To the Editor:
The article by Versmissen et al.1 revealed the mutual influences of both low-density lipoprotein receptor mutation and apoE4 homozygosity in attenuating coronary heart disease (CHD) risk, but individually, both of these did not show any association with the CHD risk. Alterations of serum apoE levels significantly modify the relationship between APOE polymorphism and lipid levels.2 This study could not observe the higher CHD risk in the apoE4/E4 carriers having the low-density lipoprotein receptor mutation, which may have been missed as a consequence of unexpected masking of the effect of the APOE polymorphism by serum apoE concentrations. This study did not adjust the models with apoE levels, which modulate lipid levels, confer a 2-fold higher risks of cardiovascular disease mortality, and account for 26.07% of total cholesterol variance independent of the APOE polymorphism.3 The finding of this study would seem more reasonable if single nucleotide polymorphisms within the regulatory region of APOE were also investigated and their coordinated effect was controlled. Individual APOE polymorphism (APOE4 [rs429358] and APOE2 [rs7412]) depicts a partial story because the interactive effect of apoE4/E4 and low-density lipoprotein receptor mutation on CHD risk may differ when the impact of rs429358 is mediated by rs449647, rs405509, and rs440446. These single-nucleotide polymorphisms of the regulatory region influence transcriptional efficacy and APOE expression,4 the functional repercussions of which have been overlooked in this study. With APOE being in a tight cluster with APOCI and APOCII at 19q13.2, there is significant linkage disequilibrium between APOE and APOCI, which influences the risk of CHD differently than individual APOE polymorphisms. Possession of apoE4/E4 is protective in the low-density lipoprotein receptor mutation and may be mediated by the other members of this cluster gene, especially APOCI.5 Apropos to the previously mentioned points, if taken care of, the findings of the present study would have been more forceful.

Disclosures
None.

References
Letter by Singh et al Regarding Article, "Apolipoprotein Isoform E4 Does Not Increase Coronary Heart Disease Risk in Carriers of Low-Density Lipoprotein Receptor Mutations"

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doi: 10.1161/CIRCGENETICS.111.962274

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