

**Two common genetic variants on  
chromosome 9p21 are associated with  
myocardial infarction and type 2 diabetes  
in an Italian population**

Claudia Specchia

Dipartimento di Scienze Biomediche e Biotecnologie  
Università degli Studi di Brescia



# Introduction

Recent genome-wide association (GWA) studies have identified a genomic region on chromosome 9p21 closely associated with increased susceptibility to coronary artery disease (CAD) and to type 2 diabetes (T2D).

(Broadbent, Hum Mol Genet 2008)



# Rationale

- T2D has long been recognized as a major risk factor for atherosclerosis, and therefore for CAD, although the temporal relationship between them is not clear: while CAD usually follows diabetes mellitus, it can sometimes precede it.
- The presence of several different genetic variants within chromosome 9p21 associated with such tightly related diseases prompted us to investigate the relationship between such variants.

# Background

The PROCARDIS Consortium has undertaken a genetic analysis of markers spanning the chromosome 9p21 in 4,251 cases and 4,443 controls in 4 European populations with the aims of:

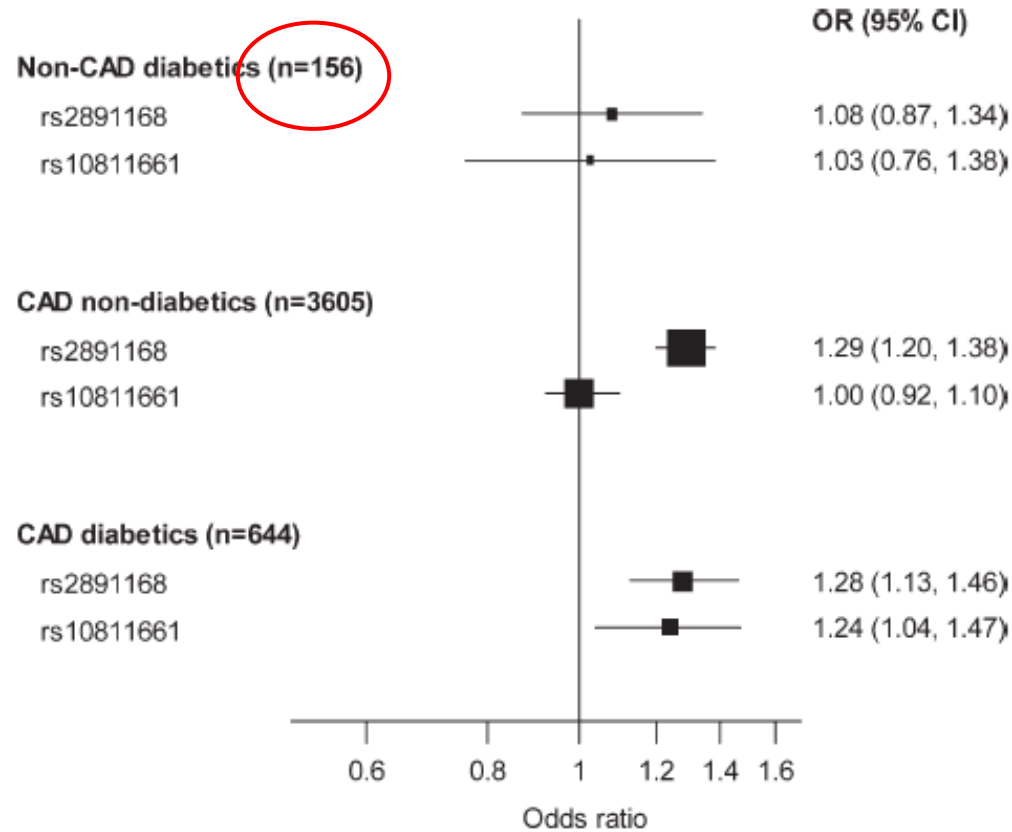
- replicate the CAD and T2D susceptibility loci reported by GWA studies
- investigate if diabetes modifies the CAD susceptibility effect

(Broadbent, Hum Mol Genet, 2008)

## **PROCARDIS results**

- Literature single nucleotide polymorphisms (SNPs) show association to CAD in single marker tests with ORs ranging from 1.26 to 1.29.
- Association between CAD and SNP rs2891168 was strongly supported and the per-G-allele odds ratio was 1.29 with no evidence for non-additive susceptibility effects and no evidence of heterogeneity of susceptibility across the four European populations.

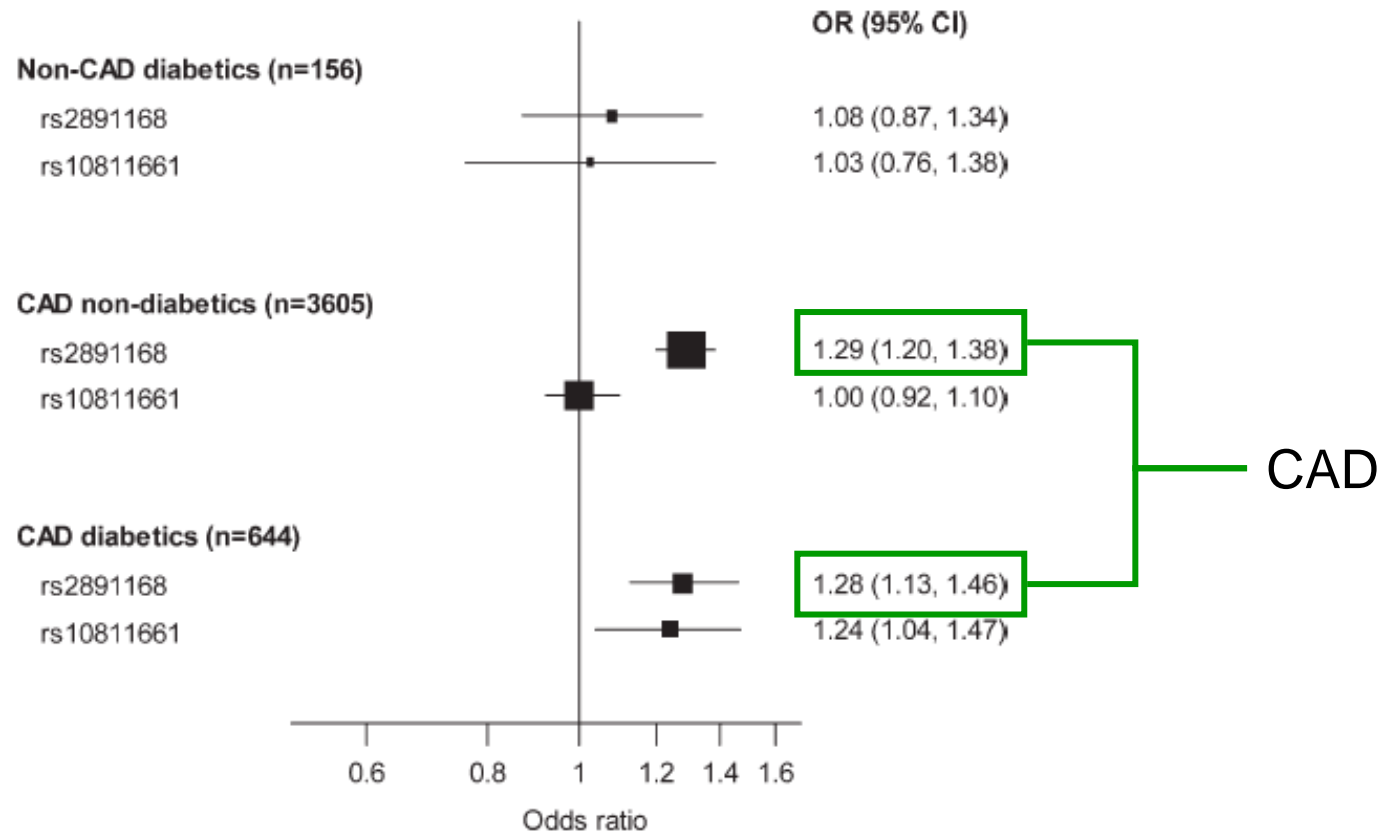
# Study limitation



non-CAD diabetics are relatively few

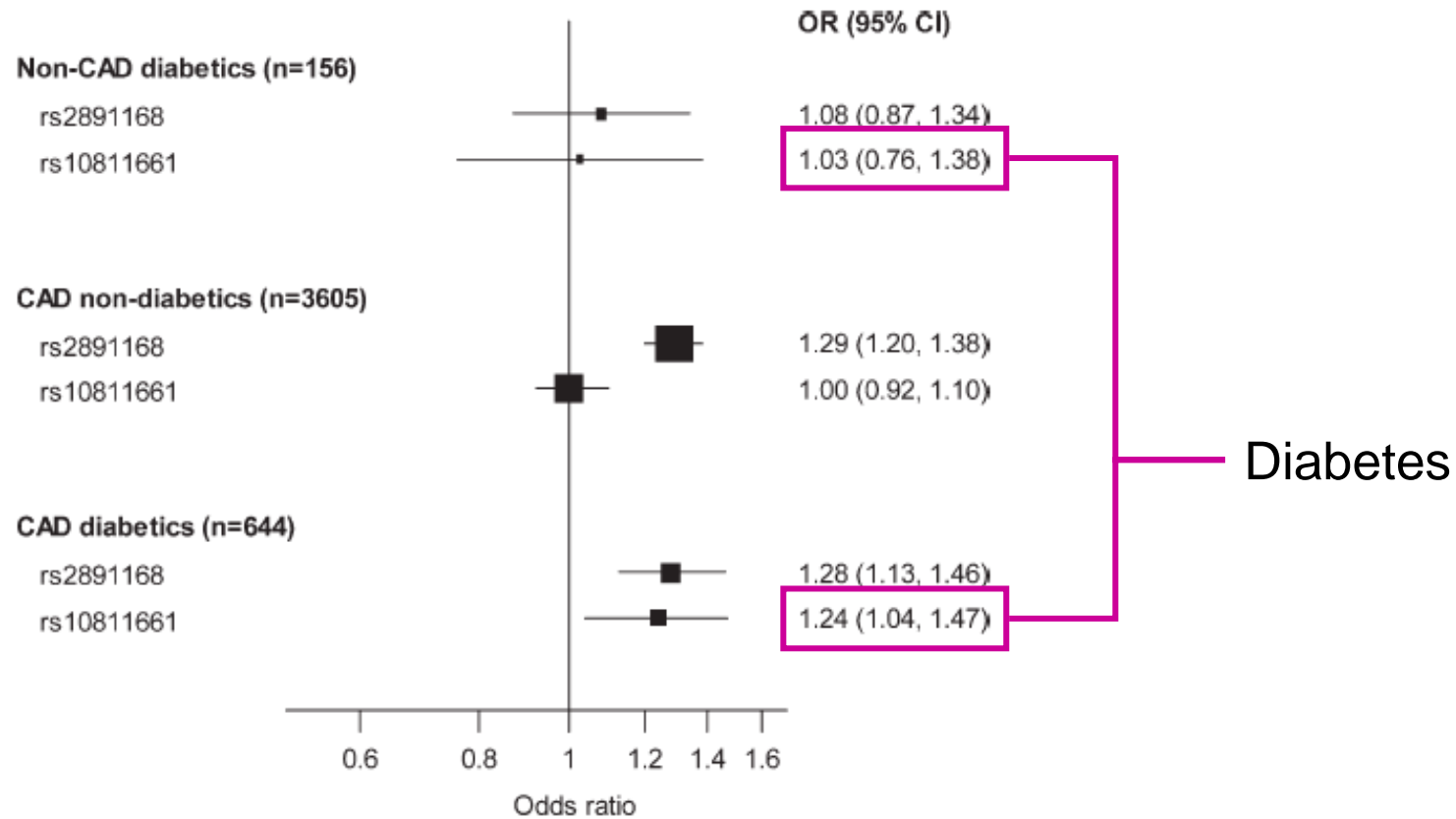
(Broadbent, Hum Mol Genet, 2008)

# Study limitation



(Broadbent, Hum Mol Genet, 2008)

# Study limitation



(Broadbent, Hum Mol Genet, 2008)

## **Aim of the present study**

- We carried out a case-control association study in an Italian population of patients with T2D only, myocardial infarction (MI) only or both diseases to test the susceptibility effects of rs2891168 and rs10811661.
- Our aim was to confirm previous results on a larger sample and to verify whether the effects of these two SNPs on susceptibility on MI and T2D were actually independent:  
rs2891168 associated with MI but not with T2D and rs10811661 associated with T2D but not with MI.

# Study population

- We enrolled all the patients (602) with T2D who had a blood sample available among those in IGLOO cohort study (Impaired Glucose intolerance & Long-term Outcomes Observational Study).
- The other case groups of 600 MI only and 600 MI & T2D were selected at random from the GISSI-Prevenzione study (GISSI-P).
- A group of 605 unmatched non-diabetic subjects with no CAD and with no family history of CAD was recruited among blood donors.

## Description of the study groups

Group	Number of subjects	Female (%)	Age (yrs) Mean (SD)
T2D	602	43.2	62.4 (7.3)
MI	600	20.8	57.5 (6.5)
MI&T2D	600	28.2	58.2 (7.5)
Controls	605	18.8	56.6 (6.5)
Total	2407	27.7	58.7 (7.3)

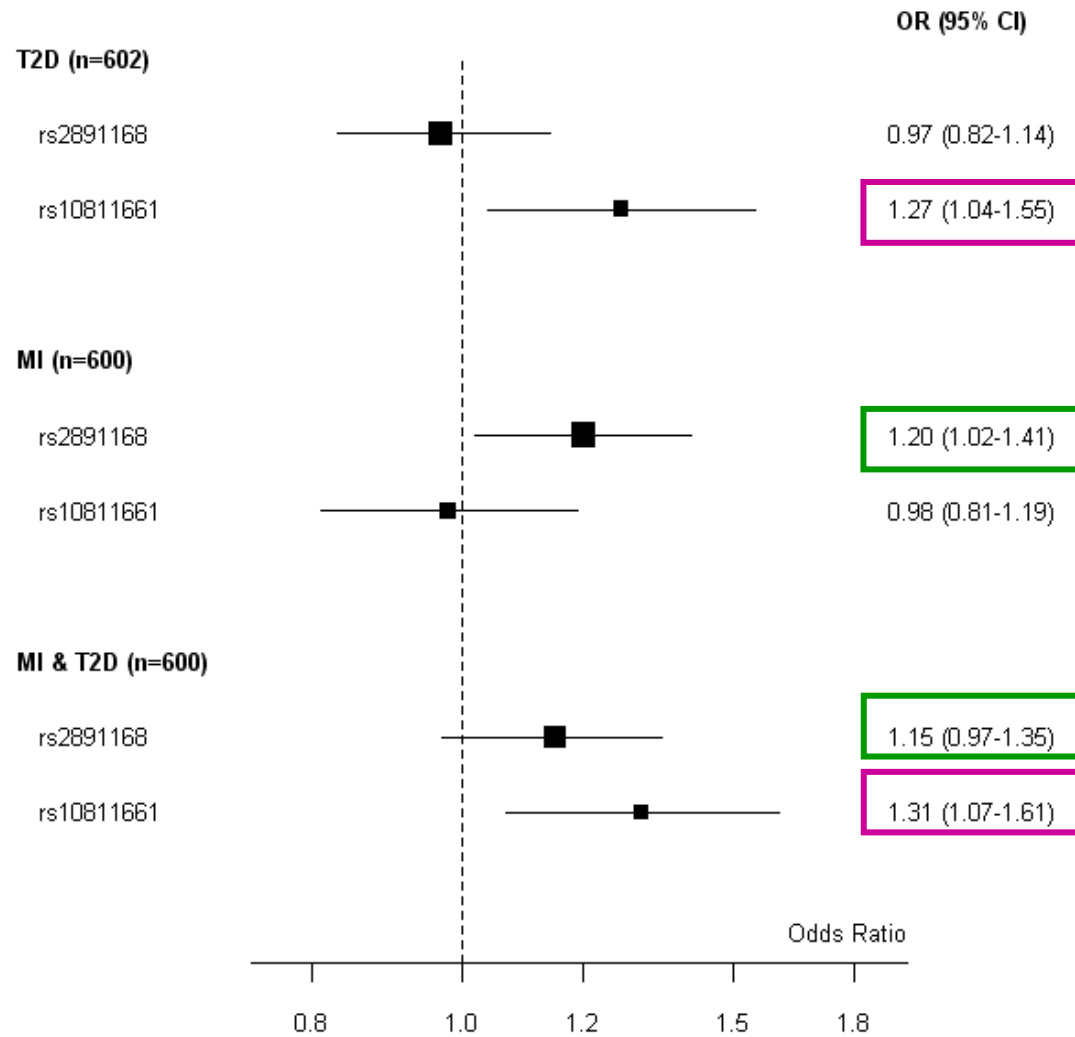
## Description of the SNPs

SNP	Position (bp)	HWE $\chi^2$ test p-value	risk allele	risk allele frequency
rs2891168	21921500	0.81	G	0.59
rs10811661	22124094	0.80	T	0.80

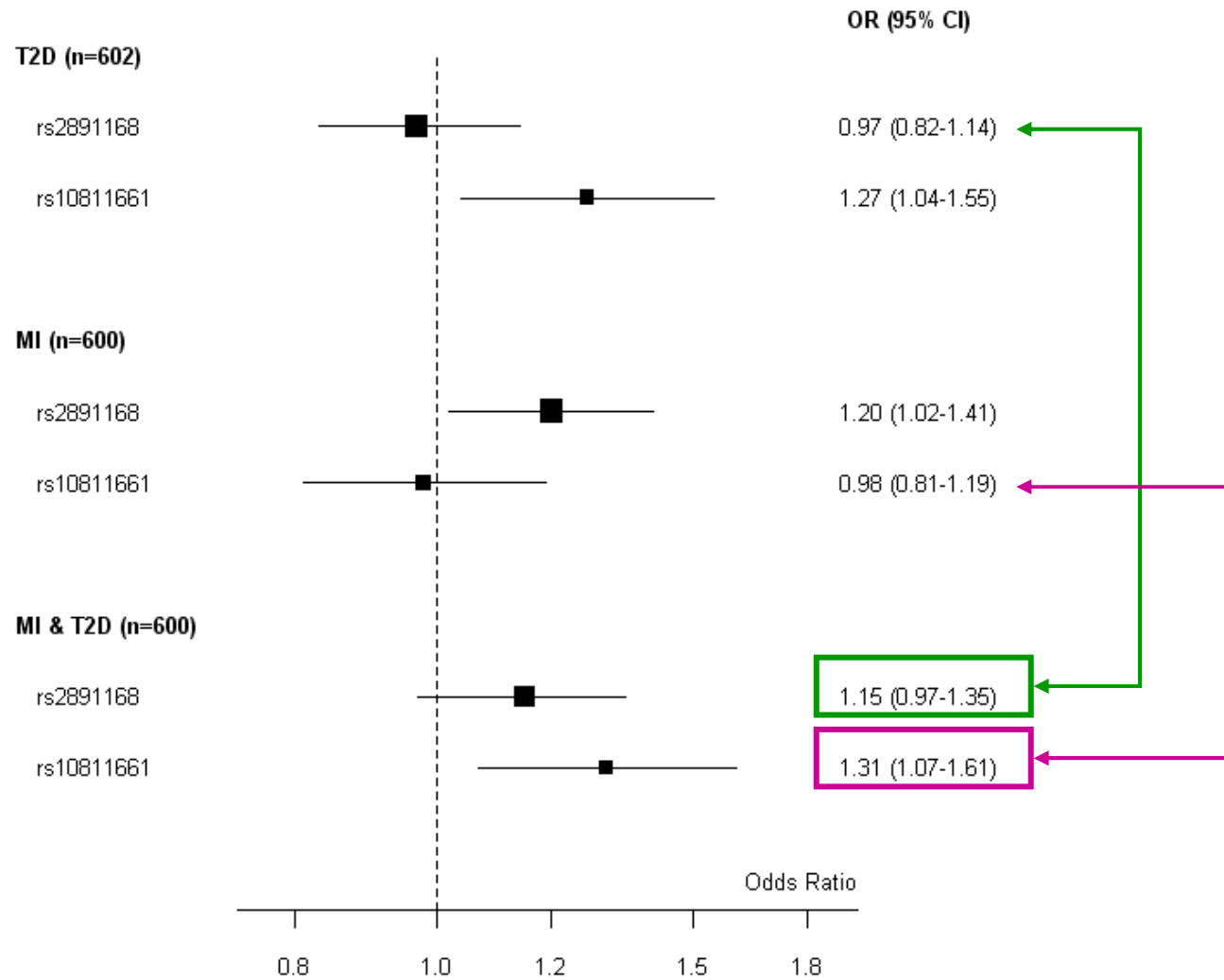
# Statistical analysis

- A model of allelic association, and a model of genotype association, were compared by the likelihood ratio test.
- Association analyses were done between the presence of rs2891168 G-allele and rs10811661 T-allele and MI, T2D and MI&T2D case groups using unconditional multinomial logistic regression.
- Homogeneity of risks among case groups was assessed using a Wald test.
- ORs estimates in the present study and in the PROCARDIS study were pooled using a fixed-effects model.

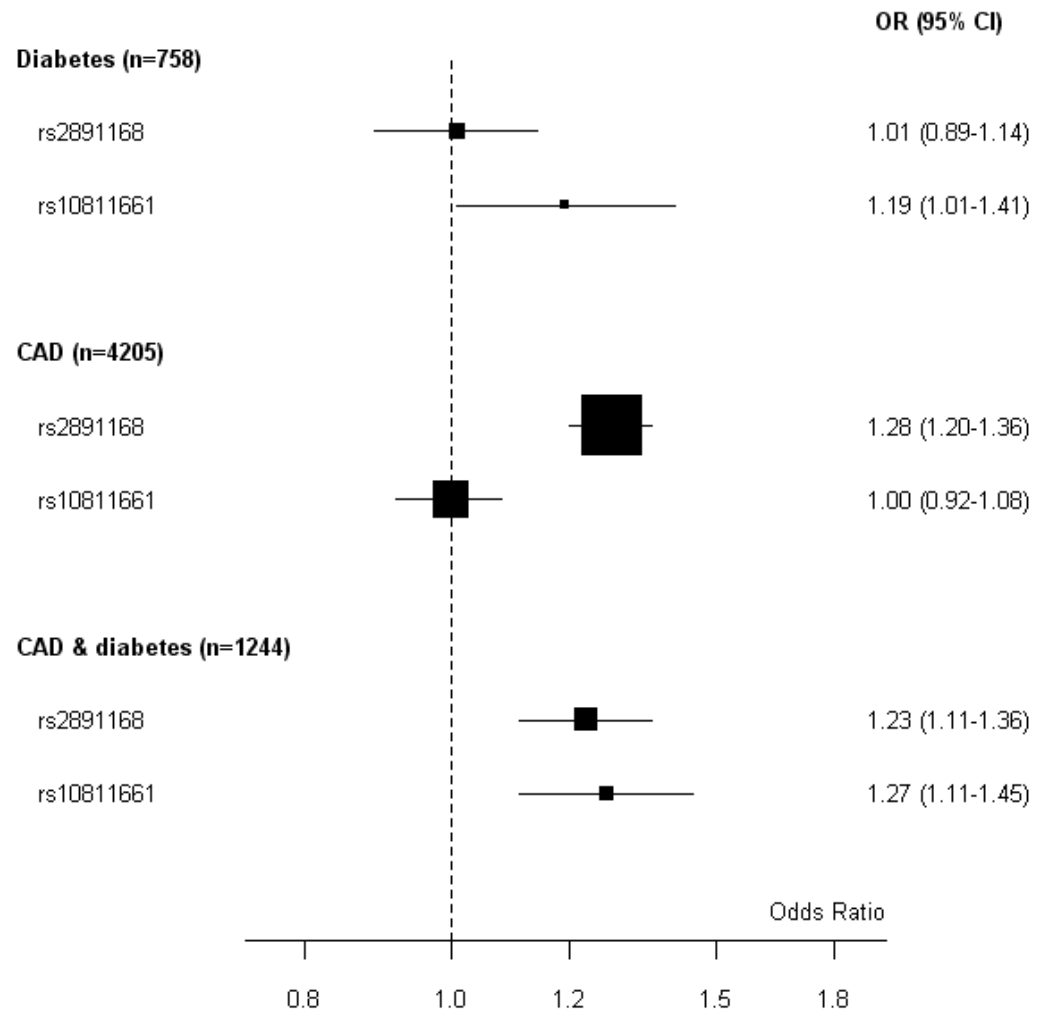
# Results



# Results



# Pooled data



# Discussion

- PROCARDIS patients had diagnoses of MI, symptomatic acute coronary syndrome, intervention for coronary revascularization, or chronic stable angina, the four major diagnostic outcomes for CAD while Italian patients are surely CAD patients but all had a clinically diagnosed MI. Moreover Italian diabetic patients are all T2D.
- The present analysis on subjects of Italian origin limits the genetic heterogeneity across different ethnic groups.

# Conclusion

- We showed that SNPs rs2891168 and rs10811661 are independently associated with MI and T2D respectively
- The main finding of the present study is therefore its ability to replicate the analysis done in the European PROCARDIS population on an independent cohort of Italians with comparable inclusion criteria.
- To clarify the molecular mechanisms and pathways underlying the associations with CAD or T2D further physiological and functional studies are needed

# Acknowledgements

Francesca Gori, Silvia Pietri, Luisa Crociati, Simona Barlera,  
Maria Grazia Franzosi  
*Istituto "Mario Negri"*

Monica Franciosi, Antonio Nicolucci  
*Consorzio Mario Negri Sud*

Stefano Signorini, Paolo Brambilla  
*Ospedale di Desio*

GISSI-Investigators

SIBioC-GISSI Prevenzione Group