Original Article

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Apolipoprotein A5 polymorphisms and risk of coronary artery disease: A meta-analysis

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Summary **The relation has not been reported consistently between the polymorphisms in the gene of apolipoprotein A5 (APO A5) and coronary artery disease (CAD). To clarify the discrepancy, we conducted a comprehensive search of PubMed and EMBASE for all available case-control studies to explore the association between two APO A5 polymorphisms and CAD. Two reviewers independently selected studies. Statistical analyses were carried out using the STATA software package v 10.0. Thirteen studies investigated the association between the APO A5 -1131T>C polymorphism and risk of CAD were selected in this meta-analysis with 5,050 cases and 7,272 controls. For the S19W APO A5 gene polymorphism, 5 studies were included with 2,196 cases and 3,933 controls. We observed a significant statistical association between Apo A5 -1131T>C polymorphism and CAD (recessive genetic model: OR = 1.73, 95% CI = 1.37-2.19; dominant genetic model: OR = 1.42, 95% CI = 1.25-1.61; allelic contrast: OR = 1.31, 95% CI = 1.22-1.39, respectively). After restricting our analysis to Chinese individuals, we found that the association was stronger. We also observed strong association between the APO A5 S19>W polymorphism and risk of CAD under a recessive genetic model. This meta-analysis reveals that the minor allele of the -1131T>C polymorphism in the promoter of APO A5 gene significantly increases the susceptibility to CAD. This effect is more pronounced in Chinese subjects.**

Keywords: Meta-analysis, gene polymorphism, coronary artery disease, apolipoprotein A5

1. Introduction

Coronary artery disease (CAD) is the leading cause of death and disability, which is believed to have a multifactorial genetic basis involving a number of genes and environmental factors that interact to contribute towards individual susceptibility (*1*). Epidemiological and clinical studies have shown that increased triglyceride (TG) concentrations are an independent risk factor of CAD (*2,3*). TG levels may be altered by a variety of genetic and environmental factors, and twin studies have also shown a strong genetic contribution to TG levels (*4*). Apolipoprotein gene cluster APOA1/C3/A4/A5 on chromosome 11q23 plays a pivotal role in TG metabolism (*5*), and apolipoprotein A5 (APO A5) has emerged as an important modulator of serum TG concentration (*6*). The APO A5 protein is predominantly synthesized in the liver. Overexpression of the APO A5 gene in mice resulted in elevated levels of plasma APO A5 and a marked decrease in plasma TG concentration. A 4-fold increase of serum TG levels can be found in the APO A5 knockout mice (*6,7*). In humans, variations of the

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APO A5 gene have been found to be associated with serum TG concentrations across ethnic groups (*8-10*).

APO A5 -1131T>C and S19W polymorphisms have been reported to be associated with an increased risk of CAD in multiple ethnic populations probably through its association with hypertriglyceridemia (*11-14*). However, there are also discrepant reports of no association between APO A5 -1131T>C and S19W polymorphisms and CAD risk (*15-17*). Therefore, the relation between APO A5 -1131T>C and S19W polymorphisms and risk of CAD remains controversial. To elucidate this discrepancy, we performed a meta-analysis of all available case-control studies to explore the association between the APO A5 polymorphisms and risk of CAD.

2. Materials and Methods

2.1. *Study Selection*

To identify all the articles that examined association of APO A5 polymorphisms with coronary artery disease, we conducted a comprehensive search of PubMed and EMBASE (the last searching update was May 28, 2011). Search terms included *apolipoprotein A-V or apolipoprotein AV or apolipoprotein A5 or APOAV or APOA-V or APO A5; gene, polymorphism, or genetic variant; and myocardial infarct, myocardial infarction, coronary artery disease, coronary heart disease, myocardial ischemia, ischemic heart disease, angina, acute coronary syndrome, acute coronary syndromes, ACS, coronary calcification, coronary flow reserve, ischemic heart failure, heart failure, or ischemic cardiomyopathy*. We also screened references of the retrieved articles and review articles by a hand search.

Eligible studies were included that fulfilled the following criteria: (i) association studies using an unrelated case-control design; (ii) complete data with genotype and allele frequencies. Cases were CAD, with the diagnosis based on angiographic or clinical criteria. Data from a study presented only in the form of an abstract and duplication studies were not included. Studies without genotype frequency were not included if the relevant information could not be obtained from the authors.

2.2. *Data extraction*

For each study, that met our criteria, the following information was collected: first author, year of publication, country of origin, ethnicity, criteria of diagnosis, number of cases and controls, genotype distribution, genotyping methods and allele frequency. All the searching work and data extraction work were conducted by two independent investigators (Zhang and Peng), and they reached a consensus on all items.

2.3. *Statistical analysis*

The strength of association between APO A5 polymorphisms and CAD was measured by odds ratio (OR) corresponding to a 95% confidence interval (CI) according to the method of Woolf (*18*). Heterogeneity between studies was assessed by Cochran's χ^2-based Q statistic test (*19*). Where *p*-value for heterogeneity was less than 0.05, a random-effects model using the DerSimonian and Laird method (*20*) was used to pool the results; otherwise, a fixed-effects model using the Mantel-Haenszel method was adopted (*21*). In order to better evaluate the extent of heterogeneity between studies, the I^2 test was also used. This statistic yields results ranged from 0 to 100% (I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2 = 50-75%, large heterogeneity; I^2 = 75-100%, extreme heterogeneity) (*22*). For the APO A5 -1131T>C promoter polymorphism, we investigated associations between the genetic variant and coronary artery disease risk in a recessive genetic model (C/C *vs.* C/T + T/T), dominant genetic model (C/C + C/T *vs.* T/T) and allelic contrast (C *vs.* T). For the APO A5 S19>W polymorphism, we investigated associations between the genetic variant and coronary artery disease risk in a recessive genetic model (W/W *vs.* W/S + S/S), dominant genetic model (W/W + W/S *vs.* S/S) and allelic contrast (W *vs.* S). The significance of the pooled OR was determined by the Z-test ($p < 0.05$ suggests a significant association).

Hardy-Weinberg equilibrium (HWE) was tested by χ^2 test at a significant level of $\alpha < 0.05$. Publication bias was investigated by funnel plots (*23*) and by Egger's linear regression test (*24*).

To examine specific subsets in these studies, separate analyses were used. A sensitivity analysis was performed to assess the influence of each study in which an individual study was removed each time. Likewise, a cumulative analysis was performed according to the ascending date of publication to identify influence of the first published study on subsequent publications and evolution of the combined estimates over time (*25*). Statistical analyses were all carried out using the STATA software package v 10.0 (Stata Corporation, College Station, TX). All *p*-values were two sided.

3. Results

3.1. *Study characteristics*

One hundred and thirty-three eligible studies were identified by our search strategy. One hundred and eight studies were excluded after title and abstract screening using the predefined inclusion and exclusion criteria. Then full text articles were retrieved for assessment in detail. In the end, 13 studies which investigated the association between the APO A5 -1131T>C

polymorphism and risk of CAD were selected in this meta-analysis with 5,050 cases and 7,272 controls (*11,12,14,16,17,26-33*). For the S19W APOA5 gene polymorphisms, 5 studies were included in the meta-analysis with 2,196 cases and 3,933 controls (*14,16, 17,27,34*). Characteristics of included studies are summarized in Table 1 and Table 2. Polymerase chain reaction-restriction fragment length polymorphism was the most commonly used genotyping method in these studies.

3.2. *Main Results, Sensitivity, and Cumulative Analyses*

For the APO A5 -1131T>C polymorphism and its relationship to CAD, significant heterogeneity was found under the recessive genetic model (I^2 = 52.2%, p = 0.014), and dominant genetic model (I^2 = 51.6%, p = 0.016). Therefore, the random-effects model (DerSimonian and Laird) was applied. No significant heterogeneity was found under allelic contrast (I^2 = 26.4%, p = 0.177) by the Mantel-Haenszel fixed effects model.

Significant statistical association was observed between the APO A5 -1131T>C polymorphism and CAD under the recessive genetic model (C/C *vs.* C/T + T/T, OR = 1.73, 95% CI = 1.37-2.19) (Figure 1). The same overall patterns were also observed under the dominant genetic model (C/C + C/T *vs.* T/T, OR = 1.42, 95% CI = 1.25-1.61) (Figure 2) and allelic contrast (C *vs.* T, OR = 1.31, 95% CI = 1.22-1.39) (data not shown).

After restricting our analysis to Chinese individuals, associations were found stronger under the recessive genetic model (C/C *vs.* C/T + T/T, OR = 1.84, 95% CI = 1.47-2.30) and allelic contrast (C *vs.* T, OR = 1.39, 95% CI = 1.21-1.60) (data not shown).

When stratified by status of HWE (the presence or absence of HWE in controls), no significant heterogeneity was found under the recessive genetic model (presence of HWE: I^2 = 26.5%, p = 0.192; absence of HWE: I^2 = 0%, p = 0.376) in both groups, and the positive association still existed (data not shown). The same patterns were also observed under the dominant genetic model (data not shown).

To investigate the influence of individual data of the APO A5 -1131T>C polymorphism sets on the pooled ORs, we deleted a single study involved in the meta-analysis each time. No individual study had an undue influence on the summary ORs under the recessive genetic model, dominant genetic model or allelic contrast (Table 3). We also performed a cumulative meta-analysis to identify the influence of the initial study on the subsequent publications. The influential role of the study of Bi *et al*. (*11*) was obvious in the cumulative random effects meta-analysis under the recessive genetic model, and the study of Hubacek *et al.* (*27*) was obvious under the dominant genetic model (Table 3).

For the APO A5 S19>W polymorphism and its relationship to CAD, significant heterogeneity was found under the dominant genetic model (I^2 = 76.3%, p = 0.002) and allelic contrast (I^2 = 75.7%, p = 0.002), but not found under the recessive genetic model (I^2 = 76.3%, p = 0.002). We observed no statistical association between APO A5 S19>W polymorphism and risk of CAD under the dominant genetic model (W/W + W/S *vs.* S/S, OR = 1.23, 95% CI = 0.76-2.00) and allelic contrast (W *vs.* S, OR = 1.30, 95% CI = 0.83-2.05), but strong association under the recessive genetic model (W/W *vs.* W/S + S/S, OR = 6.39, 95% CI = 2.68-15.24).

3.3. *Publication bias*

For the APO A5 -1131T>C polymorphism, the shape of funnel plots showed no obvious asymmetry and the result of the Egger's test did not show statistical evidence for bias either (Figure 3). For the APO A5 S19>W polymorphism, no publication bias was detected (data not shown).

4. Discussion

To the authors' knowledge, this is the first meta-analysis investigating the association between the APO A5 polymorphisms and CAD. In the present study, the effect of allele frequency and the effects of the dominant and recessive models were estimated. This meta-analysis reveals that the minor allele frequency of the -1131T>C polymorphism in the promoter of the APO A5 gene significantly increased the susceptibility for CAD. This effect was more pronounced in Chinese subjects.

The APO A5 -1131T>C polymorphism has been reported to be associated with the risk of CAD. This association has been shown to be mediated by TG levels in human studies. Bi *et al.* (*11*) found that CC homozygotes had approximately a twofold CAD risk compared with subjects with the TT genotype and the -1131C allele was correlated with increased levels of plasma TG in Chinese subjects. In a recent study, Jang *et al.* (*32*) reported that the homozygosity of the -1131C allele was associated with 47% higher TG as compared with TT subjects in Korean CAD patients. Similarly, our findings suggest that there is a modest association between the APO A5 -1131T>C polymorphism and CAD (recessive genetic model: OR = 1.73, 95% CI = 1.37-2.19; dominant genetic model: OR = 1.42, 95% CI = 1.25-1.61; allelic contrast: OR = 1.31, 95% CI = 1.22-1.39, respectively). In a recent meta-analysis of the association of the APO A5 -1131T>C polymorphism and fasting blood lipids, Zhao *et al*. found a strong association of the APO A5 -1131 T>C polymorphism with higher levels of TG (*35*). The -1131T>C polymorphism is located in the promoter

Table 1. Characteristics of included studies of APO A5 -1131T>C polymorphism

Author	Year	Population	Average age		Gender component*	Number of sample			Genotypes for Cases, *n*			Genotypes for Controls, *n*			Frequency of C Allele		HWE in Control	
			Case	Control		Case	Control	Total	TT	TC	CC	TT	TC	CC	Case	Control	χ^2	*p*
Bi *et al.* (*11*)	2004	Chinese	60.2	58.9	209/103/191/126	312	317	629	108	159	45	136	151	30	0.399	0.333	1.671	0.196
Hubacek *et al.* (*27*)	2004	Caucasians	55.1	49.0	435/0/1,191/1368	435	2,559	2,994	366	46	23	2,164	355	40	0.106	0.085	29.905	0.000
Szalai *et al.* (*12*)	2004	Hungarian	57.5	58.5	236/72/235/75	308	310	618	248	53	7	277	31	2	0.109	0.056	1.165	0.281
Liu *et al.* (*14*)	2005	Chinese	54.2	54.4	285/198/276/226	483	502	985	181	226	76	246	212	44	0.391	0.299	0.031	0.861
Tang *et al.* (*28*)	2005	Chinese	63.6	60.9	158/77/163/99	235	262	497	80	120	35	107	130	25	0.404	0.344	2.627	0.105
Yan *et al.* (*29*)	2005	Chinese	65.0	52.0	46/67/70/85	113	155	268	41	60	12	83	58	14	0.372	0.277	0.689	0.407
Hsu *et al.* (*26*)	2006	Chinese	61.6	61.0	161/50/242/75	211	317	528	104	83	24	145	156	16	0.310	0.297	10.221	0.001
Yu *et al.* (*30*)	2007	Chinese	52.1	51.5	94/46/97/59	140	156	296	46	67	27	67	75	14	0.432	0.330	1.181	0.277
Martinelli *et al.* (*17*)	2007	Italian	60.7	58.7	544/125/168/76	669	244	913	545	118	6	204	37	3	0.097	0.088	0.776	0.378
Jang *et al.* (*32*)	2009	Korean	55.2	55.2	665/76/6,65/76	741	741	1,482	320	343	78	382	295	64	0.337	0.285	0.428	0.513
Ashokkumar *et al.* (*31*)	2009	Indian	53.2	53.6	322/94/315/101	416	416	832	191	183	42	239	155	22	0.321	0.239	0.235	0.628
Prochaska *et al.* (*16*)	2010	Brazilian	60.1	58.3	112/68/95/75	180	170	350	150	27	3	147	22	1	0.092	0.071	0.032	0.858
Park *et al.* (*33*)	2010	Korean	56.9	56.1	658/149/880/243	807	1,123	1,930	363	367	77	566	455	102	0.323	0.293	0.587	0.444

*Gender component: number of male cases/number of female cases/number of male controls/number of female controls.

Table 2. Characteristics of included studies of APO A5 S19>W polymorphism

Author	Year	Population	Average age		Gender component*	Number of sample			Genotypes for Cases, *n*			Genotypes for Controls, *n*			Frequency of W Allele		HWE in Control	
			Case	Control		Case	Control	Total	SS	SW	WW	SS	SW	WW	Case	Control	χ^2	*p*
Hubacek *et al.* (*27*)	2004	Caucasians	55.1	49	435/0/1191/1,368	435	2,559	2,994	369	56	10	2,198	352	9	0.087	0.072	1.66	0.197
Liu *et al.* (*14*)	2005	Chinese	54.2	54.4	285/198/276/226	483	502	985	439	43	1	502	0	0	0.047	0	-	-
Dallongeville *et al.* (*34*)	2006	French	-	-	429/0/458/0	429	458	887	368	56	5	414	44	0	0.077	0.048	1.17	0.28
Martinelli *et al.* (*17*)	2007	Italian	60.7	58.7	544/125/168/76	669	244	913	605	59	5	219	25	0	0.052	0.051	0.71	0.399
Prochaska *et al.* (*16*)	2010	Brazilian	60.1	58.3	112/68/95/75	180	170	350	157	23	0	145	25	0	0.064	0.074	1.07	0.301

*Gender component: number of male cases/number of female cases/number of male controls/number of female controls.

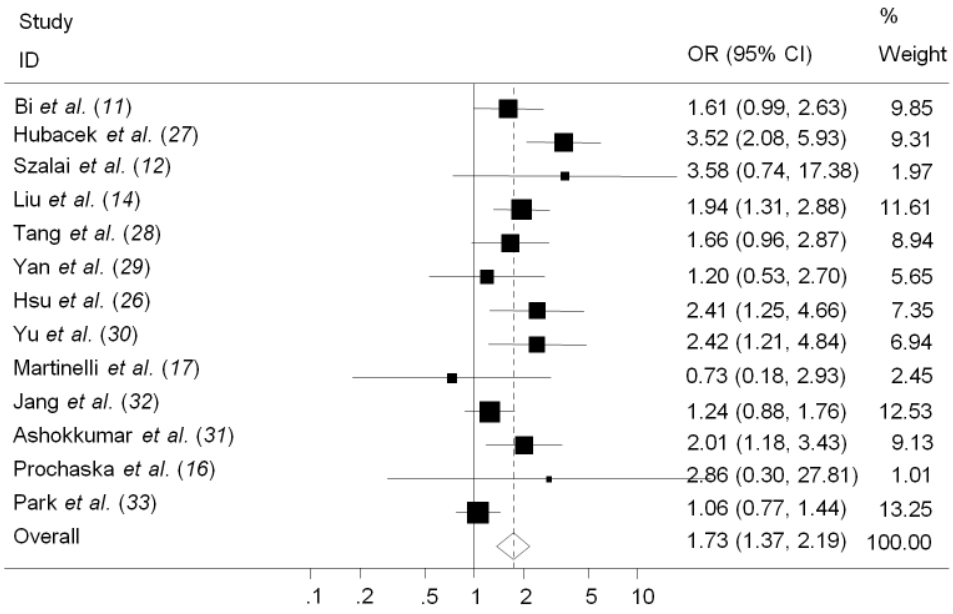

Figure 1. Random effects odds ratio (OR) for association between the APO A5 -1131T>C polymorphism and risk of CAD (C/C *vs.* C/T + T/T). Size of the gray box is proportional to weight of the corresponding study. Pooled estimate is displayed as a diamond. Bars, 95% confidence interval (CI).

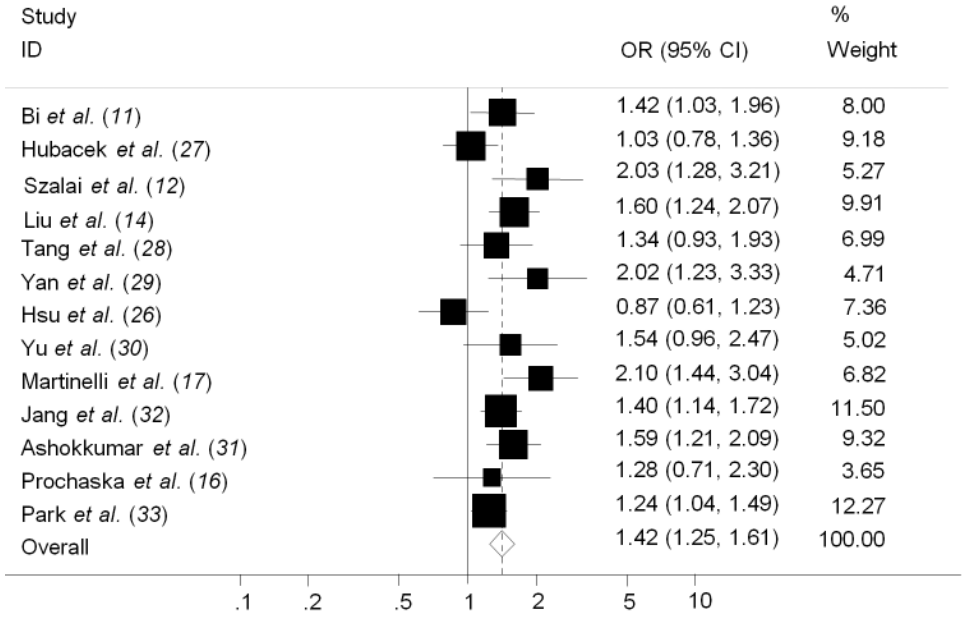

Figure 2. Random effects odds ratio (OR) for association between the APO A5 -1131T>C polymorphism and risk of CAD (C/C + C/T vs T/T). Size of the gray box is proportional to weight of the corresponding study. Pooled estimate is displayed as a diamond. Bars, 95% CI.

region of the APO A5 gene and there is no transcription factor binding sites identified in this location. Therefore, it is justified that the -1131T>C variant may not be functional. However, -1131C may affect the transcriptional activity of the APO A5 gene. In addition, Vaessen *et al.* (*10*) has suggested that association of -1131T>C with CAD is likely attributable to linkage disequilibrium with APOC3 variants or to other closely linked genetic variations.

In the present study, the minor allele frequency of the APO A5 -1131T>C polymorphism has been found to be a stronger association with the risk of CAD in Chinese subjects. This may due to higher frequency of the C allele in Chinese as compared with others (case: 0.372-0.432; control: 0.277-0.344, respectively). As the CAD mortality rates in China have dramatically increased in recent years (*36*), the presence of the APO A5 -1131C allele may have more impact on CAD risk

Table 3. Sensitivity and cumulative analyses for contrast of different genetic models of APO A5 -1131T>C polymorphism

Authors	Sensitivity analysis			Cumulative analysis		
	C/C *vs.* C/T + T/T (recessive genetic model)	C/C + C/T *vs.* T/T (dominant genetic model)	C *vs.* T (allelic contrast)	C/C *vs.* C/T + T/T (recessive genetic model)	C/C + C/T *vs.* T/T (dominant genetic model)	C *vs.* T (allelic contrast)
Bi *et al.* (*11*)	1.60 (1.37, 1.86)	1.38 (1.26, 1.50)	1.30 (1.22, 1.39)	1.61 (0.98, 2.63)	1.41 (1.02, 1.95)	1.33 (1.05, 1.67)
Hubacek *et al.* (*27*)	1.50 (1.28, 1.74)	1.42 (1.30, 1.55)	1.31 (1.22, 1.40)	2.32 (1.62, 3.32)	1.18 (0.95, 1.46)	1.31 (1.11, 1.54)
Szalai *et al.* (*12*)	1.59 (1.37, 1.84)	1.36 (1.25, 1.48)	1.29 (1.21, 1.38)	2.37 (1.67, 3.36)	1.30 (1.07, 1.57)	1.38 (1.19, 1.62)
Liu *et al.* (*14*)	1.55 (1.32, 1.82)	1.36 (1.24, 1.48)	1.28 (1.19, 1.37)	2.17 (1.67, 2.82)	1.40 (1.20, 1.63)	1.43 (1.27, 1.61)
Tang *et al.* (*28*)	1.59 (1.37, 1.86)	1.38 (1.27, 1.51)	1.30 (1.22, 1.39)	2.06 (1.63, 2.61)	1.39 (1.21, 1.60)	1.41 (1.26, 1.57)
Yan *et al.* (*29*)	1.61 (1.39, 1.87)	1.37 (1.25, 1.49)	1.30 (1.21, 1.38)	1.98 (1.57, 2.48)	1.43 (1.25, 1.64)	1.42 (1.28, 1.57)
Hsu *et al.* (*26*)	1.56 (1.35, 1.82)	1.42 (1.30, 1.55)	1.32 (1.24, 1.41)	2.02 (1.63, 2.50)	1.34 (1.18, 1.52)	1.36 (1.24, 1.50)
Yu *et al.* (*30*)	1.57 (1.35, 1.82)	1.38 (1.26, 1.50)	1.30 (1.21, 1.38)	2.05 (1.67, 2.52)	1.35 (1.19, 1.52)	1.38 (1.25, 1.51)
Martinelli *et al.* (*17*)	1.61 (1.39, 1.87)	1.35 (1.24, 1.47)	1.31 (1.23, 1.40)	2.01 (1.64, 2.46)	1.41 (1.25, 1.58)	1.36 (1.24, 1.49)
Jang *et al.* (*32*)	1.69 (1.44, 1.98)	1.38 (1.26, 1.51)	1.31 (1.22, 1.41)	1.78 (1.49, 2.12)	1.40 (1.27, 1.55)	1.33 (1.23, 1.44)
Ashokkumar *et al.* (*31*)	1.57 (1.35, 1.83)	1.36 (1.25, 1.49)	1.29 (1.20, 1.38)	1.80 (1.52, 2.12)	1.43 (1.30, 1.57)	1.35 (1.26, 1.46)
Prochaska *et al.* (*16*)	1.59 (1.38, 1.85)	1.38 (1.27, 1.50)	1.30 (1.22, 1.39)	1.80 (1.53, 2.13)	1.42 (1.29, 1.56)	1.35 (1.26, 1.45)
Park *et al.* (*33*)	1.80 (1.52, 2.13)	1.42 (1.29, 1.56)	1.35 (1.26, 1.45)	1.60 (1.38, 1.85)	1.38 (1.27, 1.50)	1.30 (1.22, 1.39)

*Gender component: number of male cases/number of female cases/number of male controls/number of female controls.

Figure 3. Begg's funnel plot for publication bias test of the APO A5 -1131T>C polymorphism with pseudo 95% confidence limits. (A) recessive genetic model. **(B)** dominant genetic model. Each point represents a separate study for the indicated association. Horizontal line represents the mean effects size.

in Chinese subjects. When stratified by status of HWE, the positive association still existed, but significant heterogeneity losses were found in both groups, suggesting that the status of HWE might be a potential source of between-study heterogeneity.

The present meta-analysis also supported an association between the APO A5 S19>W polymorphism and its relationship to CAD: the minor allele under a recessive model provided evidence of risk. This result should be interpreted with some degree of caution, because the numbers of studies and participants were relatively small.

The present study has some limitations. First, though we have collected all eligible studies, the number of qualified studies was not large. Second, all included studies had a case-control design. Third, although we had designed our study to evaluate effects of environmental modification such as smoking, alcohol intake, physical activities, and diets, few investigators reported the effects of these environmental factors and the definition of each stratum varied too much among studies. We failed to analyze modification of the effects of this polymorphism by environment factors.

In spite of the limitations, our meta-analysis has some key advantages. First, the results should be more reliable than those from a single study, as cases and controls were pooled from different studies and statistical power of analysis was significantly increased. Second, no publication bias was found. Sensitive analyses conducted by deselecting studies one by one in chronological order found no significant changes and reversal of results, which suggested the result of the present meta-analysis, was stable and reliable.

In conclusion, this meta-analysis suggests that the minor allele of the APO A5 -1131T>C polymorphism is a risk factor for CAD, especially in the Chinese population. Primary studies of a large population are required to further evaluate gene-gene and gene-environment interactions of this polymorphism on CAD risk in different ethnicities.

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