CD14 C-260T gene polymorphism and ischemic heart disease susceptibility: A HuGE review and meta-analysis

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Abstract: The *CD14* gene C-260T polymorphism has been reported to be associated with ischemic heart disease, but results were conflicting. To evaluate the role of the *CD14* C-260T polymorphism in ischemic heart disease, we performed meta-analyses of all available data. Comprehensive searches for studies on the association between the genotypes (CC, CT, TT) distributions and ischemic heart disease risk were performed. Patients with acute coronary syndrome, prior myocardial infarction, stable angina pectoris, or angiographic coronary artery stenosis were included. Potential sources of heterogeneity were explored by meta-regression. Analyses were performed under European, East Asian, and Indian studies, respectively. Data were available for 19 studies involving 11,813 cases and 6,196 controls. The summary odds ratio under the recessive model was 1.53 (95% confidence interval: 1.20–1.96) for East Asian studies published in English language journals on overall ischemic heart disease. Pooled odds ratios under the codominant model were about 1.81 (95% confidence interval: 1.36–2.40) and 1.70 (95% confidence interval: 1.26–2.29) for Chinese studies on overall ischemic heart disease and other ischemic heart disease (angina pectoris and angiographic coronary artery stenosis), respectively. No significant association was found in a European population, an Indian population, or the vulnerable plaque ischemic heart disease (acute coronary syndrome and prior myocardial infarction) subgroup of an East Asian population. It is probable that T allele and TT genotype are associated with ischemic heart disease in the East Asian population but not in the European or Indian populations. Further studies are warranted to assess these associations in greater details, especially in East Asian and Indian populations.
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Key Words: *CD14, ischemic heart disease, polymorphism, susceptibility, meta-analysis*

Atherosclerosis is a partly heritable disorder,[1] although the genes involved and the associated risks are still unclear.[2] Ischemic heart disease (IHD) is a group of diseases mainly caused by coronary atherosclerosis. It is widely accepted that inflammation and infection play a key role in atherosclerosis and IHD.[3–6] Immune cells are thought to be involved in many aspects related to IHD (e.g., lipoprotein retention and activation of oxidized low-density lipoprotein, plaque development and rupture) and dominate the atherosclerotic lesions.[6] Infection has also been reported to be involved in inflammation and plaque activation, thus infection affects the progressions of atherosclerosis and IHD and elicits clinical symptoms.[6] The *CD14* gene has been proposed as a susceptibility gene for IHD.[7] It is located on chromosome 5q31 and encodes CD14, a protein which is a component of lipopolysaccharide receptor complex mainly expressed by monocytes and macrophages.[8] By binding to lipopolysaccharide, CD14 mediates the activation of inflammatory cells and is thus involved in inflammatory reactions and contributes to the production of inflammatory mediators and cytokines.[9]

GENE VARIANT

Baldini et al.[10] first reported the existence of a single nucleotide polymorphism in the 5′ genomic region of *CD14* at position -260 (allele C and T) with respect to the translation start site (-159 when counting from the transcription start site) and found that the frequencies of the two alleles were similar in the white population from Tucson. The -260T allele was soon reported to be associated with myocardial infarction (MI).[7] The substitution of C → T leads to an increased transcriptional activity, which is paralleled by a decreased affinity of DNA/protein interactions between the Sp1, 2, 3 proteins and the GC box in the *CD14* promoter. This may be important for the pathogenesis of inflammatory diseases.[11] A higher expression of CD14 on the surface of monocytic lineage cells has been observed in TT homozygotes carriers.[7,10] All of these lead to the hypothesis that the increased activity of the *CD14* promoter results in a higher expression of CD14, hence triggers production of inflammatory cytokines and increases IHD risk.

OBJECTIVES

Many studies have been carried out to investigate the association between the *CD14* C-260T polymorphism and IHD risk, but the results were inconsistent. This may be partly because of small sample size, different IHD endpoints (e.g., MI and angiographic coronary artery stenosis [CAS]), and different populations (e.g., European, East Asian, and others). Demonstration of an association may require a much larger number of subjects, which may be beyond the resources of one single study site. IHD continues to be the leading cause of morbidity and mortality worldwide, affecting about 9.4% US white men, 6.0% US white women, 3.8% Asians, and 2.5% American Indians.[12] We thus conducted meta-analyses of all available data in accordance with the guidelines of the Human Genome Epidemiology Network (HuGENet™)[13,14] to clarify the role of the *CD14* C-260T polymorphism in IHD. To help elucidate the gene effect

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in different ethnicities, we performed the analyses based on ethnicities.[15]

METHOD

Selection criteria

For inclusion, studies had to be case-controlled or cohort in design, use proper IHD diagnosis criteria (e.g., angiographically confirmed; elevations of cardiac enzymes, changes of electrocardiographic and clinical symptoms according to the World Health Organizations criteria; a documented history of coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or percutaneous coronary intervention), involve unrelated participants, and examine the association between IHD and the presence of *CD14* C-260T polymorphism. IHD was defined as acute coronary syndrome (ACS), prior MI, stable angina pectoris (AP), and angiographic CAS.[16–18] If essential information of a study was not presented, authors were contacted for details. The study would be excluded if the information could not be obtained.

Search strategy

All studies reporting the association between the *CD14* C-260T polymorphism and IHD risk published before December 2008 were identified by comprehensive computer-based searches of Medline, EMBase, BIOSIS, Global Health, LILACS (http://bases.bireme.br), CBMDisc (http://cbmwww.imicams.ac.cn), and HuGENet.[19] Terms used for the searches were "*CD14*," "ischemic heart disease," "coronary heart disease," "coronary artery disease," "acute coronary syndrome," "myocardial infarction," and "angina pectoris," combined with "gene," "genetic," "variant," "mutation," or "polymorphism." Hand searches for related articles were also performed.

Data extraction

The first author, published year, country, populations, mean age of participants, study design, sample size, outcome, diagnostic criteria, genotyping method, characteristics of the controls, allele frequencies, genotype distributions, and cardiovascular risk factors were extracted independently by two authors (H.-F.Z. and B.-L.Z.). Results were then compared, and disagreements were resolved by discussion.

Quality score assessment

The quality of included studies was assessed independently by the same two authors using modified quality assessment scores reported previously.[20] Dissensions were resolved by discussion. Scores ranged from 0 (lowest) to 13 (highest).

Statistical analysis

First, deviance from Hardy-Weinberg equilibrium (HWE) was assessed for the controls of each study using Fisher's exact test. Second, genotype distributions of controls were used to estimate the frequency of the putative risk allele (-260T) in various ethnic groups (if the ethnicity of participants was not indicated in the study, ethnicity was assumed according to geographical location from which the participants were recruited) using the inverse variance method.[20] Third, estimation of the gene effect on IHD was performed by a logistic regression approach described previously.[21] Briefly, a Cochrane Q-test[22] for heterogeneity with a significance level of $P < 0.1$ rather than 0.05 was used separately for three odds ratios (ORs): TT versus CC (OR_1), CT versus CC (OR_2), and TT versus CT (OR_3). If there was heterogeneity on at least one of the three ORs, the sources of heterogeneity were explored by fitting a covariable (e.g., ethnicity, sample size, published language, outcome, or quality score) in the meta-regression model.[23–25] If there was no heterogeneity, logistic regression with the fixed-effects model was used to evaluate the overall gene effect; or else, the random-effects model was used. A likelihood ratio (LR) test, but not the three ORs, was used to estimate whether the overall gene effect was significant. If a significant overall gene effect was observed, further comparisons of OR_1, OR_2, and OR_3 were made and the indicated genetic models were selected as follows:

1. Dominant model if $OR_1 = OR_2 \neq 1$ and $OR_3 = 1$.
2. Recessive model if $OR_1 = OR_3 \neq 1$ and $OR_2 = 1$.
3. Overdominant model if $OR_2 = 1/OR_3 \neq 1$ and $OR_1 = 1$.
4. Codominant model if $OR_1 > OR_2 > 1$ and $OR_1 > OR_3 > 1$ (or $OR_1 < OR_2 < 1$ and $OR_1 < OR3 < 1$).

Finally, once the appropriate genetic model was identified, results were pooled again under this genetic model.

Publication bias was assessed using Egger's test.[26] In addition, subgroup analysis based on whether the IHD was related to vulnerable plaque or not was performed.[27–29] ACS and prior MI were defined as vulnerable plaque IHD, whereas AP and angiographic CAS were indicated as other IHD.[27–29] Sensitivity analysis was carried out by including studies that deviated from HWE.

All analyses were performed using STATA software, version 9.2 (StataCorp. 2005. Stata Statistical Software: Release 9. College Station, TX: StataCorp LP).

RESULTS

Study inclusion and characteristics

The combined searches yielded 603 records. Of the 603, 531 were excluded by reading titles and abstracts. Finally, 19 studies were included.[7,27,30–46] One Chinese study[47] met the inclusion criteria but was excluded, because the author obviously misunderstood the locus and no additional information could be obtained by contacting authors. One European study[7] was used only for sensitivity analysis because both the cases and the controls in this study might overlap with the latter study by Lorenzova et al.,[45] which had a larger sample size.[7,45,48]

All the included studies used either case-control or nested case-control design. ACS, prior MI, AP, and angiographic CAS cases were included. Appropriate diagnosis criteria and proper genotyping methods were used in most of the studies. Of the 19 studies, 11 involved European populations,[7,30–34,36,38,39,41,45] one involved an Indian population,[43] and seven involved East Asian populations,[27,35,37,40,42,44,46] of which five were published in Chinese journals.[37,40,42,44,46] Fourteen studies involved vulnerable plaque IHD patients. Of the 14, 10 included European populations,[7,30–32,34,36,38,39,41,45] one included an Indian population,[43] and three included East Asian populations,[27,35,40] of which one was published in a Chinese journal.[40] Twelve studies involved other IHD cases, including six involving European populations[30,32–34,38,39] and six involving East Asian populations,[27,37,40,42,44,46] of which five were published in Chinese journals.[37,40,42,44,46] Genotype distributions deviated from HWE in one study.[42] The characteristics of included studies are listed in Table 1, and the sources of participants, as well as the geographic location of the studies, are listed in **Supplemental Table, Supplemental Digital Content 1**, http://links.lww.com/A842.

Table 1 Characteristics of eligible studies in the meta-analysis

			Cases				Control						
				Genotypes				Genotypes			HWE		
Study	Country	Design	*N*	CC	CT	TT	*N*	CC	CT	TT	*P*	Outcome	Score
European													
Zee et al.[31]	America	NCC	387	98	215	74	387	108	193	86	1.00	MI	12
Hubacek et al.[7a]	CZ	CC	178	52	77	49	135	61	53	21	0.13	MI	6
Lorenzova et al.[45]	CZ	CC	230	63	116	51	562	166	268	128	0.35	AMI	4
Espliguro et al.[39]	England	CC	334	79	163	92	94	31	42	21	0.40	ACS, CSA	12
Morange et al.[41]	England	CC	54	12	28	14	70	24	31	15	0.47	MI	8
Morange et al.[41]	FR	CC	99	20	57	22	121	29	53	39	0.20	MI	8
Morange et al.[38]	FR, NIE	NCC	128	43	59	26	253	69	113	71	0.10	MI	13
Morange et al.[38]	FR, NIE	NCC	123	31	58	34	243	61	124	58	0.80	AP	13
Unkelback et al.[30]	Germany	CC	1727	491	864	372	501	140	240	121	0.37	MI, CAD	12
Koch et al.[32]	Germany	CC	1791	505	888	398	340	88	177	75	0.51	MI, CAD	12
Koenig et al.[33]	Germany	CC	312	75	164	73	476	126	243	107	0.65	CAD	11
Nauck et al.[34]	Germany	NCC	4158	1119	2020	1019	697	188	358	151	0.45	MI, CAD	8
Longobardo et al.[36]	Italy	CC	215	44	101	70	215	55	101	59	0.41	AMI	12
Morange et al.[41]	Italy	CC	194	42	98	54	197	39	104	54	0.47	MI	8
Morange et al.[41]	Sweden	CC	179	60	94	25	176	65	77	34	0.21	MI	8
Subtotal			10,109	2734	5002	2373	4467	1250	2177	1040			
East Asian													
Shimada et al.[27]	Japan	CC	128	27	49	52	83	21	43	19	0.83	AMI, AP	9
Hohda et al.[35]	Japan	CC	502	97	242	163	527	115	278	134	0.22	MI	8
Pan et al.[37b]	PRC	CC	50	14	21	15	90	45	31	14	0.05	CAD	5
Li et al.[40b]	PRC	CC	162	24	75	63	196	54	89	53	0.20	MI, CAD	8
Hu et al.[42b]	PRC	CC	218	48	57	113	227	117	39	71	<0.01	CAD	5
Li et al.[44b]	PRC	CC	193	29	95	69	225	47	124	54	0.14	CAD	5
Xie et al.[46b]	PRC	CC	241	49	127	65	149	56	65	28	0.24	CAD	5
Subtotal			1494	288	684	540	1497	455	669	373			
Indian													
Banerjee et al.[43]	India	CC	210	45	116	49	232	38	126	68	0.14	MI, UA	7
Total			11,813	3067	5802	2962	6196	1743	2972	1481			

[a]The study was used in sensitivity analysis.
[b]These articles were published in Chinese.
N, sample size; HWE, Hardy-Weinberg Equilibrium; CC, case-control; NCC, nested case-control; MI, myocardial infarction; CAD, coronary artery disease; AMI, acute myocardial infarction; ACS, acute coronary syndrome; CSA, chronic stable angina; AP, angina pectoris; UA, unstable angina; CZ, Czech Republic; FR, France; NIE, Northern Ireland; PRC, People's Republic of China.

Pooled prevalence of CD14-260T in the controls

The -260T allele frequency could be obtained in all included studies. Two European studies reported two[38] and four subgroups[41] containing different control subjects, respectively.

There was no heterogeneity among the 10 European population studies ($\chi^2_{13} = 11.01$, $P = 0.61$). The pooled frequency using the fixed-effects model was 48.03% (95% confidence interval [CI]: 46.54–49.51%); a sensitivity analysis including the study by Hubacek et al.[7] showed a similar result (47.60% [95% CI: 46.14–49.07]). The pooled -260T frequencies were 46.88% (95% CI: 41.41–52.36%), 51.39% (95% CI: 47.43–55.36%), and 45.70% (95% CI: 36.48–52.62%) for overall East Asian studies (random-effects model; $\chi^2_5 = 17.21$, $P < 0.01$), East Asian studies published in English language journals[27,35] (fixed-effects model; $\chi^2_1 = 0.26$, $P = 0.61$) and Chinese studies[37,40,44,46] (random-effects model; $\chi^2_3 = 12.80$, $P < 0.01$),

respectively. An inclusion of the study by Hu et al.[42] did not change the result significantly. The -260T allele frequency was 56.47% (95% CI: 50.09–62.85%) in Indian population.[43]

Association between *CD14* C-260T polymorphism and IHD risk

Meta-analysis of European studies

All included studies reported the association between genotype distributions and IHD risk. The summary $OR_1/OR_2/OR_3$ and Q-test results are listed in Table 2. No significant heterogeneity for OR_1, OR_2, or OR_3 was detected among the 10 European descent studies. The logistic regression with the fixed-effects model comprised 14,263 subjects yielded a nonsignificant overall gene effect ($LR_2 = 0.85$, $P = 0.66$), indicating no association between the polymorphism and IHD risk in this population. Egger's test showed that publication bias was significant for OR_2 but not for OR_1 or OR_3 ($P = 0.75$ for OR_1; $P = 0.04$ for OR_2 and $P = 0.16$ for OR_3). A sensitivity analysis including the study by Hubacek et al.[7] involving 14,576 subjects did not change the results significantly (data not shown).

An initial analysis of a vulnerable plaque IHD subgroup including 10 European studies involving 8738 subjects yielded homogenous results (Table 2). The logistic regression with the fixed-effects model showed a nonsignificant overall gene effect ($LR_2 = 0.33$, $P = 0.85$), indicating no association between the polymorphism and vulnerable plaque IHD. An inclusion of the study[7] showed very similar results (data not shown). A meta-analysis of other IHD subgroup including six studies involving 7157 subjects showed a similar outcome ($LR_2 = 0.17$, $P = 0.92$).

Meta-analysis of East Asian studies

A Q-test of the six East Asian studies in HWE[27,35,37,40,44,46] including 2546 subjects, showed a significant heterogeneity and published language was found to be the source of it (Q-test for OR_1, $P = 0.27$; Q-test for OR_2, $P = 0.05$, meta-regression $P < 0.01$; Q-test for OR_3, $P = 0.67$). We further performed subgroup analyses of English or Chinese studies. A meta-analysis of the two English studies[27,35] including 1240 subjects showed a significant overall gene effect ($LR_2 = 11.46$, $P < 0.01$). The estimated OR_1, OR_2, and OR_3 suggested a recessive model (Table 2). The pooled OR under this genetic model indicated that East Asians who had the TT genotype were about 53% more likely to have IHD (Table 2). A meta-analysis of the four Chinese studies involving 1306 subjects showed a significant overall gene effect ($LR_2 = 36.54$, $P < 0.01$). The estimated ORs (Table 2) implied a codominant model. The pooled OR under this genetic model indicated that both TT and CT genotypes conferred increased susceptibility to the disease (Table 2). A sensitivity analysis including the study[41] that deviated from HWE did not change the results significantly (data not shown).

A Q-test of the two East Asian studies published in English language journals on vulnerable plaque IHD[27,35] involving 1193 subjects showed a significant heterogeneity (Table 2) and the

Table 2 Estimated ORs for *CD14* polymorphism and ischemic heart disease risk

	ORs (95% CI)			*P* value of Q-test for ORs			
Population	OR_1	OR_2	OR_3	OR_1	OR_2	OR_3	OR under indicating Genetic model
Overall IHD							
European	1.03 (0.92–1.15)	1.05 (0.95–1.15)	0.98 (0.89–1.09)	0.43	0.56	0.23	NS
	1.06 (0.95–1.19)[a]	1.07 (0.97–1.17)[a]	1.00 (0.90–1.10)[a]	0.07[a]	0.37[a]	0.18[a]	NS[a]
	1.54 (1.12–2.12)[b]	1.01 (0.76–1.35)[b]	1.53 (1.17–1.98)[b]	0.37[b]	0.70[b]	0.14[b]	1.53 (1.20–1.96), $P < 0.01$[b,c]
East Asian	2.63 (1.91–3.61)[d]	1.81 (1.36–2.41)[d]	1.45 (1.11–1.89)[d]	0.81[d]	0.42[d]	0.81[d]	TT vs CC: 2.53 (1.84–3.50), $P < 0.01$[d,e]
							CT vs CC: 1.81 (1.36–2.40), $P < 0.01$[d,e]
Vulnerable plaque IHD							
European	1.02 (0.90–1.16)	1.03 (0.93–1.15)	0.99 (0.89–1.11)	0.25	0.39	0.12	NS
	1.06 (0.94–1.20)[a]	1.06 (0.95–1.17)[a]	1.01 (0.90–1.12)[a]	0.03[a]	0.23[a]	0.09[a]	NS[a]
East Asian	1.60 (1.16–2.12)[b]	0.98 (0.73–1.32)[b]	1.63 (1.25–2.13)[b]	0.17[b]	0.27[b]	<0.01[b]	NS
Other IHD							
European	1.03 (0.89–1.20)	1.01 (0.89–1.14)	1.02 (0.90–1.17)	0.46	0.57	0.21	NS
East Asian	2.46 (1.75–3.46)[d]	1.71 (1.27–2.31)[d]	1.44 (1.08–1.92)[d]	0.72[d]	0.35[d]	0.81[d]	TT vs CC: 2.35 (1.68–3.31), $P < 0.01$[d,e]
							CT vs CC: 1.70 (1.26–2.29), $P < 0.01$[d,e]

Other IHD including stable angina pectoris and angiographic coronary artery stenosis.
[a]Sensitivity analysis by including the study by Hubacek et al.[7]
[b]Included studies were published in English journals.
[c]Pooled OR by recessive model.
[d]Included studies were published in Chinese journals.
[e]Pooled OR by codominant model.
OR, odds ratio; NS, overall gene effect is not significant by LR-test; IHD, ischemic heart disease.

logistic regression with the random-effects model showed a nonsignificant overall gene effect, but the Chinese study[39] on vulnerable plaque IHD reported a significant difference. The four Chinese studies[37,40,44,46] on other IHD involving 1210 subjects showed a homogenous result (Table 2) and the logistic regression with the fixed-effects model showed a significant overall gene effect ($LR_2 = 27.97$, $P < 0.01$). The pooled ORs (Table 2) indicated a codominant model. The estimated OR under this genetic model indicated that both TT and CT genotypes were associated with IHD risk (Table 2). An inclusion of the study[42] that deviated from HWE did not change the result significantly (data not shown). However, the English study on other IHD showed a nonsignificant result.[27]

DISCUSSION

A large number of studies have been carried out to test the hypothesis that the *CD14* C-260T polymorphism might be associated with the risk of IHD, but data have yielded conflicting results. There is concern that a positive association might be spurious; on the other hand that a negative result might be due to a small sample size. To produce a more precise result, we explored sources of heterogeneity by meta-regression and performed meta-analyses in various populations to evaluate the association between the polymorphism and IHD risk.

Population stratification because of ethnicities may lead to inconsistency, especially when both allele frequencies and incidence rates of the diseases vary across ethnic groups.[49] In the present study, results from populations with different genetic backgrounds were not the same. The combinations of the European studies showed nonsignificant results. We further found that the genotype distributions between the cases and the controls were almost the same (proportions of CC, CT, and TT were 26.88%, 49.60%, 23.18% and 27.24%, 49.02%, 23.35%, respectively, for cases and controls) in this population. This indicates that the *CD14* C(-260)T polymorphism might be of little importance for clinical practice and public health. The use of this polymorphism as a predictor for the risk of IHD may not be efficient and the screening utility of this genetic variant in asymptomatic individuals may not be warranted in European population. Results from East Asian studies were distinct and the pooled *CD14*-260T allele frequency of the controls showed a modest difference across ethnicities (European studies: 48.03%; East Asian studies published in English language journals: 51.39%; Chinese studies: 45.70%; Indian study: 56.47%). These may be explained by the different genetic backgrounds across ethnicities or a much smaller sample size in the East Asian and Indian studies.

Evidence of heterogeneity was found among East Asian studies and genetic backgrounds may not account for it.[15] Published language was found to be the main source and a larger genetic effect was observed in most Chinese studies. Besides the small sample size, the plausible explanations may be that there is a publication bias in favor of positive results, selection bias in pursuing a significant finding for which the Chinese language may be a marker[50]; on the other hand, there may be differences in methods for selecting controls used in these studies.[35,37,40,42,44,46] Subgroup analysis of English or Chinese studies indicated that the -260T allele was associated with overall IHD risk. However, there is chance, because of a relatively small sample size and publication bias[50] this might lead to spurious results. The indicated genetic models[21] were also different between English and Chinese studies involving East Asian subjects, for which the publication bias[50] and relative small sample size may account. Interestingly, heterogeneity was not found in the analysis of overall IHD but was observed in the subgroup analysis of vulnerable plaque IHD of the two East Asian studies published in English language journals. This might be explained by the much smaller sample size of the study.[27] Results from East Asian studies published in English language journals on overall IHD and vulnerable plaque IHD were also different, which was probably because the random-effects model produced a more conservative result. Therefore, given that a combination of heterogeneous studies may lead to a less clear result,[22] the potential risk of publication bias may lead to a deviation from the true effect size[50–54] and the relative small sample, results drawn from the East Asian studies should be interpreted with caution.

Evidence of publication bias was significant for OR_2 but not for OR_1 or OR_3 among European studies. Many have argued that Egger's test[26] has been likely to yield a false-positive result because of high type I error rate, especially when used for a binary outcome with a larger OR.[55] Moreover, we further explored publication bias for all genetic models using Egger's test, and found that it was significant for the dominant model with a larger OR but not for the other genetic models with smaller ORs (data not shown). Therefore, the evidence of publication bias by Egger's test was probably false-positive.

Some limitations of the meta-analyses should be considered. First, the phenotypes that could be affected by both the low-penetrance susceptibility gene[56] and other risk factors of IHD (e.g., environment factors) might not be the same even though the genotypes were the same and this might lead to the misclassification bias.[56,57] Second, the relatively small sample size, representativeness of controls, potential heterogeneity, and publication bias might affect results drawn from East Asian studies; in addition, there was only one study with a relatively small sample size involving an Indian population. Third, there might be eligible studies that were not published, not indexed by electronic databases, or published in the journals we did not cover. Lastly, a lack of individual participants' data has restricted further adjustments by other covariables, such as specific outcome, sex, smoking, diabetes, dyslipidemia, etc.

Despite limitations, the present study has suggested a possible association between the *CD14* C-260T polymorphism and IHD risk in an East Asian population but not in European and Indian populations. In addition, there is a need for larger and more rigorous studies than is now customary, and a need to support the publication of negative results. There is also a greater need for updated genetic epidemiology quantitative systematic reviews with proper methodology,[13] to help minimize random error, explore heterogeneity, address publication bias and enhance statistical power; thereby helping to better understand the association between the *CD14* C-260T polymorphism and IHD risk.

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