5 0.42	00001) Total 4 22 31 21 20 4 12 8 45 13 9 13 8 13 8 13 8	<u>Mean</u> 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36 0.38 0.47 0.33 0.47 0.33 0.39 0.26	Total 63 115 92 228 100 48 172 243 137 201 99 59	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 8.4% 7.5% 6.7% 4.1% 3.8%	Mean Difference IV, Random, 95% CI 0.37 [-0.92, 0.76] 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.13 [-0.25, 0.51] 0.44 [-0.25, 0.63] 0.12 [-0.16, 0.40] 0.14 [-0.01, 0.29] 0.09 [-0.26, 0.08] 0.16 [-0.03, 0.35] 0.27 [-0.01, 0.59]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% CI
С	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.16 1.21 1.29 1.27	> < 0.0 TT SD 0.39 0.48 0.63 0.44 0.29 0.39 0.29 0.39 0.47 0.27 0.28 0.5 0.42 0.49	00001) 4 22 31 21 20 4 12 8 45 13 9 9 13 8 9 9 13 8 9 9	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36 0.36 0.33 0.47 0.33 0.47 0.33 0.47 0.33 0.47 0.33	Total 63 115 92 228 100 48 172 243 137 201 99 59 115	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 8.4% 7.5% 6.7% 4.1% 3.8% 3.4%	Mean Difference IV. Random, 95% CL 0.37 [-0.02, 0.76] 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.13 [-0.25, 0.63] 0.13 [-0.25, 0.63] 0.12 [-0.16, 0.40] 0.14 [-0.01, 0.29] -0.09 [-0.26, 0.08] 0.16 [-0.03, 0.35] 0.21 [-0.07, 0.49] 0.29 [-0.01, 0.59] 0.27 [-0.06, 0.60]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J H 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Vang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang T 2013 Zhang T 2013	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.16 1.21 1.29 1.27 1.18	 < 0.0 TT SD 0.39 0.48 0.63 0.4 0.29 0.38 0.29 0.39 0.47 0.27 0.28 0.5 0.42 0.49 0.51 0.21 	00001) 4 22 31 21 20 4 12 8 45 13 9 13 8 9 13 8 9	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36 0.36 0.36 0.47 0.33 0.47 0.33 0.26 0.33 0.26 0.33 0.47 0.33 0.47 0.36 0.47 0.36 0.36 0.36 0.36 0.36 0.36 0.36 0.36 0.36 0.36 0.36 0.37 0.36 0.32	Total 63 115 92 228 100 48 172 243 137 201 99 59 115 42	Weight 2.5% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 8.4% 7.5% 6.7% 4.1% 3.8% 2.3%	Mean Difference IV. Random. 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.13 (-0.25, 0.51) 0.44 (0.25, 0.63] 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35] 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.18 (-0.24, 0.60) 0.40 (-0.24	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J H 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Vang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2013 Zhang YT 2014 Zhu JR 2012	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.16 1.29 1.27 1.18 1.27 1.18 1.27 1.18	 < 0.0 TT SD 0.39 0.48 0.63 0.4 0.29 0.38 0.29 0.38 0.29 0.47 0.27 0.28 0.5 0.42 0.49 0.51 0.38 0.39 	00001) 4 22 31 21 20 4 12 8 45 13 9 13 8 9 13 8 9 6 9 28	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.36 0.38 0.47 0.33 0.47 0.33 0.47 0.33 0.47 0.33 0.47 0.33 0.49 0.32	Total 63 115 92 228 100 48 172 243 137 201 99 59 115 42 124 42 124	Weight 2.5% 5.9% 5.2% 6.6% 4.3% 8.4% 7.5% 6.7% 4.1% 3.8% 3.4% 3.4% 5.2%	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.13 (-0.25, 0.51) 0.14 (-0.25, 0.51) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.07, 0.49) 0.29 (-0.07, 0.49) 0.29 (-0.07, 0.49) 0.29 (-0.07, 0.49) 0.29 (-0.07, 0.49) 0.27 (-0.06, 0.60) 0.18 (-0.24, 0.60) 0.12 (-0.12, 0.36) 0.17 (-0.26, 0.36) 0.17 (-0.26, 0.36)	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Test for overall effect: 2 : Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhang YT 2014 Zhu JR 2012 Özer M 2013	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.27 1.16 1.21 1.29 1.27 1.18 1.12 1.29	 < 0.0 TT SD 0.39 0.48 0.63 0.4 0.29 0.39 0.39 0.47 0.29 0.47 0.27 0.28 0.5 0.42 0.49 0.51 0.35 0.35 0.35 0.35 0.35 0.24 	Total 4 22 311 20 4 12 8 4 5 13 9 13 8 9 13 8 9 6 9 9 28 28	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.38 0.38 0.37 0.36 0.36 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.32 0.32 0.32 0.32	Total 63 115 92 228 100 48 172 243 137 201 99 115 42 124 146 40	Weight 2.5% 5.9% 5.2% 6.6% 4.3% 8.4% 7.5% 6.7% 4.1% 3.8% 3.4% 2.3% 5.2% 8.2%	Mean Difference IV. Random. 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.16 (0.03, 0.29) 0.13 (-0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.12 (-0.12, 0.36) 0.12 (-0.12, 0.36) 0.17 (0.02, 0.32) 0.20 (0.04, 0.36)	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Test for overall effect: 2 = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Liang R 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhang XT 2014 Zhang ZH 2013 Özer M 2013	Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.27 1.28 1.29 1.27 1.18 1.12 1.29 1.27 1.18	SD SD 0.39 0.48 0.63 0.48 0.63 0.49 0.38 0.29 0.38 0.29 0.39 0.47 0.28 0.55 0.42 0.49 0.51 0.38 0.24	Total 4 22 31 21 20 4 12 8 45 13 9 13 8 9 9 6 9 28 28	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.37 0.36 0.33 0.26 0.33 0.27 0.36 0.33 0.27 0.36 0.32 0.33 0.26 0.33 0.26 0.33 0.26 0.37 0.33 0.26 0.33 0.32 0.32 0.33 0.32 0.33 0.32 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.32 0.33 0.36 0.33 0.32 0.33 0.33 0.33 0.33 0.33 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.33 0.36 0.36 0.36 0.33 0.36 0.56	Total 63 115 92 228 100 48 172 243 137 201 959 115 42 124 146 40	Weight 2.5% 5.9% 5.2% 6.6% 4.3% 6.5% 4.3% 6.5% 6.7% 4.1% 3.4% 2.3% 5.2% 8.2% 7.7%	Mean Difference IV. Random. 95% CI 0.37 (-0.92, 0.76) 0.18 (-0.03, 0.39) 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 (-0.25, 0.63] 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.21 (-0.07, 0.49] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 (-0.24, 0.60] 0.12 (-0.12, 0.36] 0.17 [0.02, 0.32] 0.20 [0.04, 0.36]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J H 2012 Li S 2015 Liang R 2012 Liang R 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Vang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI)	6.90 (F Mean 1.37 1.18 1.58 1.23 1.16 1.21 1.29 1.21 1.22 1.17 1.23	SD SD 0.39 0.48 0.63 0.44 0.29 0.38 0.29 0.38 0.29 0.38 0.29 0.38 0.29 0.38 0.47 0.27 0.28 0.42 0.42 0.42 0.42 0.42 0.43 0.42 0.43 0.42 0.42 0.42 0.42 0.42 0.42 0.42 0.42 0.42 0.38 0.24	00001) Total 4 22 311 21 20 4 12 8 45 13 9 13 8 9 28 18 28 28 18 28 28 18 28 28 28 28 28 28 28 28 28 2	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.38 0.47 0.33 0.38 0.47 0.33 0.27 0.36 0.32 0.32 0.38	Total 63 115 92 228 100 48 172 243 137 201 99 59 115 42 124 146 40 2106	Weight 2.5% 5.9% 5.2% 6.6% 6.5% 4.3% 4.3% 6.7% 4.1% 3.8% 2.3% 5.2% 8.2% 7.7%	Mean Difference IV, Random, 95% CI 0.37 [-0.02, 0.76] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.13 [-0.25, 0.51] 0.44 [0.25, 0.63] 0.12 [-0.16, 0.40] 0.14 [-0.01, 0.29] -0.09 [-0.26, 0.08] 0.16 [-0.03, 0.35] 0.21 [-0.01, 0.59] 0.27 [-0.06, 0.60] 0.18 [-0.24, 0.60] 0.12 [-0.12, 0.36] 0.17 [0.02, 0.32] 0.20 [0.13, 0.27]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
C	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J H 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Vang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.4	6.90 (F Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.41 1.12 1.14 0.91 1.27 1.18 1.29 1.27 1.18 1.12 1.17 1.20 0.1 0.1 0.1 0.1 0.1 0.1	TT SD 0.39 0.48 0.63 0.49 0.38 0.29 0.39 0.39 0.39 0.47 0.27 0.27 0.27 0.42 0.42 0.49 0.42 0.49 0.42 0.49 0.42 0.42 0.42 0.42 0.42 0.42 0.42 0.42	00001) Total 4 22 31 21 20 4 12 8 4 12 8 4 13 9 13 8 9 6 9 28 18 280 77, df = 20001	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.38 0.38 0.38 0.38 0.38 0.38 0.33 0.38 0.26 0.33 0.27 0.36 0.32 0.32 0.38	Total 63 115 92 82 228 100 48 172 243 137 299 59 115 42 124 146 40 2106 2 ¹	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 8.3% 4.1% 3.8% 3.4% 5.2% 8.2% 7.7% 100.0%	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.13 (-0.25, 0.51) 0.14 (-0.25, 0.51) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.18 (-0.24, 0.60) 0.12 (-0.12, 0.36) 0.17 ([0.02, 0.32] 0.20 [0.013, 0.27]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang R 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneilty: Tau ² = 0.1 Test for overall effect: Z store	6.90 (F Mean 1.37 1.8 1.58 1.23 1.16 1.13 1.44 1.12 1.14 0.91 1.27 1.18 1.29 1.27 1.18 1.12 1.17 1.20 1.17 1.20 1.21 1.20 1.27 1.18 1.20 1.17 1.20 1.17	SD SD O.39 0.48 0.63 0.44 0.29 0.39 0.47 0.29 0.39 0.47 0.28 0.51 0.35 0.38 0.24	00001) Total 4 22 31 21 20 4 12 8 45 13 9 13 8 9 9 13 8 9 9 28 18 280 77, df = 280 280 280 280 280 280 280 280	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.38 0.47 0.33 0.26 0.33 0.26 0.33 0.27 0.36 0.32 0.38 0.27 0.36 0.32 0.38 0.27 0.36 0.32 0.38 0.27 0.36 0.39 0.39 0.39 0.38 0.48 0.37 0.38 0.48 0.38 0.38 0.38 0.38 0.38 0.38 0.38 0.38 0.36 0.36 0.36 0.36 0.36 0.36 0.37 0.38 0.36 0.38 0.37 0.36 0.38 0.37 0.38 0.39 0.32 0.39 0.32 0.33 0.26 0.33 0.39 0.32 0.39 0.32 0.32 0.39 0.32 0.32 0.32 0.32 0.33 0.32 0.32 0.33 0.27 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.36 0.32 0.32 0.36 0.32 0.32 0.36 0.32 0.38 0.32 0.32 0.38 0.32 0.32 0.38 0.32 0.38 0.32 0.38 0.32 0.38 0.32 0.32 0.38 0.38 0.48	Total 63 115 92 82 228 100 48 172 201 99 115 42 124 201 99 115 42 124 146 40 2106 12 21 24 124 125 42 124 124 124 124 124 124 124 124 124 124 126 127 128 129 129 129 1201 129 129 129 129 129 129	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 6.5% 4.3% 6.7% 4.1% 3.8% 3.4% 3.8% 3.4% 5.2% 8.2% 7.7% 100.0%	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.13 (-0.25, 0.51) 0.14 (-0.01, 0.29) 0.13 (-0.26, 0.08) 0.14 (-0.01, 0.29) 0.29 (-0.01, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.12 (-0.12, 0.36) 0.12 (-0.12, 0.36) 0.12 (-0.12, 0.36) 0.12 (-0.13, 0.27]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Test for overall effect: 2 = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang Y 2013 Zhang Y 2014 Zhang Y 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	= 6.90 (F Mean 1.37 1.18 1.58 1.23 1.16 1.13 1.44 0.91 1.14 0.91 1.29 1.27 1.18 1.12 1.13 1.14 1.15 1.16 1.17 1.18	SD SD O.39 0.48 0.63 0.44 0.29 0.38 0.29 0.39 0.47 0.29 0.39 0.47 0.27 0.28 0.51 0.35 0.38 0.24 = 31.0 > < 0.0	00001) Totall 4 22 31 21 20 4 4 12 8 8 4 5 13 8 9 9 13 8 9 9 6 9 8 28 0 7, df = 20001)	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.38 0.47 0.33 0.26 0.33 0.27 0.36 0.32 0.38 0.27 0.36 0.32 0.38 0.27 0.36 0.32 0.38 0.47 0.38 0.47 0.33 0.44 0.38 0.45 0.38 0.45 0.36 0.36 0.36 0.36 0.36 0.36 0.37 0.36 0.38 0.38 0.38 0.38 0.38 0.38 0.38 0.38	Total 63 115 92 228 100 48 172 243 137 201 99 59 115 42 124 146 40 2106 P ² 245 4 2 1 5 1 1 5 1 1 1 1 1 1 1 1	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 8.4% 6.7% 4.1% 6.7% 4.1% 3.8% 3.4% 2.3% 5.2% 8.2% 7.7% 100.0%	Mean Difference IV. Random. 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 (0.35, 0.81) 0.23 (0.04, 0.42) 0.16 (0.03, 0.29) 0.13 (-0.25, 0.51) 0.44 (-0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.60, 0.60) 0.12 (-0.12, 0.36] 0.17 (0.02, 0.32] 0.20 (0.04, 0.36] 0.20 (0.13, 0.27] Mean Difference	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Test for overall effect: 2 = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li JH 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup	Mean 1.37 1.18 1.58 1.18 1.23 1.16 1.13 1.44 1.12 1.14 1.14 1.14 1.14 1.14 1.12 1.14 1.12	TT SD 0.39 0.48 0.63 0.44 0.29 0.38 0.29 0.39 0.38 0.29 0.39 0.38 0.29 0.39 0.38 0.29 0.39 0.38 0.29 0.38 0.29 0.39 0.38 0.29 0.39 0.39 0.48 0.29 0.39 0.39 0.48 0.29 0.39 0.39 0.48 0.29 0.39 0.39 0.39 0.48 0.29 0.39 0.39 0.39 0.39 0.48 0.29 0.39 0.39 0.39 0.39 0.39 0.39 0.39 0.39 0.38 0.29 0.39 0.39 0.39 0.39 0.39 0.38 0.29 0.39 0.47 0.27 0.28 0.49 0.53 0.42 0.49 0.53 0.42 0.49 0.53 0.38 0.49 0.53 0.42 0.49 0.55 0.38 0.22 0.38 0.24 0.49 0.55 0.38 0.24 0.38 0.24 0.55 0.38 0.24 0.29 0.39 0.49 0.55 0.38 0.24 0.27 0.28 0.38 0.24 0.27 0.28 0.38 0.24 0.27 0.28 0.38 0.24 0.27 0.28 0.38 0.24 0.27 0.28 0.38 0.24 0.29 0.38 0.24 0.29 0.38 0.24 0.38 0.38 0.24 0.27 0.28 0.38 0.24 0.38 0.24 0.27 0.28 0.38 0.24 0.29 0.38 0.24 0.38 0.24 0.27 0.28 0.38 0.24 0.27 0.28 0.38 0.24 0.27 0.28 0.38 0.24 0.29	00001) Total 4 22 31 21 20 4 4 12 8 8 45 13 8 9 9 13 8 9 9 13 8 8 9 9 13 8 8 9 9 13 13 8 8 9 9 13 13 13 13 13 13 13 13 13 13	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.38 0.38 0.37 0.36 0.33 0.37 0.36 0.33 0.27 0.36 0.32 0.32 0.38 0.27 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.34 0.34 0.34 0.36 0.37 0.36 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.38 0.37 0.36 0.37 0.36 0.37 0.36 0.38 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.32	Total 63 115 92 82 100 48 137 201 99 59 115 42 124 146 40 2106 12 2016 12 59 515 42 124 146 40 2106 12 24 7 124 124 124 124 126 127 2106 12 24 12 2 12 14 146 147 148 149 149 149 140 140 1	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 8.4% 2.3% 5.2% 6.7% 4.1% 3.8% 3.4% 2.3% 5.2% 8.2% 7.7% 100.0% %	Mean Difference IV. Random. 95% CI 0.37 (-0.02, 0.76) 0.18 (-0.03, 0.39) 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 [-0.25, 0.51] 0.44 [0.25, 0.63] 0.12 [-0.16, 0.40] 0.14 [-0.01, 0.29] -0.09 [-0.26, 0.08] 0.16 [-0.03, 0.35] 0.21 [-0.07, 0.49] 0.29 [-0.01, 0.59] 0.27 (-0.60, 0.60] 0.18 [-0.24, 0.60] 0.18 [-0.24, 0.60] 0.18 [-0.24, 0.60] 0.19 [-0.12, 0.36] 0.20 [0.04, 0.36] 0.20 [0.13, 0.27] Mean Difference IV. Fixed, 95% CI	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang Y 2013 Zhang Y 2014 Yu SH 2014 Zhang YT 2014 Zhang YT 2014 Zhang YT 2014 Zhang YT 2014 Zhaug Y 2012 Zhang YT 2014 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014	Mean 1.37 1.81 1.58 1.53 1.61 1.23 1.13 1.58 1.23 1.13 1.13 1.13 1.13 1.14 1.12 1.14 1.14 0.91 1.11 1.29 1.11 1.29 1.11 1.29 1.11 1.29 1.11 1.29 1.11 1.20 1.12 1.11 1.20 1.11 1.20 1.11 1.20 1.21 1.22 1.23 1.37 1.23 1.31 1.31 1.32 1.32 1.33 1.33 1.33	TT SD 0.39 0.48 0.63 0.44 0.29 0.38 0.29 0.38 0.29 0.39 0.47 0.28 0.51 0.42 0.49 0.51 0.35 0.42 0.49 0.51 0.38 0.24 TT SD 0.38 0.48 0.29 0.48 0.29 0.39 0.48 0.29 0.39 0.48 0.29 0.39 0.48 0.29 0.39 0.48 0.29 0.39 0.48 0.29 0.39 0.48 0.29 0.39 0.48 0.29 0.47 0.27 0.28 0.47 0.28 0.49 0.47 0.27 0.48 0.49 0.47 0.27 0.42 0.49 0.51 0.38 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.51 0.38 0.38 0.24 0.38 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.49 0.51 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.38 0.52 0.49 0.	00001) Total 4 22 31 1 20 4 4 12 20 4 4 12 20 4 4 12 20 4 1 2 0 7 4 2 8 8 9 9 9 2 8 8 9 9 2 8 18 2 8 0 7 0 ff = 00001) Total 4 4 2 2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.38 0.37 0.36 0.36 0.33 0.27 0.33 0.27 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.34 0.4 0.38 0.4 0.38 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.37 0.36 0.37 0.37 0.36 0.37 0.37 0.36 0.37 0.37 0.37 0.36 0.37 0.37 0.36 0.37 0.37 0.36 0.37 0.32 0.37 0.36 0.37 0.32 0	Total 63 115 92 228 100 1172 228 100 48 172 201 99 115 42 124 146 40 2106 12 124 146 307 2016 12 124 12 124 124 146 40 20106	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 7.5% 6.7% 4.1% 3.8% 3.4% 5.2% 8.2% 7.7% 100.0% %	Mean Difference IV, Random, 95% CI V, Random, 95% CI 0.37 (-0.02, 0.76] 0.18 (-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 (-0.25, 0.51] 0.44 [0.25, 0.63] 0.12 (-0.10, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 [-0.24, 0.60] 0.18 [-0.24, 0.60] 0.18 [-0.24, 0.60] 0.19 (0.02, 0.32] 0.20 [0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.20 (0.04, 0.66]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J H 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang Y 2013 Zhang Y 2014 Zhang Y 2013 Zhang Y 2012 Zhang Y 2013 Zhang Y 2012 Zhang Y 2013 Zhang Y 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014	Mean 1.37 1.18 1.58 1.58 1.18 1.58 1.13 1.13 1.13 1.13 1.13 1.13 1.14 1.13 1.44 0.91 1.44 0.91 1.27 1.14 0.91 1.29 1.21 1.18 1.22 1.17 1.29 1.27 1.18 1.29 1.27 1.18 1.29 1.27 1.18 1.29 1.17 1.20 1.21 1.22 1.23 1.37 1.38 1.58	> < 0.0 TT SD 0.39 0.48 0.63 0.48 0.63 0.49 0.39 0.47 0.27 0.28 0.39 0.47 0.27 0.28 0.51 0.51 0.35 0.42 0.49 0.51 0.51 0.38 0.24 TT SD 0.47 0.51 0.51 0.38 0.52 0.42 0.49 0.51 0.52 0.42 0.49 0.51 0.52 0.42 0.43 0.51 0.52 0.42 0.43 0.51 0.53 0.38 0.54 0.51 0.52 0.48 0.52 0.54 0.51 0.52 0.48 0.63 0.63	00001) Total 4 22 311 20 4 12 8 5 13 9 9 13 3 8 9 9 6 6 9 9 8 280 00001) Total 4 222 31	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC <u>SD</u> 0.33 0.4 0.38 0.26 0.36 0.36 0.38 0.47 0.38 0.47 0.38 0.26 0.38 0.26 0.33 0.26 0.33 0.26 0.33 0.26 0.33 0.26 0.33 0.26 0.33 0.26 0.33 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.32 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.36 0.32 0.37 0.36 0.32 0.37 0.36 0.32 0.37 0.36 0.37 0.36 0.32 0.37 0.36 0.37 0.36 0.32 0.37 0.36 0.37 0.36 0.32 0.37 0.36 0.37 0.36 0.37 0.36 0.32 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.36 0.37 0.37 0.58 0.57 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.58 0.57 0.58 0.5	Total 63 115 92 228 100 48 172 243 137 201 99 115 42 210 42 137 201 99 115 42 211 89 99 115 42 218 201 99 115 42 201 99 115 42 201 99 115 42 201 99 115 42 201 99 115 42 201 99 115 42 201 99 115 42 201 99 115 42 201 99 115 42 201 99 115 42 201 100 100 100 100 100 100 10	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 7.5% 6.7% 4.1% 3.8% 3.4% 2.3% 5.2% 8.2% 8.2% 8.2% 8.2% 5.2% 8.2% 5.4% 4.1%	Mean Difference IV, Random, 95% CI IV, Random, 95% CI 0.37 (-0.2, 0.76] 0.18 (-0.3, 0.39] 0.58 (0.35, 0.81] 0.23 (0.04, 0.42] 0.16 (0.03, 0.29] 0.13 (-0.25, 0.51] 0.44 (0.25, 0.63] 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.07, 0.49] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 (-0.24, 0.60] 0.12 (-0.12, 0.36] 0.17 (0.02, 0.32] 0.20 (0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.35 (0.10, 0.60]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl -0.5 -0.25 0 0.25 0.5 Favours [experimental] Favours [control] Mean Difference IV. Fixed, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012	Mean 1.37 1.18 1.58 1.53 1.68 1.58 1.18 1.23 1.16 1.13 1.13 1.14 1.13 1.44 1.12 1.14 0.91 1.27 1.29 1.27 1.29 1.27 1.29 01; Chi ² Mean 1.37 1.18 1.58 1.23	SOL SOL 0.39 0.48 0.63 0.48 0.63 0.48 0.63 0.44 0.29 0.38 0.29 0.38 0.29 0.38 0.29 0.39 0.39 0.47 0.27 0.27 0.28 0.51 0.35 0.38 0.24 0.51 0.35 0.38 0.24 -<0.0	00001) Total 4 22 31 21 20 4 12 8 8 45 5 13 9 9 13 13 8 9 9 28 18 280 07, df = 280 0001) Total 4 220 12 12 12 12 12 12 12 12 12 12	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.33 0.27 0.36 0.32 0.33 0.27 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.33 0.37 0.36 0.32 0.34 0.32 0.32 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.37 0.34 0.31 0.34 0.31	Total 63 115 92 228 100 48 172 201 137 1201 137 142 124 144 0 2106 1 ² = 45 ⁴ 37 80 117 85	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 6.5% 4.3% 3.8% 3.4% 3.8% 3.4% 5.2% 8.2% 7.7% 100.0% %	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.37 (-0.02, 0.76) 0.38 (-0.35, 0.81) 0.23 (-0.04, 0.42) 0.16 (-0.03, 0.29) 0.13 (-0.25, 0.51) 0.44 (-0.25, 0.51) 0.44 (-0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.12 (-0.72, 0.36) 0.12 (-0.12, 0.36) 0.12 (-0.12, 0.36) 0.12 (-0.12, 0.36) 0.12 (-0.12, 0.36) 0.12 (-0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62) 0.29 (-0.3, 0.41] 0.35 (0.10, 0.60) 0.23 (0.05, 0.41]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang Y 2013 Cozer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Ling SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012	Mean 1.37 1.8 1.58 1.18 1.58 1.18 1.58 1.18 1.23 1.16 1.13 1.16 1.13 1.14 1.21 1.14 1.22 1.21 1.21 1.21 1.21 1.21 1.22 1.21 1.17 1.22 1.17 1.22 1.17 1.21 1.17 1.22 1.17 1.21 1.17 1.22 1.37 1.18 1.18 1.18 1.18 1.23 1.16	> < 0.0 TT SD 0.39 0.39 0.39 0.48 0.63 0.44 0.29 0.38 0.29 0.39 0.48 0.29 0.39 0.42 0.51 0.38 0.24 TT SD 0.39 0.48 0.63 0.48 0.63 0.49 0.39 0.42	00001) Total 4 22 31 21 20 4 12 12 12 20 4 4 12 13 13 9 9 13 3 8 9 9 13 3 8 9 9 28 8 280 0 0 0 11 12 1 20 12 1 20 12 12 12 12 12 12 12 12 12 12	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.37 0.36 0.33 0.39 0.23 0.33 0.27 0.36 0.32 0.33 0.32 0.33 0.33 0.33 0.33 0.33 0.33 0.35 0.32 0.35 0.32 0.35 0.32 0.35 0.32 0.32 0.32 0.32 0.32 0.34 0.32 0.32 0.32 0.32 0.32 0.34 0.32 0.32 0.34 0.32 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.34 0.34 0.34 0.35 0.34 0.35 0.34 0.34 0.35 0.34 0.35 0.34 0.35 0.35 0.34 0.35 0.25 0.35 0.35 0.35 0.35 0.35 0.25 0.35	Total 63 3115 92 228 100 48 172 201 359 115 59 115 59 124 124 146 40 2106 216 216 217 80 37 80 31 78 50 104	Weight 2.5% 5.9% 5.2% 9.0% 2.6% 4.3% 8.4% 2.3% 5.2% 8.4% 2.3% 5.2% 100.0% %	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.37 (-0.02, 0.76) 0.38 (0.35, 0.81) 0.58 (0.35, 0.81) 0.58 (0.35, 0.41) 0.53 (0.04, 0.42) 0.16 (-0.03, 0.29) 0.13 (-0.25, 0.51) 0.44 (0.25, 0.63) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.12 (-0.12, 0.36] 0.17 (0.02, 0.32) 0.20 (0.04, 0.36] 0.20 (0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.19 (-0.03, 0.41] 0.35 (0.10, 0.60] 0.23 (0.05, 0.41] 0.36 (-0.08, 0.20]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang R 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Fest for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Le KE 2012 Li JH 2012 Li JL 2015 Krishna Kumar D 2014 Le KE 2012 Li JL 2012 Li JL 2012 Li JL 2012	Mean 1.37 1.8 1.58 1.23 1.68 1.23 1.13 1.44 1.12 1.13 1.44 1.12 1.13 1.44 1.12 1.14 1.21 1.21 1.21 1.21 1.21 1.21 1.21 1.21 1.21 1.22 1.23 1.24 1.27 1.28 1.27 1.28 1.27 1.28 1.27 1.28 1.37 1.58 1.28 1.28 1.28 1.26 1.28 1.28 1.29	SD O.039 0.39 0.38 0.63 0.4 0.29 0.38 0.40 0.29 0.38 0.29 0.39 0.47 0.27 0.28 0.47 0.27 0.28 0.55 0.35 0.38 0.24 0.49 0.51 0.35 0.38 0.24 0.39 0.48 0.63 0.48 0.63 0.48 0.48 0.29 0.48 0.29 0.48 0.29 0.48 0.29 0.48 0.29	00001) Total 4 22 311 20 4 4 22 8 9 9 9 9 9 28 280 280 280 280 280 28 4 4 222 31 20 20 4 4 4 22 31 20 20 4 4 4 22 31 3 20 20 20 20 20 20 20 20 20 20 20 20 20	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.36 0.36 0.33 0.26 0.33 0.39 0.33 0.27 0.33 0.22 0.38 0.227 0.36 0.32 0.32 0.32 0.38 0.02); CT SD 0.36 0.32 0.36 0.32 0.35 0.32 0.35 0.32 0.35 0.35 0.35 0.35 0.35 0.35 0.35 0.36 0.32 0.36 0.32 0.36 0.32 0.35	Total 63 63 115 92 228 100 48 172 243 137 201 99 115 42 124 146 40 2016 12 124 146 40 0 2106 7 80 117 85 104 54 104	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 7.5% 6.7% 4.1% 3.8% 3.4% 7.5% 5.2% 7.7% 100.0% %	Mean Difference IV, Random, 95% CI 0.37 (-0.92, 0.76) 0.18 (-0.03, 0.39) 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 [-0.25, 0.51] 0.44 [0.25, 0.63] 0.12 [-0.16, 0.40] 0.14 [-0.01, 0.29] -0.09 [-0.26, 0.08] 0.16 (-0.03, 0.35] 0.21 [-0.07, 0.49] 0.29 (-0.01, 0.59] 0.27 (-0.60, 0.60] 0.18 [-0.24, 0.60] 0.18 [-0.24, 0.60] 0.18 [-0.24, 0.60] 0.19 [-0.03, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.35 [0.10, 0.60] 0.24 [-0.37, 0.39]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang Y 2013 Zhang Y 2012 Zhang Y 2012 Zhang Y 2013 Cozer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Li Jang R 2012	Mean 1.37 1.13 1.37 1.13 1.13 1.13 1.13 1.13 1.13 1.13 1.13 1.13 1.14 1.12 1.14 1.14 0.11 1.12 1.14 1.21 1.21 1.22 1.11 1.29 0.11 ChiPiP 0.12 1.13 1.14 0.201 1.13 1.13 1.13 1.58 1.23 1.13 1.13 1.14 1.13 1.14 1.13 1.14 1.13 1.14 1.13 1.14 1.13 1.14 <tr td=""></tr>	SD 0.39 0.39 0.48 0.63 0.44 0.63 0.44 0.29 0.38 0.29 0.39 0.38 0.29 0.39 0.47 0.27 0.28 0.47 0.27 0.28 0.55 0.38 0.55 0.38 0.24 0.51 0.35 0.38 0.24 TT SD 0.48 0.63 0.44 0.29 0.38 0.29 0.38 0.29 0.38 0.29	00001) Total 4 22 31 12 20 4 4 12 8 8 9 9 9 8 8 8 9 9 9 8 8 8 8 9 9 9 8 8 8 8 9 9 9 8 8 8 8 8 9 9 9 9 8 8 8 8 8 8 9 9 9 8 8 8 8 8 8 9 9 9 9 8 8 8 8 8 9 9 9 8 8 8 8 8 9 9 9 8 8 8 8 8 8 8 9 9 9 8 8 8 8 8 8 8 8 8 8 8 8 8	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.36 0.36 0.36 0.36 0.33 0.26 0.33 0.32 0.33 0.27 0.33 0.26 0.33 0.26 0.33 0.32 0.32 0.32 0.38 0.32 0.32 0.36 0.37 0.58 0.32 0.36 0.32 0.36 0.37 0.58 0.32 0.36 0.32 0.36 0.37 0.58 0.32 0.36 0.32 0.36 0.36 0.36 0.36 0.36 0.37 0.58 0.32 0.32 0.36 0.32 0.36 0.36 0.32 0.36 0.32 0.36 0.32 0.36 0.32 0.36 0.36 0.32 0.36 0.36 0.32 0.36	Total 63 63 115 92 82 228 100 115 92 28 172 221 14 137 99 59 115 42 124 144 144 144 144 144 146 146 146 147 55 104 37 80 117 85 104 54 55	Weight 2.5% 5.9% 5.2% 6.6% 4.3% 8.4% 7.5% 6.7% 4.1% 3.8% 3.4% 7.5% 5.2% 8.2% 8.2% 7.7% 100.0% %	Mean Difference IV, Random, 95% CI IV, Random, 95% CI 0.37 (-0.02, 0.76] 0.18 (-0.03, 0.39] 0.58 (0.35, 0.81] 0.23 (0.04, 0.42] 0.16 (0.03, 0.29] 0.13 (-0.25, 0.51] 0.44 (0.25, 0.53] 0.12 (-0.10, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 (-0.24, 0.60] 0.18 (-0.24, 0.60] 0.18 (-0.24, 0.60] 0.18 (-0.24, 0.60] 0.19 (-0.26, 0.36] 0.20 (0.04, 0.36] 0.20 (0.04, 0.36] 0.20 (0.013, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.19 (-0.30, 0.41] 0.35 (0.10, 0.60] 0.23 [0.05, 0.41] 0.35 (0.10, 0.60] 0.23 [0.05, 0.41] 0.66 (-0.38, 0.20] 0.10 (-0.37, 0.39] 0.28 [0.08, 0.48] 0.10 (-0.48, 0.48] 0.10 (-0.48, 0.48] 0.10 (-0.48, 0.48] 0.10 (-0.48, 0.48] 0.10 (-0.48, 0.48] 0.10 (-0.48, 0.48]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang YT 2012 Zhang YT 2013 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2015 Liang R 2012 Liang R 2012 Liang R 2012 Liang Y 2013 Lou Y 2014	Mean 1.37 1.18 1.58 1.58 1.18 1.58 1.13 1.16 1.13 1.16 1.13 1.14 1.13 1.14 1.13 1.44 0.91 1.27 1.14 0.91 1.29 1.21 1.21 1.22 1.21 1.22 1.21 1.22 1.23 1.18 1.25 01: ChP Mean 1.37 1.18 1.23 1.13 1.23 1.14 1.23 1.14 1.14	> < 0.0 TT SD 0.39 0.48 0.63 0.47 0.29 0.38 0.47 0.27 0.28 0.39 0.38 0.51 0.52 0.49 0.51 0.38 0.38 0.38 0.38 0.39 0.48 0.63 0.48 0.63 0.48 0.63 0.48 0.48 0.48 0.48 0.47	00001) Total 4 22 311 20 4 4 22 8 8 4 5 4 5 5 4 5 5 7 6 9 9 9 9 7 7 , df = 7 7 , df = 7 7 , df = 1 2 0 0 0001) 4 2 2 3 1 3 1 2 0 4 4 2 2 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.38 0.39 0.26 0.33 0.39 0.26 0.32 0.32 0.32 0.32 0.32 0.32 0.34 0.37 0.34 0.37 0.58 0.34 0.37 0.34 0.37 0.34 0.34 0.34 0.37 0.34 0.34 0.37 0.34 0.37 0.34 0.37 0.34 0.37 0.34 0.37 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32	Total 63 115 92 228 100 48 172 201 137 107 42 124 146 40 2106 1 ² = 45 ⁴ 37 80 117 85 104 45 55 104 107 85 107 107 107 107 107 107 107 107	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 6.5% 4.3% 7.5% 6.7% 4.1% 3.8% 3.4% 2.3% 5.2% 8.2% 8.2% 4.2% 7.7% 100.0% %	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76] 0.37 (-0.02, 0.76] 0.38 (0.35, 0.81] 0.23 (0.04, 0.42] 0.16 [0.03, 0.29] 0.13 (-0.25, 0.51] 0.44 (0.25, 0.63] 0.12 (-0.16, 0.40] 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.21 (-0.07, 0.49] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 (-0.24, 0.60] 0.12 (-0.12, 0.36] 0.17 (0.02, 0.32] 0.20 [0.13, 0.27] Mean Difference IV. Fixed, 95% CI 0.22 (-0.18, 0.62] 0.19 (-0.30, 0.41] 0.35 (0.10, 0.60] 0.23 (0.05, 0.41] 0.36 (-0.8, 0.20] 0.28 (0.08, 0.48] 0.10 (-0.18, 0.38] 0.10 (-0.18, 0.38] 0.10 (-0.18, 0.32]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Frang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li JH 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009	Mean 1.37 1.81 1.53 1.61 1.23 1.61 1.23 1.61 1.23 1.61 1.23 1.61 1.23 1.61 1.21 1.21 1.22 1.21 1.29 1.27 1.29 1.27 1.29 1.27 1.29 1.27 1.29 1.27 1.29 1.27 1.29 1.27 1.29 1.27 1.29 1.21 1.12 1.137 1.18 1.23 1.61 1.13 1.44 1.12 1.44 1.12 1.44 1.12 1.14	> 0.039 SD 0.39 0.39 0.48 0.63 0.4 0.29 0.38 0.29 0.39 0.47 0.27 0.28 0.51 0.38 0.51 0.38 0.24 0.42 0.47 0.43 0.51 0.38 0.24 0.38 0.24 0.39 0.39 0.48 0.63 0.48 0.29 0.39 0.48 0.639 0.49 0.39 0.49 0.39 0.49 0.39 0.49 0.39 0.49 0.39 0.49 0.39 0.49 0.39 0.49 0.39 0.49 0.39 0.49 0.49 0.27	00001) Total 4 22 31 21 20 4 12 13 13 9 9 13 8 9 9 13 8 9 9 13 8 9 9 13 13 8 9 9 13 13 8 9 9 13 13 14 12 12 1 20 4 4 5 13 13 14 12 12 12 12 12 12 12 12 12 12	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.36 0.38 0.38 0.39 0.33 0.39 0.27 0.36 0.32 0.38 0.22 0.38 0.22 0.38 0.22 0.38 0.22 0.34 0.32 0.32 0.34 0.37 0.34 0.37 0.36 0.32 0.32 0.34 0.32 0.32 0.32 0.34 0.26 0.32 0.32 0.35 0.32 0.35 0.32 0.32 0.32 0.32 0.32 0.32 0.35 0.35 0.35 0.35 0.35 0.35 0.35 0.35	Total 63 3115 92 228 100 48 172 201 39 99 9115 54 2124 146 40 2106 1 ² = 45 ⁴ 2106 1 ² = 45 ⁴ 37 80 117 85 104 55 104 55 104 85 82 88 88 88 88 88 88 88 88 88 88 88 88	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 8.4% 2.3% 5.2% 8.4% 2.3% 5.2% 8.2% 100.0% %	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.37 (-0.02, 0.76) 0.38 (-0.35, 0.81) 0.23 (-0.04, 0.42] 0.16 (-0.03, 0.29] 0.13 (-0.25, 0.51) 0.44 (-0.25, 0.51) 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60) 0.12 (-0.7, 0.49) 0.29 (-0.01, 0.59] 0.27 (-0.60, 0.60) 0.12 (-0.24, 0.60) 0.12 (-0.24, 0.60) 0.12 (-0.24, 0.60) 0.12 (-0.24, 0.60] 0.12 (-0.12, 0.36] 0.20 (0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.39 (0.10, 0.60] 0.23 (0.05, 0.41] 0.36 (-0.08, 0.20] 0.01 (-0.37, 0.39] 0.28 (0.08, 0.48] 0.07 (-0.88, 0.22] 0.12 (-0.30, 0.66]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C_	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J H 2012 Li S 2015 Liang R 2012 Liang R 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Liang R 2012	Mean 1.37 1.8 1.58 1.23 1.18 1.58 1.13 1.16 1.13 1.16 1.13 1.44 1.12 1.14 1.29 1.27 1.12 1.17 1.29 0.1; Chi ² 1.12 1.17 1.29 1.27 1.18 1.12 1.17 1.29 0.1; Chi ² 1.12 1.14 1.58 1.23 1.44 1.12 1.14 1.13 1.44 0.91 1.12 1.14 1.12 1.14 1.12 1.14 0.91 1.12 1.12 1	> < 0.0 TT SD 0.39 0.48 0.63 0.48 0.63 0.48 0.29 0.39 0.47 0.27 0.28 0.39 0.48 0.48 0.39 0.48 0.48 0.61 0.39 0.48 0.48 0.62 0.39 0.48 0.48 0.648 0.62 0.62 0.39 0.42 0.48 0.48 0.62 0.42 0.39 0.47 0.48 0.62 0.62 0.62 0.62 0.62 0.62	00001) Total 4 22 31 21 20 4 4 22 31 12 12 20 4 4 12 13 3 9 9 9 28 8 9 9 28 8 9 9 28 8 280 0 0 0 1 1 20 1 20 4 4 22 20 20 4 4 20 20 4 4 20 20 4 20 20 4 20 20 4 20 20 4 20 20 4 20 20 20 20 20 20 20 20 20 20	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.36 0.36 0.38 0.39 0.26 0.33 0.39 0.26 0.33 0.39 0.26 0.33 0.39 0.32 0.38 0.32 0.38 0.32 0.34 0.32 0.32 0.34 0.32 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.32 0.34 0.37 0.54 0.32 0.34 0.37 0.54 0.34 0.37 0.55 0.34 0.26 0.34 0.37 0.55 0.34 0.36 0.32 0.34 0.37 0.55 0.34 0.35 0.34 0.36 0.32 0.34 0.37 0.55 0.34 0.35 0.34 0.35 0.47 0.55	Total 63 63 115 92 28 100 42 137 201 99 59 115 42 124 146 146 42 100 2106 17 59 101 78 102 104 55 120 200 85 100 85	Weight 2.5% 5.9% 5.2% 9.0% 2.6% 6.5% 4.3% 8.4% 2.3% 5.2% 8.2% 7.7% 100.0% % Weight 1.6% 5.4% 3.2% 1.7% 6.4% 3.2% 1.1% 7.6% 6.7%	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.37 (-0.02, 0.76) 0.38 (0.35, 0.81) 0.23 (0.04, 0.42) 0.16 (0.03, 0.29) 0.13 (-0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08) 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.11, 0.59) 0.27 (-0.60, 0.60) 0.12 (-0.12, 0.36] 0.17 (0.02, 0.32) 0.20 (0.04, 0.36] 0.20 (0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62) 0.19 (-0.3, 0.41] 0.35 (0.10, 0.60] 0.23 (0.05, 0.41] 0.36 (-0.8, 0.22) 0.21 (-0.18, 0.38] 0.07 (-0.08, 0.48] 0.10 (-0.18, 0.38] 0.07 (-0.08, 0.48] 0.07 (-0.21, 0.30, 0.66] 0.22 (-0.17, 0.21]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
C	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang Y 2013 Zhang Y 2014 Yu SH 2014 Zhang YT 2014 Phu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Liar X 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2015 Liang R 2012 Li J 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Wang Z 2011	Mean 1.37 1.81 1.58 1.23 1.16 1.13 1.14 1.13 1.14 1.12 1.13 1.44 1.12 1.13 1.44 1.12 1.14 0.91 1.27 1.18 1.12 1.17 1.201; Chi ² Mean 1.37 1.18 1.58 1.23 1.58 1.23 1.61 1.58 1.23 1.61 1.72 1.13 1.58 1.23 1.61 1.21 1.44 1.12 1.13 1.14 1.12 1.13 1.14 1.12 1.14<	SO 0.39 SD 0.39 0.43 0.49 0.46 0.29 0.38 0.49 0.39 0.47 0.27 0.28 0.47 0.27 0.28 0.55 0.42 0.51 0.38 0.24 0.38 0.24 0.39 0.48 0.38 0.24 0.39 0.63 0.40 0.29 0.38 0.49 0.38 0.49 0.47 0.27 0.38 0.63 0.47 0.29 0.38 0.47 0.29 0.38 0.47 0.27 0.28 0.52 0.47 0.28 0.47 0.28 0.47 0.28 0.47 0.28	00001) Total 4 22 311 200 4 4 22 31 12 200 4 4 28 9 9 9 8 280 07, df = 200001) Total 4 22 8 8 8 9 9 9 8 280 07, df = 21 200 4 4 5 13 13 8 8 280 07, df = 21 200 4 200 200 200 200 200 200	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.36 0.37 0.36 0.38 0.45 0.33 0.38 0.27 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32	Total 63 115 92 82 228 100 48 172 201 99 59 115 42 124 40 2016 12 42 146 40 2106 12 37 80 117 85 104 55 104 55 102 200 85 120 200 85 120 200 85 107 84	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 7.5% 6.7% 4.1% 3.8% 3.4% 5.2% 8.2% 7.7% 100.0% % Weight 1.6% 5.4% 4.2% 7.5% 5.4% 4.2% 5.2% 8.2% 5.2% 8.2% 7.7% 10.0% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2	Mean Difference IV, Random, 95% CI IV, Random, 95% CI 0.37 (-0.02, 0.76] 0.18 (-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 (-0.25, 0.51] 0.44 [0.25, 0.53] 0.12 (-0.10, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 [-0.24, 0.60] 0.12 (-0.12, 0.36] 0.20 [0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 [-0.18, 0.62] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.36 [-0.38, 0.22] 0.10 [-0.18, 0.38] 0.07 [-0.08, 0.22] -0.12 [-0.30, 0.6] 0.22 [-0.7, 0.31] 0.26 [-0.27, 0.31]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
D	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J H 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Vang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% Cl) Heterogeneity: Tau² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lie KE 2012 Li J 2015 Liang R 2012 Li J 2015 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Ybano HY 2012	Mean 1.37 1.18 1.58 1.58 1.18 1.58 1.13 1.18 1.13 1.13 1.14 1.13 1.44 1.13 1.44 0.91 1.29 1.14 1.29 1.21 1.18 1.22 1.17 1.29 1.18 1.29 1.17 1.29 1.18 1.29 1.17 1.29 1.18 1.20 1.17 1.21 1.33 1.44 1.21 1.21 1.21 1.21 1.21 1.21 1.21 1.21 1.21 1.21 1.21	SO O TT SD SD 0.39 0.48 0.63 0.47 0.29 0.38 0.29 0.39 0.48 0.29 0.39 0.38 0.29 0.39 0.47 0.27 0.28 0.49 0.51 0.38 0.24 0.38 0.24 T SD 0.39 0.48 0.63 0.49 0.39 0.48 0.63 0.49 0.39 0.48 0.63 0.49 0.38 0.49 0.38 0.49 0.38 0.49 0.38 0.49 0.38 0.49 0.38 0.49 0.39 0.48 0.49 0.51 0.40 0.29 0.40 0.49	00001) Total 4 22 311 20 4 4 22 8 5 4 5 13 9 9 8 9 9 8 280 0 0001) Total 4 22 2 31 1 20 0 0001) 4 22 2 31 3 3 8 8 280 0 4 4 22 2 3 1 3 3 8 8 2 8 3 8 3 8 8 3 8 8 8 8 8 8 8 8	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.36 0.38 0.37 0.36 0.38 0.38 0.32 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32	Total 63 115 92 228 1000 48 172 228 100 48 172 201 42 124 146 40 2106 17 85 100 117 85 100 117 85 100 117 85 100 115 100 115 100 100 115 100 100	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 7.5% 6.7% 4.1% 3.8% 3.4% 7.5% 6.7% 3.2% 7.7% 100.0% % Weight 1.6% 5.4% 4.2% 6.7% 3.3% 6.4% 3.3% 6.4% 3.2% 11.1% 7.6% 6.4% 3.2%	Mean Difference IV, Random, 95% CI IV, Random, 95% CI 0.37 (-0.2, 0.76] 0.18 (-0.3, 0.39] 0.58 (0.35, 0.81] 0.23 (0.04, 0.42] 0.16 (0.3, 0.29] 0.13 (-0.25, 0.51] 0.44 (0.25, 0.63] 0.12 (-0.16, 0.40] 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.3, 0.35] 0.29 (-0.10, 0.59] 0.29 (-0.10, 0.59] 0.29 (-0.10, 0.59] 0.29 (-0.10, 0.59] 0.29 (-0.10, 0.59] 0.27 (-0.06, 0.60] 0.18 (-0.24, 0.60] 0.12 (-0.12, 0.36] 0.20 (0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.35 (0.10, 0.60] 0.35 (0.10, 0.60] 0.32 (0.05, 0.41] 0.35 (0.10, 0.60] 0.32 (0.05, 0.41] 0.35 (0.10, 0.60] 0.32 (0.05, 0.41] 0.35 (0.10, 0.60] 0.28 (0.08, 0.48] 0.10 (-0.18, 0.38] 0.10 (-0.17, 0.39] 0.28 (0.08, 0.48] 0.10 (-0.27, 0.31] 0.02 (-0.27, 0.31] 0.02 (-0.27, 0.31] 0.02 (-0.27, 0.33] 0.02 (-0.27, 0.38] 0.18 (-0.15, 0.51)	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
D	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2015 Liang R 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang HY 2012 Zhang HY 2012 Zhang HY 2012	Mean 1.37 1.18 1.58 1.58 1.18 1.58 1.13 1.16 1.13 1.16 1.13 1.14 1.12 1.14 1.29 1.27 1.18 1.29 1.27 1.18 1.17 1.20 01: ChP Mean 1.37 1.18 1.28 1.29 1.37 1.18 1.28 1.21 1.32 1.16 1.33 1.44 1.21 1.24 1.21 1.22 1.21 1.22 1.21 1.22 1.21 1.22 1.21 1.22 1.22	> 0.039 SD 0.039 0.39 0.48 0.63 0.4 0.29 0.38 0.32 0.39 0.38 0.4 0.29 0.39 0.30 0.47 0.27 0.28 0.47 0.24 0.39 0.48 0.63 0.39 0.48 0.63 0.69 0.38 0.48 0.63 0.48 0.69 0.38 0.48 0.63 0.47 0.27 0.28 0.38 0.51 0.47 0.27 0.28 0.51 0.42 0.51	00001) Total 4 22 311 200 4 12 8 8 45 5 13 9 9 6 28 0 77, df = 00001) Total 4 22 31 20 0 4 4 22 31 3 3 8 9 9 13 3 8 9 9 13 8 8 9 9 13 8 8 9 9 13 8 8 9 9 13 8 8 9 9 13 8 9 9 13 8 8 9 9 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.37 0.36 0.39 0.26 0.33 0.39 0.27 0.36 0.32 0.32 0.32 0.32 0.32 0.34 0.37 0.34 0.37 0.34 0.37 0.34 0.37 0.34 0.33 0.32 0.42 0.45 0.32 0.42 0.45 0.33 0.32 0.42 0.33 0.32 0.32 0.32 0.34 0.33 0.32 0.33 0.32 0.33 0.32 0.33 0.32 0.34 0.33 0.34 0.33 0.34 0.35 0.34 0.35 0.34 0.35 0.35 0.35 0.35 0.35 0.35 0.35 0.35	Total 63 115 92 228 100 48 172 201 95 9 59 137 1201 137 1201 142 40 2106 1 ² = 45 ⁴ 37 80 11 ⁷ 201 1 ² = 45 ⁴ 37 80 11 ⁷ 104 55 104 55 104 45 55 104 45 55 104 45 55 104 45 55 104 45 55 104 45 55 104 45 105 105 105 105 105 105 105 10	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 4.3% 8.4% 4.3% 3.4% 2.3% 5.2% 8.2% 8.2% 8.2% 5.2% 8.2% 4.1% 7.7% 100.0% %	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76] 0.37 (-0.02, 0.76] 0.37 (-0.02, 0.76] 0.38 (0.35, 0.81] 0.23 (0.04, 0.42] 0.16 [0.03, 0.29] 0.13 (-0.25, 0.51] 0.14 (-0.01, 0.29] -0.09 [-0.26, 0.08] 0.14 (-0.01, 0.29] -0.09 [-0.26, 0.08] 0.16 [-0.03, 0.35] 0.21 (-0.07, 0.49] 0.29 [-0.01, 0.59] 0.27 [-0.06, 0.60] 0.12 [-0.12, 0.36] 0.10 [-0.22, 0.32] 0.20 [0.41, 0.36] 0.20 [0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 [-0.18, 0.62] 0.19 [-0.30, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.36 [-0.38, 0.20] 0.01 [-0.37, 0.39] 0.28 [0.08, 0.48] 0.10 [-0.18, 0.38] 0.07 [-0.08, 0.22] -0.12 [-0.30, 0.06] 0.02 [-0.17, 0.21] 0.02 [-0.27, 0.31] 0.07 [-0.24, 0.38] 0.10 [-0.18, 0.38] 0.10 [-0.24, 0.38] 0.10 [-0.27, 0.31] 0.27 [-0.30, 0.66] 0.22 [-0.11, 0.53] 0.41 [-0.31, 0.51] 0.41 [-0.31, 0.51] 0.41 [-0.31, 0.53]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
D	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhang YT 2013 Cozer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang HY 2013 Zhang YT 2014	Mean 1.37 1.8 1.58 1.18 1.58 1.13 1.18 1.58 1.13 1.18 1.23 1.16 1.13 1.14 1.21 1.14 1.22 1.14 1.29 1.27 1.21 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.18 1.18 1.18 1.18 1.18 1.12 1.14 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 <	SO O SD O.39 0.39 0.48 0.63 0.44 0.29 0.38 0.29 0.39 0.47 0.27 0.28 0.51 0.37 0.42 0.40 0.51 0.38 0.24 0.42 0.49 0.38 0.24 0.42 0.40 0.38 0.42 0.42 0.49 0.39 0.47 0.29 0.39 0.42 0.49 0.42 0.49 0.51 0.35	00001) Total 4 22 31 21 20 4 12 8 8 45 5 13 9 9 13 3 8 9 9 28 18 280 0 7, df = 20 7, df = 20 231 21 20 4 4 22 31 21 20 4 4 12 1 21 20 4 12 1 2 1 20 4 12 1 2 1 2 0 4 1 2 1 2 1 2 0 4 9 9 1 3 8 8 9 9 1 3 8 8 9 9 1 3 8 8 9 9 1 3 8 8 9 9 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.36 0.38 0.38 0.39 0.32 0.38 0.27 0.36 0.32 0.38 0.22 0.38 0.22 0.38 0.22 0.38 0.22 0.38 0.22 0.32 0.32 0.32 0.32 0.34 0.37 0.34 0.37 0.51 0.32 0.34 0.33 0.32 0.34 0.33 0.32 0.34 0.35 0.34 0.35 0.34 0.35 0.35 0.35 0.35 0.35 0.35 0.35 0.35	Total 63 115 92 228 100 48 172 201 99 9115 59 124 124 146 42 124 146 146 127 2106 12 = 45' 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 55 104 105 105 105 105 105 105 105 105	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 8.4% 2.3% 5.2% 8.4% 2.3% 5.2% 8.2% 100.0% %	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.37 (-0.02, 0.76) 0.38 (-0.35, 0.81) 0.23 (-0.04, 0.42] 0.16 (-0.03, 0.29] 0.13 (-0.25, 0.51] 0.14 (-0.25, 0.51] 0.14 (-0.25, 0.53] 0.12 (-0.16, 0.40] 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.12 (-0.17, 0.36] 0.17 (0.02, 0.32] 0.20 (0.04, 0.36] 0.20 (0.13, 0.27] Mean Difference IV. Fixed, 95% CI 0.22 (-0.18, 0.62] 0.19 (-0.03, 0.41] 0.35 (0.10, 0.60] 0.23 (0.05, 0.41] 0.36 (-0.08, 0.20] 0.41 (-0.18, 0.38] 0.41 (-0.18, 0.38] 0.41 (-0.18, 0.38] 0.47 (-0.24, 0.38] 0.48 (-0.45, 0.51] 0.41 (-0.41, 0.53] 0.44 (-0.45, 0.55]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
D	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang YT 2013 Zhang YT 2014 Zhang YT 2014 Zhang YT 2014 Zhang YT 2014 Did Strong YT 2014 Phorag YT 2014 Phorag YT 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang TY 2013	Mean 1.37 1.81 1.58 1.23 1.13 1.44 1.52 1.13 1.44 1.12 1.13 1.44 1.12 1.13 1.44 1.12 1.13 1.44 1.12 1.14 0.91 1.27 1.18 1.12 1.17 1.2 Mean 1.37 1.18 1.58 1.23 1.61 1.33 1.61 1.33 1.61 1.33 1.61 1.21 1.44 1.22 1.14 1.22 1.16 1.21 1.22 1.12 1.12 1.12 <	> < 0.0 TT SD 0.39 0.48 0.63 0.47 0.29 0.39 0.48 0.63 0.49 0.37 0.28 0.50 0.47 0.27 0.28 0.50 0.42 0.38 0.24 0.38 0.24 0.39 0.48 0.63 0.48 0.29 0.39 0.47 0.28 0.39 0.47 0.28 0.49 0.41 0.35 0.42 0.43 0.44 0.38 0.55 0.42 0.38 0.38 0.38 0.49 0.51 0.38	00001) Total 4 22 311 200 4 4 22 8 8 9 9 9 8 8 280 9 9 9 8 280 9 9 9 8 280 133 8 8 9 9 9 8 280 10 11 20 13 13 8 8 9 9 9 8 8 280 13 13 8 280 13 13 13 8 8 9 9 9 8 280 281 13 13 13 8 280 280 280 281 13 13 13 8 280 280 280 281 201 13 13 8 280 280 280 281 201 13 13 8 280 280 281 201 13 13 8 280 280 281 201 13 201 13 200 201 13 200 201 13 201 201 201 201 201 201 201 201	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.36 0.36 0.36 0.38 0.33 0.38 0.33 0.32 0.38 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32	Total 63 115 92 82 228 115 92 212 28 122 28 137 201 14 40 2106 21 24 40 2106 12 24 37 80 2000 85 104 55 104 55 107 84 33 73 73 74 86	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 7.5% 6.7% 4.1% 3.8% 3.2% 7.7% 100.0% % Weight 1.6% 5.4% 4.2% 7.7% 100.0% %	Mean Difference IV, Random, 95% CI V, Random, 95% CI 0.37 (-0.2, 0.76) 0.18 (-0.3, 0.39) 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.16 [0.03, 0.29] 0.13 (-0.25, 0.51] 0.44 [0.25, 0.63] 0.12 (-0.10, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 (-0.24, 0.60] 0.18 (-0.24, 0.60] 0.18 (-0.24, 0.60] 0.19 (-0.2, 0.32] 0.20 [0.04, 0.36] 0.20 [0.13, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.19 (-0.38, 0.41] 0.35 [0.10, 0.60] 0.23 [0.50, 0.41] 0.35 [0.10, 0.60] 0.23 [0.50, 0.41] 0.35 [0.10, 0.60] 0.23 [0.50, 0.41] 0.36 (-0.88, 0.22] -0.12 (-0.37, 0.39] 0.28 [0.08, 0.48] 0.07 (-0.08, 0.22] -0.12 (-0.37, 0.31] 0.02 (-0.27, 0.31] 0.07 (-0.24, 0.38] 0.19 (-0.15, 0.55] 0.15 (-0.11, 0.31]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
D	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Zhang Y 2013 Zhang Y 2014 Yu SH 2014 Zhang Y 2012 Zhang Y 2013 Zhang Y 2013 Zhang Y 2012 Zhang Y 2013 Zhang Y 2014 MT Lee 2009 Total (95% Cl) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2015 Liang R 2012 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang Y 2012 Zhang Y 2013	Mean 1.37 1.8 1.58 1.58 1.58 1.58 1.58 1.13 1.13 1.13 1.14 1.13 1.44 1.12 1.13 1.44 1.12 1.13 1.14 0.91 1.27 1.18 1.12 1.29 0.1 ChiPa 6.5.73 (F Mean 1.37 1.18 1.38 1.33 1.44 1.12 1.13 1.14 0.29 1.23 1.44 1.21 1.22 1.14 0.29 1.21 1.21 1.22 1.21 1.21 <	> < 0.0 TT SD 0.39 0.4 0.29 0.48 0.63 0.47 0.29 0.38 0.29 0.38 0.29 0.39 0.47 0.27 0.28 0.51 0.38 0.24 0.38 0.24 TT 0.39 0.44 0.29 0.38 0.44 0.29 0.38 0.24 TT 0.38 0.47 0.38 0.47 0.28 0.51 0.38 0.52 0.47 0.28 0.51 0.38 0.38 0.38 0.38 0.38 0.38	00001) Total 4 22 311 200 4 4 22 31 12 20 4 4 22 31 13 8 8 9 9 9 8 280 07, df = 280 280 13 13 8 8 9 9 9 8 280 280 13 13 8 5 280 280 280 280 280 280 280 280	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.37 0.36 0.38 0.37 0.36 0.33 0.27 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32	Total 63 115 92 228 100 48 172 2115 59 115 99 59 124 146 40 2106 12 2106 12 37 80 117 85 100 85 101 55 102 200 85 107 84 33 73 373 73 744 49	Weight 2.5% 5.9% 5.2% 6.6% 4.3% 8.4.3% 8.4% 7.5% 6.7% 4.1% 3.8% 3.4% 7.5% 6.7% 7.7% 100.0% % Weight 1.6% 5.4% 4.2% 7.5% 1.1.6% 6.4% 3.2% 11.1% 7.6% 6.4% 3.2% 11.1% 7.6% 6.4% 3.1% 2.3% 5.2% 1.4% 4.2% 7.5% 5.4% 7.5% 5.2% 7.5% 5.2% 7.7% 1.1% 7.5% 6.4% 7.5% 5.2% 7.7% 7.6% 7.5% 5.2% 7.7% 7.6% 7.5% 7.7% 7.6% 7.5% 7.7% 7.6% 7.6% 7.6% 7.6% 7.6% 7.6% 7.6	Mean Difference IV, Random, 95% CI IV, Random, 95% CI 0.37 (-0.2, 0.76] 0.18 (-0.3, 0.39] 0.58 (0.35, 0.81] 0.23 (0.04, 0.42] 0.16 (0.03, 0.29] 0.13 (-0.25, 0.51] 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.29 (-0.01, 0.59] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.18 (-0.24, 0.60] 0.12 (-0.12, 0.36] 0.17 ([0.02, 0.32] 0.20 (0.04, 0.36] 0.20 (0.04, 0.36] 0.22 (-0.18, 0.62] 0.22 (-0.18, 0.62] 0.22 (-0.18, 0.62] 0.35 (0.10, 0.60] 0.35 (0.10, 0.60] 0.32 (0.05, 0.41] 0.06 (-0.08, 0.22] 0.10 (-0.18, 0.38] 0.07 (-0.08, 0.22] 0.12 (-0.17, 0.29] 0.28 [0.08, 0.48] 0.10 (-0.18, 0.38] 0.07 (-0.24, 0.38] 0.10 (-0.18, 0.38] 0.02 (-0.17, 0.21] 0.02 (-0.27, 0.31] 0.02 (-0.27, 0.31] 0.01 (-0.35, 0.51] 0.11 (-0.31, 0.53] 0.10 (-0.15, 0.55] 0.15 (-0.01, 0.31] -0.03 (-0.21, 0.15]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
D	Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhu JR 2012 Özer M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang YT 2012 Zhang Y 2012 Zhang Y 2013 Cout S 2015 Liang R 2012 Liang HY 2012 Zhang Y 2013	Mean 1.37 1.18 1.58 1.58 1.18 1.58 1.13 1.16 1.13 1.16 1.13 1.14 1.13 1.14 0.91 1.22 1.14 0.91 1.27 1.14 0.91 1.22 1.21 1.22 1.21 1.22 1.17 1.22 01; ChP Mean 1.37 1.18 1.23 1.16 1.13 1.24 1.23 1.14 0.91 1.27 1.29 1.21 1.22 1.23 1.44 0.91 1.27 1.28 <tr td=""></tr>	SO CO TT SD SD 0.39 0.39 0.48 0.63 0.4 0.29 0.38 0.37 0.27 0.29 0.39 0.30 0.47 0.27 0.228 0.49 0.51 0.38 0.51 0.38 0.24 T SD 0.39 0.48 0.63 0.49 0.39 0.48 0.63 0.49 0.39 0.48 0.63 0.47 0.27 0.28 0.38 0.47 0.27 0.28 0.47 0.27 0.22 0.49 0.51 0.38 0.52 0.42 0.47 0.27 0.28 0.51 0.38 0.24	00001) Total 4 22 311 200 4 4 12 8 4 4 5 13 3 9 9 28 8 9 9 28 8 280 7, df = 280 4 4 22 8 9 9 28 13 13 13 13 13 13 13 13 13 13	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.37 0.36 0.39 0.26 0.33 0.32 0.32 0.32 0.32 0.32 0.32 0.32	Total 63 115 92 228 100 48 172 201 959 115 42 124 146 00 2016 Total 37 80 117 12 124 40 2016 12 142 40 2106 12 145 55 1200 200 85 100 200 85 107 84 33 37 37 37 37 37 37 37 37 37 37 37 37<	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 9.0% 2.6% 7.5% 6.7% 3.8% 2.3% 5.2% 8.2% 100.0% % Weight 1.6% 5.4% 4.2% 1.6% 5.4% 4.2% 1.6% 5.4% 4.1% 9.5% 1.4% 3.1% 1.4% 9.5%	Mean Difference IV, Random, 95% CI 0.37 (-0.2, 0.76] 0.37 (-0.2, 0.76] 0.38 (0.35, 0.81] 0.23 (0.40, 0.42] 0.16 (0.03, 0.29] 0.13 (-0.25, 0.51] 0.44 (0.25, 0.63] 0.12 (-0.16, 0.40] 0.14 (-0.01, 0.29] -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35] 0.21 (-0.07, 0.49] 0.29 (-0.01, 0.59] 0.27 (-0.06, 0.60] 0.12 (-0.12, 0.36] 0.12 (-0.12, 0.36] 0.12 (-0.12, 0.36] 0.12 (-0.13, 0.27] Mean Difference IV. Fixed, 95% CI 0.22 (-0.18, 0.62] 0.19 (-0.3, 0.41] 0.35 (0.10, 0.60] 0.23 (0.05, 0.41] 0.35 (0.10, 0.60] 0.23 (0.08, 0.48] 0.10 (-0.18, 0.38] 0.10 (-0.18, 0.38] 0.10 (-0.21, 0.31] 0.02 (-0.27, 0.31] 0.07 (-0.24, 0.38] 0.11 (-0.31, 0.53] 0.11 (-0.31, 0.53] 0.10 (-0.15, 0.55] 0.15 (-0.01, 0.31] -0.03 (-0.21, 0.15]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
D	Study or Subgroup Fang SJ 2014 Hiral K 2015 Krishna Kumar D 2014 Lee KE 2012 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2014 MT Lee 2009 Tan SL 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang YT 2014 Zhang YT 2014 Zhang YT 2014 Zhang YT 2014 Zhu JR 2012 Zhang YT 2014 Zhu JR 2012 Diar M 2013 Total (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Fang SJ 2014 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Li J 2012 Li J 2012 Liang R 2012 Liang R 2012 Liang R 2012 Liang R 2012 Wang Z 2011 Yu SH 2014 Zhang HY 2012 Zhang HY 2012	Mean 1.37 1.18 1.58 1.58 1.18 1.58 1.13 1.16 1.13 1.16 1.13 1.14 1.12 1.14 1.29 1.21 1.21 1.22 1.27 1.14 1.29 1.27 1.17 1.20 01: Chi ² Mean 1.37 1.18 1.22 1.33 1.66 1.33 1.61 1.33 1.62 1.33 1.44 1.22 1.21 1.44 1.22 1.21 1.22 1.22 1.21 1.22 1.21 1.22 1.21 <td>SO O SD O.39 0.39 0.48 0.63 0.4 0.29 0.38 0.29 0.39 0.38 0.4 0.29 0.39 0.47 0.27 0.28 0.55 0.42 0.51 0.38 0.51 0.38 0.24 0.39 0.48 0.63 0.39 0.48 0.63 0.69 0.38 0.48 0.55 0.42 0.47 0.27 0.28 0.51 0.35 0.48 0.55 0.42 0.47 0.27 0.28 0.51 0.35 0.42 0.42 0.42 0.42 0.42 0.42</td> <td>00001) Total 4 22 311 200 4 4 22 8 8 9 9 9 9 9 9 9 9 9 9 9 9 9</td> <td>Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td> <td>CC SD 0.33 0.4 0.38 0.26 0.36 0.37 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32</td> <td>Total 63 115 92 228 100 48 172 201 99 99 115 42 124 146 00 2106 12 = 45% 700 117 75 104 55 100 2000 85 104 54 55 100 2000 85 107 84 33 74 86 9 1480</td> <td>Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 8.4% 2.5% 5.2% 8.2% 7.5% 7.2% 100.0% % 1.6% 5.4% 4.2% 7.5% 3.5% 1.1% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 1.4% 9.5% 8.1% 100.0%</td> <td>Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.37 (-0.02, 0.76) 0.38 (0.35, 0.81) 0.23 (0.04, 0.42) 0.16 (0.03, 0.29) 0.13 (-0.25, 0.51) 0.44 (0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.12 (-0.12, 0.36) 0.21 (-0.24, 0.60) 0.12 (-0.12, 0.36] 0.20 (0.41, 0.36] 0.20 (0.43, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.23 (0.05, 0.41] 0.35 (0.10, 0.60] 0.23 (0.05, 0.41] 0.36 (0.08, 0.20] 0.01 (-0.37, 0.39) 0.28 (0.8, 0.48] 0.10 (-0.18, 0.38] 0.07 (-0.08, 0.22] -0.12 (-0.30, 0.66] 0.02 (-0.17, 0.23] 0.20 (0.24, 0.38] 0.10 (-0.18, 0.38] 0.07 (-0.24, 0.38] 0.10 (-0.15, 0.35] 0.10 (-0.15, 0.35] 0.10 (-0.15, 0.35] 0.10 (-0.21, 0.15] 0.10 (0.05, 0.15]</td> <td>Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl </td>	SO O SD O.39 0.39 0.48 0.63 0.4 0.29 0.38 0.29 0.39 0.38 0.4 0.29 0.39 0.47 0.27 0.28 0.55 0.42 0.51 0.38 0.51 0.38 0.24 0.39 0.48 0.63 0.39 0.48 0.63 0.69 0.38 0.48 0.55 0.42 0.47 0.27 0.28 0.51 0.35 0.48 0.55 0.42 0.47 0.27 0.28 0.51 0.35 0.42 0.42 0.42 0.42 0.42 0.42	00001) Total 4 22 311 200 4 4 22 8 8 9 9 9 9 9 9 9 9 9 9 9 9 9	Mean 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	CC SD 0.33 0.4 0.38 0.26 0.36 0.37 0.36 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32	Total 63 115 92 228 100 48 172 201 99 99 115 42 124 146 00 2106 12 = 45% 700 117 75 104 55 100 2000 85 104 54 55 100 2000 85 107 84 33 74 86 9 1480	Weight 2.5% 5.9% 5.2% 6.6% 9.0% 2.6% 6.5% 4.3% 8.4% 2.5% 5.2% 8.2% 7.5% 7.2% 100.0% % 1.6% 5.4% 4.2% 7.5% 3.5% 1.1% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 1.4% 9.5% 8.1% 100.0%	Mean Difference IV, Random, 95% CI 0.37 (-0.02, 0.76) 0.37 (-0.02, 0.76) 0.38 (0.35, 0.81) 0.23 (0.04, 0.42) 0.16 (0.03, 0.29) 0.13 (-0.25, 0.51) 0.44 (0.25, 0.63) 0.12 (-0.16, 0.40) 0.14 (-0.01, 0.29) -0.09 (-0.26, 0.08] 0.16 (-0.03, 0.35) 0.21 (-0.07, 0.49) 0.29 (-0.01, 0.59) 0.27 (-0.06, 0.60) 0.12 (-0.12, 0.36) 0.21 (-0.24, 0.60) 0.12 (-0.12, 0.36] 0.20 (0.41, 0.36] 0.20 (0.43, 0.27] Mean Difference IV, Fixed, 95% CI 0.22 (-0.18, 0.62] 0.23 (0.05, 0.41] 0.35 (0.10, 0.60] 0.23 (0.05, 0.41] 0.36 (0.08, 0.20] 0.01 (-0.37, 0.39) 0.28 (0.8, 0.48] 0.10 (-0.18, 0.38] 0.07 (-0.08, 0.22] -0.12 (-0.30, 0.66] 0.02 (-0.17, 0.23] 0.20 (0.24, 0.38] 0.10 (-0.18, 0.38] 0.07 (-0.24, 0.38] 0.10 (-0.15, 0.35] 0.10 (-0.15, 0.35] 0.10 (-0.15, 0.35] 0.10 (-0.21, 0.15] 0.10 (0.05, 0.15]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl

Figure 2. Forest plots for the association between the *CYP4F2* rs2108622 polymorphism and warfarin maintenance dose. The brackets represent 95% CI and the size of each box is proportional to the number of included patients. (A) CT vs. CC carriers. (B) T carriers (CT or TT) vs. CC carriers. (C) TT vs. CC carriers. (D) CT vs. TT carriers. SD, standard deviation of normalized warfarin doses associated with each genotype; CI, confidence interval.

Sensitivity analyses were performed by two methods. The first method removed studies one by one, and the second switched the meta-analysis between the fixed-effect model and random-effect model. Begg's funnel plot and Egger's linear regression test were applied to evaluate the publication bias with the use of STATA software version 12.0 (StataCorp LP, College Station, TX, USA), and P<0.05 was considered to indicate a statistically significant difference.

Subgroup analyses were carried out to identify the potential explanatory variables. The Chinese and non-Chinese Asian population studies were defined as two separate subgroups. As age was an important influence factor, the data was also divided into two according to the mean age of <60 years old and >60 years old. The main analysis was repeated separately in each subgroup.

Results

Literature selection. Fig. 1 shows the selection process of the eligible studies. A total of 379 candidate studies were included in the initial search. Following exclusion of the repeated and unfitted studies, 22 studies with a total of 4,549 patients conformed to the inclusion criteria for the qualitative data analysis.

Study characteristics. Table I expresses the characteristics of these 22 studies included in the meta-analysis. The publication years of the eligible studies ranged between 2009 and 2015. Among the included studies, the majority were of Chinese patients (10-15,20-25). Five studies were of non-Chinese populations (26-30) and one was for an Asian population (31). The main indications of warfarin were heart valve replacement, AF, DVT, pulmonary embolism and stroke.

Allele frequencies. There were 3,646 Chinese and 903 non-Chinese Asian patients included in the final analysis. On average, the frequencies of CC, CT and TT were 0.53, 0.39 and 0.08 in all the selected Asian patients. The frequencies of CC, CT and TT were 0.57, 0.37 and 0.06 in the Chinese patients and 0.44, 0.45 and 0.11, respectively, in the non-Chinese Asian patients. SPSS 18.0 (SPSS, Inc., Chicago, IL, USA) was used to assess the difference of allele frequencies between the two subgroups, and there was a significantly statistical difference (P<0.05).

Meta-analysis results. Fig. 2 shows the influence of each *CYP4F2* genotype on the warfarin maintenance dose. Compared with individuals with the homozygous CC genotype, warfarin doses in patients with genotype CT, TT and T carriers were significantly higher by 9 [95% confidence interval (CI), 6.0-13.0], 20 (95% CI, 13.0-27.0) and 11% (95% CI, 8.0-14.0), respectively (test for overall effect was P<0.05). Additionally, compared with the CT carriers, the TT carriers required a higher warfarin dose by 10% (95% CI, 5.0-15.0) with statistical significance (P<0.05).

Heterogeneity analysis. Only one meta-analysis showed no statistical heterogeneity (Cochran's Q test P=0.22, I^2 value 15%), and a fixed-effects model was used in the analysis. However, statistical heterogeneity was evident across the other meta-analyses in which the random-effects model was applied.

0.5-0-0--0.5-

Begg's funnel plot with pseudo 95% confidence limits

Figure 3. Funnel plot of the publication bias for the association between the CYP4F2 rs2108622 polymorphism and warfarin maintenance dose. The solid horizontal line shows the summary effect estimate, for exhibiting the center of the plot in the absence of bias. The diagonal lines denote the 95% confidence limits.

s.e. of: SMD

0'2

0'

ò

0.3

Sensitive analysis and publication bias. The first method of sensitivity analysis was performed by deselecting each study one at a time. When deselecting the study of Luo *et al* (2013, unpublished data), the I² decreased from 74 to 42%, indicating that the study is the source of statistical heterogeneity. Further analysis showed that the heterogeneity may have been due to several design differences among the studies, including lower mean age and the definition of stable warfarin dose in the inclusion criteria. Following this, the study was excluded in the final analysis. Subsequently, the sensitivity was analyzed using the random-effect model, in which the results of the parameter analysis were in accordance with those using the fixed-effect model, suggesting that the results were stable.

Publication bias was evaluated by Begg's funnel plot and Egger's linear regression test. Fig. 3 showed the Begg's funnel plot of the main studies included in the meta-analysis. One study was outside the excepted 95% CI. The Egger regression test indicated no significant publication bias across the studies (t=1.65, P=0.119).

Subgroup analysis. Considering the multiple difference between Chinese and non-Chinese Asian populations, a subgroup analysis was performed and the results are presented in Fig. 4. Non-Chinese CT and TT carriers showed an ~1 and 12% larger effect on warfarin dose requirement compared to Chinese patients. Non-Chinese T carriers showed ~6% larger effect by comparison with Chinese patients. Fig. 5 shows the subgroup analyses of different age intervals. CT and TT carriers <60 years old showed an ~5 and 4% larger effect on warfarin dose requirement than that of patients >60 years. However, these differences were not significant (P>0.05).

Discussion

The incidence of thromboembolic disease ranks first among various diseases, showing an increasing tendency each year. New oral anticoagulants, such as rivaroxaban and apixaban, have the advantage of safe, effective and significant reduction

 Study or Subgroup
 Mean

 5.1.1 Chinese
 Fang SJ 2014
 1.15

 Li JH 2012
 1.1
 1

 Li S 2015
 1.12
 Liang R 2012
 1.16

 Liang R 2012
 1.16
 1.02
 Lou Y 2013
 1.02

 Lou Y 2013
 1.02
 1.04
 1.07
 Tan SL 2012
 1.14

 Vai SH 2012
 1.14
 1.02
 2.011
 1.19
 Yu SH 2014
 1.22

 Zhang H 2013
 1.07
 Zhang H 2014
 1.02
 Zhu JR 2012
 1.04
 1.02

 Zhang H 2014
 1.02
 Zhu JR 2014
 1.02
 Zhu JR 2014
 1.02

 Subtotal (95% CI)
 Heterogeneity: Tau² = 0.00; Chi² = Test for overall effect: Z = 5.91 (P
 5.1.2 other Asians
 CT SD Total Mean CC SD Total Weight Mean Difference IV. Random, 95% Cl Mean Difference V. Random. 95% Cl IV. Rand $\begin{array}{c} \text{Kandem}, \text{ 497. a } \text{ --} \\ \text{0.15} [0.01, 0.29] \\ \text{0.10} [0.04, 0.16] \\ \text{0.12} [0.04, 0.16] \\ \text{0.12} [0.01, 0.23] \\ \text{0.16} [0.04, 0.31] \\ \text{0.07} [-0.01, 0.15] \\ \text{0.07} [-0.01, 0.15] \\ \text{0.07} [-0.01, 0.16] \\ \text{0.07} [-0.01, 0.16] \\ \text{0.08} [-0.02, 0.20] \\ \text{0.14} [0.06, 0.22] \\ \text{0.09} [0.07, 0.31] \\ \text{0.09} [0.06, 0.22] \\ \text{0.09} [0.06, 0.22] \\ \text{0.09} [0.06, 0.12] \\ \text{0.09} [0.06, 0.13] \\ \end{array}$
 1.15
 0.34

 1.1
 0.26

 1.12
 0.32

 1.16
 0.42

 1.02
 0.4

 1.07
 0.45

 1.14
 0.35

 1.19
 0.43

 1.22
 0.33

 1.09
 0.38

 1.07
 0.43

 1.02
 0.39
 37 104 54 55 120 200 85 107 84 33 73 37 74 86 1149 $\begin{array}{cccc} 1 & 0.33 \\ 1 & 0.26 \\ 1 & 0.37 \\ 1 & 0.36 \\ 1 & 0.38 \\ 1 & 0.47 \\ 1 & 0.33 \\ 1 & 0.39 \\ 1 & 0.26 \\ 1 & 0.33 \\ 1 & 0.27 \\ 1 & 0.36 \\ 1 & 0.32 \end{array}$ 4.2% 9.6% 5.5% 3.7% 7.0% 7.9% 4.3% 5.0% 4.5% 5.8% 4.3% 6.4% 81.3% 228 100 48 172 243 137 201 99 59 115 42 124 146 1777 df = 001) 5.1.2 other Asians 0.99 0.37 80 1.23 0.58 117 1 0.31 85 1.23 0.49 49 331 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Özer M 2013 Subtotal (95% CI) 1 0.4 1 0.38 1 0.38 1 0.38 115 92 82 40 329 5.6% 4.5% 5.9% 2.8% 18.7% -0.01 [-0.12, 0.10] 0.23 [0.10, 0.36] 0.00 [-0.11, 0.11] 0.23 [0.05, 0.41] 0.10 [-0.03, 0.23] Subtotal (95% Cl) Heterogeneity: Tau² = 0.01; Chi² = 12.50, df = 3 (P = 0.006); I² Test for overall effect: Z = 1.53 (P = 0.13) = 76% 100.0% 0.09 [0.06, 0.13] ٠ -0.5 -0.25 Favours [experimental] 0.25 0.5 Favours [control] CT+TT cc Mean Difference Mean Difference В Study or Subgroup 5.2.1 Chinese Cen HJ 2010 Fang SJ 2014 Li JH 2012 Li S 2015 IV. Random, 95% CI m. 95% CI Mean SD Total Mean SD Total Weight IV. Rand
 1.1
 0.38

 1.1
 0.34

 1.1
 0.26

 1.21
 0.32

 1.21
 0.41

 1.02
 0.4

 1.03
 0.48

 1.04
 0.48

 1.05
 0.44

 1.23
 0.34

 1.23
 0.34

 1.23
 0.34

 1.21
 0.39

 1.06
 0.39

 1.04
 0.27

 0.10 [-0.00, 0.20]

 0.10 [0.05, 0.31]

 0.18 [0.05, 0.31]

 0.10 [0.04, 0.16]

 0.12 [0.07, 0.35]

 0.21 [0.07, 0.35]

 0.02 [-0.07, 0.31]

 0.04 [0.01, 0.33]

 0.05 [0.07, 0.35]

 0.01 [-0.11, 0.13]

 0.32 [0.07, 0.32]

 0.32 [0.07, 0.33]

 0.33 [0.08, 0.32]

 0.33 [0.08, 0.32]

 0.34 [-0.06, 0.22]

 0.34 [-0.06, 0.22]

 0.34 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

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 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.32]

 0.35 [-0.06, 0.35]

 0.35 [-0.06, 0.35]

 0.35 [-0.06, 0.35]

 <td $\begin{array}{cccc} 1 & 0.38 \\ 1 & 0.33 \\ 1 & 0.26 \\ 1 & 0.36 \\ 1 & 0.36 \\ 1 & 0.36 \\ 1 & 0.38 \\ 1 & 0.47 \\ 1 & 0.33 \\ 1 & 0.26 \\ 1 & 0.27 \\ 1 & 0.36 \\ 1 & 0.32 \\ 1 & 0.32 \\ 1 & 0.32 \\ 1 & 0.3 \end{array}$ 5.1% 3.7% 4.6% 3.4% 5.8% 6.4% 4.0% 4.0% 4.0% 4.3% 4.9% 3.6% 4.7% 5.7% 6.4% 107 41 124 58 67 128 245 98 116 97 41 82 43 83 114 115 63 228 100 48 172 243 137 201 99 59 115 42 42 124 146 121 2013 = 0.09);
 Test for overall endow

 5.2.2 other Asians

 5.2.2 other Asians

 Hirai K 2015
 1.03
 0.4
 102
 1
 0.4

 Krishna Kumar D 2014
 1.3
 0.6
 148
 1
 0.38

 Lee KE 2012
 1.04
 0.34
 106
 1
 0.38

 Nakamura K 2012
 1.23
 0.59
 68
 1
 0.35

 Özer M 2013
 1.22
 0.44
 67
 1
 0.38

 Heterogeneity: Tau² = 0.01; Chi² = 16.05, df = 4 (P = 0.003); P²
 Test for overall effect: Z = 2.67 (P = 0.008)
 P
 0.03 [-0.08, 0.14] 0.30 [0.18, 0.42] 0.04 [-0.06, 0.14] 0.23 [0.06, 0.40] 0.22 [0.06, 0.38] 0.16 [0.04, 0.27] 115 92 82 58 40 387 4.8% 4.0% 4.9% 2.7% 75% 0.11 [0.08, 0.14] -0.5 -Favours [exp -0.25 0.25 0.5 Introl ntall Favo Study or Subgroup 5.3.1 Chinese Fang SJ 2014 Li JH 2012 Li S 2015 Liang R 2012 Liang Y 2013 Lou Y 2013 MT Lee 2009 MT Lee 2009 Wang Z 2011 Wang Z 2014 Zhang HY 2012 Zhang YT 2014 Zhang YT 2014 Zhang YT 2013 Zhang YT 2014 Hotorogeneity: Tau² J тт cc Mean Differend Mean Differen C . SD Total Mean SD Total Weight IV. Random, 95% CI IV. Rar n. 95% Cl $\begin{array}{c} \text{Kardem, } 9.7 \\ \text{Co.02, } 0.76 \\ \text{O, 16 } [0.03, 0.29] \\ \text{O, 17 } [0.03, 0.29] \\ \text{O, 13 } [-0.25, 0.63] \\ \text{O, 14 } [-0.25, 0.63] \\ \text{O, 14 } [-0.07, 0.29] \\ \text{O, 14 } [-0.07, 0.29] \\ \text{O, 16 } [-0.03, 0.35] \\ \text{O, 21 } [-0.07, 0.49] \\ \text{O, 29 } [-0.07, 0.49] \\ \text{O, 29 } [-0.07, 0.49] \\ \text{O, 29 } [-0.07, 0.59] \\ \text{O, 27 } [-0.06, 0.60] \\ \text{O, 18 } [-0.24, 0.60] \\ \text{O, 14 } [-0.22, 0.32] \\ \text{O, 17 } [0.02, 0.32] \\ \text{O, 17 } [0.02, 0.32] \end{array}$ 0.33 0.26 0.37 0.36 0.38 0.47 0.33 0.26 0.33 0.26 0.33 0.27 0.36 0.32 2.5% 2.6% 6.5% 4.3% 7.5% 6.7% 4.1% 3.8% 3.4% 2.3% 5.2% 8.2% 74.5% 4 20 42 85 13 9 13 8 9 6 9 228 100 48 172 243 137 201 99 59 115 42 124 146 1777 28 188 188 0.01; Chi² = 19.43, df = 13 (F Z = 4.65 (P < 0.00001) Heterogeneity: Tau² = 0. Test for overall effect: Z 0.11): F = 33% 5.3.2 other Asians 5.3.2 other Asians Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Özer M 2013 Subtotal (95% CI) 1.18 0.48 1.58 0.63 1.23 0.4 1.2 0.24 1 0.4 1 0.38 1 0.38 1 0.38 0.18 [-0.03, 0.39] 0.58 [0.35, 0.81] 0.23 [0.04, 0.42] 0.20 [0.04, 0.36] 0.29 [0.12, 0.45] 22 31 21 18 92 115 92 82 40 329 5.9% 5.2% 6.6% 7.7% 25.5% Subtotal (95% Cl) 329 Heterogeneity: Tau² = 0.02; Chi² = 8.26, df = 3 (P = 0.04); I² = 64% Test for overall effect: Z = 3.42 (P = 0.0006) $\begin{array}{cccc} \textbf{Total (95\% Cl)} & \textbf{280} & \textbf{2106} & \textbf{100} \\ \textbf{Heterogeneity: } \texttt{Tau}^a = 0.01; \ \textbf{Ch}^a = 31.07, \ \textbf{df} = 17 \ (\textbf{P} = 0.02); \ \textbf{l}^a = 45\% \\ \textbf{Test for overall effect: } Z = 5.73 \ (\textbf{P} < 0.00001) \\ \textbf{Test for suboroup differences: } \textbf{Ch}^a = 1.57, \ \textbf{df} = 1 \ (\textbf{P} = 0.21), \ \textbf{l}^a = 36.3\% \end{array}$ 0.20 [0.13, 0.27] 100.0% -0.5 Favours [expe -0.25 erimer 0 0.25 0.5 Favours [control] ntall
 Study or Subgroup

 5.4.1 Chinese

 Fang SJ 2014

 Li JH 2012

 Liang R 2012

 Liang Y 2013

 Lou Y 2014

 MT Lee 2009

 Tan SL 2012

 Wang Z 2011

 Yu SH 2014

 Zhang HY 2012

 Zhang T 2013

 Zhang Y 2012

 Zhang Y 2013

 Zhang Y 2014

 Zhang Y 2013
 тт D ст Mean Difference Mean Difference IV. Random. 95% Cl Mean SD Total Mean SD Total Weight IV. Random. 95% CI 0.22 [-0.18, 0.62] 0.06 [-0.08, 0.20] 0.01 [-0.37, 0.39] 0.28 [0.08, 0.48] 0.10 [-0.18, 0.38] 0.10 [-0.18, 0.38] 0.10 [-0.18, 0.38] 0.12 [-0.17, 0.21] 0.02 [-0.17, 0.21] 0.02 [-0.17, 0.31] 0.07 [-0.24, 0.38] 0.18 [-0.15, 0.53] 0.11 [-0.31, 0.53] 0.15 [-0.01, 0.31]
 1.37
 0.39

 1.16
 0.29

 1.13
 0.38

 1.44
 0.29

 1.12
 0.38

 1.14
 0.47

 0.91
 0.27

 1.16
 0.28

 1.21
 0.5

 1.29
 0.42

 1.29
 0.49

 1.18
 0.51

 1.12
 0.35

 1.17
 0.38
 4 20 4 12 8 45 13 9 13 8 9 6 9 1.15 1.1 1.12 1.02 1.07 1.03 1.14 1.19 1.22 1.09 1.07 1.02 0.34 0.26 0.32 0.42 0.45 0.51 0.35 0.43 0.33 0.33 0.33 0.33 0.42 0.39 37 104 54 55 120 200 85 107 84 33 73 37 74 1.9% 1.6% 11.6% 2.0% 6.6% 3.6% 10.1% 7.5% 6.8% 3.5% 3.0% 2.6% 1.7% 4.5% _
 Zhang YT 2014
 1.12
 0.00

 Zhu JR 2012
 1.17
 0.38
 28

 Subtotal (95% CI)
 188
 188
 188

 Heterogeneity: Tau² = 0.00; Chi² = 10.89, df =
 10.90; df =
 10.90; df =

 Test for overall effect: Z = 2.68 (P = 0.007)
 10.00; df =
 10.00; df =
 1.02 9.0% 74.3% 0.15 [-0.01, 0.31] 0.08 [0.02, 0.14] 5.4.2 other Asians 1.18 0.48 1.58 0.63 1.23 0.4 1.2 0.24 Hirai K 2015 Krishna Kumar D 2014 Lee KE 2012 Özer M 2013 22 31 21 18 92 0.99 0.37 1.23 0.58 1 0.31 1.23 0.49 80 117 85 49 331 5.7% 4.6% 7.5% 7.9% 25.7% 0.19 [-0.03, 0.41] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] -0.03 [-0.21, 0.15] 0.17 [0.01, 0.33] Subtotal (95% CI) Subtotal (95% Cl) 92 Heterogeneity: Tau² = 0.02; Chi² = 7.39, df = 3 (P = 0.06); $|^{2}$ Test for overall effect: Z = 2.13 (P = 0.03) 59% 0.10 [0.05, 0.16]

Figure 4. Forest plots of the subgroup analysis between Chinese and non-Chinese Asian populations. SD, standard deviation; CI, confidence interval.

-0.5 -0.25 Favours [experimental]

0 0.25 0.5 Favours [control]

Mean Difference V. Random, 95% CI Mean Difference IV. Random. 95% CI Study or Subgroup. 6.1.1 age<60 Fang SJ 2014 Krishna Kumar D 201 Lee KE 2012 Li J 2015 Liang Y 2013 Lou Y 2014 Tan SL 2014 Zhang HY 2012 Özer M 2014 Subtotal (95% CI) Heterogeneity: Tau² ст CC SD Total Weight Mean SD Total Mean IV. Rand 0.15 [0.01, 0.29] 0.23 [0.10, 0.36] 0.00 [-0.11, 0.11] 0.10 [0.04, 0.16] 0.12 [0.04, 0.16] 0.22 [0.07, 0.11] 0.02 [-0.07, 0.11] 0.7 [-0.01, 0.15] 0.14 [0.06, 0.22] 0.22 [0.09, 0.35] 0.09 [-0.02, 0.20] 0.23 [0.05, 0.41] 0.11 [0.07, 0.15] $\begin{array}{ccccc} 1.15 & 0.34 \\ 1.23 & 0.58 \\ 1 & 0.31 \\ 1.1 & 0.26 \\ 1.12 & 0.32 \\ 1.02 & 0.4 \\ 1.07 & 0.45 \\ 1.14 & 0.35 \\ 1.24 & 0.33 \\ 1.29 & 0.38 \\ 1.23 & 0.49 \\ \end{array}$ 63 92 82 37 117 85 104 54 120 200 107 33 73 49 979 0.33 0.38 0.26 0.37 0.36 0.38 0.33 0.26 0.33 0.38 4.2% 4.5% 9.6% 5.5% 7.0% 7.9% 7.7% 4.5% 5.8% 2.8% 65.3% . nr D 2014 82 228 100 172 243 201 59 115 40 1395 _ • Heterogeneity: Tau² = 0.00; Chi² = 17.67, df = Test for overall effect: Z = 5.28 (P < 0.00001) 10 (P = 0.06); 43% 6.1.2 age>60
 6.1.2 age>60

 Hirai K 2015
 0.99
 0.37

 Liang R 2012
 1.16
 0.42

 M T Lee 2009
 1.03
 0.51

 Wang Z 2011
 1.19
 0.43

 Zhang T 2013
 1.07
 0.33

 Zhang YT 2014
 1.02
 0.42

 Subtotal (05% c1)
 1.02
 0.43

 Heterogeneity: Tau² = 0.00; Chi² = 9.12, dt
 Test for overall effect: Z = 2.15 (P = 0.03)
 80 55 85 84 37 74 86 501 , df = 6 (P 1 0.4 1 0.36 1 0.47 1 0.39 1 0.27 1 0.36 1 0.32 -0.01 [-0.12, 0.10] 0.16 [0.01, 0.31] 0.03 [-0.10, 0.16] 0.19 [0.07, 0.31] 0.07 [-0.06, 0.20] 0.02 [-0.09, 0.13] 0.02 [-0.08, 0.12] 0.06 [0.01, 0.12] 5.6% 3.7% 4.3% 5.0% 4.3% 5.3% 6.4% 34.7% 115 48 137 99 42 124 146 711 0.17): 12 $\begin{array}{cccc} \mbox{Total (95\% Cl)} & 1480 & 2106 & 100.0\% \\ \mbox{Heterogeneity: } Tau^a = 0.00; \mbox{ Chi}^a = 29.51, \mbox{ df} = 17 \ (P = 0.03); \mbox{ l}^a = 42\% \\ \mbox{Test for overall effect: } Z = 5.45 \ (P < 0.00001) \\ \mbox{Test for suboroud differences: } \mbox{ Chi}^a = 1.83, \mbox{ df} = 1 \ (P = 0.18), \mbox{ l}^a = 45.5\% \\ \end{array}$ 0.09 [0.06, 0.13] • -0.5 -0.25 Favours [experimental] 0.25 Favours [control] 0.5 CT+TT cc Mean Differenc Mean Difference В n. 95% CI Study or Subgroup SD Total Mean SD Total Weight IV. Random, 95% CI IV. Rand Mean
 Candom.
 D37.
 D

 0.10
 [-0.00, 0.20]
 0.18
 [0.05, 0.31]

 0.30
 [0.18, 0.42]
 0.04
 [-0.06, 0.14]

 0.12
 [0.01, 0.23]
 0.22
 [-0.07, 0.11]

 0.08
 [0.00, 0.16]
 0.38
 [0.00, 0.16]

 0.12
 [0.01, 0.23]
 [0.11, 0.35]
 [0.11, 0.35]

 0.23
 [0.11, 0.35]
 [0.13]
 [0.08, 0.07]
 6.2.1 age<60 Cen HJ 2010 Fang SJ 2014 Krishna Kumar D 2014 Lee KE 2012 107 41 106 124 58 128 245 116 41 82 67 1263 115 63 92 82 0.38 0.33 0.38 0.26 0.37 0.36 0.38 0.33 0.26 0.33 0.26 0.33 5.0% 3.7% 4.0% 4.8% 7.5% 4.6% 5.7% 6.3% 6.3% 4.0% 4.8% 2.9% 59.4% Lee KE 2012 Li JH 2012 Li S 2015 Liang Y 2013 Lou Y 2014 Tan SL 2012 Yu SH 2014 Zhang HY 2012 Özer M 2013 Subtotal (95% CI) Heteroceneity: Tauj 228 100 172 243 201 59 115 40 1510 _ Heterogeneity: Tau² = 0.00; Chi² = 22.94, df = Test for overall effect: Z = 6.03 (P < 0.00001) = 0.02); | 52% 6.2.2 age>60 Hirai K 2015 Liang R 2012 MT Lee 2009 Nakamura K 2012 Singh O 2011 Wang Z 2011 Zhang YT 2014 Zhu JR 2012 Zhuang WF 2015 Subtotal (95% CI) Heterogeneity: Tau' 0.03 [-0.06, 0.14] 0.21 [0.07, 0.35] 0.01 [-0.11, 0.13] 0.23 [0.06, 0.40] 0.25 [0.02, 0.48] 0.20 [0.08, 0.32] 0.08 [-0.06, 0.22] 0.03 [-0.06, 0.14] 0.06 [-0.03, 0.15] 0.04 [-0.04, 0.12] 1.03 102 0.4 0.36 0.47 0.35 0.61 0.39 0.27 0.36 0.32 0.3 115 48 137 58 83 99 42 124 146 121 **973** 4.7% 3.4% 3.9% 2.7% 1.6% 4.3% 3.6% 4.6% 5.6% 6.2% 40.6% $\begin{array}{cccc} 1.03 & 0.4 \\ 1.21 & 0.41 \\ 1.01 & 0.49 \\ 1.23 & 0.59 \\ 1.25 & 0.61 \\ 1.2 & 0.44 \\ 1.08 & 0.36 \\ 1.03 & 0.41 \\ 1.06 & 0.39 \\ 1.04 & 0.27 \end{array}$ 1111111111 67 98 68 41 97 43 83 114 90 803 Subtotal (95% CI) 803 Heterogeneity: Tau² = 0.00; Chi² = 16.64, df = 9 (P Test for overall effect: Z = 3.57 (P = 0.0004) = 0.05); 1 = 46% 100.0% 0.11 [0.08, 0.14] ٠ -0.5 -0.25 Favours [experim 0.25 Favours [control] 0.5 ental]
 TT
 TT

 6.3.1 age<60</td>
 8.0 T

 Pang SJ 2014
 1.57
 0.39

 Krishe Komar D 2014
 1.58
 0.63

 Li JM 2012
 1.23
 0.4

 Li JM 2012
 1.23
 0.4

 Li S2 015
 1.13
 0.38

 Liang Y 2013
 1.12
 0.39

 Lou Y 2013
 1.12
 0.39

 Yu SH 2014
 1.24
 0.42

 Zhang HY 2012
 1.27
 0.49

 Gozer M 2013
 1.2
 0.24

 Subtotal (95% CI)
 1.20.00
 Ch² = 12.93,

 Test for overall effect: Z = 5.84 (P < 0.000</td>
 0.000
 CC ean SD Total Mean Difference IV. Random. 95% CI Mean Difference IV. Random, 95% CI тт С Mean SD Total Me Weight 4 31 20 4 8 45 9 8 9 1111 0.33 0.38 0.26 0.37 0.36 0.38 0.33 0.26 0.33 0.26 0.33 63 92 82 228 100 172 243 201 59 115 40 1395 2.5% 5.2% 6.6% 9.0% 2.6% 4.3% 8.4% 6.7% 3.8% 3.4% 7.7% **60.3%** 0.37 [-0.02.0.76] $\begin{array}{c} 0.37 \ [-0.02, 0.76]\\ 0.58 \ [0.35, 0.61]\\ 0.23 \ [0.04, 0.42]\\ 0.16 \ [0.03, 0.29]\\ 0.13 \ [-0.25, 0.51]\\ 0.12 \ [-0.16, 0.40]\\ 0.14 \ [-0.01, 0.29]\\ 0.16 \ [-0.03, 0.35]\\ 0.29 \ [-0.01, 0.50]\\ 0.27 \ [-0.06, 0.60]\\ 0.20 \ [0.04, 0.36]\\ 0.20 \ [0.04, 0.36]\\ \end{array}$ 1 18 177 df = 10 001) 0.20 [0.04, 0.36] 0.22 [0.15, 0.29] -0.23); 0.18 [-0.03, 0.39] 0.44 [0.25, 0.63] -0.09 [-0.26, 0.08] 0.21 [-0.07, 0.49] 0.18 [-0.24, 0.60] 0.12 [-0.12, 0.36] 0.17 [0.02, 0.32] 0.17 [0.03, 0.31] 0.4 0.36 0.47 0.39 0.27 0.36 0.32 5.9% 6.5% 7.5% 4.1% 2.3% 5.2% 8.2% 39.7% 115 48 137 99 42 124 146 711 = 0.009); I
 Total (95% Cl)
 280
 2106
 1

 Heterogeneity: Tau³ = 0.01; Chi² = 31.07, df = 17 (P = 0.02); l² = 45%
 Test for overall effect: Z = 5.73 (P < 0.00001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
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 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
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 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
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 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effect: Z = 0.73 (P < 0.0001)</td>
 Test for overall effec 0.20 [0.13, 0.27] 100.0% -0.5 -0.25 Favours [experimental] 0 0.25 Favours (co 0.5 (trol] Study or Subaroup 6.4.1 age-60 Fang SJ 2014 Krishna Kumar D 201-Lee KC 2012 Li S 2015 Li S 2015 Lou Y 2013 Lou Y 2014 Tan SL 2014 Zhang HY 2012 Özer M 2013 Subtotal (95% CI) Heterogeneily: Tau² E TT CT Mean SD Total Mean SD Total Weight Mean Difference IV. Random. 95% CI D Mean Difference IV. Random. 95% CI 0.22 [-0.18, 0.62] 0.35 [0.10, 0.60] 0.23 [0.05, 0.41] 0.06 [-0.08, 0.20] 0.01 [-0.37, 0.39] 0.07 [-0.08, 0.22] 0.02 [-0.17, 0.21] 0.07 [-0.24, 0.38] 0.18 [-0.15, 0.51] 0.10 [0.03, 0.16] $\begin{array}{ccccc} 1.37 & 0.39 \\ 1.58 & 0.63 \\ 1.23 & 0.4 \\ 1.16 & 0.29 \\ 1.13 & 0.38 \\ 1.12 & 0.39 \\ 1.14 & 0.47 \\ 1.16 & 0.28 \\ 1.29 & 0.42 \\ 1.27 & 0.49 \\ 1.2 & 0.24 \end{array}$ 1.15 1.23 1 1.1 1.12 1.02 1.07 1.14 1.22 1.09 1.23 0.34 0.58 0.31 0.26 0.32 0.4 0.45 0.35 0.33 0.38 0.49 37 117 85 104 54 120 200 107 33 73 49 979 4 31 20 4 8 45 9 8 9 1.9% 4.6% 7.5% 11.6% 2.0% 3.6% 10.1% 6.8% 3.0% 2.6% 7.9% 61.6% nar D 2014 18 177 -Heterogeneity: $Tau^2 = 0.00$; Chi² Test for overall effect: Z = 2.94 (f 9.94, df = 10 (P 0.003) 0.45); 1
 6.4.2 age>60

 Hirai K 2015
 1.18
 0.48

 Liang R 2012
 1.44
 0.29

 MT Lee 2009
 0.91
 0.27

 Wang Z 2011
 1.21
 0.5

 Zhang T 2013
 1.18
 0.51

 Zhang YT 2014
 1.12
 0.35

 Subtotal (95% CI)
 1.17
 0.38

 Heterogeneity: Tau² = 0.01; Chi² = 1.06,
 Test for overall effect: Z = 1.88 (P = 0.06)
 0.99 1.16 1.03 1.19 1.07 1.02 1.02 0.37 0.42 0.51 0.43 0.33 0.42 0.39 5.7% 6.6% 7.5% 3.5% 1.7% 4.5% 0.19 [-0.03, 0.41] 0.28 [0.08, 0.48] -0.12 [-0.30, 0.06] 0.02 [-0.27, 0.31] 0.11 [-0.31, 0.53] 0.10 [-0.15, 0.35] 0.15 [-0.01, 0.31] 22 12 13 13 6 9 80 55 85 84 37 74 28 103 86 501 9.0% 38.4% 0.15 [-0.01, 0.31] $df = 6 (P = 0.12); I^2$ 40%

Figure 5. Forest plots of the subgroup analysis between ages <60 and >60 years old.

0.10 [0.05, 0.16]

-0.5

-0.25

entall

Irs [expe

0.25 Favours [control]

0.5

 $\begin{array}{cccc} \textbf{Total (95\% CI)} & 280 & \textbf{1480} & \textbf{100.0\%} \\ \text{Heterogeneity: Tau^a = 0.00; Chi^a = 20.04, df = 17 (P = 0.27); l^a = 15\% \\ \text{Test for overall effect: $2 = 3.56 (P = 0.0004)$} \\ \text{Test for subaroup differences: Chi^a = 0.03, df = 1 (P = 0.87), l^a = 0\% \end{array}$

in intracranial hemorrhage and no requirement for routine laboratory monitoring. However, they have the defects of higher drug prices and the absence of a suitable antidote. Currently, warfarin remains the primary anticoagulation drug for treatment of AF and other thromboembolic diseases. There is a large individual difference in warfarin dose requirement. Genetic variation shows a clinically important impact on stable warfarin dose. The association between CYP2C9, VKORC1 and warfarin dose has been investigated in several meta-analysis (19,32-34), and the influence of these two genes on warfarin dose has been confirmed. Data showed that CYP2C9 and VKORC1 together with clinical factors such as age, weight and drug combination can explain only ~50% of warfarin dose variability, suggesting that 50% uncertain factors remain to be considered. Thus far, only CYP2C9 and VKORC1 as genetic factors are included in a multitude of pharmacogenetic models, and CYP4F2 may have the third major influence among genetic factors. Studies regarding whether CYP4F2 affects warfarin dose requirement are consecutive; however, the results of different studies are controversial, particularly for Asian population studies. One possible explanation could be that the sample size in these studies is too small. Therefore, summarizing the scattered sample data to analyze the association between CYP4F2 and warfarin dose requirement in Asian populations is likely to get effectual results.

Although the findings regarding the correlation between the *CYP4F2* polymorphism and warfarin dose in the Asian population are inconsistent, the results of the present systematic review and meta-analysis showed a strong association between *CYP4F2* polymorphisms and warfarin maintenance dose. Using a systematic search strategy, 22 studies that met the prespecified eligibility criteria were selected. Carriers of the CT and TT genotypes required 9 and 20% higher warfarin doses compared to carriers of the CC genotype, respectively. Additionally, T carriers required a warfarin dose 11% higher than the CC genotype. Furthermore, TT carriers required a 10% higher warfarin dose compared to the CT group (all P<0.05).

With regard to the sensitivity analysis, following the exclusion of the study by Luo *et al*, any significant change or revision in findings was not identified, and the results of the parameter analysis using the random-effect model were in accordance with those using the fixed-effect model, so therefore, the meta-analysis results of the impact of *CYP4F2* genotype on warfarin dose requirements were considered stable and reliable.

Limdi *et al* (35) proposed that the effect of predictors including clinical and genetic factor on warfarin dose differs by ethnicities. In the subgroup analyses, minor but no significant differences were observed between the Chinese and non-Chinese population. The results were similar in different age ranges. However, the heterogeneity of the Chinese group was reduced compared with the undifferentiated patients, and there was a significant difference in the allele gene frequencies of *CYP4F2* between Chinese and non-Chinese Asian populations. The aforementioned results are indicative of a minor difference between the Chinese and non-Chinese patients. Due to the small number of non-Chinese Asian patients included in the present analysis, the results required further verification.

The systematic review and meta-analysis confirmed the association between warfarin and CYP4F2 rs2108622 in the Asian population. The results will aid further research of pharmacogenetics model, and improve the antithrombotic therapy of warfarin. To the best of our knowledge, this is the first study to explore the association between CYP4F2 and the warfarin stable dose solely for the Asian population. As opposed to the studies by Danese *et al* (16) and Liang *et al* (17), a statistical difference was observed between the CT and TT genotype, which may be an indication of a larger effect of CYP4F2 on the warfarin dose in the Asian population.

There are several limitations to the present meta-analysis. Firstly, the data for warfarin mean maintenance dose in the meta-analysis was not adjusted for other predictors. Secondly, certain studies were not included in the meta-analysis due to the absence of sufficient data. Thirdly, data of certain non-Chinese Asian studies was unavailable, leading to a smaller number of studies for the non-Chinese Asian population.

More studies with larger sample sizes are required in the future to investigate the effect of *CYP4F2* on a stable warfarin dose requirement, particularly considering the adjustment for the *CYP2C9* and *VKORC1* genes.

In conclusion, the present meta-analysis provides evidence that *CYP4F2* rs2108622 may influence the maintenance dose of warfarin in the Asian population and can address the controversy that has emerged in recent years to a certain extent. However, whether the impact of *CYP4F2* on warfarin dose is clinically important requires further investigation.

Acknowledgements

The authors would like to thank Dr Chen and Dr Hirai for providing original data. The study was supported by the International Science and Technology Cooperation Program of China (grant no. 2014DFA30900), the National Scientific Foundation of China (grant nos. 81373476, 81301924 and 81302851), the Scientific Foundation of Hunan Province (grant nos. 11JJ2054 and 14JJ7016) and the Science and Technology Plan of Changsha (grant no. k1403065-31).

References

- Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, Limdi NA, Page D, Roden DM, Wagner MJ, *et al*; International Warfarin Pharmacogenetics Consortium: Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 360: 753-764, 2009.
- Zhu Y, Shennan M, Reynolds KK, Johnson NA, Herrnberger MR, Valdes R Jr and Linder MW: Estimation of warfarin maintenance dose based on VKORC1 (-1639 G>A) and CYP2C9 genotypes. Clin Chem 53: 1199-1205, 2007.
- Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM, Milligan PE, Grice G, Lenzini P, Rettie AE, *et al*: Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther 84: 326-331, 2008.
- 4. Ohno M, Yamamoto A, Ono A, Miura G, Funamoto M, Takemoto Y, Otsu K, Kouno Y, Tanabe T, Masunaga Y, *et al*: Influence of clinical and genetic factors on warfarin dose requirements among Japanese patients. Eur J Clin Pharmacol 65: 1097-1103, 2009.
- 5. Cini M, Legnani C, Cosmi B, Guazzaloca G, Valdrè L, Frascaro M and Palareti G: A new warfarin dosing algorithm including VKORC1 3730 G>A polymorphism: Comparison with results obtained by other published algorithms. Eur J Clin Pharmacol 68: 1167-1174, 2012.

- 6. Huang SW, Chen HS, Wang XQ, Huang L, Xu DL, Hu XJ, Huang ZH, He Y, Chen KM, Xiang DK, et al: Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: A prospective study in Chinese patients. Pharmacogenet Genomics 19: 226-234, 2009.
- Teichert M, Eijgelsheim M, Rivadeneira F, Uitterlinden AG, van Schaik RH, Hofman A, De Smet PA, van Gelder T, Visser LE and Stricker BH: A genome-wide association study of acenocoumarol maintenance dosage. Hum Mol Genet 18: 3758-3768, 2009.
- McDonald MG, Rieder MJ, Nakano M, Hsia CK and Rettie AE: CYP4F2 is a vitamin K1 oxidase: An explanation for altered warfarin dose in carriers of the V433M variant. Mol Pharmacol 75: 1337-1346, 2009.
- 9. Caldwell MD, Awad T, Johnson JA, Gage BF, Falkowski M, Gardina P, Hubbard J, Turpaz Y, Langaee TY, Eby C, *et al*: CYP4F2 genetic variant alters required warfarin dose. Blood 111: 4106-4112, 2008.
- Lee MT, Chen CH, Chou CH, Lu LS, Chuang HP, Chen YT, Saleem AN, Wen MS, Chen JJ, Wu JY, *et al*: Genetic determinants of warfarin dosing in the Han-Chinese population. Pharmacogenomics 10: 1905-1913, 2009.
- Liang R, Li L, Li C, Gao Y, Liu W, Hu D and Sun Y: Impact of CYP2C9*3, VKORC1-1639, CYP4F2rs2108622 genetic polymorphism and clinical factors on warfarin maintenance dose in Han-Chinese patients. J Thromb Thrombolysis 34: 120-125, 2012.
- Li JH, Ma GG, Zhu SQ, Yan H, Wu YB and Xu JJ: Correlation between single nucleotide polymorphisms in CYP4F2 and warfarin dosing in Chinese valve replacement patients. J Cardiothorac Surg 7: 97, 2012.
 Liang Y, Chen Z, Guo G, Dong X, Wu C, Li H, Wang T and
- Liang Y, Chen Z, Guo G, Dong X, Wu C, Li H, Wang T and Xu B: Association of genetic polymorphisms with warfarin dose requirements in Chinese patients. Genet Test Mol Biomarkers 17: 932-936, 2013.
- 14. Li S, Zou Y, Wang X, Huang X, Sun Y, Wang Y, Dong L and Jiang H: Warfarin dosage response related pharmacogenetics in Chinese population. PLoS One 10: e0116463, 2015.
- 15. Zhuang W, Wen W, Xuan B, Chen Y, Cao Y, Sun Z and Ma J: Effect of CYP2C9, CYP4F2 and VKORC1 genetic polymorphisms on pharmacokinetics and pharmacodynamics of mean daily maintenance dose of warfarin in Chinese patients. Blood Coagul Fibrinolysis 26: 167-174, 2015.
- 16. Danese E, Montagnana M, Johnson JA, Rettie AE, Zambon CF, Lubitz SA, Suarez-Kurtz G, Cavallari LH, Zhao L, Huang M, et al: Impact of the CYP4F2 p.V433M polymorphism on coumarin dose requirement: Systematic review and meta-analysis. Clin Pharmacol Ther 92: 746-756, 2012.
- Liang R, Wang C, Zhao H, Huang J, Hu D and Sun Y: Influence of CYP4F2 genotype on warfarin dose requirement-a systematic review and meta-analysis. Thromb Res 130: 38-44, 2012.
- Little J, Bradley L, Bray MS, Clyne M, Dorman J, Ellsworth DL, Hanson J, Khoury M, Lau J, O'Brien TR, *et al*: Reporting, appraising, and integrating data on genotype prevalence and gene-disease associations. Am J Epidemiol 156: 300-310, 2002.
- Lindh JD, Holm L, Andersson ML and Rane A: Influence of CYP2C9 genotype on warfarin dose requirements - a systematic review and meta-analysis. Eur J Clin Pharmacol 65: 365-375, 2009.
- 20. Cen HJ, Zeng WT, Leng XY, Huang M, Chen X, Li JL, Huang ZY, Bi HC, Wang XD, He YL, *et al*: CYP4F2 rs2108622: A minor significant genetic factor of warfarin dose in Han Chinese patients with mechanical heart valve replacement. Br J Clin Pharmacol 70: 234-240, 2010.

- 21. Lou Y, Han L, Li Y, Zhang X, Liu Z, Tang M, Yu H, Wang W, Xu J, Liu H and Li Y: Impact of six genetic polymorphisms on Warfarin maintenance dose variation in Chinese Han population. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 31: 367-371, 2014 (In Chinese).
- 22. Zhang HY, Luo WW, Fang HR, Yang XQ, Xu LH and Ma SM: Influence of VKORC1, CYP2C9, CYP4F2 and EPHX1 gene polymorphisms on warfarin dose. China Pharmacy 34: 3201-3205, 2012.
- 23. Zhu JR, Zhu YB, Xie DJ, Ye F and Tao YF: Effects of CYP4F2, CYP2C9 and VKORC1 genetic polymorphisms on maintenance dosage of warfarin in Chinese Han nationality patients with non-valve atrial fibrillation. China Pharmacy 44: 4161-4164, 2012.
- 24. Wang Z, Yang D, Li YL, *et al*: Influence of CYP4F2 gene polymorphisms on warfarin dose. Guangdong Medical Journal: 3091-3094, 2011.
- 25. Zhang YT, Liang X, Dong F, *et al*: Effect of CYP4F2 polymorphism on warfarin anticoagulant in Chinese population. Clinical Medication Journal: 41-59, 2014.
- 26. Krishna Kumar D, Shewade DG, Loriot MA, Beaune P, Balachander J, Sai Chandran BV and Adithan C: Effect of CYP2C9, VKORC1, CYP4F2 and GGCX genetic variants on warfarin maintenance dose and explicating a new pharmacogenetic algorithm in South Indian population. Eur J Clin Pharmacol 70: 47-56, 2014.
- 27. Özer M, Demirci Y, Hizel C, Sarikaya S, Karalti İ, Kaspar Ç, Alpan S and Genç E: Impact of genetic factors (CYP2C9, VKORC1 and CYP4F2) on warfarin dose requirement in the Turkish population. Basic Clin Pharmacol Toxicol 112: 209-214, 2013.
- 28. Hirai K, Yamada Y, Hayashi H, Tanaka M, Izumiya K, Suzuki M, Yoshizawa M, Moriwaki H, Akimoto T, Tsuji D, et al: Plasma vitamin K concentrations depend on CYP4F2 polymorphism and influence on anticoagulation in Japanese patients with warfarin therapy. Thromb Res 135: 861-866, 2015.
- 29. Nakamura K, Obayashi K, Araki T, Aomori T, Fujita Y, Okada Y, Kurabayashi M, Hasegawa A, Ohmori S, Nakamura T, *et al*: CYP4F2 gene polymorphism as a contributor to warfarin maintenance dose in Japanese subjects. J Clin Pharm Ther 37: 481-485, 2012.
- 30. Lee KE, Chang BC, Kim HO, Yoon IK, Lee NR, Park HY and Gwak HS: Effects of CYP4F2 gene polymorphisms on warfarin clearance and sensitivity in Korean patients with mechanical cardiac valves. Ther Drug Monit 34: 275-282, 2012.
- 31. Singh O, Sandanaraj E, Subramanian K, Lee LH and Chowbay B: Influence of CYP4F2 rs2108622 (V433M) on warfarin dose requirement in Asian patients. Drug Metab Pharmacokinet 26: 130-136, 2011.
- 32. Jorgensen AL, FitzGerald RJ, Oyee J, Pirmohamed M and Williamson PR: Influence of CYP2C9 and VKORC1 on patient response to warfarin: A systematic review and meta-analysis. PLoS One 7: e44064, 2012.
- 33. Yang L, Ge W, Yu F and Zhu H: Impact of VKORC1 gene polymorphism on interindividual and interethnic warfarin dosage requirement - a systematic review and meta analysis. Thromb Res 125: e159-e166, 2010.
- Res 125: e159-e166, 2010.
 34. Jin B, Hong Y, Zhu J, Li Y and Shi HM: The impact of VKORC1-1639G>A genetic polymorphism upon warfarin dose requirement in different ethnic populations. Curr Med Res Opin 30: 1505-1511, 2014.
- Limdi NA, Brown TM, Yan Q, Thigpen JL, Shendre A, Liu N, Hill CE, Arnett DK and Beasley TM: Race influences warfarin dose changes associated with genetic factors. Blood 126: 539-545, 2015.