Reviewer's report

Title: Association between polymorphisms in the adiponectin gene and cardiovascular disease: a meta-analysis

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Reviewer: Christina Wassel

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This paper meta-analyzes data from 34 different studies which examined the associations of 3 common polymorphisms of the adiponectin gene (ADIPOQ) with cardiovascular disease (CVD). These SNPs have been studied extensively, but there are conflicting results as to the strength and direction of the associations with CVD. Studies contributing to the meta-analysis represented different ethnic groups, both men and women, and a varying sample sizes. Studies were given quality scores based on the NCI-NHGRI Working Group on Replication in Association Studies guidelines, and the MOOSE guidelines were followed in the meta-analysis. The three SNPs, rs2241766, rs1501299, and rs266729 had significant but weak associations with CVD in the meta-analysis, and the authors conclude that further high quality studies are still needed, especially for rs2241766.

Overall a well-written and well done paper, but there are some points to clarify or improve upon.

Major Comments

The authors are missing several papers from the literature on the association of adiponectin and CHD which found inverse associations (i.e. Laughlin et al, Kanaya et al, among others).

The quality scores seem low for these studies. Is this typical with use of the the NCI-NHGRI Working Group on Replication in Association Studies guidelines? What are average scores using this metric for assessing quality?

Figure 1 states that one of the reasons 65 papers were excluded was “detail data unavailable”. Can the authors better define what this means? How many papers were excluded for this reason? As it stands, this is a bit vague.

What about population stratification? Did any of these studies adjust for population stratification within ethnic groups? This could be contributing to the between study heterogeneity!

Use of the word “risk” throughout the manuscript is too loose – these are case-control studies, and odds ratios, which do not equate to relative risk. More appropriate to say “greater odds” rather than “greater risk”.

Why do authors use random effects? As Lebrec et al (Dealing with heterogeneity
between cohorts in genomewide SNP association studies. Stat Appl Genet Mol Biol. 2010;9(1):Article 8) point out, the random effects hypothesis is appropriate for clinical trials but results in relatively reduced power for genetic association/GWAS detection of SNPs which show association in at least one study. The random effects model has less power to detect effects than fixed effects in almost all situations (Han et al, Random-effects model aimed at discovering associations in meta-analysis of genome-wide association studies. Am J Hum Genet. 2011 May 13;88(5):586-98), thus does not improve the ability to detect additional associations. It would probably be more appropriate to just use fixed effects for all 3 SNPs in this situation based on the work of Lebrec et al and Han et al.

Also what meta-analysis method exactly is used to combine the odds ratios from each study, i.e. inverse variance weighted? Please give a little more detail of Ref 24 since many readers may not be familiar?

Minor Comments

In paragraph 2 of the introduction – would say “also found significant inverse associations” rather than negative associations.

Page 5, first line of statistical analysis section, “compare contrasts” does not make sense – maybe the authors just mean “compare”?

Page 6, second line, “…consist of 36 case-control studies…” – should be “consisting”

Page 6, third line, should be ‘polymorphisms” instead of “polymorphism”

Table 2 – may consider labeling the column “studies” as “No. Studies” to make it clear that this is the number of studies contributing to that particular analysis.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.