meta-analysis

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GST null polymorphisms may affect the risk of coronary artery disease: evidence from a



Hongling Su^{*}, Yunshan Cao, Jing Li, Yan Zhu and Xuming Ma

Abstract

Background: Whether glutathione S-transferase (GST) null polymorphisms, namely GSTM1 null, GSTP1 null and GSTT1 null polymorphisms, influence the risk of coronary artery disease (CAD) or not remains unclear. Thus, the authors performed a meta-analysis to more robustly estimate associations between GST null polymorphisms and the risk of CAD by integrating the results of previous publications.

Methods: Medline, Embase, Wanfang, VIP and CNKI were searched comprehensively for eligible studies, and 45 genetic association studies were finally selected to be included in this meta-analysis.

Results: We found that GSTM1 null polymorphism was significantly associated with the risk of CAD in overall population (OR = 1.37, p = 0.003) and mixed population (OR = 1.61, p = 0.004), GSTP1 null polymorphism was significantly associated with the risk of CAD in overall population (OR = 1.23, p = 0.03), whereas GSTT1 null polymorphism was significantly associated with the risk of CAD in overall population (OR = 1.23, p = 0.02), Caucasians (OR = 1.23, p = 0.02) and East Asians (OR = 1.38, p < 0.0001).

Conclusions: This meta-analysis demonstrated that GSTM1 null, GSTP1 null and GSTT1 null polymorphisms were all significantly associated with an increased risk of CAD.

Keywords: Glutathione S-transferase (GST), Null polymorphisms, Coronary artery disease (CAD), Meta-analysis

Background

Coronary artery disease (CAD) is featured by stenosis or even occlusion of coronary arteries, and their associated myocardial ischemia or infarction [1, 2]. The exact cause and pathogenesis of CAD are still nuclear despite extensive researches. Nevertheless, accumulating evidence supports that genetic factors play a crucial part in its development. First, family aggregation of CAD has been observed extensively, and past twin studies have demonstrated that the heredity grade of CHD can be as high as 50% [3, 4]. Second, numerous genetic polymorphisms have been found to be associated with an increased risk

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of CAD by previous genetic association studies, and screening of common causal mutations has also been demonstrated to be an efficient way to predict the individual risk of developing CAD [5, 6]. Overall, these findings jointly indicate that genetic architecture is important for the occurrence and development of CAD.

Oxidative stress, characterized by accumulation of free radicals, membrane lipid peroxidation and DNA damage, has been found to play a critical role in the pathogenesis of various atherothrombotic disorders including CAD [7, 8]. Glutathione-S-transferases (GSTs) are a group of enzymes that play vital roles in regulating cellular detoxification of various exogenous toxins [9]. Moreover, it has been shown that GSTs have anti-oxidation effects and they can protect cells against oxidative stress and its associated DNA

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damage [10]. Previous experimental studies have demonstrated that *GST* null polymorphisms, which include null polymorphisms of *GSTM1* (mu), *GSTP1* (pi) and *GSTT1* (theta) can result in a diminished gene expression level and a reduced enzymatic activity of GST [11, 12]. Consequently, it is biologically plausible that *GST* null polymorphisms may also affect the risk of CAD. Over the last decade, investigators across the world have repeatedly attempted to assess the associations between *GST* null polymorphisms and the risk of CAD, with inconsistent findings. So a metaanalysis was performed by us to more robustly estimate the associations between *GST* null polymorphisms and the risk of CAD by integrating the results of previous publications.

Methods

This meta-analysis was conducted in accordance with the PRISMA guideline [13].

Literature search and inclusion criteria

Medline, Embase, Wanfang, VIP and CNKI were comprehensively searched by the authors using the below keywords: (glutathione S-transferase OR GST) AND (polymorphism OR polymorphic OR variation OR variant OR mutant OR mutation OR SNP OR genotypic OR genotype OR allelic OR allele) AND (coronary atherosclerotic heart disease OR coronary heart disease OR coronary artery disease OR ischemic heart disease OR angina pectoris OR acute coronary syndrome OR myocardial infarction OR CHD OR CAD OR IHD OR ACS OR MI). Moreover, we also manually screened the references of retrieved publications to make up for the potential incompleteness of literature searching from electronic databases.

Selection criteria of this meta-analysis were listed below: 1. Studies of case-control or cohort design; 2. Give genotypic frequencies of *GST* null polymorphisms in cases with CAD and population-based controls; 3. The full manuscript with detailed genotypic frequencies of *GST* null polymorphisms is retrievable or buyable. Articles would be excluded if one of the following three criteria is satisfied: 1. Studies without complete genotypic data of *GST* null polymorphisms in cases with CAD and population-based controls; 2. Narrative or systematic reviews, meta-analysis or comments; 3. Case series of subjects with CAD only. If duplicate reports are retrieved, we would only include the most complete one for integrated analyses.

Data extraction and quality assessment

The authors extracted the following data items from eligible studies: 1. Last name of the leading author; 2. Year of publication; 3. Country and ethnicity of study population; 4. The number of cases with CAD and populationbased controls; 5. Genotypic frequencies of *GST* null polymorphisms in cases with CAD and population-based controls. The quality of eligible publications was assessed by the Newcastle-Ottawa scale (NOS) [14], and these with a score of 7 - 9 were considered to be of good quality. Two authors extracted data and assessed quality of eligible literatures in parallel. A thorough discussion until a consensus is reached would be endorsed in case of any discrepancy between two authors.

Statistical analyses

All statistical analyses in this meta-analysis were performed with the Cochrane Review Manager software. Associations between GST null polymorphisms and the risk of CAD were explored by using odds ratio and its 95% confidence interval. The statistically significant pvalue was set at 0.05. The authors used I² statistics to estimate heterogeneities among included studies. The authors would use DerSimonian-Laird method, which is also known as the random effect model, to integrate the results of eligible studies if I^2 is larger than 50%. Otherwise, the authors would use Mantel-Haenszel method, which is also known as the fixed effect model, to integrate the results of eligible studies. Meanwhile, the authors also conduct subgroup analyses by ethnic groups. The overall population (with all study subjects of eligible studies for each polymorphism included) can be divided into Caucasians, Asians or the mixed populations. If the authors specify the ethnic origin of study subjects in their publications, then we would use these data to divide the publications into different subgroups. But if the authors failed to specify the ethnic origin of study subjects in their publications, then we would use the location of the authors' affiliations to divide the publications into different subgroups. For the mixed population, since the authors failed to specify the ethnic origin of study subjects and we could not judge the ethnic origin of study subjects from authors' affiliations neither, it may have several scenarios, which can be a mixture of Caucasians and Africans, a mixture of Caucasians and Asians, a mixture of Africans and Asians, or a mixture of Caucasians, Asians and Africans. Stabilities of integrated results were tested by deleting one study each time, and then integrating the results of the rest of eligible studies. Publication biases were evaluated by assessing symmetry of funnel plots.

Results

Characteristics of included studies

One hundred and eighty-four publications were retrieved by using our searching strategy. Among these publications, nine duplicate reports as well as one hundred and four unrelated publications (papers that were not about *GST* null polymorphisms and the risk of CAD) were omitted, and 71 publications were then selected to screen for eligibility. Seventeen reviews and seven case series were further excluded, and another two publications without complete genotypic data were further excluded by the authors. Totally 45 studies met the inclusion criteria, and were finally enrolled for integrated analyses (Fig. 1). The eligible studies were published between 1996 and 2020. Data extracted from eligible studies were summarized in Table 1.

GSTM1 null polymorphism and the risk of CAD

Thirty-seven studies (17,054 cases and 36,630 controls) assessed relationship between *GSTM1* null polymorphism and the risk of CAD. The integrated analyses demonstrated that *GSTM1* null polymorphism was significantly associated with the risk of CAD in overall population (OR = 1.37, p = 0.003) and mixed population (OR = 1.61, p = 0.004) (see Table 2 and Fig. 2).

GSTP1 null polymorphism and the risk of CAD

Eleven studies (4595 cases and 4390 controls) assessed relationship between *GSTP1* null polymorphism and the risk of CAD. The integrated analyses demonstrated that *GSTP1* null polymorphism was significantly associated with the risk of CAD in overall population (OR = 1.23, p = 0.03) (see Table 2 and Fig. 2).

GSTT1 null polymorphism and the risk of CAD

Thirty-nine studies (17,120 cases and 38,115 controls) assessed relationship between *GSTT1* null polymorphism



Table 1 The characteristics of included studies in this meta-analysis

First author, year	Country	Ethnicity	Type of disease	Sample size	Null genotype	[n(%)]	NOS
				Case/Control	Cases Controls	;	score
GSTM1 null							
Abu-Amero 2006	Saudi Arabia	Mixed	Coronary artery disease (CAD)	1054/762	655 (62.1%)	117 (15.3%)	7
Bazo 2011	Brazil	Mixed	Coronary artery disease (CAD)	297/96	160 (53.8%)	40 (41.7%)	7
Bhat 2016	India	Mixed	Coronary artery disease (CAD)	200/200	62 (31.0%)	36 (18.0%)	8
Bhatti 2018	India	Mixed	Coronary artery disease (CAD)	562/564	217 (38.6%)	127 (22.5%)	7
Cora 2013	Turkey	Caucasian	Myocardial infarction (MI)	324/296	182 (56.1%)	143 (48.3%)	8
Cornelis 2007	Canada	Caucasian	Myocardial infarction (MI)	2042/2042	980 (48.0%)	1041 (51.0%)	7
Evans 1996	Saudi Arabia	Mixed	Coronary artery disease (CAD)	90/884	57 (63.3%)	484 (54.8%)	7
Girisha 2004	India	Mixed	Coronary artery disease (CAD)	197/198	46 (23.4%)	41 (20.7%)	7
Hayek 2006	Israel	Mixed	Coronary artery disease (CAD)	193/2399	88 (45.6%)	1142 (47.6%)	8
Kadıoğlu 2016	Turkey	Caucasian	Coronary artery disease (CAD)	29/30	17 (58.6%)	14 (46.7%)	7
Kariž 2012	Slovenia	Caucasian	Myocardial infarction (MI)	206/257	142 (69.0%)	166 (64.6%)	7
Kim 2008	Korea	East Asian	Coronary artery disease (CAD)	356/336	198 (55.6%)	191 (56.8%)	7
Li 2000	USA	Mixed	Coronary artery disease (CAD)	400/790	178 (44.5%)	354 (44.8%)	7
Macie 2009	Brazil	Mixed	Coronary artery disease (CAD)	869/1573	557 (64.1%)	789 (50.2%)	7
Manfredi 2007	Italy	Caucasian	Coronary artery disease (CAD)	169/53	99 (58.6%)	24 (45.3%)	7
Manfredi 2009	Italy	Caucasian	Coronary artery disease (CAD)	184/47	108 (58.7%)	18 (38.3%)	7
Martin 2009	USA	Mixed	Coronary artery disease (CAD)	67/63	41 (61.2%)	19 (30.2%)	7
Masetti 2003	Italy	Caucasian	Coronary artery disease (CAD)	308/122	163 (52.9%)	66 (54.1%)	8
Mir 2016	India	Mixed	Coronary artery disease (CAD)	100/100	42 (42.0%)	26 (26.0%)	8
Nomani 2011	Iran	Mixed	Coronary artery disease (CAD)	209/108	100 (47.8%)	57 (52.8%)	8
Norskov 2011	Denmark	Caucasian	Coronary artery disease (CAD)	4930/21684	2052 (41.6%)	11,362 (52.4%)	7
Olshan 2003	USA	Mixed	Coronary artery disease (CAD)	526/868	252 (47.9%)	352 (40.6%)	8
Pašalić 2017	Croatia	Caucasian	Coronary artery disease (CAD)	71/174	29 (40.8%)	69 (39.7%)	7
Phulukdaree 2012	India	Mixed	Coronary artery disease (CAD)	102/100	37 (36.3%)	18 (18.0%)	7
Pourkeramati 2020	Iran	Mixed	Coronary artery disease (CAD)	244/281	128 (52.5%)	138 (49.1%)	8
Ramprasath 2011	India	Mixed	Coronary artery disease (CAD)	290/270	128 (44.1%)	56 (20.7%)	7
Salama 2002	USA	Mixed	Coronary artery disease (CAD)	130/90	45 (34.6%)	33 (36.7%)	7
Singh 2011	India	Mixed	Myocardial infarction (MI)	230/300	56 (24.3%)	65 (21.7%)	8
Tamer 2004	Turkey	Caucasian	Coronary artery disease (CAD)	148/247	67 (45.3%)	103 (41.7%)	7
Tang 2009	China	East Asian	Coronary artery disease (CAD)	277/277	89 (32,.1%)	59 (21.3%)	7
Taspinar 2012	Turkey	Caucasian	Coronary artery disease (CAD)	122/142	51 (41.8%)	66 (46.5%)	7
Wang 2002	Australia	Caucasian	Coronary artery disease (CAD)	612/256	343 (56.0%)	153 (59.8%)	7
Wang 2008	China	East Asian	Coronary artery disease (CAD)	277/277	89 (32.1%)	59 (21.3%)	8
Wilson 2000	UK	Caucasian	Myocardial infarction (MI)	356/187	191 (53.7%)	107 (57.2%)	8
Wilson 2003	UK	Mixed	Coronary artery disease (CAD)	170/203	70 (41.2%)	107 (52.7%)	7
Yeh 2013	Taiwan	East Asian	Coronary artery disease (CAD)	458/209	253 (55.2%)	121 (57.9%)	8
Zhang 2011	China	East Asian	Coronary artery disease (CAD)	255/145	120 (47.1%)	46 (31.7%)	7
GSTP1 null							
Bhat 2016	India	Mixed	Coronary artery disease (CAD)	200/200	132 (66.0%)	104 (52.0%)	8
Bhatti 2018	India	Mixed	Coronary artery disease (CAD)	560/545	366 (65.4%)	307 (56.3%)	7
Cornelis 2007	Canada	Caucasian	Myocardial infarction (MI)	2042/2042	817 (40.0%)	817 (40.0%)	7
Kariž 2012	Slovenia	Caucasian	Myocardial infarction (MI)	206/257	135 (65.5%)	140 (54.5%)	7

Table 1 The characteristics of included studies in this meta-analysis (Continued)

First author, year	Country	Ethnicity	Type of disease	Sample size Case/Control	Null genotype	e [n(%)]	NOS score
	Hungany	Caucacian	Muccardial infarction (MI)	E 4 /70)) ())) ())	7
Novacs 2014	Hungary	Caucasian	Coronany artony disease (CAD)	24/78	27 (50.0%)	20 (33.3%)	/
Phulukdaroo 2012	India	Mixed	Coronary artery disease (CAD)	102/100	36 (35 30%)	52 (52.0%)	7
Phulukualee 2012	Inuia	Mixed	Coronary artery disease (CAD)	244/201	50 (55.5%)	52 (52.0%)	0
Pourkeramati 2020	India	Mixed	Coronary artery disease (CAD)	244/201	04 (20.2%)	50 (19.9%) 152 (56.20()	0
Gineb 2011	Inula	Mixed	Coronary artery disease (CAD)	290/2/0	190 (07.0%)	132 (30.3%)	/
Singn 2011		IVIIXed		230/300	90 (39.1%)	117 (39.0%)	8
Yen 2013	Taiwan	East Asian	Coronary artery disease (CAD)	458/209	125 (27.3%)	59 (28.2%)	8
	Cauali Analaia	Minad		1054/760	462 (42.00()		7
Abu-Amero 2006		IVIIXed	Coronary artery disease (CAD)	1054/762	463 (43.9%)	66 (8.7%)	/
Bazo 2011	Brazil	Mixed	Coronary artery disease (CAD)	29//100	69 (23.2%)	19 (19.0%)	/
Bhat 2016	India	Mixed	Coronary artery disease (CAD)	200/200	12 (6.0%)	25 (12.5%)	8
Bhatti 2018	India	Mixed	Coronary artery disease (CAD)	562/564	86 (15.3%)	129 (22.9%)	/
Cora 2013	Turkey	Caucasian	Myocardial infarction (MI)	324/296	106 (32.7%)	63 (21.3%)	8
Cornelis 2007	Canada	Caucasian	Myocardial infarction (MI)	2042/2042	388 (19.0%)	408 (20.0%)	7
Decharatchakul 2020	Thailand	East Asian	Coronary artery disease (CAD)	279/735	115 (41.9%)	242 (32.9%)	8
García 2018	Mexico	Mixed	Coronary artery disease (CAD)	79/101	15 (19.0%)	8 (7.9%)	7
Girisha 2004	India	Mixed	Coronary artery disease (CAD)	197/198	15 (7.6%)	36 (18.2%)	7
Hayek 2006	Israel	Mixed	Coronary artery disease (CAD)	193/2399	30 (15.5%)	392 (16.3%)	8
Kadıoğlu 2016	Turkey	Caucasian	Coronary artery disease (CAD)	29/30	6 (20.7%)	5 (16.7%)	7
Kariž 2012	Slovenia	Caucasian	Myocardial infarction (MI)	206/257	77 (37.4%)	108 (42.0%)	7
Kim 2008	Korea	East Asian	Coronary artery disease (CAD)	356/336	196 (55.0%)	187 (55.7%)	7
Li 2000	USA	Mixed	Coronary artery disease (CAD)	400/890	74 (18.5%)	166 (18.7%)	7
Lakshmi 2012	India	Mixed	Coronary artery disease (CAD)	352/282	81 (23.0%)	39 (13.8%)	7
Levinsson 2014	Sweden	Caucasian	Coronary artery disease (CAD)	112/1221	11 (9.8%)	168 (13.8)	7
Macie 2009	Brazil	Mixed	Coronary artery disease (CAD)	869/1573	209 (24.1%)	337 (21.4%)	7
Manfredi 2007	Italy	Caucasian	Coronary artery disease (CAD)	169/53	95 (56.2%)	13 (24.5%)	7
Manfredi 2009	Italy	Caucasian	Coronary artery disease (CAD)	184/47	84 (45.7%)	13 (27.7%)	7
Martin 2009	USA	Mixed	Coronary artery disease (CAD)	67/63	12 (17.9%)	12 (19.7%)	7
Masetti 2003	Italy	Caucasian	Coronary artery disease (CAD)	308/122	117 (38.0%)	40 (32.8%)	8
Mir 2016	India	Mixed	Coronary artery disease (CAD)	100/100	23 (23.0%)	16 (16.0%)	8
Nomani 2011	Iran	Mixed	Coronary artery disease (CAD)	209/108	16 (7.7%)	17 (15.7%)	8
Norskov 2011	Denmark	Caucasian	Coronary artery disease (CAD)	4930/21684	740 (15.0%)	3161 (14.6%)	7
Olshan 2003	USA	Mixed	Coronary artery disease (CAD)	526/868	75 (14.3%)	165 (19.0%)	8
Palmer 2003	UK	Caucasian	Coronary artery disease (CAD)	51/57	40 (78.4%)	35 (61.4%)	7
Pašalić 2017	Croatia	Caucasian	Coronary artery disease (CAD)	68/177	17 (25.0%)	54 (30.5%)	7
Pourkeramati 2020	Iran	Mixed	Coronary artery disease (CAD)	244/281	129 (52.9%)	143 (50.8%)	8
Ramprasath 2011	India	Mixed	Coronary artery disease (CAD)	290/492	136 (46.9%)	118 (24.0%)	7
Salama 2002	USA	Mixed	Coronary artery disease (CAD)	130/90	32 (26.7%)	14 (15.6%)	7
Singh 2011	India	Mixed	Myocardial infarction (MI)	230/300	23 (10.0%)	61 (20.3%)	8
Tamer 2004	Turkey	Caucasian	Coronary artery disease (CAD)	148/247	48 (32.4%)	70 (28 3%)	- 7
Tang 2009	China	Fast Asian	Coronary artery disease (CAD)	277/277	77 (27.8%)	53 (19 1%)	, 7
Taspinar 2012	Turkey	Caucacian	Coronary artery disease (CAD)	122/142	77 (∠7.070) 28 (23.0%)	25 (17.6%)	, 7
Wang 2009	China	Eact Acian	Coronary artery disease (CAD)	122/172 277/277	20 (23.070)	52 (10.10/)	, 0
wang 2008	CHILID	east Asidi)	Coronary artery disease (CAD)	2///2//	// (∠/.ठ%)	JJ (19.1%)	0

First author, year	Country	Ethnicity	Type of disease	Sample size	Null genotype	[n(%)]	NOS
				Case/Control	Cases Controls	5	score
Wilson 2000	UK	Caucasian	Myocardial infarction (MI)	356/187	90 (25.3%)	36 (19.3%)	8
Wilson 2003	UK	Mixed	Coronary artery disease (CAD)	170/203	34 (20.0%)	44 (21.7%)	7
Yeh 2013	Taiwan	East Asian	Coronary artery disease (CAD)	458/209	276 (60.3%)	110 (52.6%)	8
Zhang 2011	China	East Asian	Coronary artery disease (CAD)	255/145	141 (55.3%)	60 (41.4%)	7

Table 1 The characteristics of included studies in this meta-analysis (Continued)

Abbreviations: HWE Hardy-Weinberg equilibrium, NOS Newcastle-Ottawa scale, NA Not available

and the risk of CAD. The integrated analyses demonstrated that *GSTT1* null polymorphism was significantly associated with the risk of CAD in overall population (OR = 1.23, p = 0.02), Caucasians (OR = 1.23, p = 0.02) and East Asians (OR = 1.38, p < 0.0001) (see Table 2 and Fig. 2).

Sensitivity analyses

The authors examined stabilities of integrated analyses results by deleting one study each time, and then integrating the results of the rest of studies. The trends of associations were not significantly altered in sensitivity analyses, which indicated that from statistical perspective, our integrated analyses results were reliable and stable (Relevant datasets can be found at https://osf.io, username: suhonglingxxx@163. com, password: suhonglingxxx@).

Publication biases

The authors examined potential publication biases in this meta-analysis by assessing symmetry of funnel plots. Funnel plots were found to be generally symmetrical, which indicated that our integrated analyses results were not likely to be severely deteriorated by publication biases (see Fig. 3).

Discussion

To our knowledge, this is so far the very first metaanalysis regarding associations of *GSTM1* and *GSTP1* null polymorphisms with the risk of CAD, and this is also so far the most complete meta-analysis regarding *GSTT1* null polymorphism and the risk of CAD. The integrated analyses showed that *GSTM1* null, *GSTP1* null and *GSTT1* null polymorphisms were all significantly associated with an increased risk of CAD. Sensitivity analyses suggested that the positive associations observed were quite statistically robust, and no publication bias was detected.

The following points are worth noting when interpreting our integrated findings. Firstly, based on the findings of previous observational studies, we speculated that the investigated *GST* null polymorphisms may lead to a diminished gene expression level of *GST*, which may subsequently affect biological functions of *GST*, result in excessive oxidative stress and ultimately increase the risk of CAD [11, 12]. Secondly, considering that the functional significances of investigated *GST* null polymorphisms are well established. Our pooled analyses may be still statistically inadequate to detect the actual associations between *GST* null polymorphisms and CAD in certain ethnic subgroups. Therefore, further studies with larger sample sizes in different populations still

Table 2 Integrated a	alyses for	GSI nu	ll po	lymorphisms	and	CAL
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Polymorphisms	Population	Sample size	Null genotype vs. Present genotype				
		(Cases/ controls)	P value	OR (95%CI)	l ² statistic		
GSTM1 null	CAD	17,054/36630	0.003	1.37 (1.11-1.70)	95%		
	Caucasian	9501/25537	0.72	1.04 (0.85-1.26)	84%		
	East Asian	1623/1244	0.07	1.35 (0.97-1.88)	76%		
	Mixed population	5930/9849	0.004	1.61 (1.16-2.22)	94%		
GSTP1 null	CAD	4595/4390	0.03	1.23 (1.02-1.48)	70%		
	Caucasian	2302/2377	0.17	1.35 (0.88-2.07)	76%		
	Mixed population	1835/1804	0.11	1.23 (0.96-1.59)	68%		
GSTT1 null	CAD	17,120/38115	0.02	1.23 (1.03-1.46)	89%		
	Caucasian	9049/26562	0.02	1.23 (1.03-1.47)	67%		
	East Asian	1902/1979	< 0.0001	1.38 (1.20-1.59)	36%		
	Mixed population	6169/9574	0.61	1.11 (0.76-1.62)	94%		

Abbreviations: OR Odds ratio, CI Confidence interval, NA Not available, CAD Coronary artery disease

The values in bold represent there is statistically significant differences between cases and controls

	Experim						
		ental	Contro	4		Odds Ratio	Odds Batio
Study or Subgroup	Events	Total	Events	Total \	Weight	M-H. Random, 95% C	I M-H, Random, 95% Cl
Abu-Amero 2006 Bazo 2011	655 160	1054	117	762 96	2.9%	9.05 [7.17, 11.42]	
Bhat 2016	62	200	36	200	2.7%	2.05 [1.28, 3.27]	
Bhatti 2018	217	562	127	564	2.9%	2.16 [1.67, 2.81]	L
Cornelis 2007	182	324 2042	143	296 2042	2.9%	1.37 [1.00, 1.88] 0.89 [0.78, 1.00]	
Evans 1996	57	90	484	884	2.7%	1.43 [0.91, 2.24]	
Girisha 2004	46	197	41	198	2.6%	1.17 [0.72, 1.88]	±
Hayek 2006 Kadioğlu 2016	88	193	1142	∠399 30	2.9%	0.92 [0.69, 1.24] 1.62 I0.58, 4 531	
Kariž 2012	142	206	166	257	2.8%	1.22 [0.82, 1.80]	+-
Kim 2008	198	356	191	336	2.9%	0.95 [0.70, 1.28]	±
LI 2000 Macie 2009	178	400	354	790	2.9%	0.99 [0.78, 1.26]	T-
Manfredi 2009	99	169	24	53	2.4%	1.71 [0.92, 3.18]	
Manfredi 2009	108	184	18	47	2.4%	2.29 [1.19, 4.42]	
Martin 2009	41	67	19	63	2.2%	3.65 [1.76, 7.57]	
Masetti 2003 Mir 2016	163	308	66 26	122	2.7%	0.95 [0.63, 1.45]	
Nomani 2011	100	209	57	108	2.7%	0.82 [0.52, 1.31]	-+
Norskov 2011	2052	4930	11362 2	21684	3.0%	0.65 [0.61, 0.69]	•
Olshan 2003 Račalić 2017	252	526	352	868	3.0%	1.35 [1.08, 1.68]	
Phulukdaree 2012	37	102	18	100	2.4%	2.59 [1.35, 4.97]	
Pourkeramati 2020	128	244	138	281	2.8%	1.14 [0.81, 1.61]	
Ramprasath 2011	128	290	56	270	2.8%	3.02 [2.08, 4.39]	
Salama 2002 Singh 2011	45	230	33 65	300	2.5%	1.16 [0.77, 1.75]	+
Tamer 2004	67	148	103	247	2.7%	1.16 [0.77, 1.74]	+
Tang 2009	89	277	59	277	2.8%	1.75 [1.19, 2.56]	
Taspinar 2012	51	122	66	142	2.6%	0.83 [0.51, 1.35]	
Wang 2002	89	277	59	277	2.8%	1.75 [1.19, 2.56]	
Wilson 2000	191	356	107	187	2.8%	0.87 [0.61, 1.24]	-+
Wilson 2003	70	170	107	203	2.7%	0.63 [0.42, 0.95]	
Yeh 2013 Zhang 2011	253	458	121	209	2.8%	0.90 [0.64, 1.25]	
2011	120	200	40	.40	a 1 70		
Total (95% CI)		17054	3	6630	100.0%	1.37 [1.11, 1.70]	•
Total events	8092		17809			0.544	
Test for overall effect	Z = 2.93 /F	= 743.19 = 0.003	, at = 36 (F	- < 0.00	1001); I ^z =	93%	0.01 0.1 1 10 100
	E 2100 (1	01000	/				Favours [experimental] Favours [control]
		For	act plat	of G	STMI	null nolumore	higm and CAD
	â	i. 1'0ľ	est pioi	. 01 0	SIMI	nan porymorp	
	Experim	ental	Contro	d		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total V	Neight	M-H, Random, 95% C	I M-H, Random, 95% CI
Bhatt 2016 Bhatti 2018	132	200	104	200	8.8%	1.79 [1.20, 2.68]	-
Cornelis 2007	817	2042	817	2042	13.9%	1.00 [0.88, 1.13]	+
Kariž 2012	135	206	140	257	9.2%	1.59 [1.09, 2.32]	
Kovacs 2014	27	54	26	78	4.7%	2.00 [0.98, 4.07]	
Phulukdaree 2012	118	209	52	108	6.3%	1.04 [0.65, 1.66]	
Pourkeramati 2020	64	244	56	281	8.7%	1.43 [0.95, 2.15]	
Ramprasath 2011	196	290	152	270	9.9%	1.62 [1.15, 2.28]	-
Singh 2011	90	230	117	300	9.7%	1.01 [0.71, 1.43]	Ŧ
.012013	120	+36	09	209	0.076	0.00 [0.00, 1.37]	
Total (95% CI)	0400	4595	1000	4390 1	100.0%	1.23 [1.02, 1.48]	•
Heterogeneity: Tau ²	2106 = 0.06; Chi ²	= 33.19.	1890 df = 10 (P	= 0.000	03); l ² = 7(0%	
Test for overall effect	Z = 2.16 (F	P = 0.03)					0.01 0.1 1 10 100 Favours [experimental] Favours [control]
	1	b. For	est plo	t of C	GSTP1	null polymorp	hism and CAD
	-						
Church and Carbon and	Experim	nental	Contro	N Total 1	Weight	Odds Ratio	Odds Ratio
Study or Subdroup	Events	Total	events	I Otal 1		M-H. Random, 95% C	M-H. Random, 95% CI
Abu-Amero 2006	Events 463	<u>Total</u> 1054	Events 66	762	3.0%	M-H. Random. 95% C 8.26 [6.24, 10.93]	M-H, Random, 95% CI
Abu-Amero 2006 Bazo 2011	Events 463 69	Total 1054 297	66 19	762 100	3.0% 2.4%	M-H. Random, 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28]	M-H, Kandom, 95% Cl
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhatti 2019	Events 463 69 12	Total 1054 297 200	66 19 25	762 100 200	3.0% 2.4% 2.1%	M-H, Random, 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 0.61 [0.45 0.022]	M-H, Kandom, 95% Cl
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhatti 2018 Cora 2013	Events 463 69 12 86 106	Total 1054 297 200 562 324	66 19 25 129 63	762 100 200 564 296	3.0% 2.4% 2.1% 3.0% 2.9%	M-H. Random, 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 0.61 [0.45, 0.82] 1.80 [1.25, 2.58]	MH, Kandom, 35% SI
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhatti 2018 Cora 2013 Cornelis 2007	Events 463 69 12 86 106 388	Total 1054 297 200 562 324 2042	66 19 25 129 63 408	762 100 200 564 296 2042	3.0% 2.4% 2.1% 3.0% 2.9% 3.2%	M-H, Random, 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 0.61 [0.45, 0.82] 1.80 [1.25, 2.58] 0.94 [0.80, 1.10]	M+5, Kandom, 957, 51
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhatti 2018 Cora 2013 Cornelis 2007 Decharatchakul 2020	Events 463 69 12 86 106 388 115	Total 1054 297 200 562 324 2042 279	66 19 25 129 63 408 242	762 100 200 564 296 2042 735	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0%	M-H, Random, 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 0.61 [0.45, 0.82] 1.80 [1.25, 2.58] 0.94 [0.80, 1.10] 1.43 [1.08, 1.90]	M-H, Kandom, 353, 51
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhatti 2018 Cora 2013 Cornelis 2007 Decharatchakul 2020 García 2018 Girisha 2004	Events 463 69 12 86 106 388 115 15 15	Total 1054 297 200 562 324 2042 279 79 197	66 19 25 129 63 408 242 8 36	762 100 200 564 296 2042 735 101 198	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.3%	M-H. Random, 95% C 8.26 [6.24, 10.93] 1.29 (0.73, 2.28] 0.45 [0.22, 0.92] 0.61 [0.45, 0.82] 1.80 [1.25, 2.58] 0.94 [0.80, 1.10] 1.43 [1.08, 1.90] 2.72 [1.09, 6.80] 0.37 [0.20, 0.70]	M-H, Kandom, 357, 51
Abu-Amero 2006 Bazo 2011 Bhati 2018 Cora 2013 Cornelis 2007 Decharatchakul 2020 García 2018 Girisha 2004 Hayek 2006	Events 463 69 12 86 106 388 115 15 15 15 30	Total 1054 297 200 562 324 2042 279 79 197 193	66 19 25 129 63 408 242 8 36 392	762 100 200 564 296 2042 735 101 198 2399	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.3% 2.8%	MH, Random, 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 1.80 [1.25, 2.58] 0.94 [0.80, 1.10] 1.43 [1.08, 1.90] 2.72 [1.09, 6.80] 0.37 [0.20, 0.70] 0.94 [0.63, 1.41]	M-H. Kandom. 353. Cl
Abu-Amero 2006 Bazo 2011 Bhatt 2016 Cora 2013 Cornelis 2007 Decharatchakul 2020 Garcia 2018 Girisha 2004 Hayek 2006 Kadioğlu 2016	Events 463 69 12 86 106 388 115 15 15 30 6	Total 1054 297 200 562 324 2042 279 79 197 193 29	66 19 25 129 63 408 242 8 36 392 5	762 100 200 564 296 2042 735 101 198 2399 30	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.3% 2.8% 1.2%	M.H. Random. 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 1.80 [1.25, 2.58] 0.94 [0.80, 1.10] 1.43 [1.08, 1.90] 2.72 [1.09, 6.80] 0.37 [0.20, 0.70] 0.94 [0.63, 1.41] 1.30 [0.35, 4.86]	M-H, Kandom, 353, 51
Abu-Amero 2006 Bazo 2001 Bhat 2016 Bhat 2016 Bhatti 2018 Cornelis 2007 Decharatchakul 2020 Garcia 2018 Girisha 2004 Hayek 2006 Kariz 2012 Kariz 2012	Events 463 69 12 86 106 388 115 15 15 30 6 777	Total 1054 297 200 562 324 2042 279 79 197 193 29 206 255	66 19 25 129 63 408 242 8 36 392 5 108	762 100 200 564 296 2042 735 101 198 2399 30 257 326	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.3% 2.8% 1.2% 2.8% 3.0%	M-H. Random. 95% C 8.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 1.61 [0.45, 0.82] 1.80 [1.25, 2.58] 0.94 [0.80, 1.10] 1.43 [1.08, 1.90] 2.72 [1.99, 6.80] 0.37 [0.20, 0.70] 0.94 [0.63, 1.41] 1.30 [0.35, 4.86] 0.82 [0.57, 1.20]	M+H, Kandom, 357, Cl
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhat 2016 Bhat 2016 Cora 2013 Cornelis 2007 Decharatchakul 2020 Garcia 2018 Girisha 2004 Hayok 2006 Kadroğlu 2016 Kaniž 2012 Kim 2008 Lakshmi 2012	Events 463 69 12 86 106 388 115 15 15 30 6 77 196 81	Total 1054 297 200 562 324 2042 279 79 197 193 29 206 356 352	66 19 25 129 63 408 242 8 36 392 5 108 187 39	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.8% 1.2% 2.8% 3.0% 2.7%	M-H. Random. 95% C 8.26 (6.24, 10.93) 1.29 (0.73, 2.28) 0.45 (0.22, 0.92) 0.61 (0.45, 0.82) 1.80 (1.25, 2.58) 0.94 (0.80, 1.10) 1.43 (1.08, 1.90) 2.72 (1.09, 6.80) 0.37 (0.20, 0.70) 0.94 (0.63, 1.41) 1.30 (0.35, 4.86] 0.82 (0.57, 1.20) 0.98 (0.72, 1.32) 1.86 (1.22, 2.83)	M-H. Kandom. 353. Cl
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhat 2016 Bhat 2016 Cora 2013 Cornelis 2007 Decharatchakul 2020 Garcia 2018 Girisha 2004 Hayek 2006 Kadroğlu 2016 Kadrž 2012 Kim 2008 Lakshmi 2012 Lewinsson 2014	Events 463 69 12 86 106 388 115 15 5 15 30 6 77 196 81 11	Total 1054 297 200 562 324 2042 279 79 197 193 29 206 356 352 112	Events 66 19 25 129 63 408 242 8 36 392 5 108 187 39 168	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.8% 1.2% 2.8% 3.0% 2.7% 2.3%	M:H. Random. 95% C 8.26 [6.24, 10.93] 0.45 [0.22, 0.92] 0.61 [0.45, 0.82] 1.80 [1.25, 2.58] 0.94 [0.80, 1.10] 1.43 [1.08, 1.90] 2.72 [1.09, 6.80] 0.37 [0.20, 0.70] 0.94 [0.63, 1.41] 1.30 [0.35, 4.86] 0.82 [0.75, 1.20] 0.98 [0.72, 1.32] 1.86 [1.22, 2.83] 0.68 [0.36, 1.30]	M-H, Kandom, 353, 51
Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhat 2016 Bhat 2016 Cora 2013 Cornelis 2007 Decharatchakul 2020 Garcia 2018 Girisha 2004 Hayek 2006 Kadi 2012 Kadi 2012 Kadi 2012 Lakshmi 2012 Lakshmi 2012 Lakshmi 2015 Lakshmi 2016 Lakshmi 2016	Events 463 69 12 86 106 388 8115 15 15 15 15 30 0 6 77 7196 811 11 74	Total 1054 297 200 562 324 2042 279 79 197 193 299 206 356 352 112 400 000 000 000 000 000 000 00	Events 66 19 25 129 63 408 242 8 36 392 5 108 187 39 168 168 237	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221 890	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.3% 2.8% 1.2% 2.8% 3.0% 2.7% 2.3% 3.0% 2.7% 2.3% 3.0%	MH-L Random, 95% C 44, 10.33 8.26 (6.24, 10.33) 1.29 (0.73, 2.28) 0.45 (0.22, 0.92] 1.80 (1.25, 2.58) 0.44 (0.80, 1.10) 1.43 (1.08, 1.30) 2.72 (109, 6.80) 0.37 (0.20, 0.70) 0.54 (0.63, 1.41) 1.30 (0.55, 4.86] 0.52 (0.57, 1.20) 0.58 (0.72, 1.32) 1.86 (1.22, 1.83) 0.68 (0.36, 1.30) 0.98 (0.72, 1.32) 1.86 (1.22, 1.83) 0.68 (0.36, 1.30) 0.68 (0.36, 1.30)	M-H. Kandom. 353. Cl
Situly of Subgroup. Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhat 2016 Bhat 2016 Cora 2013 Cornelis 2007 Decharatichakul 2020 Garcia 2018 Kastoglu 2016 Kastoglu 2016 Kastoglu 2016 Kastoglu 2016 Kastoglu 2016 Lakshmi 2012 Lakshmi 2012 Li 2000 Macie 2009 Macie 2009	Events. 463 69 12 86 106 388 115 15 15 30 6 6 77 71 96 81 1 11 11 74 209 95	Total 1054 297 200 562 324 2042 279 79 197 193 299 206 356 352 112 400 869 169	Events 66 19 25 129 63 408 242 8 36 392 5 108 187 189 168 166 337 13 13	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221 890 1573 53	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.3% 2.8% 1.2% 2.8% 3.0% 2.7% 2.3% 3.0% 3.1% 3.1%	MH.H.andom. 955.C 44, 10.33) 1.29 (0.73, 2.28) 0.45 (0.22, 0.92) 0.45 (0.22, 0.92) 0.41 (0.45, 0.62) 1.80 (1.25, 2.58) 0.94 (0.80, 1.10) 1.43 (1.08, 1.50) 0.37 (0.20, 0.70) 0.34 (0.43, 1.41) 1.30 (0.35, 4.86) 0.32 (0.25, 1.22) 0.84 (0.43, 1.41) 1.30 (0.35, 4.86) 0.48 (0.26, 1.32) 1.86 (1.22, 2.83) 0.88 (0.36, 1.30) 0.99 (0.73, 1.34) 1.16 (0.55, 1.41) 1.69 (0.73, 1.34) 1.16 (0.55, 1.41) 1.30 (0.77, 1.20)	M-H. Kandom. 353. Cl
-study cor subgroup. Abu-Amero 2006 Bazo 2011 Bhat 2016 Bhat 2016 Bhat 2016 Correlis 2007 Garcia 2018 Girisha 2004 Hayek 2005 Kanż 2012 Kim 2008 Lakshmi 2012 Lakshmi 2012 Lakshmi 2014 Li Levinsson 2014 Li Levinsson 2014 Li Levinsson 2014 Li Levinsson 2014	Events. 463 69 12 86 106 388 115 15 30 6 77 7 196 81 11 11 11 74 209 95 84	Total 1054 290 562 324 2042 279 79 197 193 29 206 356 352 112 400 869 184	Events 66 19 25 129 63 408 242 8 36 392 5 108 187 187 108 186 166 337 13	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221 890 1573 53 47	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.2% 3.0% 1.7% 2.8% 1.2% 2.8% 2.8% 3.0% 3.0% 3.1% 2.2% 2.1%	MH:H.Random. 955.C 6.26 [6.24, 10.93] 1.29 [0.73, 2.28] 0.45 [0.22, 0.92] 0.61 [0.45, 0.62] 1.80 [125, 2.58] 0.44 [0.80, 1.10] 1.27 [1.96, 6.60] 0.37 [0.20, 0.70] 0.44 [0.83, 1.41] 1.30 [0.35, 4.86] 0.28 [0.77, 1.20] 1.86 [122, 2.83] 0.86 [0.72, 1.32] 1.86 [122, 6.36] 0.88 [0.72, 1.32] 1.86 [122, 6.36] 0.86 [0.56, 6.13] 0.96 [0.71, 1.32] 1.86 [122, 6.36] 0.87 [0.72, 1.32] 1.86 [0.86, 1.30] 0.87 [0.72, 1.32] 1.86 [0.86, 1.30] 0.87 [0.72, 1.32] 0.88 [0.72, 1.32] 1.86 [0.86, 1.30] 0.99 [0.73, 1.34] 1.80 [0.85, 1.41] 3.95 [1.97, 7.92] 2.20 [1.09, 4.43]	M-H, Kandom, 955 Cl
-Study Cor Subjective Bana 2011 Bhara 2016 Bhara 2011 Bhara 2018 Bhara 2018 Bhara 2018 Garcia 2018 Garcia 2018 Garcia 2018 Kana 2006 Kana 2012 Kim 2006 Kana 2012 Levinson 2014 Levinson 2014 Levinson 2014 Levinson 2014 Levinson 2014 Levinson 2014 Levinson 2014 Mantreal 2009 Martine 2009	Events 463 69 12 86 106 388 115 15 30 6 77 7 196 81 11 11 74 4 209 95 84 4 12	Total 1054 290 562 324 2042 279 79 197 193 29 206 356 352 112 400 869 184 67	Events 66 19 25 129 3 408 242 8 36 392 5 108 187 39 168 166 337 13 12	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221 890 1573 53 47 63	3.0% 2.4% 2.1% 3.0% 3.2% 3.2% 3.2% 3.0% 2.8% 3.0% 2.8% 3.0% 2.8% 3.0% 3.1% 2.2% 3.0% 3.1% 2.1% 1.8%	$\begin{array}{l} \underbrace{\textbf{MH}} \textbf{Random, 955.C} \\ \textbf{6.26} \ [6.24, 10.83] \\ \textbf{1.29} \ [0.73, 2.24] \\ \textbf{0.45} \ [0.22, 0.92] \\ \textbf{0.45} \ [0.22, 0.92] \\ \textbf{0.51} \ [1.64, 0.162] \\ \textbf{0.45} \ [1.62, 2.58] \\ \textbf{0.44} \ [1.68, 1.56] \\ \textbf{0.71} \ [1.68, 1.56] \\ \textbf{0.72} \ [1.67, 1.23] \\ \textbf{0.86} \ [1.62, 1.56] \\ \textbf{0.86}$	
-Study Cor Study Cours Baco 2016 Baco 2011 Bhat 2016 Corra 2013 Bhat 2016 Corra 2013 Grinba 2017 Decharatishaku 2020 Garcia 2018 Grinba 2004 Hayek 2006 Kari 2012 Kari 2012 Kari 2012 Kari 2012 Kari 2012 Kari 2012 Manfred 2009 Manfred 2009 Manfred 2009 Manfred 2009	Events. 463 699 12 86 106 388 115 15 15 15 15 30 6 77 196 81 11 74 209 95 84 12 217 77	Total 1054 297 200 562 324 2042 279 79 197 193 29 206 3566 3522 112 400 869 169 184 67 308	Events 66 19 25 129 3 408 242 8 36 392 5 108 187 39 168 187 39 168 1337 13 12 40 40	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221 890 1573 53 47 63 122	3.0% 2.4% 2.1% 3.0% 3.2% 3.2% 3.2% 3.2% 2.8% 2.8% 2.8% 2.8% 3.0% 2.7% 2.8% 3.0% 3.1% 2.2% 2.1% 1.8% 2.1%	$\begin{array}{c} \underbrace{\textbf{MH}, \textbf{H}, \textbf{mandrom}, \textbf{mS5C}, \textbf{C}}{\textbf{S}, 26 (6, 24, 10, 03)}\\ \textbf{L}, 29 (0, 73, 2, 28)\\ \textbf{L}, 20 (0, 73, 2, 28)\\ \textbf{L}, 20 (1, 25, 2, 58)\\ \textbf{L}, 30 (1, 25, 2, 58)\\ \textbf{L}, 30 (1, 25, 2, 58)\\ \textbf{L}, 31 (1, 68, 1, 50)\\ \textbf{L}, 71 (1, 96, 1, 60)\\ \textbf{L}, 13 (1, 96, 1, 96)\\ \textbf{L}, 14 (1, 96, 1, 16)\\ \textbf{L}, 14 (1, 96, 1, 16)\\ \textbf{L}, 16 (1, 96, 1, 14)\\ \textbf{L}, 16 (1, 96, 1, $	M-H. Kandom. 353. Cl
-Study Cor Subjectives Abu-Americ 2006 Basic 2011 Beharit 2018 Cornelis 2017 Beharit 2018 Cornelis 2007 Decharatchaku 2020 Garicla 2018 Garicla 2018 Carcia 2018 Carcia 2018 Carcia 2018 Carcia 2018 Kini 2008 Lakshmi 2012 Levinson 2014 Levinson 2014 Manteeli 2009 Martin 2009	Events. 463 69 12 866 106 388 115 15 15 300 6 81 117 74 209 95 84 12 117 23 16	Total 1054 297 200 562 324 2042 279 79 197 193 29 206 356 352 112 400 869 169 184 67 308 100 209	Events 66 66 19 25 129 63 408 242 8 36 392 108 168 168 166 337 13 129 40 16 16	762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221 890 1573 53 53 47 63 122 100 108	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 2.8% 1.2% 2.8% 2.8% 2.7% 2.3% 3.0% 2.7% 2.3% 3.1% 2.2% 2.1%	$\begin{array}{c} \underbrace{\textbf{MH}, \textbf{H}, \textbf{and, m}, \textbf{S5X}, \textbf{C}}{\textbf{a}_{2} \in \{4, 10, 33\}}\\ \textbf{h}_{2} \in \{2, 4, 10, 33\}\\ \textbf{h}_{2} \in \{0, 73, 2, 24\}\\ \textbf{h}_{3} \in \{1, 0, 45, 0, 62\}\\ \textbf{h}_{4} \in \{1, 0, 22, 0, 52\}\\ \textbf{h}_{4} \in \{1, 0, 45, 0, 62\}\\ \textbf{h}_{4} \in \{1, 0, 16, 16, 16\}\\ \textbf{h}_{4} \in \{1, 0, 16, 16\}\\ \textbf{h}_{4} \in \{1, 0, 16\}\\ \textbf{h}_{4} \in \{1, 0, 16\}\\ \textbf{h}_{4} \in \{1, 0, 16\}\\ \textbf{h}_{4} \in \{1, 16\}\\ \textbf{h}_{4} \in \{1$	M-H. Kandom. 353. Cl
	Events. 463 69 12 866 106 388 115 15 15 30 6 6 77 196 81 11 11 11 11 11 11 11 11 11 11 209 95 5 84 12 209 95 12 84 12 20 6 12 15 15 15 15 15 15 15 15 15 15 15 15 15	Total 1054 297 200 562 324 2042 279 797 193 299 206 356 352 112 400 869 169 169 169 169 169 169 169 1	Events 666 19 255 129 63 408 242 8 366 392 5 108 187 39 168 166 337 13 13 13 12 40 16 17 3161	Total 762 100 200 564 296 2042 735 101 198 2399 30 257 336 282 1221 890 1573 53 63 122 108 21684	3.0% 2.4% 2.1% 3.0% 3.2% 3.2% 3.0% 1.7% 2.3% 2.8% 3.0% 2.8% 3.0% 2.7% 2.3% 3.1% 2.2% 2.1% 2.7% 2.1% 3.2%	$\begin{array}{l} \underbrace{\textbf{HH}} & \textbf{Handsom}, \underbrace{\textbf{S5C}}_{2} \\ \textbf{6}, 26 \\ \textbf{6}, 24 \\ \textbf{6}, 24 \\ \textbf{10}, \textbf{3}, 129 \\ \textbf{0}, \textbf{7}, 220 \\ \textbf{0}, \textbf{5}, 104 \\ \textbf{5}, 202 \\ \textbf{0}, \textbf{5}, 104 \\ \textbf{5}, 202 \\ \textbf{0}, \textbf{5}, 104 \\ \textbf{5}, 202 \\ \textbf{0}, \textbf{5}, 104 \\ \textbf{5}, 114 $	M-H. Kandom. 353. Cl
-Study Cor Subjective Aba-Americ 2006 Baca 2011 Baca 2011 Baca 2011 Baca 2013 Cornelis 2007 Decharatchaku 2020 Garcia 2018 Garcia 2018 Garcia 2018 Garcia 2018 Garcia 2018 Karat 2005 Karat 2012 Lashanni 2012 Lashanni 2012 Lashanni 2012 Manfredi 2009 Manfredi 2009 Manfr	Events. 463 699 12 866 106 3888 115 15 15 15 300 6 77 196 811 11 74 209 95 84 4 12 117 23 16 74 20 75 86 87 10 77 10 75 86 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 196 77 74 196 74 74 209 95 84 115 74 74 74 74 74 72 74 74 74 75 75 76 77 76 76 77 77 74 76 77 74 76 77 77 76 76 77 77 76 76 77 77	Tetal 1054 297 200 562 324 2042 279 197 193 299 206 3556 3552 112 400 869 184 67 3088 1000 2090 4930 526	Events 66 19 25 129 63 408 242 8 366 392 5 108 187 39 166 337 13 12 40 16 177 3161 165	Iotal 762 100 200 206 296 2042 735 201 198 2399 30 2577 336 2862 2577 336 282 1573 53 47 63 122 100 108 108 21684 868	3.0% 2.4% 2.1% 3.0% 3.2% 3.2% 3.0% 1.7% 2.8% 1.2% 2.8% 1.2% 2.8% 3.0% 3.1% 2.2% 3.0% 3.1% 2.2% 3.2% 3.2%	$\begin{array}{c} {\rm MH}, {\rm H}, {\rm anatom}, {\rm m} {\rm S5.C}, {\rm G}, {\rm a}, {\rm a}, {\rm c}, {\rm a}, {$	M-H. Kandom. 353. Cl
	Events. 463 69 12 86 106 388 115 15 15 15 15 30 6 77 196 811 111 74 2009 95 84 122 117 205 84 122 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 81 117 196 84 117 106 106 117 117 116 117 116 117 116 117 116 117 116 117 116 117 117	Total 1054 297 200 562 2799 979 971 93 206 356 356 356 356 112 400 869 184 67 108 100 2099 4930 526 51 52	Events 66 19 25 129 63 408 242 8 366 392 5 108 187 391 168 166 17 3161 165 5	Joian 762 100 200 564 296 2042 735 101 2399 30 257 336 282 1221 1880 1573 53 47 63 122 100 108 21684 868 57 177	3.0% 2.4% 2.1% 3.0% 2.9% 3.2% 3.0% 1.7% 2.8% 1.2% 2.8% 1.2% 2.8% 2.7% 2.3% 3.0% 3.0% 3.1% 2.1% 2.1% 2.1% 2.1% 3.0% 1.8% 2.1% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0	$\begin{array}{c} \underbrace{\textbf{MH}, \textbf{H}, \textbf{mandrom}, \textbf{mS5C}, \textbf{C}}{\textbf{S}, 26 \left[6.24, 10.83 \right]} \\ \textbf{h}, 26 \left[6.24, 10.83 \right] \\ \textbf{h}, 26 \left[10.73, 2.24 \right] \\ \textbf{h}, 20 \left[10.75, 2.88 \right] \\ \textbf{h}, 20 \left[10.85, 2.88 \right] \\ \textbf{h}, 20 \left[10.75, 1.23 \right] \\ \textbf{h}, 20 \left[10.95, 4.43 \right] \\ \textbf{h}, 20 \left[10.95, 4.53 \right] \\ \textbf{h}, 20 \left[10.95, 4.55 $	
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Fig. 2 Forest plots for this meta-analysis



need to confirm our findings. Thirdly, we want to study all polymorphic loci of the GST gene initially. Nevertheless, our comprehensive literature searching did not reveal sufficient eligible studies to support integrated analyses for any other polymorphic loci of the GST gene, so we only explored associations with the risk of CAD for three most commonly investigated polymorphisms of the GST gene in this metaanalysis. Fourthly, it is worth noting that previously, Song et al. [15] also tried to investigate associations between GSTT1 null polymorphism and the risk of CAD through a meta-analysis. Nevertheless, this previous meta-analysis only covered relevant genetic association studies that were published before 2014. Since our literature searching revealed that many related studies were published after 2014, an updated meta-analysis like ours is warranted to get more reliable findings. Consistent with the previous meta-analysis, a similar significant finding for GSTT1 null polymorphism was observed in our integrated analyses. Considering that our updated analyses were derived from more eligible studies, our observations should be considered as a valuable confirmation for pre-existing literatures. Fifthly, GST null polymorphisms have also been found to be closely associated with the risk of diabetes, essential hypertension and other types of atherothrombotic disorders such as ischemic stroke or peripheral artery disease [16-20]. Considering that the above mentioned diseases are either considered to be conventional risk factors of CAD or usually manifest as co-morbid conditions of CAD, it would be interesting to perform some stratified analyses accordingly. Nevertheless, due to the fact that the vast majority of eligible studies failed to report genotypic data according to co-morbid conditions, it is impossible for us to conduct such analyses, and we highly recommend future genetic association studies to carry out stratified analyses according to the co-morbid status of these diseases.

The major limitations of our integrated analyses were listed below. Firstly, our integrated analyses results were derived from unadjusted pooling of previous studies. Without access to raw data of eligible studies, we can only assess associations between GST null polymorphisms and the risk of CAD based on re-calculations of raw genotypic frequencies provided by eligible studies, and we need to admit that lack of further adjustment for baseline characteristics such as age, gender or co-morbid conditions may possibly influence reliability of our findings [21]. Secondly, environmental factors such as smoking status, eating habits or exercise levels may also influence associations between polymorphisms in GST null polymorphisms and the risk of CAD. However, since most of previous studies only paid attention to genetic associations, it is almost impossible for us to explore genetic-environmental interactions in a metaanalysis based on these previous literatures [22]. Thirdly, we did not select 'grey literatures' that were not formally published in peer-reviewed scientific journals for integrated analyses because these literatures are generally considered to be incomplete and it is almost impossible for us to extract all necessary data items from these literatures or assess their quality through the NOS scale. Nevertheless, since we did not select 'grey literatures' for integrated analyses, despite that funnel plots were found to be overall symmetrical, it should be acknowledged that publication biases still may influence reliability of our integrated analyses results [23].

Conclusion

In conclusion, this meta-analysis demonstrated that *GSTM1* null, *GSTP1* null and *GSTT1* null polymorphisms were all significantly associated with an increased risk of CAD. These findings suggested that *GSTM1* null, *GSTP1* null and *GSTT1* null polymorphisms may have the potential to serve as genetic biomarkers of CAD and they may be used to identify subjects at higher risk of developing CAD. Further studies with larger sample sizes in different populations are still needed to confirm our findings. Moreover, experimental studies are also warranted to reveal the exact underlying mechanisms of the positive associations observed between above mentioned *GST* null polymorphisms and the risk of CAD in the future.

Abbreviations

GST: Glutathione S-transferase; CAD: Coronary artery disease; HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa scale; OR: Odds ratios; CI: Confidence intervals

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Authors' contributions

HS and YC conceived and designed this meta-analysis. YC and JL searched literatures. YZ and XM analyzed data. HS and YC wrote the manuscript. All authors have approved the final manuscript as submitted.

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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