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ORIGINAL ARTICLE

A46G and C79G polymorphisms in the β2-adrenergic receptor gene (*ADRB2*) and essential hypertension risk: a meta-analysis

Yuqing Lou[1,4], Jinghua Liu[2,4], Yan Huang[3], Jielin Liu[1], Zuoguang Wang[1], Ya Liu[1], Zhizhong Li[2], Yao Li[3], Yi Xie[3] and Shaojun Wen[1,5]

No consensus has been reached on the association between the β2-adrenergic receptor polymorphisms A46G and C79G and essential hypertension risk. We performed a meta-analysis to confirm the possible association. After reviewing 303 reports in PubMed and 359 reports in Embase, we included in our meta-analysis 18 articles (20 studies) that met our inclusion criteria. The fixed-effects model and the random-effects model were applied for dichotomous outcomes to combine the results of the individual studies. There was no statistical association between A46G and hypertension risk in all subjects, Asians or Caucasians. However, an association was observed in the dominant genetic model (AA *vs.* (AG+GG)) (P=0.04, odds ratio (OR)=1.38, 95% confidence interval (CI) 1.01–1.87, $P_{heterogeneity}$=0.98, fixed-effects model) in the subgroup of mixed Africans. No overall statistical association could be found between C79G and hypertension risk or any ethnic subgroup. In the research conducted on severe hypertension (systolic blood pressure ⩾160 mm Hg and/or diastolic blood pressure ⩾95 mm Hg hypertensive population), significant association was found in the dominant genetic model (CC *vs.* (CG+GG)) (P=0.04, OR=1.38, 95% CI 1.02–1.86, $P_{heterogeneity}$=0.03, random-effects model), and there was also a borderline significance between the C79 allele and severe hypertension (P=0.05, OR=1.26, 95% CI 1.00–1.57, $P_{heterogeneity}$=0.04, random-effects model). No association could be found in this study between the two polymorphisms and stage 2 hypertension. More studies stratified for different ethnicities and different stages of hypertension should be performed in the future.
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Keywords: adrenergic receptor; meta-analysis; polymorphism

INTRODUCTION

Essential hypertension is an escalating problem in modern society. It is widely considered a complex genetic trait caused by multiple susceptibility genes, the effects of which are modulated by gene–environment and gene–gene interactions.[1] As a consequence, many gene polymorphisms have been assessed as candidate determinants of the risk of hypertension.

At the molecular level, the role of the β2-adrenergic receptor, *ADRB2*, in hypertension has been extensively evaluated, paying particular attention to the rs1042713 (Arg16Gly, A46G) and rs1042714 (Gln27Glu, C79G) single-nucleotide polymorphisms on chromosome 5q31 to 32.[2] *In vitro*, compared with wild-type A46, the G46 allele displayed normal agonist binding and functional coupling to Gs, resulting in the stimulation of adenylyl cyclase activity. Similar results were found in the comparison between the C79 and G79 alleles.[3] In clinical and epidemiologic populations, some studies have indicated that the A46G polymorphism[4–10] as well as the C79G polymorphism[5,6,8,10,11] in the *ADRB2* gene is associated with essential hypertension (or BP level). Other studies have been unable to replicate these findings.[12–20] Therefore, in spite of the large number of previous reports about the association between these two polymorphisms and hypertension, the conclusion remains unclear. To clarify the effect of A46G and C79G polymorphisms on the risk of hypertension, we conducted a meta-analysis from all eligible case–control studies published to date.

[1]Department of Hypertension Research, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing, PR China; [2]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, PR China and [3]State Key Laboratory of Genetic Engineering, Institute of Genetics, School of Life Sciences, Fudan University, Shanghai, PR China
[4]These authors contributed equally to this work.
[5]Member of International Society of Hypertension.
Correspondence: Dr S Wen, Department of Hypertension Research, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart Lung and Blood Vessel Diseases, 2 Anzhen Road, Beijing 100029, PR China.
E-mail: wenshaojun@yahoo.com.cn
or Dr Y Xie, School of Life Sciences, Institute of Genetics, Fudan University, Room 605 Science Building, 220 Handan Road, Shanghai 200433, PR China.
E-mail: yxie@fudan.edu.cn
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MATERIALS AND METHODS

Identification and eligibility of relevant studies

To identify all the studies that examined the association of A46G and C79G polymorphisms with hypertension, we conducted a computerized literature search of PubMed and Embase databases (before January 2010) using the following keywords and subject terms: 'adrenergic' or 'adrenoceptor', 'polymorphism' and 'hypertension'. References of retrieved articles were also screened. If an article reported results on different ethnic sub-populations, each sub-population was treated as a separate study in our meta-analysis. Studies included in the meta-analysis had to meet all the following criteria: (i) use of an unrelated case–control design, (ii) available genotype frequency, (iii) the genotype distribution of the control population must be in Hardy–Weinberg equilibrium (HWE) and (iv) hypertension defined as systolic blood pressure (SBP) $\geqslant$ 140 mm Hg and/or diastolic blood pressure (DBP) $\geqslant$ 90 mm Hg and/or treatment with antihypertensive medication; stage 2 hypertension was defined as SBP $\geqslant$ 160 mm Hg and/or DBP $\geqslant$ 100 mm Hg.[21–22] To minimize bias in the selection of studies, two observers independently extracted the information from each study. Disagreements were resolved in consensus by discussion between the authors. If a paper did not provide relevant data, or if the data provided were not sufficient, we contacted corresponding or original authors by e-mail in order to obtain the raw data.

Data extraction

Data were collected on the genotype of A46G and C79G according to ethnicity. First author, year of publication, diagnostic standards of each study, number of cases and controls, number and frequency of genotypes, and allele frequency of both polymorphisms in cases and controls are described in Tables 1, 2a and b.

Statistical analysis

The strength of the association of A46G and C79G with hypertension was measured by an odds ratio (OR) corresponding to a 95% confidence interval (CI), which was calculated according to the method used by Woolf.[23] We examined the association between allele A of A46G and hypertension, as well as the dominant genetic model (AA *vs.* GG + AG), the recessive genetic model (AA + AG *vs.* GG) and homozygote comparison (AA *vs.* GG). The same method was applied to analysis of the C79G polymorphism. In our study, two models of meta-analysis were applied for dichotomous outcomes in Review-Manager 4.2 software (The Cochrane Collaboration, Oxford, UK): the fixed-effects model and the random-effects model. The fixed-effects model, using the Mantel–Haenszel method, assumed that studies were sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance. The random-effects model, using the DerSimonian and Laird method, assumed that studies were taken from populations with varying effect sizes and calculated study weights both from in-study and between-study variances, with consideration of the extent of variation or heterogeneity. We performed a X^2-based Q statistic test to assess the between-study heterogeneity.[24] Heterogeneity was considered significant for $P<0.10$ because of the low power of the statistic. The random-effects model (if $P<0.10$) or the fixed-effects model (if $P>0.10$) was used to pool the results.[25] The significance of the pooled OR was determined by the Z test and a P-value of <0.05 was considered significant. For each genetic comparison, subgroup analysis according to ethnicity was considered for Asian, Caucasian and mixed African populations to estimate ethnic-specific OR. The subgroup 'mixed African' included the African-American population and the Black South African population. Subgroup analysis according to different stages of hypertension was considered for stage 2 hypertension and severe hypertension. We defined the criterion of SBP $\geqslant$ 160 mm Hg and/or DBP $\geqslant$ 95 mm Hg as 'severe hypertension' based on stage 2 hypertension, in order to expand the sample size by including the research of Kato *et al.*[16]

When unexpected heterogeneity was detected, sensitivity analysis was performed to examine specific sensitivity of the findings. This was done by examining and recalculating the pooled association sizes and joint values of P in homogeneous subgroups, as well as after excluding studies one by one.

Publication bias was investigated by funnel plot, in which the standard error of the log (OR) of each study was plotted against its OR. Funnel plot suggested possible publication bias, which was also assessed by Egger's linear regression test.[26] In addition, we performed a t-test to determine the significance of the intercept, and a P-value of <0.05 was considered significant.

HWE was tested by the X^2-test for goodness of fit based on a web program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Analyses were performed using the software Stata version 7 (Stata, College Station, TX, USA) and ReviewManager 4.2. All P-values were two-sided.

Table 1 Characteristics of eligible studies considered in the meta-analysis

Ethnicity	*First author (year)*	*Single-nucleotide polymorphism*	*Case no.*	*Control no.*	*Diagnostic standard*
Asian	Misonoa (2009)[7]	A46G	194	208	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Asian	Yu (2008)[9]	A46G, C79G	58	58	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Asian	Mo (2007)[11]	C79G	288	149	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Asian	Wu CHN-Hani (2006)[5]	A46G, C79G	172	133	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Asian	Wu CHN-Yi (2006)[5]	A46G, C79G	99	134	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Asian	Ge (2005)[10]	C79G	503	504	SBP $\geqslant$ 160, DBP $\geqslant$ 100
Asian	Kato (2001)[16]	A46G, C79G	1141	852	SBP $\geqslant$ 160, DBP $\geqslant$ 95
Caucasian	Gjesing (2007)[20]	A46G, C79G	2511	3984	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Caucasian	Bartels (2007)[15]	A46G, C79G	258	171	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Caucasian	Pojoga (2006)[6]	A46G, C79G	280	65	DBP $\geqslant$ 90 (with treatment) or DBP $\geqslant$ 100
Caucasian	Filigheddu (2004)[4]	A46G	517	184	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Caucasian	Castellano (2003)[8]	A46G, C79G	324	247	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Caucasian	Sunder-Plassmann (2002)[13]	A46G, C79G	182	182	DBP $\geqslant$ 120
Caucasian	Herrmann SM (2002)[17]	A46G, C79G	707	290	DBP $\geqslant$ 100
Caucasian	Herrmann V (2000)[18]	A46G	36	101	SBP $\geqslant$ 140, DBP $\geqslant$ 95
Caucasian	Xie (2000)[14]	A46G, C79G	201	179	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Caucasian	Jia (2000)[19]	C79G	298	298	SBP $\geqslant$ 160, DBP $\geqslant$ 90
Mixed African	Tang (2003)[27]	A46G	134	143	SBP $\geqslant$ 160, DBP $\geqslant$ 100
Mixed African	Xie (2000)[14]	A46G, C79G	155	128	SBP $\geqslant$ 140, DBP $\geqslant$ 90
Mixed African	Candy (2000)[12]	A46G, C79G	192	123	DBP $\geqslant$ 90

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2a Characteristics of studies and the distribution of *ADRB2* A46G genotypes and alleles among hypertension of cases and controls in the meta-analysis

	Genotype						*Allele*			
A46G	*AA*		*AG*		*GG*		*A*		*G*	
Author	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*
Misonoa[7]	51	60	82	112	61	36	184	232	204	184
Yu[9]	15	29	34	21	9	8	64	79	52	37
Wu (CHN-Hani)[5]	53	32	72	64	47	37	178	128	166	138
Wu (CHN-Yi)[5]	53	28	34	66	12	40	140	122	58	146
Kato[16]	277	214	550	420	314	218	1104	848	1178	856
Gjesing[20]	350	569	1204	1810	939	1581	1904	2948	3082	4972
Bartels[15]	34	25	121	76	103	70	189	126	327	216
Pojoga[6]	37	9	120	29	123	27	194	47	366	83
Filigheddu[4]	122	33	198	91	197	60	442	157	592	211
Castellano[8]	45	33	155	118	124	96	245	184	403	310
Sunder-Plassmann[13]	24	31	90	85	68	66	138	147	226	217
Herrmann SM[17]	109	34	327	135	254	108	545	203	835	351
Herrmann V[18]	8	26	13	42	15	33	29	94	43	108
Xie (Caucasian)[14]	45	35	86	81	70	63	176	151	226	207
Tang[27]	41	34	58	76	35	33	140	144	128	142
Xie (African)[14]	48	31	72	57	35	40	168	119	142	137
Candy[12]	50	26	94	67	48	30	194	119	190	127

Table 2b Characteristics of studies and the distribution of *ADRB2* C79G genotypes and alleles among hypertension of cases and controls in the meta-analysis

	Genotype						*Allele*			
C79G	*CC*		*CG*		*GG*		*C*		*G*	
Author	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*
Yu[9]	45	51	11	7	2	0	101	109	15	7
Mo[11]	237	130	48	19	3	0	522	279	54	19
Wu (CHN-Hani)[5]	164	122	7	11	1	0	335	255	9	11
Wu (CHN-Yi)[5]	87	103	11	28	1	3	185	234	13	34
Ge[10]	456	410	39	88	8	6	951	908	55	100
Kato[16]	986	720	127	112	7	5	2099	1552	141	122
Gjesing[20]	772	1215	1257	1965	482	804	2801	4395	2221	3573
Bartels[15]	67	42	117	85	74	44	251	169	265	173
Pojoga[6]	99	24	124	27	57	14	322	75	238	55
Castellano[8]	126	92	158	123	40	32	410	307	238	187
Sunder-Plassmann[13]	30	26	87	82	65	74	147	134	217	230
Herrmann SM[17]	269	100	329	147	109	43	867	347	547	233
Xie (Caucasian)[14]	89	78	80	76	32	25	258	232	144	126
Jia[19]	96	88	144	143	58	67	336	319	260	277
Xie (African)[14]	102	88	49	34	4	6	253	210	57	46
Candy[12]	112	85	65	34	13	4	289	204	91	42

RESULTS

Selection of studies

Through literature search and selection based on the inclusion criteria, 19 articles (23 studies) were identified by reviewing 303 articles in PubMed and 359 articles in Embase.[4–20,27,28] Of the 19 eligible articles, the study of Gu *et al.*[28] was replaced by their earlier report,[10] as these two articles reported the same data. Wu *et al.*[5] provided data on two Chinese minorities, the Hani and Yi, residents of the remote rural area of Yunnan, China.[29] The population of the two minorities was also grouped in to Asian.[30] Tang *et al.*,[27] Herrmann *et al.*[18] and Xie *et al.*[14] provided data on two ethnicities: Caucasian American and African-American. The genotyping data of the normotensive controls in the population Caucasian-American in Tang *et al.*[27] (P_{HWE}=0.048), and the African-American control subjects studied in Herrmann *et al.*[18] (P_{HWE}=0.027) deviated from HWE. The same occurred with the data provided in Mo *et al.*[11] ($P_{HWE}<0.001$), Ge *et al.*[10] (P_{HWE}=0.040) and

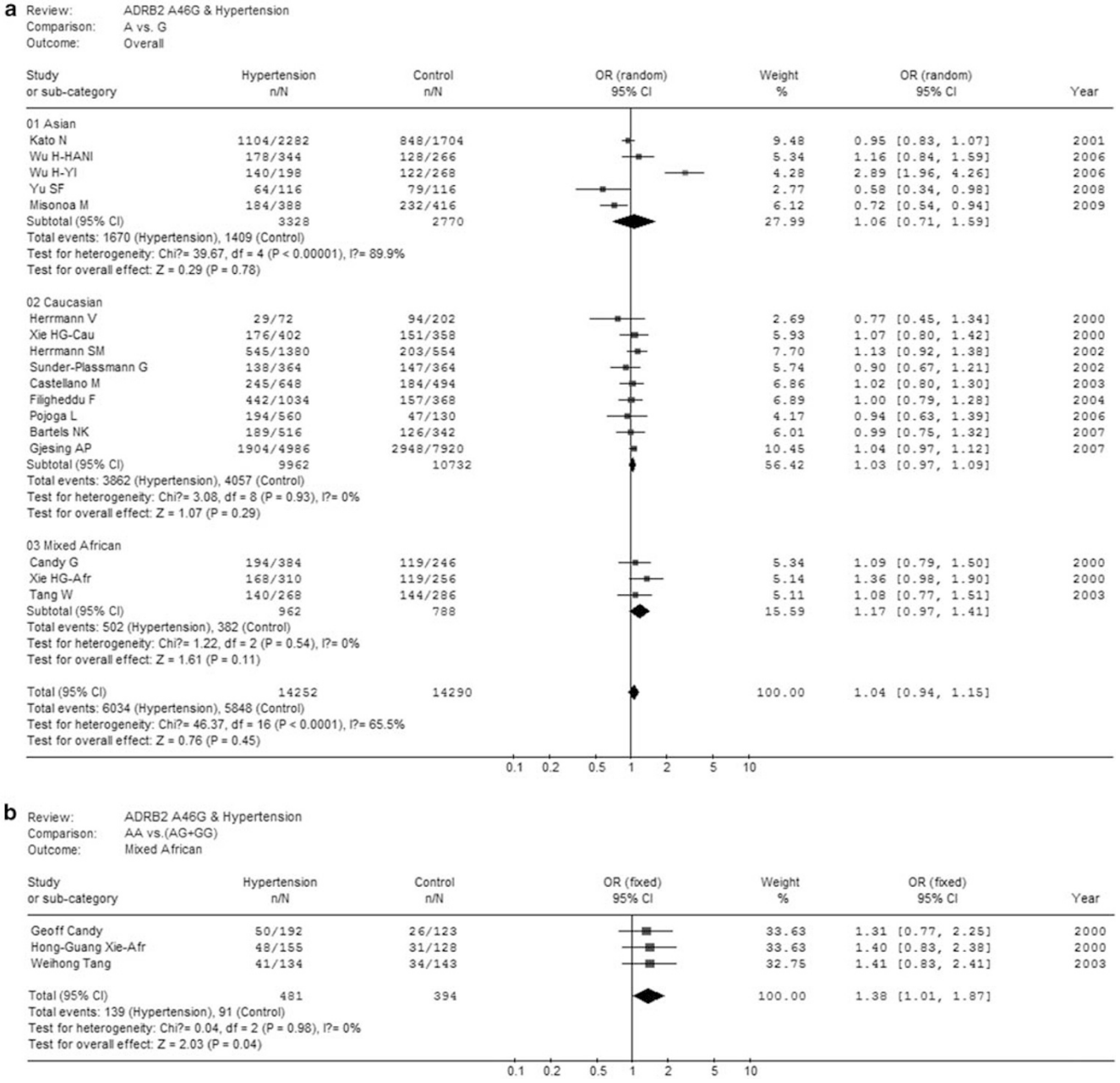


Figure 1 (**a**) Meta-analysis of the overall association between the A46G polymorphism and hypertension comparing A *vs.* G. *n* indicates the total number of A alleles; *N* indicates the total number of A alleles plus G alleles. (**b**) Meta-analysis for the association between the A46G polymorphism and hypertension comparing AA *vs.* AG+GG in the subgroup of mixed Africans. *n* indicates the total number of the AA genotype; *N* indicates the total number of the AA genotype plus the AG+GG genotype.

Jia *et al.*[19] (P_{HWE}=0.041) for the A46G polymorphism. Thus, those sub-population studies were excluded. No study of the C79G polymorphism was excluded because the data deviated from HWE. Finally, 18 articles (20 studies) were included in our analysis (Table 1). All studies used blood samples for genotyping.

Summary statistics

A total of 7126 hypertension patients and 7145 controls for A46G, as well as 7346 hypertension patients and 7482 controls for C79G, were investigated. The allele frequencies were calculated for controls from the corresponding genotype distributions (Tables 2a and b). A46G allele G had a higher representation in cases and controls of Caucasians (61.2 and 62.2%, respectively) than of Asians (49.8 and 49.1%, respectively) and of the mixed African population (47.8 and 51.5%, respectively). The overall prevalence of G46 was 57.7% in cases and 59.1% in controls. C79G allele G had a much lower representation in cases and controls of Asians (6.4 and 8.1%, respectively) than of Caucasians (43.4 and 44.8%, respectively) and of the mixed African population (21.4 and 17.5%, respectively). The overall prevalence of G79 was 31.1% in cases and 35.0% in controls.

Table 3 OR (95% CI) of the association of the A46G and C79G polymorphisms and hypertension in different subgroups under various genetic contrasts

Contrast	*Comparisons (study numbers)*	$P_{heterogeneity}$	P* *value*	*OR (95% CI)*
A46G in hypertension				
A *vs.* G	Overall (17)	<0.0001	0.45[a]	1.04 (0.94–1.15)
	Asian (5)	<0.00001	0.78[a]	1.06 (0.71–1.59)
	Caucasian (9)	0.93	0.28	1.03 (0.97–1.09)
	Mixed African (3)	0.54	0.11	1.17 (0.97–1.41)
	Stage 2 hypertension (3)	0.47	0.47	1.06 (0.91–1.23)
AA *vs.* (AG+GG)	Overall (17)	0.0002	0.17[a]	1.13 (0.95–1.35)
	Asian (5)	<0.00001	0.64[a]	1.15 (0.64–2.06)
	Caucasian (9)	0.61	0.70	1.02 (0.91–1.15)
	Mixed African (3)	0.98	0.04	1.38 (1.01–1.87)
	Stage 2 hypertension (3)	0.19	0.25	1.18 (0.89–1.56)
(AA+AG) *vs.* GG	Overall (17)	0.01	0.81[a]	0.98 (0.87–1.12)
	Asian (5)	0.0005	0.96[a]	0.99 (0.60–1.62)
	Caucasian (9)	0.75	0.22	1.05 (0.97–1.14)
	Mixed African (3)	0.25	0.58	1.09 (0.80–1.48)
	Stage 2 hypertension (3)	0.68	0.89	1.02 (0.82–1.26)
AA *vs.* GG	Overall (17)	0.002	0.43[a]	1.08 (0.89–1.30)
	Asian (5)	<0.00001	0.76[a]	1.12 (0.55–2.26)
	Caucasian (9)	0.89	0.50	1.04 (0.92–1.18)
	Mixed African (3)	0.59	0.12	1.35 (0.93–1.96)
	Stage 2 hypertension (3)	0.32	0.46	1.13 (0.82–1.54)
C79G in hypertension				
C *vs.* G	Overall (16)	0.010	0.27[a]	1.06 (0.96–1.18)
	Asian (6)	0.002	0.39[a]	1.19 (0.80–1.79)
	Caucasian (8)	0.98	0.24	1.04 (0.98–1.10)
	Mixed African (2)	0.19	0.11	0.79 (0.59–1.06)
	Stage 2 hypertension (3)	0.01	0.11[a]	1.30 (0.94–1.81)
	SBP⩾160 mm Hg, DBP⩾95 mm Hg (4)[b]	0.04	0.05[a]	1.26 (1.00–1.57)
CC *vs.* (CG+GG)	Overall (16)	0.006	0.21[a]	1.10 (0.95–1.27)
	Asian (6)	0.002	0.26[a]	1.29 (0.83–2.00)
	Caucasian (8)	0.98	0.36	1.04 (0.95–1.14)
	Mixed African (2)	0.38	0.09	0.74 (0.53–1.05)
	Stage 2 hypertension (3)	0.02	0.09[a]	1.47 (0.94–2.30)
	SBP⩾160 mm Hg, DBP⩾95 mm Hg (4)[b]	0.03	0.04[a]	1.38 (1.02–1.86)
(CC+CG) *vs.* GG	Overall (16)	0.90	0.43	1.04 (0.94–1.15)
	Asian (6)	0.79	0.38	0.75 (0.39–1.44)
	Caucasian (8)	0.92	0.31	1.05 (0.95–1.17)
	Mixed African (2)	0.11	0.63	0.82 (0.37–1.83)
	Stage 2 hypertension (3)	0.55	0.75	1.05 (0.80–1.37)
	SBP⩾160 mm Hg, DBP⩾95 mm Hg (4)[b]	0.75	0.77	1.04 (0.80–1.36)
CC *vs.* GG	Overall (16)	0.93	0.40	1.05 (0.94–1.18)
	Asian (6)	0.74	0.48	0.79 (0.41–1.51)
	Caucasian (8)	0.98	0.27	1.07 (0.95–1.20)
	Mixed African (2)	0.10	0.78[a]	0.81 (0.20–3.39)
	Stage 2 hypertension (3)	0.74	0.57	1.10 (0.79–1.53)
	SBP⩾160 mm Hg, DBP⩾95 mm Hg (4)[b]	0.89	0.59	1.09 (0.79–1.50)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.
[a]Random-effects estimate.
[b]SBP⩾160 mm Hg and/or DBP⩾95 mm Hg hypertension population.
*The *P*-value of OR determined by the *Z* test.

Quantitative synthesis

ADRB2 A46G. Global statistical results: The random-effects model was used to pool the results, as the between-study heterogeneity was significant. There was no significant association between the A46 allele and hypertension in all subjects (P=0.45, OR=1.04, 95% CI 0.94–1.15, $P_{heterogeneity}<0.0001$) (Figure 1a). No evidence of association was found between A46G and hypertension in the dominant genetic model (AA *vs.* (AG+GG)) (P=0.17, OR=1.13, 95% CI 0.95–1.35, $P_{heterogeneity}$=0.0002) or in the recessive genetic model ((AA+AG) *vs.* GG) (P=0.81, OR=0.98, 95% CI 0.87–1.12, $P_{heterogeneity}$=0.01). With homozygote comparison (AA *vs.* GG), no association could be found (P=0.43, OR=1.08, 95% CI 0.89–1.30, $P_{heterogeneity}$=0.002) (Table 3).

Stratification analysis

Significant heterogeneity existed in five studies of Asian populations. The random-effects model was used to pool the results. No significant association was found between *ADRB2* A46G and hypertension in any statistical models (Table 3). The fixed-effects model was used to pool the results of the Caucasian and the mixed African populations, as the between-study heterogeneity was insignificant. In the Caucasian population, we found no significant association between *ADRB2* A46G and hypertension (Table 3). In the mixed African population, a significant association was found between the dominant genetic model (AA *vs.* (AG+GG)) (P=0.04, OR=1.38, 95% CI 1.01–1.87, $P_{heterogeneity}$=0.98) (Figure 1b), while no significant association was found in other statistic models (Table 3).

No significant heterogeneity existed in three studies of stage 2 hypertension;[13,17,27] the fixed-effects model was used to pool the results. There was no significant association between the A46 allele and stage 2 hypertension (P=0.47, OR=1.06, 95% CI 0.91–1.23, $P_{heterogeneity}$=0.47). No evidence of association between A46G and stage 2 hypertension in the dominant genetic model was found (AA *vs.* (AG+GG)) (P=0.25, OR=1.18, 95% CI 0.89–1.56, $P_{heterogeneity}$=0.19). The same was true for the recessive genetic model ((AA+AG) *vs.* GG) (P=0.89, OR=1.02, 95% CI 0.82–1.26, $P_{heterogeneity}$=0.68). In homozygote comparison (AA *vs.* GG), no association could be found (P=0.46, OR=1.13, 95% CI 0.82–1.54, $P_{heterogeneity}$=0.32) (Table 3).

ADRB2 C79G. Global statistical results: Significant between-study heterogeneity existed in 16 studies when we compared the C and G alleles of C79G in relation to hypertension. The random-effects model was used to pool the results. There was no significant association between the C79 allele and hypertension in all subjects (P=0.27, OR=1.06, 95% CI 0.96–1.18, $P_{heterogeneity}$=0.01) (Figure 2a). No evidence of association was seen between C79G and hypertension in the dominant genetic model (CC *vs.* (CG+GG)) (P=0.21, OR=1.10, 95% CI 0.95–1.27, $P_{heterogeneity}$=0.006) or in the recessive genetic model ((CC+CG) *vs.* GG) (P=0.43, OR=1.04, 95% CI 0.94–1.15, $P_{heterogeneity}$=0.90). There was no significant association in homozygote comparison (CC *vs.* GG) (P=0.40, OR=1.05, 95% CI 0.94–1.18, $P_{heterogeneity}$=0.93) (Table 3).

Stratification analysis

Significant heterogeneity existed in six studies of Asians; the random-effects model was used for allele comparison, and no significant association was found (Table 3). There was also no significant association found in other genetic models conducted using Asians (Table 3). The fixed-effects model was used to pool the results for the Caucasian and mixed African populations, as the between-study heterogeneity was insignificant. There was no significant association with hypertension found in either population (Table 3).

Meta-analysis in the subgroup of stage 2 hypertension could not find significant association with the C79G polymorphism in the three studies included.[10,13,17] No association was found between the C79 allele and stage 2 hypertension (P=0.11, OR=1.30, 95% CI 0.94–1.81, $P_{heterogeneity}$=0.01, random-effects model), in the dominant genetic model (CC *vs.* (CG+GG)) (P=0.09, OR=1.47, 95% CI 0.94–2.30, $P_{heterogeneity}$=0.02, random-effects model), in the recessive genetic model ((CC+CG) *vs.* GG) (P=0.75, OR=1.05, 95% CI 0.80–1.37, $P_{heterogeneity}$=0.55, fixed-effects model), or in the homozygote comparison (CC *vs.* GG) (P=0.57, OR=1.10, 95% CI 0.79–1.53, $P_{heterogeneity}$=0.74, fixed-effects model).

To uncover the potential association between C79G polymorphisms and hypertension, further research was conducted on severe hypertension (SBP $\geqslant$ 160 mm Hg and/or DBP $\geqslant$ 95 mm Hg hypertensive population); four studies were included[10,13,16,17] (Table 4). Significant association was found in the dominant genetic model (CC *vs.* (CG+GG)) (P=0.04, OR=1.38, 95% CI 1.02–1.86, $P_{heterogeneity}$=0.03, random-effects model) (Figure 2b), and there was also a borderline significance between the C79 allele and hypertension (P=0.05, OR=1.26, 95% CI 1.00–1.57, $P_{heterogeneity}$=0.04, random-effects model) (Figure 2c), whereas no association was found in the recessive genetic model ((CC+CG) *vs.* GG) (P=0.77, OR=1.04, 95% CI 0.80–1.36, $P_{heterogeneity}$=0.75, fixed-effects model) or in homozygote comparison (CC *vs.* GG) (P=0.59, OR=1.09, 95% CI 0.79–1.50, $P_{heterogeneity}$=0.89, fixed-effects model).

Sensitivity analysis

Between-study heterogeneity existed in all the studies using Asian subjects, but not in those using Caucasians and mixed African populations. Sensitivity analysis was conducted by sequential omission of individual studies overall and of Asians. As such, the Wu *et al.*[5] article on the Yi Chinese minority was excluded; it appeared that the overall between-study heterogeneity no longer existed for the A46G polymorphism and no association could be found (A *vs.* G, P=0.61, OR=1.01, 95% CI 0.96–1.06, $P_{heterogeneity}$=0.22, fixed-effects model). A similar result was found in the study of Ge *et al.*[10] on the Han Chinese and prevalence of the C79G, which was also excluded; it appeared there was no association found overall (C *vs.* G, P=0.29, OR=1.03, 95% CI 0.98–1.09, $P_{heterogeneity}$=0.18, fixed-effects model). However, in the Asian population, between-study heterogeneity still existed when any single study was excluded.

Publication bias

The funnel plot was applied for comparison of A46 *vs.* G46 in the OR analysis of *ADRB2* A46G, and Egger's test provided no evidence for funnel-plot asymmetry (t=−0.17, P=0.868; Figure 3a). Similarly, no publication bias was detected for the C79G polymorphism (t=−0.21, P=0.838; Figure 3b).

DISCUSSION

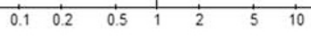
We performed a systematic review of the literature by means of a meta-analysis on the association between the *ADRB2* A46G and C79G polymorphisms and essential hypertension, without evidence of publication bias for the outcome. To avoid reporting bias, we contacted the authors for raw data. We acquired the data, including 6495 Caucasian subjects from Gjesing *et al.*,[20] but failed to gain information from two original studies[31,32] of Asians, which included 1700 subjects altogether. These two papers both indicated 'negative' results of A46G and C79G polymorphisms, which were consistent with our results of meta-analysis in Asians and overall.

Sensitivity analysis revealed that when two studies on Chinese subjects[5,10] were excluded, significant overall heterogeneity did not exist. The source of heterogeneity might be attributed to two factors. The first is the genetic difference in the sub-ethnic groups of the Chinese population. In the Wu *et al.* study,[5] the ethnic minorities Yi and Hani were recruited for the analysis but not the Han ethnic majority. The genetic differences between these populations should not be neglected.[30] Even in Han Chinese, a recent genome-wide association study suggested that certain genetic characteristics of the Han population correlated with geographical locations.[33] The genetic difference made it such that heterogeneity in the meta-analysis was inevitable. Another source of heterogeneity might be related to the quality of the studies, such as small samples and different inclusion criteria. Multicenter genome-wide association

a

Review: ADRB2 C79G & Hypertension
Comparison: C vs. G
Outcome: Overall

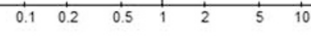
Study or sub-category	Hypertension n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI	Year
01 Asian						
Kato N	2099/2240	1552/1674		8.31	1.17 [0.91, 1.50]	2001
Ge D	951/1006	908/1008		5.92	1.90 [1.35, 2.68]	2005
Wu H-HANI	335/344	255/266		1.26	1.61 [0.66, 3.93]	2006
Wu H-YI	185/198	234/268		2.13	2.07 [1.06, 4.03]	2006
Mo W	522/576	279/298		3.02	0.66 [0.38, 1.13]	2007
Yu SF	101/116	109/116		1.16	0.43 [0.17, 1.10]	2008
Subtotal (95% CI)	4480	3630		21.80	1.19 [0.80, 1.79]	
Total events: 4193 (Hypertension), 3337 (Control)						
Test for heterogeneity: Chi?= 18.84, df = 5 (P = 0.002), I?= 73.5%						
Test for overall effect: Z = 0.86 (P = 0.39)						
02 Caucasian						
Jia H	336/596	319/596		9.06	1.12 [0.89, 1.41]	2000
Xie HG-Cau	258/402	232/358		6.96	0.97 [0.72, 1.31]	2000
Herrmann SM	867/1414	347/580		10.16	1.06 [0.87, 1.30]	2002
Sunder-Plassmann G	147/364	134/364		6.94	1.16 [0.86, 1.57]	2002
Castellano M	410/648	307/494		8.60	1.05 [0.82, 1.34]	2003
Pojoga L	322/560	75/130		5.03	0.99 [0.67, 1.46]	2006
Bartels NK	251/516	169/342		7.63	0.97 [0.74, 1.27]	2007
Gjesing AP	2801/5022	4395/7968		14.80	1.03 [0.95, 1.10]	2007
Subtotal (95% CI)	9522	10832		69.19	1.04 [0.98, 1.10]	
Total events: 5392 (Hypertension), 5978 (Control)						
Test for heterogeneity: Chi?= 1.65, df = 7 (P = 0.98), I?= 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
03 Mixed African						
Candy G	289/380	204/246		4.68	0.65 [0.44, 0.98]	2000
Xie HG-Afr	253/310	210/256		4.33	0.97 [0.63, 1.49]	2000
Subtotal (95% CI)	690	502		9.01	0.79 [0.54, 1.17]	
Total events: 542 (Hypertension), 414 (Control)						
Test for heterogeneity: Chi?= 1.73, df = 1 (P = 0.19), I?= 42.1%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)	14692	14964		100.00	1.06 [0.96, 1.18]	
Total events: 10127 (Hypertension), 9729 (Control)						
Test for heterogeneity: Chi?= 30.70, df = 15 (P = 0.010), I?= 51.1%						
Test for overall effect: Z = 1.11 (P = 0.27)						



b

Review: ADRB2 C79G & Hypertension
Comparison: CC vs.(CG+GG)
Outcome: Severe Hypertension (SBP>160mmHg and/or DBP>95mmHg)

Study or sub-category	Hypertension n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI	Year
Norihiro Kato	986/1120	720/837		30.15	1.20 [0.92, 1.56]	2001
Gere Sunder-Plassman	30/182	26/182		16.30	1.18 [0.67, 2.10]	2002
Stefan-Martin Herrma	269/707	100/290		29.09	1.17 [0.88, 1.55]	2002
D. Ge	456/503	410/504		24.47	2.22 [1.53, 3.24]	2005
Total (95% CI)	2512	1813		100.00	1.38 [1.02, 1.86]	
Total events: 1741 (Hypertension), 1256 (Control)						
Test for heterogeneity: Chi?= 8.82, df = 3 (P = 0.03), I?= 66.0%						
Test for overall effect: Z = 2.10 (P = 0.04)						



c

Review: ADRB2 C79G & Hypertension
Comparison: C vs.G
Outcome: Severe Hypertension (SBP>160mmHg and/or DBP>95mmHg)

Study or sub-category	Hypertension n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI	Year
Norihiro Kato	2099/2240	1552/1674		26.28	1.17 [0.91, 1.50]	2001
Gere Sunder-Plassman	147/364	134/364		23.12	1.16 [0.86, 1.57]	2002
Stefan-Martin Herrma	867/1414	347/580		30.06	1.06 [0.87, 1.30]	2002
D. Ge	951/1006	908/1008		20.53	1.90 [1.35, 2.68]	2005
Total (95% CI)	5024	3626		100.00	1.26 [1.00, 1.57]	
Total events: 4064 (Hypertension), 2941 (Control)						
Test for heterogeneity: Chi?= 8.53, df = 3 (P = 0.04), I?= 64.8%						
Test for overall effect: Z = 1.99 (P = 0.05)						

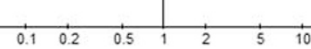


Table 4 Comparison of characteristics between cases and controls in the articles studied the association between 'severe hypertension' and *ADRB2* C79G polymorphism

First author	*Country*	*Case/control*	n, *M/F*	*Age, year*	*SBP, mm Hg*	*DBP, mm Hg*	*BMI, kg m^{-2}*
Ge[10]	China	Case	262/241	53.57 ± 9.34	177.07 ± 28.05	104.34 ± 12.28	26.32 ± 3.85
		Control	263/241	53.67 ± 9.18	117.58 ± 11.65	75.08 ± 7.96	24.34 ± 3.57
Kato[16]	Japan	Case (non-diabetic)	440/402	65.9 ± 11.0	160.3 ± 19.3	96.9 ± 10.9	23.5 ± 3.0
		Control (non-diabetic)	366/267	58.9 ± 13.2	118.7 ± 12.8	75.3 ± 9.0	22.3 ± 2.9
		Case (diabetic)	192/113	70.3 ± 9.5	156.3 ± 19.5	93.3 ± 12.6	24.5 ± 3.6
		Control (diabetic)	156/64	71.6 ± 10.0	127.3 ± 14.9	79.0 ± 8.9	23.1 ± 3.1
Sunder-Plassmann[13]	Austria	Case	91/91	55.8 ± 12.8	—	—	—
		Control	91/91	55.9 ± 12.9	—	—	—
Herrmann[17]	France, UK	Case (PEGASE study)	403/304	43.7 ± 9.8	—	—	—
	France	Control (ECTIM study)	290/0	51.1 ± 8.8	—	—	—

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; —, data not available.
Values are mean ± s.d.

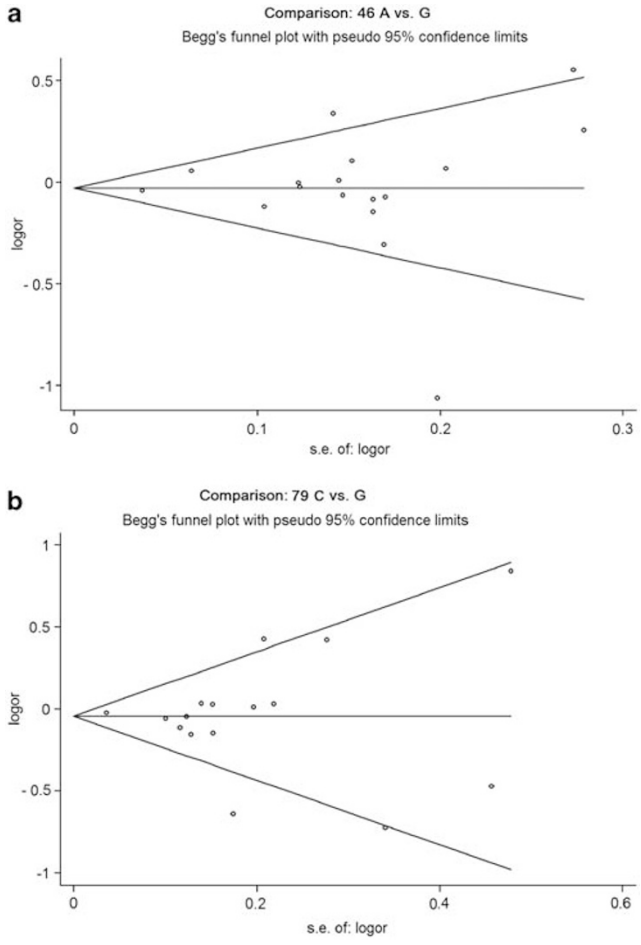


Figure 3 (**a**) Funnel plot for A *vs.* G allele comparison of the A46G polymorphism. (**b**) Funnel plot for C *vs.* G allele comparison of the C79G polymorphism.

study with larger samples might help to elucidate the association between hundreds of thousands of locus variants and hypertension, which would minimize the heterogeneity of samples and would also examine the loci rarely studied by traditional single-nucleotide polymorphism genotyping technology. However, despite our best efforts, we have not found any genome-wide association study of this locus published.

In the meta-analysis of the association between the *ADRB2* C79G polymorphism and hypertension, our results showed no overall association or an ethnicity-specific association. Similar results were found for the stage 2 hypertension population. Interestingly, the meta-analysis on 'severe hypertension' showed significant association between C79G and hypertension in the dominant genetic model (CC *vs.* (CG+GG)), as well as in the comparison of the C and G alleles. We were curious to understand why an association occurred for particular criterion in the hypertensive population, but not in the population as a whole or in the subgroups of stage 2 hypertensives. Few studies (only three articles[10,13,17]) investigated the correlation between this polymorphism and stage 2 hypertension. When we defined 'severe hypertension', the sample size expanded by more than 80%; by including the research of Kato *et al.*,[16] significant association could be found. To avoid overestimation by possible bias of other factors, we analyzed the detailed information of these four studies. Kato *et al.*'s study, involving both non-diabetic and diabetic patients (Table 4), deviated from the other three studies. To avoid potential bias because of diabetes, we excluded the diabetic subjects (294 hypertensive patients and 213 normotensive controls) and recalculated the pooled results. Significant association was stable in both models (CC *vs.* (CG+GG), P=0.01, OR=1.44, 95% CI 1.07–1.93, $P_{heterogeneity}$=0.05, random-effects model; C *vs.* G, P=0.03, OR=1.30, 95% CI 1.03–1.66, $P_{heterogeneity}$=0.03, random-effects model).

Cockcroft *et al.*[34] studied the regulation of the β_2-adrenoceptor on vessel resistance. The results indicate that homozygotes for A46 had significantly lower basal blood flow and attenuated increases in forearm blood flow compared with the G46 homozygotes, which

Figure 2 (**a**) Meta-analysis of the overall association between the C79G polymorphism and hypertension comparing C *vs.* G. *n* indicates the total number of C alleles; *N* indicates the total number of C alleles plus G alleles. (**b**) Meta-analysis for the association between the C79G polymorphism and systolic blood pressure (SBP)⩾160 mm Hg and/or diastolic blood pressure (DBP)⩾95 mm Hg hypertension comparing CC *vs.* CG+GG. *n* indicates the total number of the CC genotype; *N* indicates the total number of the CC genotype plus the CG+GG genotype. (**c**) Meta-analysis for the association between the C79G polymorphism and SBP⩾160 mm Hg and/or DBP⩾95 mm Hg hypertension comparing C *vs.* G. *n* indicates the total number of C alleles; *N* indicates the total number of C alleles plus G alleles.

could be explained by the variability in vascular responsiveness to isoproterenol in the vascular bed associated with A46G polymorphism.[35] Lang *et al.*[36] and Johnson *et al.*[37] provided a schematic diagram to explain the functional difference of vascular responsiveness in Africans and Caucasians. In Africans, the degree of vasodilatation and chronotropic effects in response to isoproterenol in the forearm was markedly higher than that of Caucasians, whereas baseline blood flow was similar in the two populations. In our meta-analysis, we demonstrated association of A46G polymorphisms with essential hypertension in the subgroup of the mixed African population, but not in Caucasians. The frequency of A46 homozygotes in the mixed African population was considerably higher in hypertensives than in normotensives, whereas no association could be found in other ethnicities. This suggests that the mechanisms responsible for blunted vasodilatation mediated by β_2-adrenoceptors in response to the administration of isoproterenol might contribute to enhanced vascular reactivity in Africans and might have a role in the pathogenesis of hypertension in Africans.

Some studies have reported that in G79 subjects, locally applied isoprenaline caused larger increases in forearm blood flow[34] and dilation of hand veins[34,35] than in C79 subjects. In other words, A46G polymorphisms and C79G polymorphisms seem to share similar mechanisms in conducting blood flow in resistance vessels. This is very likely due to the linkage disequilibrium between A46G and C79G.[38–40] Owing to linkage disequilibrium, subjects homozygous for G79 are nearly always homozygous for G46, whereas naturally occurring A46/G79 is rare.[41–43] Pojoga *et al.*[6] observed that AA46/CC79 was significantly associated with higher blood pressure, which might be attributed to the enhancement of the AA46/CC79 diplotype.

In conclusion, our meta-analysis suggests significant association between the *ADRB2* A46G polymorphism and hypertension in the mixed African population. The *ADRB2* C79G polymorphism had significant association with an SBP $\geqslant$ 160 mm Hg and/or DBP $\geqslant$ 95 mm Hg in the hypertensive population. The role of both polymorphisms might contribute to enhanced vascular reactivity to isoproterenol in capacitance vessels.[34] More studies or large case–control studies, and especially studies stratified for different ethnicities and different stages of hypertension, should be performed to clarify the association between *ADRB2* polymorphisms and essential hypertension. Studies on the pathophysiologic mechanisms of the possible roles of A46G and C79G in hypertension are important as well.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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