Association Between *GSTM1* Null Genotype and Coronary Artery Disease Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: We conducted a meta-analysis to assess the association between polymorphisms of *GSTM1* null genotype and coronary artery disease (CAD) risk.

Material/Methods: Published literature from PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) were retrieved before March 2014. All studies reporting adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of CAD risk were included.

Results: A total of 13 case-control studies, including 5453 cases and 5068 controls, were collected. There was a significant association between *GSTM1* null genotype and CAD risk (adjusted OR=1.26; 95% CI, 1.11–1.43; I^2=3%). When stratified by ethnicity, a significantly elevated risk was observed in whites. In the subgroup analysis according to disease type, a significantly increased myocardial infarction (MI) risk was observed. Subgroup analysis of smoking status showed an increased CAD risk in smokers.

Conclusions: Our results indicate that *GSTM1* null genotype is associated with an increased CAD risk.

MeSH Keywords: **Coronary Artery Disease • Glutathione Transferase • Meta-Analysis as Topic • Polymorphism, Genetic**

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Background

Coronary artery disease (CAD) is the leading health problem worldwide and is the leading cause of mortality in the United States. The role of DNA oxidative stress in the pathogenesis of atherosclerosis and its association with increased production of reactive oxygen species has been well established [1]. The mutagenic activities of cigarette smoke chemicals can cause DNA adducts in target tissues and oxidative modification and progression of atherosclerotic lesions. The glutathione S-transferases (GSTs) are a gene superfamily of phase II metabolic enzymes that detoxify free radicals, particularly in tobacco smoke [2]. *GSTM1* has been mapped to the GST mu gene cluster on chromosome 1p13.3. One variant in *GSTM1* have been identified – a deletion. This inactive form of *GSTM1* (null genotype) causes lower detoxification, which may be a risk factor for CAD. The relationship between *GSTM1* null genotype and risk of CAD has been studied for more than 10 years. Several studies found *GSTM1* null genotype to be a risk factor in CAD, but other studies showed no association between this polymorphism and risk of CAD. These studies reached inconsistent conclusions [3–15], probably due to the relatively small sample sizes. Since individual studies are usually underpowered in detecting the effect of low-penetrance genes, in this study we conducted a meta-analysis to investigate the association between *GSTM1* null genotype and the risk for CAD.

Material and Methods

Publication search

We conducted a literature search before February 2014 in PubMed, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases without restrictions. Combination of the following terms were applied: 'coronary heart disease' OR 'coronary artery disease' OR 'myocardial infarction' OR 'acute coronary syndrome' OR 'ischemic heart disease' OR 'cardiovascular disease' OR 'major adverse cardiac event' OR 'CHD' OR 'CAD' OR 'MI' OR 'ACS' OR 'IHD' OR 'MACE'; 'Glutathione S-transferases' OR 'GSTM1; 'polymorphism' OR 'variant' OR 'genetic' OR 'mutation'. We also conducted a manual search to find other articles based on references identified in the individual articles.

Inclusion criteria and data extraction

We included articles if they met all the following criteria: (1) evaluation of *GSTM1* polymorphism and CAD risk, (2) using a case-control design, and (3) adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Data were extracted by 2 authors independently. In case of conflicting evaluations, an agreement was reached following a discussion; if agreement could not be reached, another author was consulted to resolve the debate. The following information was extracted from each study: first author, year of publication, ethnicity, age, sex, disease type, sample size, smoking status, covariates, adjusted Ors, and the corresponding 95% CIs of CAD risk.

Statistical analysis

For the *GSTM1* gene, we estimated the risk of the null genotype on CAD compared with the non-null genotypes in the recessive model (null verses heterozygous + wild type). The strength of the association between the *GSTM1* gene and CAD risk was measured by ORs with 95% CIs. The ORs with corresponding 95% CIs from individual studies were pooled using random-effects models. Heterogeneity between the studies was quantified using the Cochran Q test in combination with the I^2 statistic, which represents the percentage of variability across studies that is attributable to heterogeneity rather than to chance. Heterogeneity among studies was considered significant when P was less than 0.1 for the Q-test or when the I^2 value was greater than 50%. Subgroup analyses were stratified by ethnicity, disease type, smoking status, and covariates of adjustment. Cumulative meta-analysis was performed. Sensitivity analysis was further performed by excluding single studies sequentially to assess the impact of the individual study on the pooled estimate. Funnel plots and Egger's regression test were undertaken to assess the potential publication bias [16]. Data analysis was performed using STATA 12 (StataCorp LP, College Station, Texas, USA).

Results

Study characteristics

We ultimately identified a total of 13 articles reporting the relationship between *GSTM1* null genotype and CAD risk [3–15]. A total of 5453 cases and 5068 controls were included in this meta-analysis. Table 1 summarized the main characteristics of those included studies. There were 8 case-control studies from white populations and 5 case-control studies from Asian populations.

Quantitative data synthesis

The evaluations of the association between *GSTM1* polymorphism and CAD risk are summarized in Table 2. The null genotype of *GSTM1* was associated with a significantly increased risk of CAD when compared with present genotype (adjusted OR=1.26; 95% CI 1.11–1.43; I^2=3%; Figure 1). When stratified by ethnicity, a significantly elevated risk was observed in whites (OR=1.22; 95% CI 1.06–1.41; I^2=0%) but not in Asians

Table 1. Characteristics of the case-control studies included in this meta-analysis.

First author	Year	Race	Age	Sex	Type	Smoking	Case	Control	Covariate
Li	2000	White	54	Mixed	CAD	Mixed*	400	890	Age, sex, LDL, HDL, hypertension and diabetes
Masetti	2003	White	61	Mixed	CAD	Mixed*	308	122	Sex, dyslipidemia, hypertension, diabetes, and family history
Girisha	2004	Asian	47	Mixed	CAD	Mixed*	59	132	Age, sex, smoke, alcohol, diet, cholesterol, triglyceride, HDL, LDL, VLDL, apoprotein B
Tamer	2004	White	51	Mixed	CAD	Mixed*	148	247	Smoke
Cornelis	2007	White	58	Mixed	MI	Mixed	2042	2042	Smoke, waist-to-hip ratio, income, physical activity, history of diabetes and hypertension, intake of alcohol, and energy-adjusted saturated fat and folate
Manfredi	2007	White	56	Mixed	CAD	Smoker	165	53	Age, sex, dyslipidemia, hypertension, diabetes, and family history
Kim	2008	Asian	60	Mixed	CAD	Mixed*	582	110	Age, sex, hypertension, diabetes, body mass index, and lipid profile
Wang	2008	Asian	62	Mixed	CAD	Mixed*	277	277	Age, sex, smoke, dyslipidemia, hypertension, diabetes, body mass index
Kariž	2012	White	62	Mixed	MI	Mixed	206	257	Age, sex, smoke, BMI, duration of diabetes and lipid parameters
Lakshmi	2012	Asian	68	Mixed	CAD	Mixed	352	282	Age, sex, diabetes
Taspinar	2012	White	62	Mixed	CAD	Mixed*	132	151	Age, sex, smoke, diabetes and family history
Cora	2013	Caucasian	62	Mixed	MI	Mixed*	324	296	Age, sex, smoke, diabetes, hypertension, family history and lipid profile
Yeh	2013	Asian	64	Mixed	CAD	Mixed	458	209	Age, sex, smoke, alcohol use, diabetes mellitus, levels of serum total cholesterol and high-density lipoprotein cholesterol

* Information of smoking status can be extracted. CAD – coronary artery disease; MI – myocardial infarction; LDL – low-density lipoprotein; HDL – high-density lipoprotein; VLDL – very low-density lipoprotein; BMI – body mass index.

(OR=1.20; 95% CI 0.85–1.71; I^2=50%). In the subgroup analysis according to disease type, a significantly increased myocardial infarction (MI) risk was observed (OR=1.19; 95% CI 1.01–1.40; I^2=0%). Subgroup analysis of smoking status showed that increased risks were found in smokers (OR=1.97; 95% CI 1.59–2.44; I^2=4%) but not in non-smokers (OR=1.20; 95%CI, 0.96–1.51; I^2=0%). When we limited the meta-analysis to studies that controlled for confounders such as age, sex, smoking, diabetes, hypertension, family history, and dyslipidemia, a significant association between *GSTM1* null genotype and CAD risk remained.

As shown in Figure 2, significant associations were evident with each addition of more data over time. The results showed that the pooled ORs tended to be stable. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (Figure 3).

Funnel plot and Egger's test were performed to assess the publication bias of the literature. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (data not shown). Egger's test did not find evidence of publication bias (*P*=0.68).

Discussion

The present meta-analysis, including 5453 cases and 5068 controls from 13 case-control studies, explored the associations of *GSTM1* null genotype with CAD risk. We demonstrated that this polymorphism is significantly associated with an increased CAD risk. Subgroup analyses stratified by ethnicity showed whites, but not Asians, with *GSTM1* null genotype had increased CAD risk. It was possible that different lifestyles, diets, and environments may account for this discrepancy. In the MI subgroup, we found that this polymorphism was associated with MI risk. Cigarette smoking is a pro-inflammatory stimulus and an important risk factor for CAD. Some studies

Table 2. Results of meta-analysis.

|	Test of association		Heterogeneity	
	OR (95% CI)	*P* value	*P* value	*I²* (%)
Overall	1.26 (1.11–1.43)	<0.01	0.41	3.0
Asian	1.20 (0.85–1.71)	0.30	0.09	50.0
Caucasian	1.22 (1.06–1.41)	<0.01	0.97	0.0
MI	1.19 (1.01–1.40)	0.04	0.85	0.0
Smoker	1.97 (1.59–2.44)	<0.01	0.40	4.0
Non-smoker	1.20 (0.96–1.51)	0.11	0.63	0.0
Adjusted for				
Age and sex	1.31 (1.07–1.59)	<0.01	0.23	23.0
Smoke	1.29 (1.12–1.48)	<0.01	0.50	0.0
Diabetes and hypertension	1.31 (1.15–1.50)	<0.01	0.69	0.0
Family history	1.46 (1.07–1.99)	0.02	0.50	0.0
Dyslipidemia	1.25 (1.03–1.51)	0.03	0.32	13.0

MI – myocardial infarction.
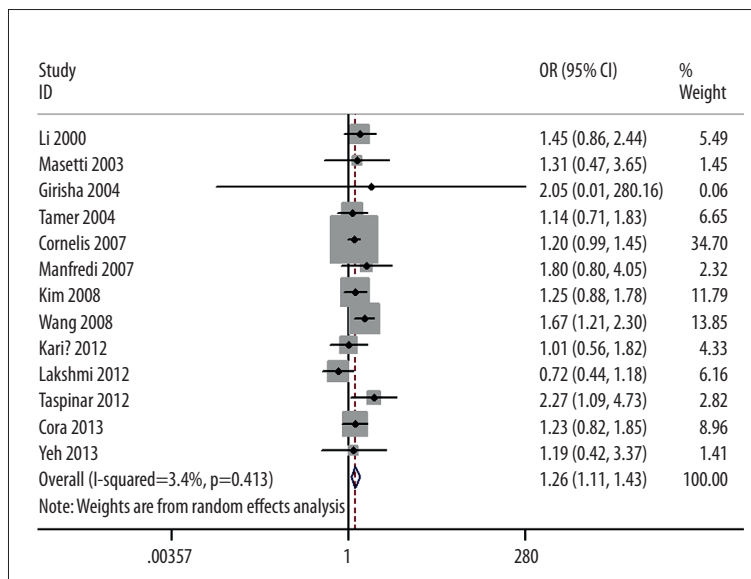
Figure 1. Forest plot for the association between CAD risk and *GSTM1* null genotype.

have explored the interaction between *GSTM1* genotype and smoking habits. Our results showed a significant association among smokers but not in non-smokers, suggesting that even the same variant in the same gene may have a different effect on the pathogenesis and occurrence of CAD in different individuals.

Previous studies have shown that individuals with *GSTM1* null genotype have a decreased capacity to detoxify certain carcinogens. Thus, impaired *GSTM1* function may lead to serious DNA damage. Toxic molecules produce DNA adducts that contribute to the development of atherosclerosis. Evidence indicates that the interaction of DNA adducts with DNA may trigger pathogenic pathways in the cell. Significant correlation was found between DNA adduct levels, which are accepted as a biomarker of exposure to environmental carcinogens, and atherogenic risk factors. Higher DNA adduct levels were detected in individuals with severe CAD [17,18] and in atherosclerotic plaques [19]. Therefore, it is biologically plausible that the *GSTM1* null genotype may increase risk of CAD.
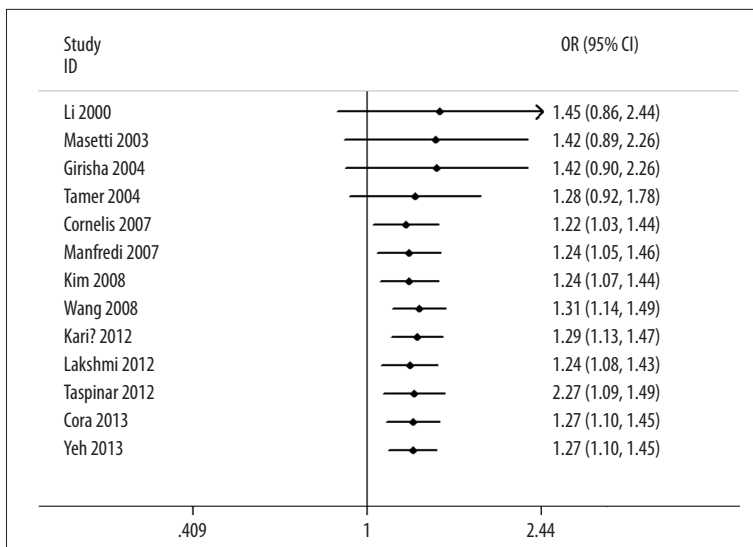
Study ID		OR (95% CI)
Li 2000		1.45 (0.86, 2.44)
Masetti 2003		1.42 (0.89, 2.26)
Girisha 2004		1.42 (0.90, 2.26)
Tamer 2004		1.28 (0.92, 1.78)
Cornelis 2007		1.22 (1.03, 1.44)
Manfredi 2007		1.24 (1.05, 1.46)
Kim 2008		1.24 (1.07, 1.44)
Wang 2008		1.31 (1.14, 1.49)
Kari? 2012		1.29 (1.13, 1.47)
Lakshmi 2012		1.24 (1.08, 1.43)
Taspinar 2012		2.27 (1.09, 1.49)
Cora 2013		1.27 (1.10, 1.45)
Yeh 2013		1.27 (1.10, 1.45)

.409   1   2.44

Figure 2. Cumulative meta-analysis for the association between CAD risk and *GSTM1* null genotype.

Meta-analysis ranodm-effects estimates (exponential form)
Study ommited

Li 2000
Masetti 2003
Girisha 2004
Tamer 2004
Cornelis 2007
Manfredi 2007
Kim 2008
Wang 2008
Kari? 2012
Lakshmi 2012
Taspinar 2012
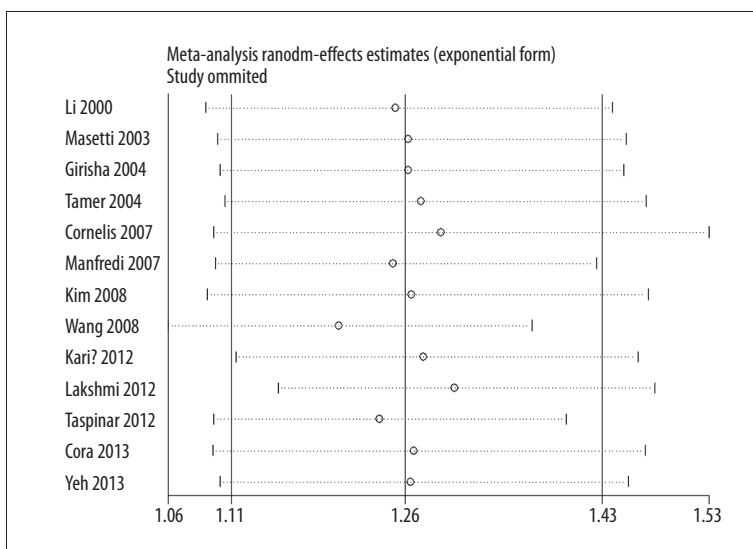Cora 2013
Yeh 2013

1.06   1.11   1.26   1.43   1.53

Figure 3. Sensitivity analysis for the association between CAD risk and *GSTM1* null genotype.

Our study has some strengths. First, it was the first meta-analysis to report the adjusted ORs between *GSTM1* null genotype and CAD risk. Second, the methodological issues for meta-analysis (e.g., subgroup analysis, cumulative meta-analysis, and sensitivity analysis) were well investigated. Third, when we limited the meta-analysis to studies that controlled for age and sex, smoking, diabetes and hypertension, family history, dyslipidemia, the significant positive association was only marginally altered. Finally, we did find significant heterogeneity and publication bias in this meta-analysis.

Some limitations in this meta-analysis should be addressed. First, the number of studies included in our meta-analysis remained small. Thus, publication bias may exist, although the funnel plots and Egger's linear regression tests indicated no remarkable publication bias. Second, lack of the original data of the eligible studies limited the evaluation of the effects of the gene-environment interactions in CAD development. Third, no prospective studies have addressed this association between *GSTM1* null genotype and CAD risk, and all included studies followed a retrospective case-control design. Thus, owing to the limitations of case-control design, we cannot exclude the possibility of undetected bias.

Conclusions

This meta-analysis supports an association between *GSTM1* null genotype and risk of CAD. Prospective studies are suggested to further ascertain the relationship between *GSTM1* null genotype and genetic predisposition to CAD.

Declaration of interest statement

The authors declare that they have no competing interests.

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