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Association between KIF6 rs20455 polymorphism and the risk of coronary heart disease (CHD): a pooled analysis of 50 individual studies including 40,059 cases and 64,032 controls

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# Abstract

**Background:** The KIF6 rs20455 polymorphism has been verified as an important genetic factor of coronary heart disease (CHD), but with controversial results. The aim of this study was to explore the association between KIF6 rs20455 polymorphism and susceptibility to CHD.

**Methods:** All eligible studies were identified by searching Medline (mainly PubMed), EMBASE, the Web of Science, Cochrane Collaboration Database, Chinese National Knowledge Infrastructure, Wanfang Database and China Biological Medicine up to October 5, 2016.Odds ratios (ORs) with 95% confidence interval (CI) were used to explore the association between KIF6 rs20455 polymorphism and CHD risk. Begg's and Egger's tests were used to examine the publication bias. Subgroup analysis and sensitivity analysis were performed to test the reliability and stability of the results. All the analyses were carried out by Stata 12.0 software.

**Results:** A total of 28 publications including 50 individual studies were analyzed in this present work. There are no significant association found between KIF6 rs20455 polymorphism and CHD risk (Homozygote model: OR = 1.007, 95% CI = 0.952–1.066, P = 0.801; Heterozygote model: OR = 1.009, 95% CI = 0.968–1.052, P = 0.636; Dominant model: OR = 1.007, 95% CI = 0.966–1.048, P = 0.753; Recessive model: OR = 0.989, 95% CI = 0.943–1. 037, P = 0.655; Allele comparison model: OR = 1.00, 95% CI = 0.971–1.030, P = 0.988). Furthermore, subgroup analyses were performed by ethnicity, source of control.

**Conclusions:** Our result suggests that KIF6 rs20455 polymorphism may not be associated with CHD susceptibility. However, additional very well-designed large-scale studies are warranted to confirm our results.

Keywords: Coronary heart disease, KIF6 rs20455, Polymorphism, Meta-analysis

# Background

Coronary heart disease (CHD), a multifactorial heart disorder resulting from both environmental and genetic factors [1], is one of the leading causes of disability and death around the world [2]. Epidemiology studies have suggested that hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking are major risk factors for CHD [3]. In recent years, more and more studies reveled that several loci and variants are strongly associated with CHD [4, 5]. It has been estimated that approximately 50% of the variability of the major risk factors for CHD is determined by genetics [6].

The KIF6 protein is one of several molecular components that mediate intracellular transport of organelles, protein complexes, and mRNAs. A common Trp719Arg (rs20455) SNP in exon 19 of the KIF6 gene has been identified as a potential risk factor for CHD [7, 8]. The



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KIF6 protein belongs to the kinesin superfamily, which is involved in the intracellular transport in a microtubule and ATP-dependent manner [9]. The rs20455 polymorphism replaces the nonpolar 'Trp' residue in codon 719 with a basic 'Arg' amino acid. This SNP lies near the putative cargo binding taildomain and may alter the cargo activity of KIF6 [10]. Carriers of the 719Arg allele exhibit a 50% increased risk of events compared with non-carriers [8, 11]. Up to now, multiple large prospective and case-control studies have reported the association between KIF6 rs20455 polymorphism and the risk of CHD. However, somestudies have not verified inconsistent results. Published studies have generally been restricted in terms of sample size and ethnic diversity, and individual studies may have in-sufficient power to achieve a comprehensive and reliable conclusion. In view of the discrepancies in the findings of previous published studies, we aimed to perform a meta-analysis of the published studies to clarify the association between KIF6 rs20455 polymorphism and CHD to get a better under-standing of this relationship.

# Methods

## Literature search

A comprehensive search for all related studies from both electric databases, such as, Medline (mainly PubMed), Embase, Web of science, China National Knowledge Infrastructure (CNKI) et al., and hand search from references of all eligible literatures. Single or combinations of the following keywords were used: "kinesin like protein 6" or "KIF6" or "rs20455" or "719Arg", "single nucleotide polymorphism, SNP or variation, mutation", "genetic association" and "coronary heart disease" or "CHD". No language and sample size were set. When more than one studies of the same population were included in several publications, only the most recent or complete studies were included in this meta-analysis.

# Selection criteria

Articles included should meet following criteria: an appropriate description of KIF6 rs20455 polymorphism in CHD cases and healthy controls; results expressed as odds ratio (OR); and studies with a 95% confidence interval (CI) for OR with sufficient data to calculate these numbers. While for the exclusion criteria provided as follows: studies without raw data; case-only studies, family-based studies, case reports, editorials, and review articles (including meta-analyses). In studies with overlapping cases/controls, the study with the higher quality score or the study with more information on the origin of the cases/controls was included in the meta-analysis.

# Data extraction

Two researchers extracted important information independently and carefully from all eligible studies according to the criteria listed above. Any disagreement will be resolved by the two authors through discussion or the third author. The following data were extracted from each included study: first author's surname, year of publication, country, ethnicity, genotyping method, source of control, total number of cases and controls, distributions of KIF6 rs20455 genotypes. Different ethnicity descents were categorized as Caucasian, Asian, and Mixed populations (the original studies didn't clarify the race of the subjects or mixed races).

# Statistical analysis

We adopted poled ORs and corresponding 95% confidence interval (CIs) to detect the association between KIF6 rs20455 polymorphism and CHD risk. Heterogeneity was explored by Q statistic [12], and the P value was <0.05 will be considered statistically significant. Heterogeneity was also assessed using the  $I^2$  statistic, which takes values between 0% and 100% with higher values denoting greater degree of heterogeneity ( $I^2 = 0-25\%$ : noheterogeneity;  $I^2 = 25-50\%$ : moderate heterogeneity;  $I^2 = 50-75\%$ : large heterogeneity;  $I^2 = 75-100\%$ : extreme heterogeneity) [13]. Different statistical models will be selected according to the result of heterogeneity. Random (Der Simonian-Laird method) [14] will be used to calculate the precise results when the P value of heterogeneity was <0.05, or the  $I^2$  > 50%. Otherwise, fixed effects model (Mantel-Haenszel method) will be adopted [15]. Five genetic comparison model were carried out and calculated as follows: homozygote model (GG vs. AA), heterozygote model (AG vs. AA), recessive model (GG vs. AG + AA), and dominant model (GG + AG vs. AA), and allele comparison model (G-allele vs. A-allele). Hardy-Weinberg equilibrium in the control group was tested by the chi-square test for goodness of fit, and a P value of <0.05 was considered significant. Subgroup analyses were performed by ethnicity, source of control, to confirm if our results were stable and robust [16]. Begg's funnel plots [17] and Egger's test [18] were explored to examine if potential publication bias were existed in this study. Sensitivity analysis was carried out by sequentially omitting each study and finding the influence on the overall summary estimate [19]. All the statistical analyses were finished by STATA software (version 12.0; Stata Corporation, College Station, TX). All the P values were two-sided.

# Results

# Characteristics of all included studies

Totally, 209 potential relevant studies were searched through several databases. Based on the including criteria listed above, only 28 articles including 50 separate studies were included finally [8, 20–46]. A flow diagram summarizing the process of study selection was present

in Fig. 1. The baseline characteristics of all included studies were listed in Table 1. Helgadottir et al. contained two individual studies [25], Samani et al. contained two individual studies [26], Assimes et al. contained 20 individual studies [31], and Wu et al. contained two separate studies [41]. Moreover, there were 37 studies from Caucasian decedent, 9 studies from Asian populations and the rest 14 studies from mixed populations. There were 20 population-based (PB) studies, 21 hospital-based (HB) studies and four family based (FB) study, three community based (CB) study, two hospital and community based (H-CB) study. Different ethnicity descents were categorized as Caucasian, Asian and Mix (the original studies didn't clarify the race of the subjects or mixed races).

# Quantitative synthesis

All the eligible data were calculated and significant heterogeneity was detected under homozygote ( $I^2 = 33.9\%$ ; P<sub>heterogeneity</sub> = 0.012), heterozygote ( $I^2 = 35.5\%$ ; P<sub>heterogeneity</sub> = 0.008), dominant ( $I^2 = 39.8$ ; P<sub>heterogeneity</sub> = 0.002), recessive ( $I^2 = 26.5\%$ ; P<sub>heterogeneity</sub> = 0.047) and allele comparison model ( $I^2 = 44.2\%$ ; P<sub>heterogeneity</sub> = 0.001) between this gene variation and the risk of CHD. So,

random-effect model was used to calculate the statistical parameters. Overall, there were no significant association existed between KIF6 rs20455 polymorphism and the risk of CHD (Homozygote model: OR = 1.007, 95% CI = 0.952–1.066, P = 0.801, Fig. 2; Heterozygote model: OR = 1.009, 95% CI = 0.968–1.052, P = 0.636, Fig. 3; Dominant model: OR = 1.007, 95% CI = 0.966–1.048, P = 0.753, Fig. 4; Recessive model: OR = 0.989, 95% CI = 0.943–1.037, P = 0.655, Fig. 5; Allele comparison model: OR = 1.00, 95% CI = 0.971–1.030, P = 0.988, Fig. 6). Furthermore, we explored the subgroup analyses by ethnicity and source of control. All the results were listed in Table 2.

# Sensitivity analysis

The sensitivity analysis was performed to evaluate the influence of each individual study on the pooled OR by omitting every single study. The analysis results reflected that our results were statistically stable and reliable.

## **Publication bias**

There was no significant publication bias found in the meta-analysis, reflected by *P* values from Begg's correlation (Heterozygote model: P = 0.089; Dominant model: P = 0.061; Allele comparison model: P = 0.052, Fig. 7)



P<sub>HWE</sub> Author Ethnicity Control Case Control Year Country Control Case source AA AG GG AA AG GG Berglund et al. Sweden ΡB Yes Caucasian Vartiainen et al. Finland PB Yes Caucasian Senti et al. Spain Caucasian ΡB Yes Yusuf et al. ΡB Several Asian Yes USA HB I ow et al. Yes Caucasian Helgadottir et al.<sup>1</sup> USA ΡB Caucasian Yes Helgadottir et al.<sup>2</sup> USA Caucasian ΡB Yes Samani et al.<sup>1</sup> ΡB Yes Germany Caucasian Samani et al.<sup>2</sup> PB Germany Caucasian Yes Meng et al. FB Ireland Caucasian Yes Meiner et al. USA ΡB Yes Caucasian PB Serre et al. Mixed Several Yes Morgan et al. USA ΗB Yes Caucasian Assimes et al. USA Caucasian ΡB Yes Vennemann et al. Germany PB Caucasian Yes Sutton et al. USA Caucasian FB Yes Martinelli et al. ΡB Italy Caucasian Yes lakoubova et al. ΡB Scottland Caucasian Yes Stewart et al. Canada Caucasian ΗB Yes ΗB Luke et al. Austria Caucasian Yes Bare et al. Costa Rican PΒ Caucasian Yes Assimes et al.<sup>1</sup> U.S.A Mixed PΒ Yes Assimes et al.<sup>2</sup> Germany Caucasian ΗB Yes Assimes et al.3 U.S.A Mixed ΗB Yes Assimes et al.4 Iceland PΒ Caucasian 24.952 11,813 10.689 Yes Assimes et al.<sup>5</sup> Finland Caucasian ΡB Yes Assimes et al.<sup>6</sup> U.S.A Mixed FB Yes Assimes et al.7 ΡB Germany Caucasian Yes Assimes et al.8 Germany Caucasian ΗB Yes Assimes et al.9 U.S.A Caucasian CB Yes Assimes et al.<sup>10</sup> Mixed H-CB Caucasian Yes Assimes et al.<sup>11</sup> Mixed Asian H-CB Yes Assimes et al.12 Ireland Caucasian FB Yes Assimes et al.<sup>13</sup> ΡB Sweden Yes Caucasian Assimes et al.14 ΗB U.S.A Caucasian Yes Assimes et al.15 U.S.A ΗB Caucasian Yes Assimes et al.<sup>16</sup> U.S.A Caucasian ΗB Yes Assimes et al.17 U.S.A ΗB Caucasian Yes Assimes et al.<sup>18</sup> Spain Caucasian CB Yes Assimes et al.<sup>19</sup> ΗB Yes Italy Caucasian Assimes et al.<sup>20</sup> U.K. Caucasian CB Yes Bhanushali et al. India Asian ΗB Yes Peng et al. China Asian ΗB Yes

Table 1 Characteristics of all studies included in this meta-analysis

 Table 1 Characteristics of all studies included in this meta-analysis (Continued)

Author	Year	Country	Ethnicity	Control source	Case	Control	Case		Control		P <sub>HWE</sub>		
							AA	AG	GG	AA	AG	GG	
Wu et al. <sup>1</sup>	2012	China	Asian	HB	356	568	104	164	88	168	268	132	Yes
Wu et al. <sup>2</sup>	2012	China	Asian	HB	114	568	16	68	30	168	268	132	Yes
Wu et al.	2014	China	Asian	HB	288	346	74	141	73	101	166	79	Yes
Hamidizadeh et al.	2015	Iran	Caucasian	HB	100	100	35	48	17	63	27	10	No
Vishnuprabu et al.	2015	India	Asian	HB	510	532	107	252	151	121	251	160	Yes
Hubacek et al.	2016	Czech	Caucasian	HB	1889	1191	691	856	302	440	543	195	Yes
Vatte et al.	2016	Saudi Arabia	Asian	HB	1002	984	277	513	212	286	464	234	Yes

1–20: represents different studies in one publication; *HB* hospital based study, *PB* population based study, *FB* family based study, *CB* community based study, *HCB* hospital and community based study, *HWE* Hardy-Weinberg equilibrium. Mix: the original studies didn't clarify the race of the subjects or mixed races

and Egger's regression (Heterozygote model: P = 0.070; Dominant model: P = 0.058; Allele comparison model: P = 0.066, Fig. 8). However, significant publication bias found in the meta-analysis, reflected by P values from Begg's correlation (Homozygote model: P = 0.046; Recessive model: P = 0.025) and Egger's regression (Homozygote model: P = 0.041; Recessive model: P = 0.040). All the results are listed in Table 2.

# Discussion

Large sample and unbiased epidemiological studies of predisposition genes polymorphisms could provide insight into the in vivo relationship between candidate genes and complex diseases. Many epidemiological studies have investigated the relationship between the KIF6 rs20455 polymorphism and the risk of CHD, but because of small sample size and the low statistical power of individual studies, results have been contradictory. In this present study, we searched all eligible studies to date and got the precise result if KIF6 rs20455 polymorphism could contribute to the risk of CHD. To the best of our knowledge, our present work was the most comprehensive one through enrolling all eligible studies.

Herein, we included 50 individual studies, including 40,059 cases and 64,032 controls. Overall, there was no association between KIF6 rs20455 polymorphism and CHD risk. Hamidizadeh et al. found that significant association was found between this gene polymorphism and CHD risk among Caucasian populations [43], and the result was verified in another study through enrolling 143,000 subjects [40]. However, no association was found in a meta-analysis, among South Asians, African-Americans, Hispanics, East Asians, and mixed decedent populations [39]. Furthermore, other recent studies were also found no association existed between this gene polymorphism and CHD risk [25, 26, 47-49]. When we got the subgroup analyses by ethnicity, there was also no association found among Caucasian and Asian populations. While decreased risk of this gene polymorphism and CHD risk was found among mixed populations. Of note, mixed populations means the original studies didn't clarify the race of the subjects or mixed races. This result may be not provided some useful information for clinical deeds. So, further studies should be performed with clearly race or ethnicity stated in their work.

Publication bias was found in some genetic models. The explanations might arise from some aspects. First, our meta-analysis took into consideration only fully published data, and the abstract and conference papers were excluded. Second, this meta-analysis only focused on papers published in Chinese and English language, and some eligible studies which were reported in other languages might be missed. Third, positive results tend to be accepted by journals while negative results are often rejected or not even submitted. We should point out that the publication bias might partly account for the results, but which were not affected deeply. When we adjusted the results using the trim and fill method, the adjusted risk estimate was attenuated but remained significant, indicating the stability of our results.

Some limitations of this meta-analysis should be addressed. Firstly, heterogeneity is a potential problem when interpreting all the results of meta-analysis. Although we minimized the likelihood by performing a careful search for published studies, using the explicit criteria for study inclusion, the significant between-study heterogeneity still existed in most of comparison. The presence of heterogeneity can result from differences in the age distribution, selection of controls, prevalence lifestyle factors and so on. Secondly, only published studies were included in this meta-analysis. Therefore, potential publication bias was existed in some genetic models. Despite the limitations, our meta-analysis significantly increased the statistical power based on substantial data from different studies. The sensitivity analyses outcomes reflected that our results were statistically stable and reliable.

In conclusion, this present meta-analysis suggests that carriers of KIF6 rs20455 polymorphism may irrelative to



atuay D		% Weight
	OK (95% CI)	weight
Berglund et al.	0.66 (0.35, 1.25)	0.41
/artiainen et al.	1.22 (0.77, 1.92)	0.73
Senti et al.	1.07 (0.76, 1.49)	1.25
/usuf et al.	1.04 (0.86, 1.26)	2.80
Low et al.	0.99 (0.67, 1.47)	0.95
Helgadottir et al.1	0.85 (0.67, 1.08)	2.02
Helgadottir et al.2	1.12 (0.88, 1.42)	2.07
Samani et al.1	1.04 (0.88, 1.24)	3.10
Samani et al.2	0.98 (0.81, 1.19)	2.80
Meng et al.	1.00 (0.77, 1.28)	1.92
Aeiner et al.	1.01 (0.78, 1.32)	1.80
Serre et al.	0.89 (0.72, 1.09)	2.49
Aorgan et al.	0.99 (0.79, 1.23)	2.28
Assimes et al.	0.91 (0.67, 1.23)	1.46
/ennemann et al.	0.99 (0.82, 1.21)	2.67
Sutton et al.	0.90 (0.74, 1.09)	2.71
Martinelli et al.	0.87 (0.68, 1.12)	1.94
akoubova et al.	1.65 (1.21, 2.26)	1.38
Stewart et al.	1.26 (1.01, 1.59)	2.23
uke et al.	0.95 (0.68, 1.34)	1.22
Bare et al.	1.12 (0.99, 1.28)	4.00
Assimes et al.1	0.87 (0.65, 1.15)	1.64
Assimes et al.2	0.99 (0.82, 1.21)	2.67
Assimes et al.3	0.84 (0.70, 1.01)	2.88
Assimes et al.4	0.92 (0.86, 0.99)	5.64
Assimes et al.5	1.22 (0.77, 1.92)	0.73
Assimes et al.6	1.04 (0.80, 1.34)	1.88
Assimes et al.7	0.98 (0.81, 1.19)	2.80
Assimes et al.8	1.04 (0.88, 1.24)	3.10
Assimes et al.9	1.01 (0.78, 1.32)	1.80
Assimes et al.10	0.89 (0.72, 1.09)	2.49
Assimes et al.11	1.04 (0.86, 1.26)	2.80
Assimes et al.12	1.00 (0.77, 1.28)	1.92
Assimes et al.13	0.66 (0.35, 1.25)	0.41
Assimes et al.14	0.85 (0.67, 1.08)	2.02
Assimes et al.15	0.99 (0.67, 1.47)	0.95
Assimes et al.16	0.99 (0.79, 1.23)	2.28
Assimes et al.17	1.12 (0.88, 1.42)	2.07
Assimes et al.18	1.07 (0.76, 1.49)	1.25
Assimes et al.19	0.87 (0.68, 1.12)	1.94
Assimes et al.20	1.07 (0.95, 1.22)	4.19
Bhanushali et al.	0.65 (0.40, 1.08)	0.62
Peng et al.	1.15 (0.81, 1.63)	1.15
Vu et al.1	0.99 (0.72, 1.35)	1.40
Vu et al.2	<b>2</b> .66 (1.50, 4.75)	0.48
Vu et al.	1.16 (0.80, 1.69)	1.04
łamidizadeh et al.	3.20 (1.71, 5.99)	0.41
/ishnuprabu et al.	1.14 (0.83, 1.55)	1.39
Hubacek et al.	1.00 (0.85, 1.18)	3.33
/atte et al.	1.14 (0.93, 1.40)	2.50
Overall (I-squared = 35.5%, p = 0.008)	1.01 (0.97, 1.05)	100.00
NOTE: Weights are from random effects analysis		



	OR (95% CI)	Weight
- 		rreight
Berglund et al.	1.29 (0.56, 3.00)	0.30
/artiainen et al.	0.98 (0.52, 1.84)	0.53
Senti et al.	1.02 (0.63, 1.64)	0.89
′usuf et al.	0.99 (0.81, 1.20)	3.43
ow et al.	1.07 (0.63, 1.81)	0.73
lelgadottir et al.1	1.05 (0.74, 1.49)	1.48
lelgadottir et al.2	1.11 (0.80, 1.54)	1.69
Samani et al.1	1.06 (0.83, 1.34)	2.70
Samani et al.2	1.01 (0.78, 1.30)	2.49
/eng et al.	0.99 (0.68, 1.45)	1.32
/einer et al.	1.24 (0.90, 1.72)	1.69
Serre et al.	1.28 (0.96, 1.70)	2.09
Norgan et al.	1.12 (0.82, 1.54)	1.81
Assimes et al.	0.60 (0.44, 0.82)	1.80
/ennemann et al.	0.88 (0.67, 1.14)	2.32
Sutton et al.	1.23 (0.93, 1.62)	2.21
Aartinelli et al.	1.28 (0.91, 1.81)	1.53
akouhova et al	1 13 (0 72 1 77)	1.00
Stewart et al	0.98 (0.84, 1.13)	4 74
	0.84 (0.67, 1.06)	2 79
	0.04 (0.78, 1.13)	3.77
	0.60 (0.45, 0.81)	1.06
	0.88 (0.67, 1.14)	1.90
ssimes et al.2	0.88 (0.67, 1.14)	2.32
	0.85 (0.74, 1.08)	5.59
	0.95 (0.85, 1.08)	5.79
Assimes et al.5	0.98 (0.52, 1.84)	0.53
Assimes et al.6	0.62 (0.48, 0.80)	2.50
Assimes et al.7	1.01 (0.78, 1.30)	2.49
Assimes et al.8	1.06 (0.83, 1.34)	2.70
Assimes et al.9	1.24 (0.90, 1.72)	1.69
Assimes et al.10	1.28 (0.96, 1.70)	2.09
Assimes et al.11	0.99 (0.81, 1.20)	3.43
Assimes et al.12	• 0.99 (0.68, 1.45)	1.32
Assimes et al.13	1.29 (0.56, 3.00)	0.30
Assimes et al.14	<b>1</b> .02 (0.71, 1.45)	1.47
Assimes et al.15	1.07 (0.63, 1.81)	0.73
Assimes et al.16	1.12 (0.82, 1.54)	1.81
Assimes et al.17	1.11 (0.80, 1.54)	1.69
Assimes et al.18	1.02 (0.63, 1.64)	0.89
Assimes et al.19	1.28 (0.91, 1.81)	1.53
Assimes et al.20	0.92 (0.78, 1.10)	4.00
Shanushali et al.	0.78 (0.47, 1.27)	0.83
Peng et al.	1.08 (0.77, 1.51)	1.61
Vu et al.1	1.08 (0.80, 1.48)	1.83
Vu et al.2	1.18 (0.74, 1.87)	0.94
Vu et al.	1.15 (0.80, 1.65)	1.40
lamidizadeh et al.	1.84 (0.80, 4.25)	0.31
/ishnuprabu et al.	0.98 (0.75, 1.28)	2.32
łubacek et al.	0.98 (0.81, 1.20)	3.44
'atte et al.	0.86 (0.70, 1.06)	3.16
Dverall (I-squared = 26.5%, p = 0.047)	0.99 (0.94, 1.04)	100.00
IOTE: Weights are from random effects analysis		



Hermosynome         Key is a strain of the strain of t	Variables	No.	Pheterogneity	Analysis model	OR (95% CI)	Р	P <sub>Begg's</sub>	P <sub>Egger's</sub>
Totol500.012Random model1.007 (12852-1.068)0.8010.1080.108Linkity <td>Homozygote mc</td> <td>del</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Homozygote mc	del						
ÉrtheolyGuacajan370.45Fixed model0.108400.622Alaina00.158Fixed model0.20840.032.115400.444Maed40.004Random model0.271 (0.57-1243)0.0731Source at control0.4840.4940.494Pile00.386Fixed model0.201 (0.57-1243)0.691File210.086Fixed model0.201 (0.56-1102)0.016File20.386Fixed model1.021 (0.956-1102)0.466Hererosycet model1.021 (0.957-1138)0.4660.0090.070File20.386Fixed model1.039 (0.958-1102)0.466Hererosycet model1.021 (0.958-1126)0.4660.0090.070Alaina90.071Fixed model0.893 (0.959-1191)0.065Alaina90.071Fixed model0.893 (0.959-1191)0.067Alaina90.071Fixed model0.979 (0.938-1121)0.316Alaina90.067Fixed model0.490 (0.956-1132)0.361Fixed model0.591 (0.941-1151)0.316Fixed model0.979 (0.938-1121)0.316Fixed model0.102 (0.961-1132)0.581Fixed model0.104 (0.956-1132)0.581Fixed model0.102 (0.961-1143)0.254Fixed model0.102 (0.961-1162)0.121Fixed model0.102 (0.971-1163)0.254Fixed model0.103 (0.971-1163)0.121 <t< td=""><td>Total</td><td>50</td><td>0.012</td><td>Random model</td><td>1.007 (0.952–1.066)</td><td>0.801</td><td>0.106</td><td>0.108</td></t<>	Total	50	0.012	Random model	1.007 (0.952–1.066)	0.801	0.106	0.108
Caucasian370.45Fixed model1.012 (0.964-1.063)0.022Asian90.158Fixed model0.203 0.033-1.1540.044Maxed40.014Random model0.203 (0.52-1.024)0.001Source of cantrol70.9981.027 (0.956-1.102)0.091FB200.038Fixed model0.202 (0.956-1.102)0.001FB30.028Fixed model1.027 (0.956-1.102)0.001CB30.027Fixed model1.027 (0.956-1.102)0.016FB30.028Fixed model1.009 (0.967-1.102)0.016FR30.028Fixed model1.009 (0.968-1.029)0.047FR00.008Random model0.955 (0.963-1.029)0.047Caucasian370.038Fixed model0.955 (0.963-1.029)0.047Source of control7777Source of control70.0650.0580.058FR30.067Fixed model0.907 (0.938-1.021)0.356FR30.091Fixed model0.070 (0.96-1.132)0.356FR30.092Fixed model0.070 (0.96-1.132)0.356FR30.054Fixed model0.070 (0.96-1.132)0.358FR30.054Fixed model0.103 (0.97-1.132)0.356FR30.054Fixed model0.103 (0.97-1.132)0.356FR30.054Fixed model	Ethnicity							
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Meed40.004Random model0.771 (0.37-1.043)0.0731Sources controlPB00.038Random model0.081 (0.895-1.07c)0.601FB10.096Fixed model0.007 (0.767-1.072)0.016FB20.038Fixed model0.109 (0.895-1.082)0.406FBC20.068Fixed model1.009 (0.895-1.082)0.406FH-CR20.088Fixed model1.009 (0.985-1.082)0.406CB0.08Random model0.905 (0.963-1.092)0.406Caucasian90.071Fixed model0.905 (0.963-1.092)0.079Asian90.071Fixed model0.905 (0.963-1.092)0.079Asian90.071Fixed model0.907 (0.993-1.01)0.051Fixed200.677Random model0.907 (0.993-1.01)0.316Fixed200.676Random model1.004 (0.957-1.182)0.356Fixed30.024Fixed model0.066 (0.857-1.182)0.254Fixed30.024Fixed model1.007 (0.966-1.081)0.367Fixed30.024Fixed model1.007 (0.967-1.182)0.254Fixed30.024Fixed model1.017 (0.984-1.162)0.361Fixed model1.007 (0.967-1.081)0.361Fixed model1.007 (0.967-1.182)0.361Fixed model1.007 (0.967-1.081)0.361Fixed model1.007 (0.967-1.182)0.361Fixe	Asian	9	0.158	Fixed model	1.038 (0.933–1.154)	0.494		
Source of controlPB200.038Random model0.981 (0.895-1.020)0.091HB40.038Fixed model1.027 (0.956-1.020)0.016CB30.427Fixed model1.019 (0.872-1.120)0.816HCR30.427Fixed model1.019 (0.872-1.120)0.816HCR30.427Fixed model1.019 (0.851-1.026)0.436Hererozynets modelTox3 (0.895-1.266)0.4630.0690.070Everosynets model1.009 (0.968.1.022)0.5360.0890.070Everosynets model0.995 (0.963-1.029)0.0471.001Everosynets model0.026Random model0.995 (0.995-1.019)0.055Maxed30.037Random model0.997 (0.998-1.021)0.051Maxed40.639Fixed model0.979 (0.998-1.021)0.051Mored0.040Random model0.979 (0.998-1.012)0.551FB30.026Fixed model0.997 (0.891-1.012)0.551CB30.924Fixed model0.997 (0.891-1.012)0.551FB30.924Fixed model1.040 (0.956-1.123)0.551CB30.924Fixed model1.040 (0.956-1.123)0.561Fixed30.924Fixed model1.013 (0.970-1.057)0.561Fixed30.924Fixed model1.013 (0.970-1.057)0.561Mixed30.936Fixed model1.013 (0.970-1.05	Mixed	4	0.004	Random model	0.771 (0.57–1.043)	0.0731		
PB200.038Pandom model0.981 (0.995-1.070)0.691HB210.006Fixed model1.027 (0.956-1.103)0.891FB40.038Fixed model0.907 (0.767-1.072)0.016HCB30.427Fixed model1.019 (0.872-1.189)0.816HCB20.368Fixed model1.007 (0.968-1.052)0.446Heterocytopt model1.009 (0.968-1.052)0.6360.0890.070Fahral300.005Random model0.955 (0.963-1.029)0.700Asian90.071Fixed model0.955 (0.963-1.029)0.070Asian90.071Fixed model0.989 (0.995-1.191)0.055Source of control1.089 (0.959-1.191)0.0651.089Source of control1.089 (0.959-1.191)0.051FB200.057Random model0.979 (0.938-1.021)0.316FB310.020Random model0.979 (0.938-1.021)0.316FB310.024Fixed model0.960 (0.859-1.081)0.558CB30.024Fixed model0.970 (0.984-1.012)0.371Dominant model1.001 (0.966-1.048)0.7530.0610.568Ethicity1.021 (0.994-1.051)0.5681.011Mixed370.034Random model1.013 (0.970-1.057)0.568Ethicity1.021 (0.998-1.015)0.7561.011Mixed40.503Fi	Source of control							
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FB40.038Fixed model0.007 (0.767-1.072)0.016GR30.027Fixed model1.019 (0.872-1.18)0.816H-GB20.008Fixed model1.007 (0.867-1.072)0.816Heterozygete mod1.003 (0.908-1.052)0.6260.0890.070EthericationNorman Mark1.009 (0.968-1.052)0.6260.0890.070EtherozymetNorman Mark0.955 (0.963-1.029)0.7900.070Succe of controlNiked0.033Fixed model0.893 (0.799-0.999)0.047Succe of controlNiked0.036Fixed model0.979 (0.938-1.021)0.316HB200.067Random model0.979 (0.938-1.021)0.316HB210.004Random model0.979 (0.938-1.021)0.356GR30.924Fixed model1.064 (0.957-1.183)0.254HCB210.061Random model0.967 (0.841-1.112)0.637CR30.924Fixed model1.007 (0.966-1.048)0.254HCB20.265Fixed model1.064 (0.957-1.183)0.254CR30.924Fixed model1.007 (0.966-1.048)0.258CR30.924Fixed model1.007 (0.966-1.048)0.254LHCB20.256Fixed model1.013 (0.970-1.057)0.568CR30.924Fixed model1.013 (0.970-1.057)0.568LHCB20.026Fixed model0.991 (	HB	21	0.096	Fixed model	1.027 (0.956–1.103)	0.891		
CB30.427Fixed model0.101 (0.872-1.189)0.816HCR3.0368Fixed model1.073 (0.895-1.286)0.446Heterozyote model500.009Random model1.009 (0.908-1.052)0.6360.0090.070Ethicity500.035Random model1.009 (0.908-1.052)0.6360.0990.070EthicitySearce and the searce and the sear	FB	4	0.038	Fixed model	0.907 (0.767–1.072)	0.016		
HCB20.368Fixed model1.073 (0.895-1286)0.446Heterozygote model <t< td=""><td>СВ</td><td>3</td><td>0.427</td><td>Fixed model</td><td>1.019 (0.872–1.189)</td><td>0.816</td><td></td><td></td></t<>	СВ	3	0.427	Fixed model	1.019 (0.872–1.189)	0.816		
Heterozyote modelToral0.0080.008Random model1.009 (0.968-1.02)0.6360.0890.009EhnorCaucasian30.031Random model0.955 (0.963-1.02)0.070Asian90.031Fixed model0.899 (0.995-1.019)0.065Mixed0.639Fixed model0.893 (0.990-1.02)0.064Source of controlSamo0.631P80.00.667Random model0.970 (0.938-1.02)0.316Fixel0.00.067Random model0.960 (0.950-1.132)0.356Fixel0.00.064Fixel model0.960 (0.950-1.132)0.558Fixel0.02Random model0.961 (0.957-1.132)0.5730.0610.958Fixel00.265Fixel model0.967 (0.956-1.048)0.7530.0610.958Fixel00.02Random model1.017 (0.966-1.048)0.7530.0610.958Fixel00.02Random model1.013 (0.970-1.057)0.7530.0610.958Fixel00.03Fixel model0.017 (0.964-1.165)0.1121.974Fixel00.054Fixel model0.917 (0.974-1.152)0.121Fixel00.054Fixel model0.917 (0.974-1.152)0.121Fixel00.054Fixel model0.917 (0.974-1.152)0.121Fixel00.021Fixel model0.919 (0.932-1.152)0.786Fixe	H-CB	2	0.368	Fixed model	1.073 (0.895–1.286)	0.446		
Total500.008Random model1.009 (0.968-1.02)0.6360.0890.070EthnicityGaucasian370.035Random model0.955 (0.963-1.02)0.790Asian90.070Fixed model0.893 (0.790-099)0.065Mixed40.630Fixed model0.893 (0.790-099)0.070Secure of control1040 (0.956-1.12)0.316Source of controlPR200.067Random model1.040 (0.957-1.132)0.356FB40.807Fixed model1.064 (0.957-1.183)0.254H-CB20.265Fixed model0.967 (0.841-1.112)0.637Deminant modelH-CB00.002Random model1.007 (0.966-1.048)0.7530.0610.058EthnicySecure of controlSecure of controlSecure of controlFacasaina370.034Random model1.013 (0.970-1.057)0.568Asian90.034Fixed model1.031 (0.970-1.057)0.568Source of controlSecure of control </td <td>Heterozygote mo</td> <td>odel</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Heterozygote mo	odel						
EthnicityCaucasian370.035Random model0.955 (0.963-1.02)0.790Asian90.071Fixed model0.890 (0.99-0.91)0.065Mixed40.630Pixed model0.890 (0.99-0.90)0.047Surrear of controlSurrear of controlPI00.670Random model0.979 (0.938-1.02)0.316FI8210.067Random model0.966 (0.859-1.085)0.558CB30.924Fixed model0.967 (0.841-1.12)0.637Dotation of the Random model0.967 (0.841-1.12)0.637Colspan="4">Colspan="4" <t< td=""><td>Total</td><td>50</td><td>0.008</td><td>Random model</td><td>1.009 (0.968–1.052)</td><td>0.636</td><td>0.089</td><td>0.070</td></t<>	Total	50	0.008	Random model	1.009 (0.968–1.052)	0.636	0.089	0.070
Caucasian370.035Random model0.955 (0.963-1.02)0.790Asian90.071Fixed model1.089 (0.995-1.191)0.065Mixed40.639Fixed model0.893 (0.799-0.999)0.047Source of controlSource of controlP80.00.040Random model0.979 (0.938-1.021)0.366HB210.004Random model1.040 (0.956-1.132)0.356FB40.807Fixed model0.666 (0.859-1.083)0.558CB30.924Fixed model0.667 (0.841-1.112)0.637Domination model1.007 (0.966-1.084)0.7530.0610.058EthicityCaucasian370.034Random model1.013 (0.970-1.057)0.568Source of controlCaucasian370.034Random model1.013 (0.970-1.057)0.568Asian90.054Fixed model0.991 (0.932-1.055)0.766Source of controlCaucasian370.026Random model1.013 (0.970-1.057)0.568FB200.054Fixed model0.991 (0.932-1.055)0.766FB200.050Random model1.0140 (0.958-1.129)0.342FB200.026Random model0.991 (0.932-1.051)0.342FB30.996Fixed model0.998 (0.943-1.037)0.765<	Ethnicity							
Asian90.071Fixed model1.089 (0.995-1.191)0.065Mixed40.639Fixed model0.893 (0.799-0.999)0.047Surce of control0.067Random model0.979 (0.938-1.021)0.316HB200.067Random model0.966 (0.859-1.085)0.558FB30.924Fixed model0.966 (0.859-1.085)0.558CB30.924Fixed model0.966 (0.841-1.112)0.6370.6110.051Dominant model20.256Fixed model1.007 (0.966-1.048)0.7530.0610.058Ethricty0.024Random model1.013 (0.970-1.057)0.5680.054Caucasian370.034Random model1.017 (0.964-1.155)0.102Mixed00.954Fixed model0.854 (0.770-0.977)0.568Surce of controlRandom model0.991 (0.922-1.055)0.786Mixed00.902Random model0.991 (0.932-1.055)0.786 </td <td>Caucasian</td> <td>37</td> <td>0.035</td> <td>Random model</td> <td>0.955 (0.963–1.029)</td> <td>0.790</td> <td></td> <td></td>	Caucasian	37	0.035	Random model	0.955 (0.963–1.029)	0.790		
Mixed40.639Fixed model0.839 (0.799-0.999)0.047Source of controlPB200.667Random model0.979 (0.938-1.021)0.316HB210.004Random model1.040 (0.956-1.132)0.356FB40.807Fixed model0.966 (0.859-1.082)0.558FLCB20.265Fixed model1.064 (0.957-1.183)0.254H-CB20.265Fixed model1.007 (0.966-1.048)0.7530.0610.058Cominant model1.007 (0.966-1.048)0.7530.0610.058EthicityVVVV0.0540.054Cacasian370.034Random model1.013 (0.970-1.057)0.568Source of controlVVVVVSource of controlVVVVVPB00.020Random model1.013 (0.970-1.057)0.568VVSource of controlVVVVVVVSource of controlVVVVVVPB00.020Random model0.919 (0.932-1.055)0.786VVFB200.020Random model0.991 (0.932-1.051)0.310VVVGLCB30.986Fixed model0.919 (0.932-1.051)0.310VVVFB40.820Fixed model0.991 (0.932-1.051)0.310VV </td <td>Asian</td> <td>9</td> <td>0.071</td> <td>Fixed model</td> <td>1.089 (0.995–1.191)</td> <td>0.065</td> <td></td> <td></td>	Asian	9	0.071	Fixed model	1.089 (0.995–1.191)	0.065		
Source of controlPB200.067Random model0.979 (0.938-1.021)0.316HB210.004Random model1.040 (0.956-1.132)0.356FB40.807Fixed model0.966 (0.859-1.083)0.558CB30.924Fixed model0.967 (0.841-1.12)0.254HCB20.265Fixed model0.967 (0.841-1.12)0.6730.0610.858Domain model1.007 (0.966-1.048)0.7530.0610.8580.8580.8580.858EthicityUURandom model1.017 (0.964-1.05)0.5580.8580.8580.854 (0.770-0.971)0.033Source of controlUVFixed model1.017 (0.964-1.165)0.12VVVPB00.503Fixed model0.917 (0.954-1.165)0.12VVVVPB00.026Fixed model0.910 (0.92-1.055)0.362VVVVPB00.026Fixed model0.910 (0.92-1.051)0.362VVVVVFR30.961Fixed model0.910 (0.92-1.051)0.362VVVVVFR30.961Fixed model0.910 (0.92-1.051)0.362VVVVVVVVVVVVVVVVVVVVVVVVVVVV<	Mixed	4	0.639	Fixed model	0.893 (0.799–0.999)	0.047		
PB200.067Random model0.979 (0.938-1.021)0.316HB210.004Random model1.040 (0.956-1.132)0.356FB40.807Fixed model0.966 (0.859-1.085)0.558CB30.924Fixed model0.967 (0.841-1.112)0.637Deminant model20.265Fixed model0.967 (0.841-1.112)0.637Deminant model50.022Random model1.007 (0.966-1.048)0.7530.0610.058Ethricity55555555Caccasian370.034Random model1.013 (0.970-1.057)0.56855Asian90.054Fixed model0.991 (0.932-1.051)0.01255BR200.026Random model0.991 (0.932-1.051)0.766555BR210.002Random model0.991 (0.932-1.051)0.3765555BR210.002Random model0.991 (0.932-1.051)0.376555	Source of control							
HB210.004Random model1.040 (0.956-1.132)0.356FB40.807Fixed model0.966 (0.859-1.085)0.558CB30.924Fixed model1.064 (0.957-1.183)0.254H-CB20.265Fixed model0.967 (0.841-1.112)0.637Dominant model0.707 (0.966-1.048)0.7530.0610.058EthicityRandom model1.007 (0.966-1.048)0.7530.0610.058Caucasian370.034Random model1.013 (0.970-1.057)0.568Asian90.054Fixed model1.013 (0.970-1.057)0.568Viral40.508Fixed model0.854 (0.770-0.947)0.003Source of controlFixed model0.991 (0.932-1.055)0.766FB200.026Random model1.040 (0.958-1.129)0.346FB210.002Random model0.991 (0.932-1.055)0.766FB30.962Fixed model0.993 (0.81-1.132)0.310 </td <td>PB</td> <td>20</td> <td>0.067</td> <td>Random model</td> <td>0.979 (0.938–1.021)</td> <td>0.316</td> <td></td> <td></td>	PB	20	0.067	Random model	0.979 (0.938–1.021)	0.316		
FB40.807Fixed model0.966 (0.859-1.08)0.558CB30.924Fixed model1.064 (0.957-1.18)0.254H-CB20.265Fixed model0.967 (0.841-1.12)0.637Dominant modelTotal500.002Random model1.007 (0.966-1.048)0.7530.0610.058EtricitCalcasian370.034Random model1.013 (0.970-1.057)0.568Asian90.054Fixed model1.011 (0.984-1.165)0.112Mixed0.508Fixed model0.991 (0.932-1.055)0.786JournousJ	HB	21	0.004	Random model	1.040 (0.956–1.132)	0.356		
CB30.924Fixed model1.064 (0.957-1.18)0.254HCB20.265Fixed model0.967 (0.841-1.12)0.637Dominant modelTotal500.002Random model1.007 (0.966-1.048)0.7530.0610.058Distribution of the second of	FB	4	0.807	Fixed model	0.966 (0.859–1.085)	0.558		
H-CB20.265Fixed model0.967 (0.841-1.12)0.637Dominant model500.002Random model1.007 (0.966-1.048)0.7530.0610.058EthrictySolan8.002Random model1.013 (0.970-1.057)0.568Asian90.054Fixed model0.071 (0.984-1.165)0.112Mixed40.054Fixed model0.911 (0.932-1.057)0.786Source of controlSixed model0.991 (0.932-1.055)0.786PB200.026Random model1.040 (0.958-1.129)0.346 </td <td>СВ</td> <td>3</td> <td>0.924</td> <td>Fixed model</td> <td>1.064 (0.957–1.183)</td> <td>0.254</td> <td></td> <td></td>	СВ	3	0.924	Fixed model	1.064 (0.957–1.183)	0.254		
Dominant modelTotal500.002Random model1.007 (0.966-1.048)0.7530.0610.058EthrictyGaucasian370.034Random model1.013 (0.970-1.057)0.568Asian90.054Fixed model1.071 (0.984-1.165)0.112Mixed40.508Fixed model0.991 (0.932-1.055)0.786Surce of controlRandom model0.991 (0.932-1.055)0.786FB200.026Random model0.904 (0.958-1.129)0.346FB410.802Random model0.948 (0.848-1.059)0.342FB30.986Fixed model0.930 (0.951-1.14)0.310FAC30.986Fixed model0.993 (0.871-1.132)0.917Recessive modelStat model0.989 (0.943-1.037)0.6550.0250.040FiredricStat model0.902 (0.959-1.048)0.919falcasian370.514Fixed model0.020 (0.959-1.048)0.919 </td <td>H-CB</td> <td>2</td> <td>0.265</td> <td>Fixed model</td> <td>0.967 (0.841-1.112)</td> <td>0.637</td> <td></td> <td></td>	H-CB	2	0.265	Fixed model	0.967 (0.841-1.112)	0.637		
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Surver of controlPB200.026Random model0.991 (0.932-1.05)0.786HB210.002Random model1.040 (0.958-1.12)0.346FB40.820Fixed model0.948 (0.848-1.059)0.342CB30.986Fixed model1.053 (0.953-1.164)0.310H-CB20.551Fixed model0.993 (0.871-1.132)0.917Recensive modelVVCalcasian370.47Asian90.511Fixed model0.983 (0.898-1.075)0.019Mixed4<0.001	Mixed	4	0.508	Fixed model	0.854 (0.770–0.947)	0.003		
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FB40.820Fixed model0.948 (0.848–1.059)0.342CB30.986Fixed model1.053 (0.953–1.164)0.310H-CB20.551Fixed model0.993 (0.871–1.132)0.917Recessive model500.047Random model0.989 (0.943–1.037)0.6550.0250.040Ethicity510.511Fixed model1.002 (0.959–1.048)0.9190.9190.919Asian90.819Fixed model0.983 (0.898–1.075)0.7050.705Mixed4<0.001	HB	21	0.002	Random model	1.040 (0.958–1.129)	0.346		
CB       3       0.986       Fixed model       1.053 (0.953-1.164)       0.310         H-CB       2       0.551       Fixed model       0.993 (0.871-1.132)       0.917         Recessive model </td <td>FB</td> <td>4</td> <td>0.820</td> <td>Fixed model</td> <td>0.948 (0.848–1.059)</td> <td>0.342</td> <td></td> <td></td>	FB	4	0.820	Fixed model	0.948 (0.848–1.059)	0.342		
H-CB       2       0.551       Fixed model       0.993 (0.871–1.132)       0.917         R=c=ssive model	СВ	3	0.986	Fixed model	1.053 (0.953–1.164)	0.310		
Recessive model         Total       50       0.047       Random model       0.989 (0.943–1.037)       0.655       0.025       0.040         Ethricity       V       V       V       V       V       0.047       0.040         Asian       9       0.819       Fixed model       0.983 (0.898–1.075)       0.705       V       V       V         Mixed       4       <0.001	H-CB	2	0.551	Fixed model	0.993 (0.871–1.132)	0.917		
Total         50         0.047         Random model         0.989 (0.943–1.037)         0.655         0.025         0.040           Ethnicity         V           Caucasian         37         0.541         Fixed model         1.002 (0.959–1.048)         0.919         V         V           Asian         9         0.819         Fixed model         0.983 (0.898–1.075)         0.705         V         V           Mixed         4         <.001         Random model         0.811 (0.592–1.111)         0.191         V	Recessive model							
Ethnicity	Total	50	0.047	Random model	0.989 (0.943–1.037)	0.655	0.025	0.040
Caucasian370.541Fixed model1.002 (0.959–1.048)0.919Asian90.819Fixed model0.983 (0.898–1.075)0.705Mixed4<0.001	Ethnicity							
Asian         9         0.819         Fixed model         0.983 (0.898–1.075)         0.705           Mixed         4         <0.001	Caucasian	37	0.541	Fixed model	1.002 (0.959–1.048)	0.919		
Mixed         4         <0.001         Random model         0.811 (0.592–1.111)         0.191	Asian	9	0.819	Fixed model	0.983 (0.898–1.075)	0.705		
	Mixed	4	<0.001	Random model	0.811 (0.592–1.111)	0.191		

Table 2 Main results of pooled ORs with 95% CI in the meta-analysis

Source of control

No.	P <sub>heterogneity</sub>	Analysis model	OR (95% CI)	Р	P <sub>Begg's</sub>	P <sub>Egger's</sub>
20	0.040	Random model	0.982 (0.902–1.069)	0.668		
21	0.796	Fixed model	0.989 (0.919–1.064)	0.715		
4	0.004	Random model	0.924 (0.661–1.291)	0.643		
3	0.287	Fixed model	1.009 (0.843–1.209)	0.883		
2	0.142	Fixed model	1.099 (0.856–1.412)	0.395		
n model						
50	0.001	Random model	1.00 (0.971–1.030)	0.988	0.052	0.066
37	0.067	Fixed model	0.999 (0.977–1.022)	0.950		
9	0.186	Fixed model	1.022 (0.968–1.079)	0.428		
4	0.009	Random model	0.855 (0.742–0.985)	<0.001		
20	0.004	Random model	0.990 (0.943–1.040)	0.690		
21	0.017	Random model	1.015 (0.967–1.066)	0.547		
4	0.045	Random model	0.877 (0.691–1.113)	0.361		
3	0.653	Fixed model	1.025 (0.953–1.102)	0.507		
2	0.776	Fixed model	1.019 (0.931–1.115)	0.687		
	No. 20 21 4 3 2 n model 50 37 9 4 20 21 4 20 21 4 3 2 2 2 3 2 2 3 3 2 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 3 2 3 3 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3	No.         Pheterogneity           20         0.040           21         0.796           4         0.004           3         0.287           2         0.142           model         50           50         0.001           37         0.067           9         0.186           4         0.009           20         0.004           21         0.017           4         0.045           3         0.653           2         0.776	No.PheterogneityAnalysis model200.040Random model210.796Fixed model40.004Random model30.287Fixed model20.142Fixed model500.001Random model370.067Fixed model90.186Fixed model40.009Random model370.067Fixed model330.653Fixed model200.004Random model210.017Random model210.017Random model210.017Random model210.017Random model30.653Fixed model20.776Fixed model	No.         P <sub>heterogneity</sub> Analysis model         OR (95% Cl)           20         0.040         Random model         0.982 (0.902–1.069)           21         0.796         Fixed model         0.989 (0.919–1.064)           4         0.004         Random model         0.924 (0.661–1.291)           3         0.287         Fixed model         1.009 (0.843–1.209)           2         0.142         Fixed model         1.009 (0.856–1.412)           n model         50         0.001         Random model         0.999 (0.977–1.022)           9         0.186         Fixed model         1.002 (0.968–1.079)           4         0.009         Random model         0.999 (0.977–1.022)           9         0.186         Fixed model         1.022 (0.968–1.079)           4         0.009         Random model         0.855 (0.742–0.985)           20         0.004         Random model         0.855 (0.742–0.985)           20         0.004         Random model         1.015 (0.967–1.040)           21         0.017         Random model         0.877 (0.691–1.113)           3         0.653         Fixed model         1.025 (0.953–1.102)           2         0.776         Fixed model         1	No.         P <sub>heterogneity</sub> Analysis model         OR (95% Cl)         P           20         0.040         Random model         0.982 (0.902–1.069)         0.668           21         0.796         Fixed model         0.989 (0.919–1.064)         0.715           4         0.004         Random model         0.924 (0.661–1.291)         0.643           3         0.287         Fixed model         1.009 (0.843–1.209)         0.883           2         0.142         Fixed model         1.099 (0.856–1.412)         0.395           n model         50         0.001         Random model         0.999 (0.977–1.022)         0.950           9         0.186         Fixed model         1.002 (0.968–1.079)         0.428           4         0.009         Random model         0.855 (0.742–0.985)         <0.001	No.         P <sub>heterogneity</sub> Analysis model         OR (95% Cl)         P         P <sub>Begg/s</sub> 20         0.040         Random model         0.982 (0.902–1.069)         0.668           21         0.796         Fixed model         0.989 (0.919–1.064)         0.715           4         0.004         Random model         0.924 (0.661–1.291)         0.643           3         0.287         Fixed model         1.009 (0.843–1.209)         0.883           2         0.142         Fixed model         1.099 (0.856–1.412)         0.395           1         model         50         0.001         Random model         1.00 (0.971–1.030)         0.988         0.052           37         0.067         Fixed model         1.002 (0.968–1.079)         0.428         0.052           37         0.067         Fixed model         0.999 (0.977–1.022)         0.950         9           9         0.186         Fixed model         0.022 (0.968–1.079)         0.428         0.001           20         0.004         Random model         0.855 (0.742–0.985)         <0.001

Table 2 Main results of pooled ORs with 95% CI in the meta-analysis (Continued)

No. number of studies, OR odds ratio, 95% CI 95% confidence interval, HB hospital based study, PB population based study, FB family based study, CB community based study, H-CB hospital and community based study





the risk of CHD. We also observed no compelling evidence of an association between the KIF6 rs20455 SNP and CHD in multiple race/ethnic groups. These findings do not support the clinical utility of testing for the KIF6 rs20455 polymorphism in the primary prevention of CHD and indirectly question whether genotype information at this locus is able to identify subjects most likely to benefit from the use of statins.

#### Abbreviations

CHD: Coronary heart disease; CHS: Cardiovascular Health Study; Cl: Confidence interval; KIF6: Kinesin-like protein 6; OR: Odds ratio; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; SNPs: Single nucleotide polymorphisms; WHS: the Women's Health Study

# Acknowledgements

We thank all our colleagues of this present work.

# Funding

Not applicable.

## Availability of data and materials

Please contact author for data requests.

## Authors' contributions

YL, ZC, HS participated in the design of the study. YL, ZC, HS carried out the literature search and data extraction. YL, ZC, HS participated in the analysis of eligible data. YL, ZC, HS wrote the manuscript All authors read and approved the final manuscript.

#### **Ethics approval and consent to participate** Not applicable.

not applicable.

# Consent for publication

Not applicable.

#### **Competing interests**

The authors declare that they have no competing interests.

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# Received: 14 February 2017 Accepted: 25 December 2017 Published online: 05 January 2018

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