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Association between apolipoprotein C3 Sst I, T-455C, C-482T and C1100T polymorphisms and risk of coronary heart disease

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ABSTRACT

Objectives: Apolipoprotein C3 (ApoC3) polymorphisms have been suggested to be associated with risk of coronary heart disease (CHD). However, the results of relevant studies were inconsistent. We aimed to systematically evaluate this issue.

Design: PubMed, EMBASE and Cochrane library databases (up to March 2013) were systematically searched to identify studies evaluating the association between ApoC3 polymorphisms and CHD risk. Two reviewers independently identified studies, extracted and analysed the data. Either a fixed-effects or a random-effects model was adopted to estimate overall ORs.

Studies reviewed: Finally, 20 studies comprising 15 591 participants were included in this systematic review. Fifteen studies with 11 539 individuals were included in the meta-analysis of Sst I polymorphism, four studies comprising 3378 individuals assessed T-455C polymorphism, four studies with 3070 participants evaluated C-482T polymorphism and C1100T polymorphism was assessed by three studies comprising 4662 participants.

Results: Under dominant model, Sst I polymorphism was borderline significantly associated with CHD risk (S1S2+S2S2 vs S1S1, pooled OR=1.19, 95% CI 1.00 to 1.42). Subgroup analyses suggested that Sst I polymorphism was significantly associated with myocardial infarction (MI) risk (pooled OR=1.42, 95% CI 1.06 to 1.91), and Sst I polymorphism was statistically associated with CHD risk among Asian population (pooled OR=1.35, 95% CI 1.08 to 1.69) and in retrospective studies (pooled OR=1.30, 95% CI 1.04 to 1.61). A significant association was observed between T-455C polymorphism and CHD risk (TC+CC vs TT, pooled OR=1.22, 95% CI 1.06 to 1.42). A borderline significant association was suggested between T-455C polymorphism and MI risk (pooled OR=1.21, 95% CI 1.00 to 1.46). C-482T and C1100T polymorphisms were not indicated to be associated with CHD risk or MI risk.

Conclusions: ApoC3 Sst I and T-455C polymorphisms might be associated with CHD risk.

Strengths and limitations of the study

- The present study comprehensively evaluated the association between apolipoprotein C3 polymorphisms, including Sst I, T-455C, C-482T, C1100T and coronary heart disease risk. The methods of this study were rigorous and were based on the guidelines for conducting and reporting systematic reviews.
- Most of the included studies were from Asia, Europe and the USA, so the conclusions may not be true for other ethnic groups. Besides, between-study heterogeneity could not be completely explained.

INTRODUCTION

The progression of coronary heart disease (CHD) is complicated and is influenced by multigenetic and environmental factors, and atherosclerosis of the coronary artery is the basic pathogenic factor of CHD.[1] Plasma lipids and lipoproteins are important risk factors for atherosclerosis, and genes involved in lipoprotein metabolism might be candidate genes for CHD susceptibility.[2 3] Apolipoprotein C3 (ApoC3) is an essential component of circulating particles in the TG-rich lipoprotein, and inhibits the hydrolysis of TG-rich particles by the lipoprotein lipase and their hepatic uptake mediated by apolipoprotein E.[4] Therefore, high levels of ApoC3 may cause hypertriglyceridaemia.[5] Previous studies supported that ApoC3 might play an important role in CHD development, and the ApoC3 concentration was also associated with CHD risk.[6 7]

Serum ApoC3 concentration was shown to be influenced by genetic and acquired factors.[8] Several polymorphisms have been found in ApoC3 gene, including C-482T, T-455C, Sst I and C1100T polymorphisms.[9–12] In recent years, studies have investigated the correlation between these polymorphisms and CHD risk, while the results were inconsistent. The aim of our meta-analysis was to assess the association between ApoC3 polymorphisms and risk of CHD.

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METHODS

Literature search

Systematic literature searches were conducted before March 2013 in PubMed, EMBASE and Cochrane library 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'; 'apolipoprotein C3' OR 'apolipoprotein C' OR 'apolipoprotein C- III' OR 'apolipoprotein C III' OR 'APO C3' OR 'APOC3" OR 'APOC' OR 'APO C III' OR 'APO C- III'; 'polymorphism' OR 'variant' OR 'SNP' OR 'mutation'. References of relevant articles were also scanned for studies potentially missed in the primary searches. Articles published in English were retrieved. And the retrieved studies were carefully examined to exclude potential duplicates or overlapping data. This meta-analysis was designed, conducted and reported according to PRISMA statement.[13]

Selection criteria, data extraction and study quality assessment

Studies retrieved from the initial search were then screened for eligible articles. Titles and abstracts were scanned and then full articles were reviewed. We included articles if they met all the following criteria: (1) evaluating the association between ApoC3 polymorphism and CAD and (or) myocardial infarction (MI); (2) OR estimates and their 95% CI were available or could be calculated; (3) each polymorphism included in the meta-analysis should be reported by at least two studies.

Data were extracted independently by two reviewers (BL and YH). The following information was extracted from each study: first author, publication year, country, study design, sample size, gender distribution, mean age, phenotype (disease), genotype of cases and controls, whether the polymorphism(s) evaluated was in Hardy-Weinberg equilibrium or not and the genotyping assay method. Any discrepancy was resolved by a third investigator. The Newcastle-Ottawa Scale (NOS) method was applied to assess the study quality.[14] The NOS contains eight items and the score ranged from 0 to 9.

Statistical analysis

Dominant model was applied in this study as this genetic model was most widely used in the included studies. Because some studies did not apply dominant model, we recalculated OR values under dominant model. Either a fixed-effects model or a random-effects model was applied to pool the OR estimates of each study, according to heterogeneity across studies. The extent of heterogeneity was checked using the χ^2 test and I^2 test; $p \leq 0.10$ and/or $I^2 > 50\%$ indicates a significant heterogeneity. When $p > 0.10$, the fixed-effects model was applied and otherwise we used the random-effects model. Subgroup analysis was applied to explore heterogeneity. Study-specific ORs of CHD were first pooled and then evaluated the association between ApoC3 polymorphisms and MI risk separately. Funnel plots were constructed and Begg's and Egger's tests were used to assess the publication bias, and $p \leq 0.10$ was considered to be significant. All analyses were conducted using the Stata software (V.11.0; StatCorp, College Station, Texas, USA).

RESULTS

Study selection and characteristics

A total of 1532 articles were identified by searching PubMed, EMBASE and Cochrane library databases. Among them, 1482 articles were excluded by screening the titles and abstracts. The remaining 50 articles were carefully evaluated as full texts and 30 articles were excluded. The reasons for exclusion were articles not on right topic (15 articles), insufficient data (six papers), relevant reviews (eight papers) and duplicate reports from the same study (one article). This meta-analysis finally included 20 articles.[9–12 15–30] The selection process was shown in figure 1 while the characteristics of those studies were listed in online supplementary table S1. Among these studies, fifteen studies assessed ApoC3 Sst I polymorphism, four studies evaluated ApoC3 T-455C polymorphism, four studies reported ApoC3 C-482T polymorphism and three investigated ApoC3 C1100T polymorphism (several studies reported more than one polymorphism). The results of quality assessment were shown in the online supplementary table S2 and the score of the included studies ranged from 5 to 9.

AOPC3 polymorphisms and risk of CHD

Meta-analysis of Sst I polymorphism

A total of 15 studies with 11 539 individuals were assessed for the association between Sst I polymorphism and CHD risk. Fourteen studies were in Hardy-Weinberg equilibrium while one study did not report whether Sst I polymorphism was in Hardy-Weinberg equilibrium or not.[22] Most of the studies used restriction fragment length

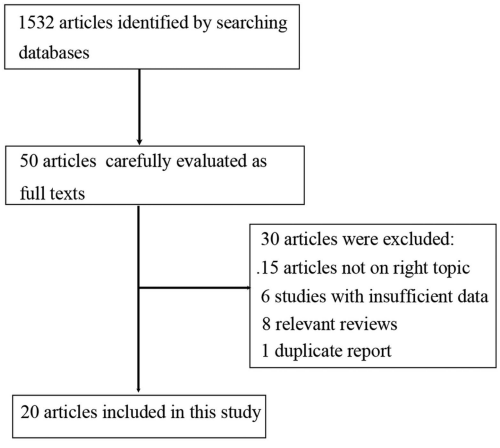

Figure 1 Flow diagram of study selection process.

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polymorphism (RFLP) method for DNA genotyping (n=14) and one study applied the immobilised oligonucleotide probes array (IOPA) method.[24] Multivariable OR could be extracted from four studies[10 20 22 24] (see online supplementary table S3). Under dominant model (S1S2+S2S2 vs S1S1), the pooled univariate OR of all studies was 1.19 (95% CI 1.00 to 1.42; figure 2 and table 1), indicating a borderline significant association between Sst I polymorphism and CHD risk. There was significant heterogeneity among studies (I^2=48.9%, p=0.017; figure 2 and table 1). The pooled multivariable OR was 1.11 (0.73 to 1.70), which did not suggest a significant association.

According to study characteristics, subgroup analysis was adopted, as shown in table 2. Pooled results showed that S1S2 and S2S2 genotyes might increase the risk of CHD in Asian population (pooled OR=1.35, 95% CI 1.08 to 1.69) but not in Caucasian population (pooled OR=1.14, 95% CI 0.92 to 1.41). Study design could also influence the result; Sst I polymorphism was significantly associated with CHD risk in retrospective studies (pooled OR=1.30, 95% CI 1.04 to 1.61) but not in prospective studies (pooled OR=0.98, 95% CI 0.75 to 1.28). Besides, Sst I polymorphism was observed to be significantly associated with MI risk (pooled OR=1.42, 95% CI 1.06 to 1.91) but not CHD risk (pooled OR=1.09, 95% CI 0.87 to 1.35). After excluding the study that did not report Hardy-Weinberg equilibrium, the pooled OR was 1.24 (95% CI 1.04 to 1.47). The pooled OR of the studies that applied RFLP method was 1.19 (95% CI 0.98 to 1.44).

Meta-analysis of T-455C polymorphism

The association between T-455C polymorphism and CHD risk was evaluated by four studies comprising 3378 individuals. All the studies were in Hardy-Weinberg equilibrium. The IOPA method was used by three studies while real-time fluorescence quantitative PCR was applied by one study.[9] Only one study reported a multivariable OR of 1.82 (95% CI 1.05 to 3.18), while the unadjusted OR was 1.15 (98% CI 0.85 to 1.55[17]; see online supplementary table S3). The results indicated a significant association between T-455C polymorphism and CHD risk (TC+CC vs TT, pooled OR=1.22, 95% CI 1.06 to 1.42; figure 3 and table 1). No significant heterogeneity among studies was indicated (I^2=0%, p=0.580; figure 3 and table 1). Two studies reported the association between T-455C polymorphism and MI risk, and the pooled result suggested a borderline significant association (pooled OR=1.21, 95% CI 1.00 to 1.46).

Meta-analysis of C-482T polymorphism

Four studies with 3070 individuals reported the association between C-482T polymorphism and CHD risk. Only one study did not report whether C-482T polymorphism was in Hardy-Weinberg equilibrium or not.[22] Two studies applied real-time fluorescence quantitative PCR method,[9 16] one study used RFLP method[22] and the other study adopted the IOPA method.[19] Multivariable OR could be extracted from two studies[16 18] (see online supplementary table S3). There was no significant association between C-482T polymorphism and CHD risk (CT+TT vs CC, pooled OR=1.06, 95% CI 0.92 to 1.22; figure 4 and table 1). No significant heterogeneity was observed (I^2=0%, p=0.788; figure 4 and table 1). Only one study reported the association between C-482T polymorphism and MI risk (OR=1.12, 95% CI 0.88 to 1.43).[19]

Meta-analysis of C1100T polymorphism

Three studies comprising 4662 participants evaluated the association between C1100T polymorphism and

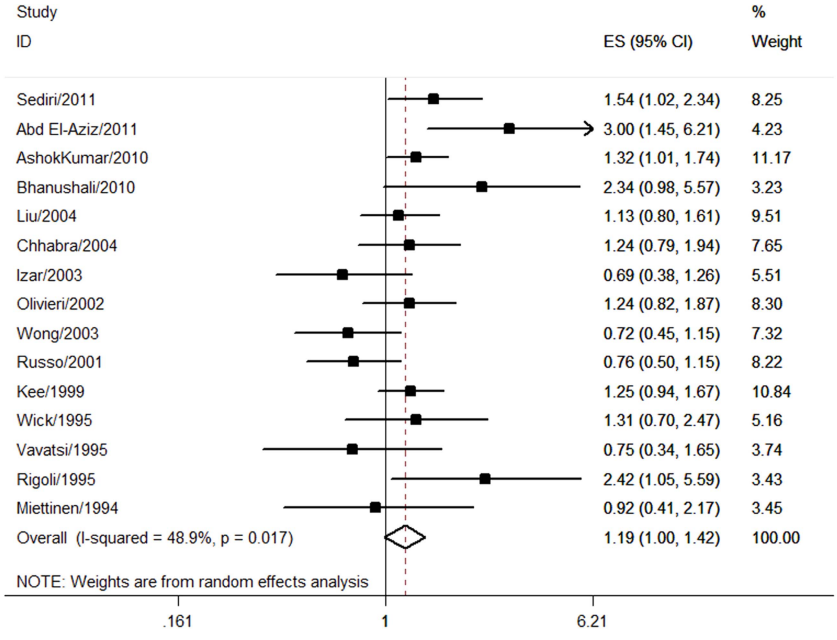

Figure 2 Association between Sst I polymorphism and coronary heart disease risk.

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Table 1 Meta-analysis results of Sst I, T-455C, C-482T and C1100T polymorphisms

Polymorphism	Number of studies	Number of participants	Comparison	OR (95% CI)	Heterogeneity I^2 (%)	Heterogeneity p Value
Sst I	15	11 539	S1S2+S2S2 vs S1S1	1.19 (1.00 to 1.42)	48.9	0.017
T-455C	4	3378	TC+CC vs TT	1.22 (1.06 to 1.42)	0	0.580
C-482T	4	3070	CT+TT vs CC	1.06 (0.92 to 1.22)	0	0.788
C1100T	3	4662	CT+TT vs CC	1.06 (0.89 to 1.27)	46.7	0.153

CHD risk. Two studies adopted the IOPA method[19 24] and one study used the RFLP method.[22] No significant association was found (CT+TT vs CC, pooled OR=1.06, 95% CI 0.89 to 1.27) and no significant heterogeneity was observed (I^2=46.7%, p=0.153; figure 5 and table 1). One study evaluated the association between C1100T polymorphism and MI risk (OR=1.18, 95% CI 0.93 to 1.51).[19]

Publication bias

Begg's and Egger's tests suggested that no publication bias was found in our meta-analyses.

DISCUSSION

ApoC3 is a glycoprotein synthesised mainly in the liver and the intestinal, and plays an essential role in regulating the serum triglyceride levels. Besides, it can strongly regulate the levels of very-low-density lipoprotein and small dense low-density lipoprotein (LDL) which potentially improves atherosclerosis.[31] The clinical research has found that ApoC3 levels were a predictor of risk for the development of CHD.[32–34] In the present study, 20 studies were included and four polymorphisms of ApoC3 were evaluated, including C-482T, T-455C, Sst I and C1100T polymorphisms. T-455C polymorphism was suggested to be significantly associated with CHD risk, and 'C' allele increased CHD risk by 22% (CT+TT vs CC, pooled OR=1.22, 95% CI 1.06 to 1.42). A borderline significant association was observed between Sst Ipolymorphism and CHD risk, while no evidence suggested a significant association between C-482T and C1100T polymorphisms and CHD risk. Subgroup analysis was applied for Sst I polymorphism, and we found that Sst I polymorphism was significantly associated with MI risk. Besides, Sst I polymorphism was significantly associated with CHD risk in Asian population but not in Caucasian population, indicating that the effect of Sst I polymorphism might be influenced by ethnicity. For retrospective studies, Sst I was indicated to be significantly associated with CHD risk but this association was not confirmed in prospective studies. So, the association between Sst I polymorphism and CHD risk should be interpreted cautiously.

Table 2 Subgroup analysis of Sst I polymorphism

Groups	OR (95% CI)	Heterogeneity I^2 (%)	Heterogeneity p Value
Ethnicity			
Caucasian	1.14 (0.92 to 1.41)	54.2	0.013
Asian	1.35 (1.08 to 1.69)	0	0.427
Study design			
Retrospective	1.30 (1.04 to 1.61)	39.0	0.098
Prospective	0.98 (0.75 to 1.28)	52.3	0.098
Phenotype			
CHD	1.09 (0.87 to 1.35)	46.0	0.047
MI	1.42 (1.06 to 1.91)	52.3	0.099

CHD, coronary heart disease; MI, myocardial infarction.

The mechanism of Sst I polymorphism in CHD susceptibility may be multiple. Sst I polymorphism is located in 3′-untranslated region of the ApoC3 gene, and it is possible that this polymorphism is in linkage disequilibrium with other functional polymorphism in the nearby region, such as T-455C polymorphism.[10] Sst I polymorphism might alter plasma lipid concentrations. Several studies showed that S2 carriers have higher plasma total cholesterol, TG and LDL-C levels,[12 35 36] though other studies did not demonstrate significant difference.[10 20 37] Besides, it has been shown that S2 allele might significantly influence dyslipidaemic state and atherosclerosis severity when patients changed their diet from saturated fatty acids to olive oil.[38] So, Sst I polymorphism plays an important role in modulating lipid levels response to dietary changes.

T-455C and C-482T polymorphisms were located in the 5′ promoter region and were in a strong linkage disequilibrium with each other. These two polymorphisms have been studied extensively because they could alter the nuclear transcript factors which mediate the insulin response. A significant association between T-455C polymorphism and risk of CHD was found under dominant model. However, it should be noted that in the four studies evaluating T-455C polymorphism, only one study[24] showed a significant association between T-455C polymorphism and CHD risk. So, more studies with large sample size are warranted to clarify this issue. For C-482T polymorphism, no significant association with CHD risk was found.

Different mechanisms could be linked to this finding. In previous works, T-455C polymorphism was associated with increased TG and ApoC3 levels.[24 39] Also, T-455C polymorphism was demonstrated to be significantly associated with metabolic syndrome.[39] Another study showed

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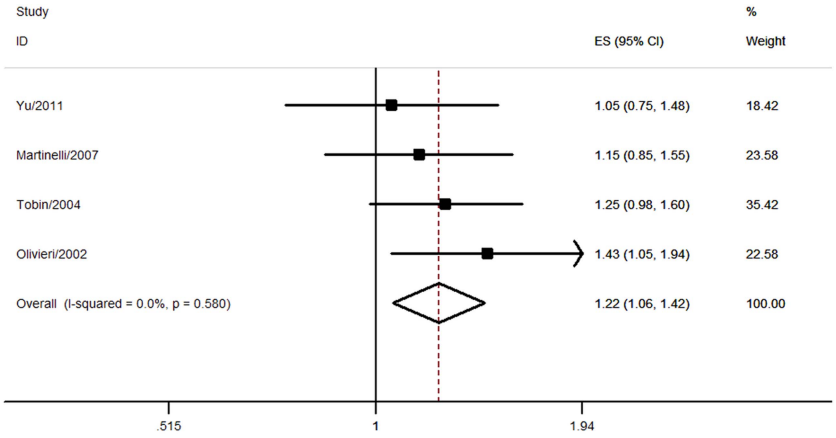

Figure 3 Association between T-455C polymorphism and coronary heart disease risk.

that T-455C polymorphism could interfere with n−3 polyunsaturated fatty acids on ApoC3 concentrations.[7] Olivieri *et al*[7] found that CC homozygous carriers were poorly responsive to the ApoC3 lowering effects of n−3 polyunsaturated fatty acids.

The present meta-analysis has several strengths. First, this study was based on the guidelines for conducting and reporting systematic reviews and the methods were rigorous. Second, we comprehensively evaluated the association between ApoC3 polymorphisms and CHD risk, and a total of four polymorphisms of ApoC3 were assessed. Besides, no publication bias was observed, indicating that the pooled results might be unbiased.

The current analysis also has several limitations. First, most of the included studies investigated Asian or Caucasian population, so the conclusions may not be true for other ethnic groups. Second, a significant heterogeneity was found and could not be completely explained when assessing some polymorphisms. Third, only PubMed, EMBASE and Cochrane library were searched for eligible articles. Finally, only articles published in English were included.

Some questions remain unanswered in the present study. Most of the studies did not report multivariable OR, so it is not clear whether ApoC3 polymorphisms could be an independent predictor of CHD risk or not. More studies are warranted to clarify this issue. Different genotyping assay methods were applied in the included studies, which might call for different results. And it should be noted that ApoC3 polymorphisms are non-modified risk factors, and little control methods over them were accessible. However, people in high-risk groups (such as S2 carriers of Sst I polymorphism) might be advised to go for regular checkups to reduce the risk of adverse cardiac event. Detecting ApoC3 polymorphisms may help people be aware of the risk of CHD. With the current level of evidence, we cannot comment on the optimal genotyping assay method and the cost-effectiveness of detecting ApoC3 polymorphisms. Further research is needed to explore the combination of variables associated with CHD risk to develop a predictive model with a high discriminative capacity.

In summary, ApoC3 Sst I and T-455C polymorphisms might be associated with CHD risk, while no evidence

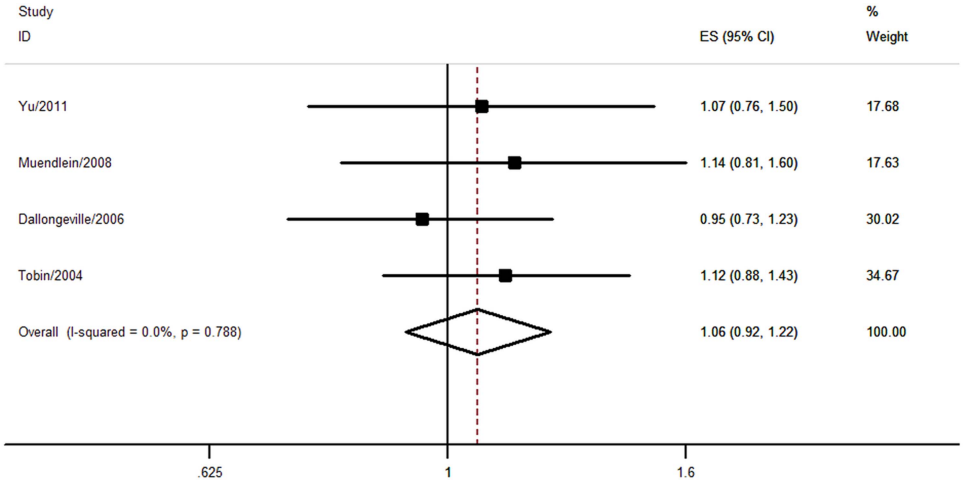

Figure 4 Association between C-482T polymorphism and coronary heart disease risk.

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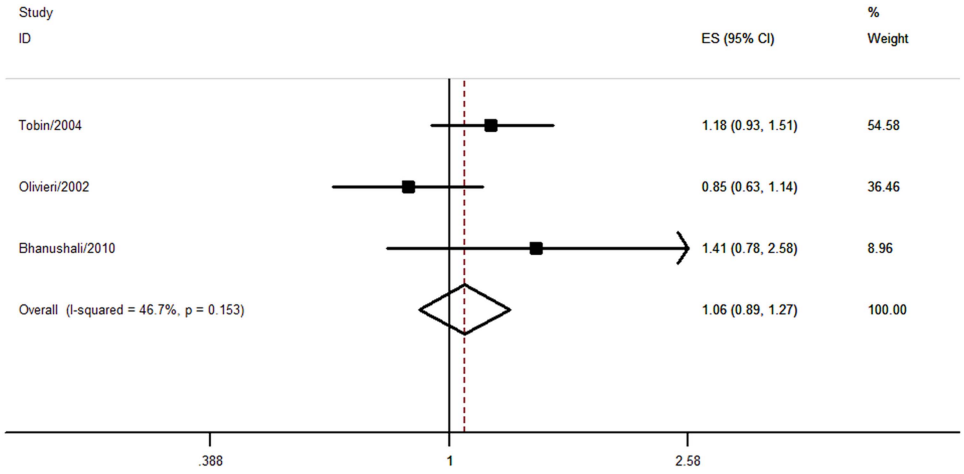

Figure 5 Association between C1100T polymorphism and coronary heart disease risk.

suggested a significant association between C-482T and C1100T polymorphisms and CHD risk.

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