Several studies have considered the potential clinical importance of genetic variation at the *PPARA* locus although most have concentrated on lipid levels and have considered the L162V variant in isolation. These studies have been inconsistent indicating that L162V may influence levels of cholesterol or other lipoproteins, depending on the population analysed [6,8,10,12,17,18], while other studies have found no evidence for such an association [19,20]. These inconsistencies may be due in large part to differing environments, genetic background and diseased status (including medications prescribed) between the populations considered. For instance the relative concentration in the diet of saturated to polyunsaturated fat has recently been demonstrated to significantly affect association of L162Vgenotype with lipoprotein profile [21,22]. Furthermore, it is likely that there will be differential usage of fibrate (as well as other lipid modifying) drugs between individuals with type 2 diabetes and non-diabetic populations which may also influence the lipid levels differentially by PPARα haplotype [23,24]. Gene/gene interactions may also be important as evidenced by the observation that variants in the *PPARD* and *APOE* genes can influence the observed association [10,20]. The inevitability of gene/environment interactions, and the observed inconsistency between studies, illustrate the difficulties of considering single measures of quantitative traits. Such measures are likely to vary considerably over an individual's lifetime, depending on health status and diet. Importantly, the clinical measures in this study were a mean of multiple measures taken over up to a three year period and therefore represent a limited integration of such temporal fluctuations.

In this study we found that the G2582C variant, but not the L162V variant, influenced lipid levels and this association was not influenced by L162V. The difference between the mean values of LDL cholesterol for GG individuals compared to CC was rather small (0.36 mmol/L) and even in this high risk population did not account for the increased cardiovascular risk associated with C2582. This was not unexpected, as in keeping with the previous studies in non-diabetic men, inclusion of total cholesterol or LDL cholesterol in the model did not affect the association with cardiovascular outcomes, indicating that the increased risk associated with the C2528 variant is not likely to be through its influence on lipid levels.

Few studies have considered cardiovascular disease or considered variants other than the L162V. One recent study also demonstrated a non significant trend towards a protective effect of V162 in individuals with diabetes [19]. This study did not consider the G2825C variant. The present study however confirms that the V162 variant is protective against nonfatal myocardial infarction, while the C2528 variant is associated with an increased risk in this population with type 2 diabetes. These observations also appear to affect overall mortality in this population. This apparent consistency across studies with respect to cardiovascular events probably reflects the small, though global, modulation in phenotype acting across an individual's lifetime due to the slight changes in activity of PPARα associated with each variant. Unlike single measures of lipids or lipoproteins, this is less likely to be effected by temporal environmental changes. This is also likely to be true for clinical events such as age of diagnosis. In the previous study that considered age of diagnosis a further variant in intron 1 of *PPARA* was used to construct haplotypes with L162V and G2825C [12].

In this study, as in ours, the C2825 was associated with an earlier age of diagnosis, with the V162 allele being associated with protection from early diagnosis, in a manner consistent with the modulation of CVD risk. This is the first study to present the association with age-of-diagnosis of type 2 diabetes in the same population with the association with cardiovascular risk, and we can state that inclusion of age of diagnosis does not modulate the observed associations with cardiovascular risk and vice-versa, demonstrating that these are independent observations. This is not surprising, as *PPARA* variation is associated with CVD risk regardless of diabetic status.

The G2825C variant is in a non-coding region (intron 7) and therefore unlikely to be a directly causal variant, however several other studies have indicated its potential biological importance [9,11,12] and also a reduced response to fibrate therapy [25]. These observations together with that of PPARα activation through fibrate therapy have given rise to the suggestion that the C2528 variant is associated with reduced RNA transcription and hence lower PPARα levels. Although this suggestion together with a mechanism remains to be demonstrated, it is probably due to a further (as yet) unidentified variant in or near the *PPARA* gene.

We have previously demonstrated a similar situation in the *PPARG* locus in which the biological effect of a variant with probable functional consequences is consistently modified in an opposing manner by the presence of a variant for which a function is difficult to ascribe [14,15]. Given the role of the PPARs as master controllers of energy metabolism it is likely, as the accumulating evidence appears to suggest, that they will manifest epistasis and balanced polymorphism allowing for rapid adaptive evolutionary response to widely differing environmental challenges. Indeed, the existence of widespread, balanced variation has recently been suggested for genes involved in complex traits [26].