

# Genetic polymorphisms of glutathione *S*-transferase genes *GSTM1*, *GSTT1* and risk of coronary heart disease

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**To clarify the role of glutathione *S*-transferases (GSTs; *GSTM1* and *GSTT1*) status in susceptibility to coronary heart disease (CHD), a meta-analysis of published studies was performed. A total of 19 studies including 8020 cases and 11 501 controls were included in this meta-analysis. In a combined analysis, the relative risks for CHD of the *GSTM1* null and *GSTT1* null polymorphisms were 1.47 [95% confidence interval (CI): 1.08–2.01] and 1.26 (95% CI: 0.90–1.75), respectively. Three potential sources of heterogeneity including ethnicity, source of control and sample size of study were also assessed. However, no significant association was found in stratified analyses. By pooling data from eight studies (2909 cases and 3745 controls) that considered combinations of *GSTT1* and *GSTM1* genotypes, a statistically significant increased risk for CHD [odds ratio (OR) = 2.38, 95% CI: 1.03–5.48] was detected for individuals with combined deletion mutations in both genes compared with positive genotypes. Results from the meta-analysis of five studies on GSTs stratified according to smoking status showed an increased risk for individuals with null genotype (OR = 2.21, 95% CI: 1.24–3.92 for *GSTM1* and OR = 3.29, 95% CI: 1.49–7.26 for *GSTT1*) versus non-null genotypes. This meta-analysis suggests that the *GSTM1* null genotype may slightly increase the risk of CHD and that interaction between unfavourable GSTs genotypes may exist.**

## Introduction

Coronary heart disease (CHD), including its most severe complication, myocardial infarction, is the leading cause of death in the industrialized world (1). Traditional risk such as hypertension, diabetes mellitus, dyslipidemia and smoking can only explain approximately two-thirds of the observed clinical events. This has maintained interest in other biochemical and genetic factors that might contribute to the underlying pathophysiology of vascular disease (2). Recent studies addressing the issue of acquired DNA mutations in the

pathogenesis of atherosclerosis suggest that the occurrence of DNA alterations contribute to the multifaceted pathogenesis of the atherogenic process. In particular, deletions or mutations of gene coding for enzymes involved in the metabolism of hazardous compounds may be responsible for individual susceptibility to genotoxic factors, predisposing to the development of DNA insults (3, 4).

The glutathione *S*-transferases (GSTs) are a gene superfamily of phase II metabolic enzymes that detoxify free radicals, particularly in tobacco smoke, products of oxidative stress and carcinogens such as benzopyrene and other polycyclic aromatic hydrocarbons (5). In addition to their role in phase II detoxification, GSTs also play an important role in modulating the induction of other enzymes and proteins for cellular functions, such as DNA repair (6). *GSTM1* and *GSTT1* are the most extensively studied genes in the GST gene superfamily. Polymorphic deletion variants in the *GSTM1* and *GSTT1* genes produce either a functional enzyme (non-deletion alleles or heterozygous deletion, *GSTM1*-1 and *GSTT1*-1) or result in the complete absence of the enzyme (homozygous deletion alleles, *GSTM1*-null and *GSTT1*-null) (7). Therefore, these enzymes may be related to the risk for atherosclerosis and CHD (8).

Indeed, several studies have investigated the associations between the *GSTT1* and *GSTM1* null genotypes and CHD susceptibility. However, these studies have yielded contradictory results, with some studies showing a significant association, while others showing no such association. Such inconsistency could be due to the small effect of the polymorphism on CHD risk and the relatively small sample size in each of the published studies. We therefore performed a meta-analysis of the published studies to clarify this inconsistency and to establish a comprehensive picture of the relationship between *GSTM1*, *GSTT1* and CHD.

## Materials and methods

### Literature search and data extraction

Papers published before the end of November 2009 were identified through a search of Pubmed and Embase using the following terms 'glutathione *S*-transferases' or 'GST' and 'coronary heart disease' or 'CHD', without restriction on language. All references cited in these studies and previously published review articles were reviewed to identify additional work not indexed by MEDLINE. Only those studies assessing the association between the CHD and the GSTs gene polymorphisms were included. The inclusion criteria were (i) original papers containing independent data, (ii) identification of CHD was confirmed pathologically, (iii) sufficient data to calculate the odds ratio (OR) or *P*-value and (iv) case–control or cohort studies. The major reasons for exclusion of studies were (i) overlapping data and (ii) case-only studies, family-based studies and review articles.

For each study, the following information was extracted independently by two investigators: first author's surname, publication date, gender, ethnicity, genotyping method, cigarette smoking status, clinical characteristics, confirmation of diagnosis, total number of cases and controls. The results were compared and disagreements were discussed and resolved with consensus. Where essential information was not presented in articles, every effort was made to contact the authors.

*Statistical analysis*

For the GSTM1 and GSTT1 gene, we estimated the risks of the null genotype on CHD compared with the non-null genotypes in the recessive model (null versus heterozygous + wild type). The strength of the association between the GSTM1 and GSTT1 gene and CHD risk was measured by ORs with 95% confidence intervals (CIs).

Cochran's  $\chi^2$  based Q-statistic test (9, 10) and  $I^2$ -test (11) were performed to assess possible heterogeneity in the combined studies. If heterogeneity existed, the random effects model (the DerSimonian and Laird method) (12), which yields wider CIs, was adopted to calculate the overall OR value. Otherwise, the fixed effects model (the Mantel-Haenszel method) was used (13). In addition, sources of heterogeneity were investigated by stratified meta-analyses based on ethnicity (Caucasian and non-Caucasian population), source of controls (population and hospital based) and sample size (number of cases > 250 or < 250). The method of Woolf (14) was used to construct 95% CIs. The significance of the overall OR was determined by the Z-test. Funnel plots and Egger's linear regression test were used to assess evidence for potential publication bias (15). In order to assess the stability of the result, sensitivity analyses were performed, each study in turn was removed from the total, and the remaining were reanalysed. The analysis was conducted using Review Manager (version 5.0, The Cochrane Collaboration, Oxford, UK). The type I error rate was set at 0.05. All *P*-values were two tailed.

**Results***Characteristics of studies*

A total of 19 studies were retrieved based on the search criteria for CHD susceptibility related to the GST polymorphisms. The main study characteristics were summarized in Table I. There are 19 studies with 8020 CHD cases and 11 501 controls concerning GSTM1 polymorphism and 17 studies with 7318 CHD cases and 10 361 controls concerning GSTT1 polymorphism.

*Meta-analysis results*

**GSTM1.** For CHD risk and the null genotype of GSTM1, our meta-analysis gave an overall OR of 1.47 (95% CI: 1.08–2.01;  $I^2 = 95%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) with statistically significant between-study heterogeneity (Figure 1). This analysis is based on pooling of data from a number of different ethnic populations. When stratifying for ethnicity, an OR of 1.43 (95% CI: 0.92–2.22;  $I^2 = 93%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) and 1.50 (95% CI: 0.93–2.43;  $I^2 = 96%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) resulted for null genotype, among Caucasians and non-Caucasians, respectively. By considering control source subgroups, the OR was 1.31 (95% CI: 0.99–1.72;  $I^2 = 91%$ ,  $P_{\text{heterogeneity}} = 0.00$ )

in population-based controls compared to 1.81 (95% CI: 0.77–4.26;  $I^2 = 97%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) in hospital controls. After stratification for sample size, we still observed positive results in big studies (data not shown).

**GSTT1.** The meta-analysis resulted in a statistically non-significant association between GSTT1 deficiency and CHD. The overall OR was 1.26 (95% CI: 0.90–1.75;  $I^2 = 93%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) (Figure 2). No significant association was found in stratified analyses according to ethnicity, source of controls and GSTT1 genotypes. The OR was 1.22 (95% CI: 0.96–1.54;  $I^2 = 49%$ ,  $P_{\text{heterogeneity}} = 0.06$ ) in Caucasians and 1.20 (95% CI: 0.68–2.10;  $I^2 = 96%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) in non-Caucasians. When stratifying for source of controls, an OR of 0.97 (95% CI: 0.82–1.14;  $I^2 = 55%$ ,  $P = 0.01$ ) and 2.09 (95% CI: 0.90–4.86;  $I^2 = 96%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) resulted for null genotype, among population- and hospital-based controls, respectively. In the stratified analysis by sample size, no significant associations were found in big studies or small studies (data not shown).

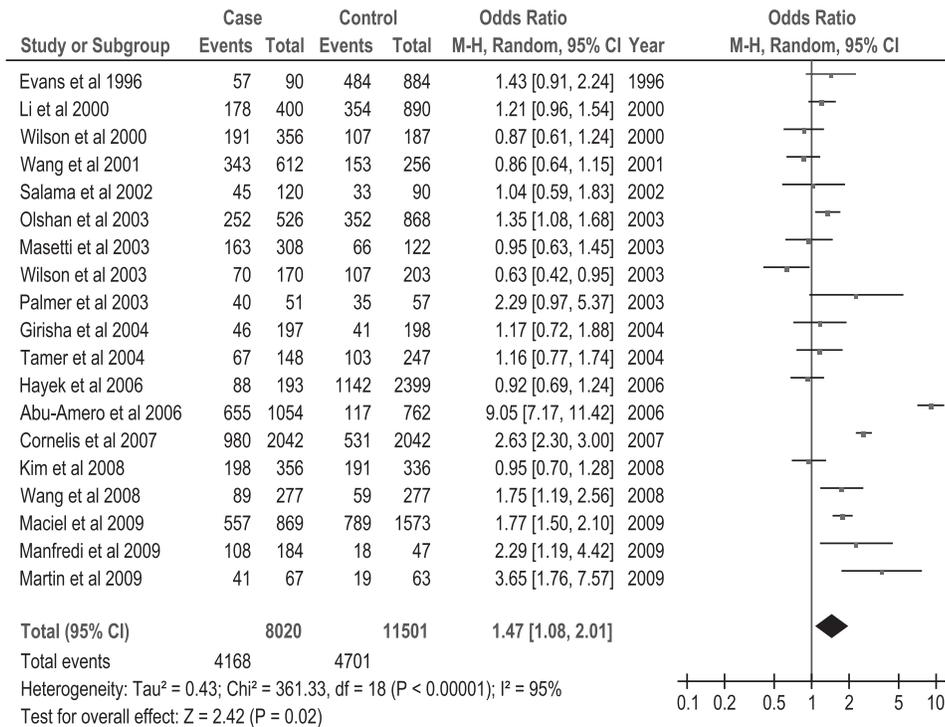
**Gene-gene interaction.** The effect of each genotype of GSTs was independently assessed. No association was established between both the null genotype of GSTM1, GSTT1 and CHD. The data on both null genotype of GSTs among cases and controls were available in eight studies, which included 2909 cases and 3745 controls. The interaction between GSTM1 null and GSTT1 null, for which an OR of 2.38 (95% CI: 1.03–5.48;  $I^2 = 96%$ ,  $P = 0.00$ ) for CHD appeared in compared with individuals with the positive genotypes.

**Gene-environment interaction.** The data on genotypes of the GSTM1 and GSTT1 among cases and controls stratified by smoking status were available in five studies. Among smokers in all five studies, individuals with the null genotype of GSTM1 or GSTT1 had a significantly increased CHD risk compared to the non-null genotypes with an OR of 2.21 (95% CI: 1.24–3.92;  $I^2 = 84%$ ,  $P_{\text{heterogeneity}} = 0.00$ ) and 3.29 (95% CI: 1.49–7.26;  $I^2 = 90%$ ,  $P_{\text{heterogeneity}} = 0.00$ ), respectively.

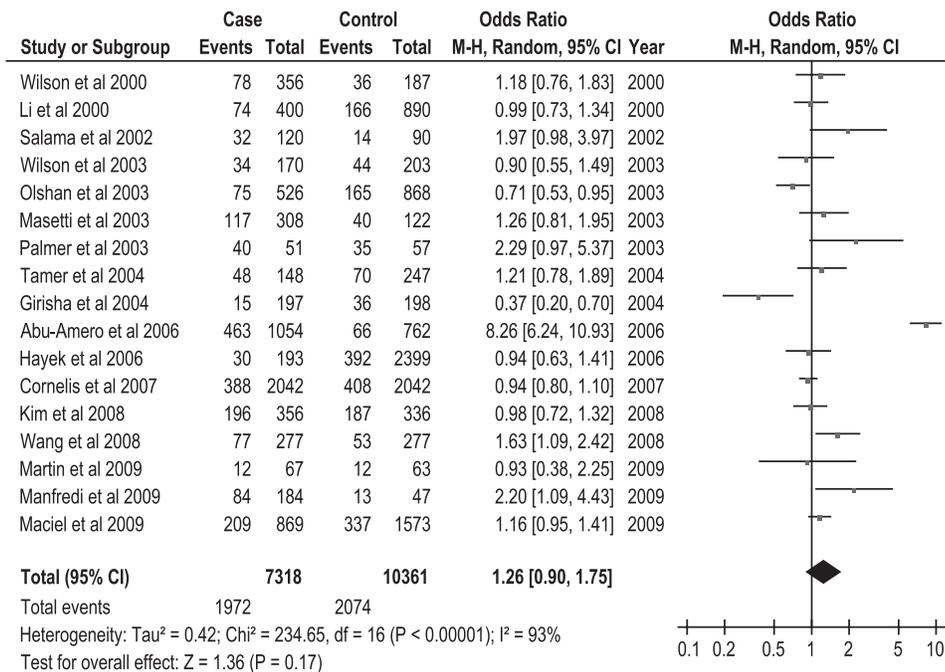
**Sensitivity analyses and publication bias.** Sensitivity analyses indicated that the studies by Abu-Amro *et al.* were the main origin of heterogeneity in overall OR. The heterogeneity was

**Table I.** Demography of the combined studies

Reference	Year	Country (ethnicity)	Genotyping method	No. of cases	No. of controls	Controls source
Evans <i>et al.</i> (16)	1996	Saudi Arabia	PCR	90	884	Population
Wilson <i>et al.</i> (17)	2000	UK	PCR	356	187	Population
Li <i>et al.</i> (5)	2000	USA	PCR	400	890	Population
Wang <i>et al.</i> (18)	2001	USA	PCR	612	256	Hospital
Salama <i>et al.</i> (19)	2002	USA	PCR	120	90	Population
Wilson <i>et al.</i> (20)	2003	South Asian	PCR	170	203	Population
Palmer <i>et al.</i> (21)	2003	UK	PCR	51	57	Hospital
Olshan <i>et al.</i> (22)	2003	USA	PCR	526	868	Population
Masetti <i>et al.</i> (23)	2003	Italy	PCR	308	122	Hospital
Girisha <i>et al.</i> (24)	2004	India	PCR	197	198	Population
Tamer <i>et al.</i> (25)	2004	Turkey	RT-PCR	148	247	Population
Hayek <i>et al.</i> (26)	2006	UK	PCR	193	2399	Population
Abu-Amro <i>et al.</i> (27)	2006	Saudi Arabia	PCR	1054	762	Hospital
Cornelis <i>et al.</i> (28)	2007	Canada	PCR	2042	2042	Population
Kim <i>et al.</i> (29)	2008	Korea	PCR	356	336	Hospital
Wang <i>et al.</i> (30)	2008	Chinese	PCR	277	277	Hospital
Martin <i>et al.</i> (31)	2009	USA	PCR	67	63	Population
Manfredi <i>et al.</i> (32)	2009	Italy	PCR	184	47	Hospital
Maciel <i>et al.</i> (33)	2009	Brazil	PCR	871	1577	Population



**Fig. 1.** Meta-analysis of GSTM1 null genotype associated with CHD. Each box represents the OR point estimate, and its area is proportional to the weight of the study. The diamond represents the overall summary estimate, with CI represented by its width.



**Fig. 2.** Effect of the GSTT1 null versus present genotype the risk of CHD.

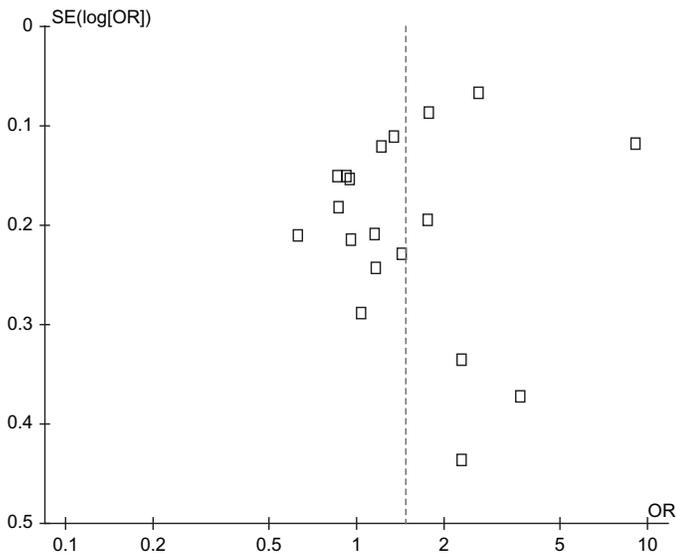
effectively decreased after exclusion of the study (GSTM1:  $I^2 = 60\%$ ; GSTT1:  $I^2 = 89\%$ ). In addition, no other single study influenced the pooled OR qualitatively, as indicated by sensitivity analyses, suggesting that the results of this meta-analysis are stable (data not shown).

Begg's funnel plot and Egger's test were performed to evaluate the publication bias of literatures. As shown in Figures 3 and 4, the shape of the funnel plots seemed symmetrical for both

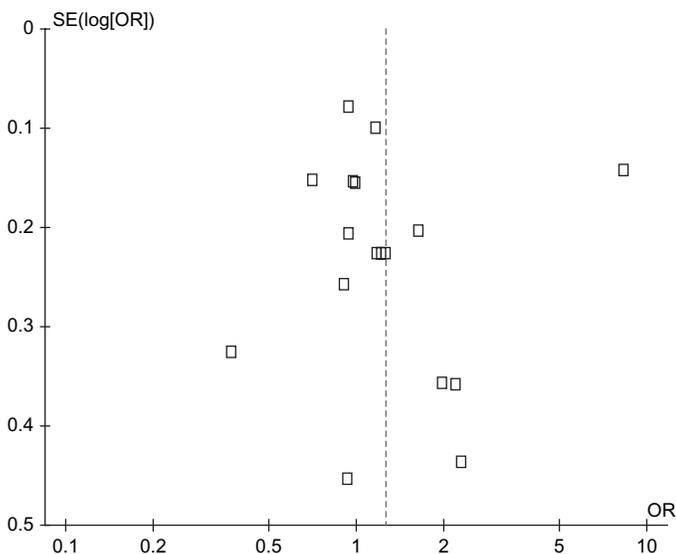
genes, suggesting no publication bias among the studies included. The statistical results still did not show publication bias ( $P > 0.05$ , for all).

## Discussion

Large sample and unbiased epidemiological studies of pre-disposition genes polymorphisms could provide insight into the



**Fig. 3.** Funnel plot of association between GSTM1 polymorphism and CHD overall individuals. Formal statistical criteria by Egger's test was also performed to investigate the symmetry of the funnel plot ( $P = 0.142$ ).



**Fig. 4.** Funnel plot of association between GSTT1 polymorphism and CHD overall individuals. Formal statistical criteria by Egger's test was also performed to investigate the symmetry of the funnel plot ( $P = 0.763$ ).

*in vivo* relationship between candidate genes and complex diseases. This meta-analysis, involving a total of 8020 CHD cases and 10 501 controls from 19 case-control studies, examined the association of two commonly studied polymorphisms of GST (M1 and T1) with CHD risk. Results indicated a significant association between null polymorphism of GSTM1 and CHD risk, whereas the GSTT1 polymorphism (null versus non-deleted) seems unrelated to CHD risk.

In meta-analysis, heterogeneity evaluation was always conducted in statistical analysis. Thus, several subgroup meta-analyses were performed according to ethnicity control source. In racial subgroups, no statistically significant association between GSTM1 or GSTT1 polymorphism and CHD appeared in Caucasians and non-Caucasians. However, the Caucasian and non-Caucasian population reports in the subgroup analysis include a mixture of populations from very

distant countries, so the result must be interpreted with caution. No significant association between variant genotypes and CHD risk was observed when the included studies were stratified by control source. Such result could be due to limited number of studies that had insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate.

If genetic susceptibility to CHD is, in part, mediated through metabolic gene polymorphisms, it is possible that the combinations of certain genotypes may be more discriminating as risk factors for CHD than a single locus genotype. Among the 19 studies included in the present meta-analysis, eight studies investigated the interaction between GSTM1 and GSTT1 polymorphism. By pooling the collected data on GSTM1 and GSTT1 genotypes, a statistically significant 2.38-fold increased risk for CHD appeared for individuals with combined deletion mutations in GSTT1 and GSTM1 genes in comparison with individuals with the positive genotypes. This result suggests that in the presence of both of the two risk factors, an important number of CHD cases would occur.

Cigarette smoking is a pro-inflammatory stimulus and an important risk factor for CHD. Unfortunately, almost all the studies did not explore the interaction between GSTs genotype and smoking habits. This was probably due to the low statistical power of the individual studies to detect interactions. Our results show a significant association among smokers subgroup between GSTM1, GSTT1 polymorphism and CHD risk. The results suggest that there could be an interaction between cigarette smoking and GSTs. One possible cause is that tobacco smoke-induced DNA damage causes smooth muscle cell proliferation in the intima of arteries, thereby contributing to atherosclerotic plaque formation (8).

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, the three subgroup meta-analyses considering interactions between GSTM1, GSTT1 null genotype and cigarette smoking, as well as between GSTT1 null and GSTM1 null genotypes, were performed on the basis of a fraction of all the possible data to be pooled, so selection bias may have occurred and our results may be over inflated. In this context, more reliable results can be expected if individual data are available for a pooled analysis. Thirdly, only published studies were included in this meta-analysis. Therefore, publication bias may have occurred, even though the use of a statistical test did not show it.

Despite these limitations, this meta-analysis suggests that GSTM1 polymorphisms may increase the risk of CHD, but no significant effect for GSTT1 polymorphisms. In addition, GSTM1 and GSTT1 polymorphisms may modulate the tobacco-related pathogenesis of CHD and the combination of unfavourable genotypes may result in an additional risk of CHD. Larger studies of different ethnic populations, especially with detailed individual information, are needed to confirm our findings.

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Conflict of interest statement: None declared.

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