Response to: The *PNPLA3* SNP rs738409:G allele is associated with increased liver disease-associated mortality but reduced overall mortality in a population-based cohort

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Sir,

We thank Meffert and co-workers [1] for their interest in our study and for providing data which support our finding of an association between carriage of rs738409:G in *PNPLA3* and the risk of liver-associated mortality, at least in men. [2] The authors evaluated the association of rs738409:G with mortality in adults participating in a population-based health study in Pomerania. The included population of 4081 was sub-classified by sex and by the absence/presence of hepatic steatosis on ultrasound. Participants were censored at death or when lost to follow-up with the length of follow-up defined as birth to censorship. The median follow-up period was 11.3 (interquartile range: 10.6-11.8) years, though this is difficult to equate with the definition of the follow-up period provided. In men carriage of the rs738409:G was associated with a fourfold increase in the hazard ratio for liver-disease-related mortality; there were too few events in women for analysis. These data corroborates not only our findings that carriage of rs738409:G is a negative risk factor for survival [2] but also the reported association with a reduction in survival in people listed for liver transplantation [3] and in those with cirrhosis and hepatocellular carcinoma [4]. The authors also showed that, in men, carriage of rs738409:G was associated with a decrease in the risk of death from coronary artery disease; there was no such effect in women [1]. Lui and colleagues [5] recently reported in an exome-wide association study in >300,000 individuals that carriage of rs738409:G was associated with a lower risk of coronary artery disease so corroborating this finding although sex-specific data were not provided.

The main point of interest in the data provided by Meffert and co-workers [1] is the apparent sex-related differences in disease-specific mortality associated with carriage of rs738409:G, which needs to be confirmed. Consequently we re-analysed our study data to

test for the presence of interactions between sex and the rs738409:G allele and medium-term mortality (90 to 450 days after initial presentation). The study populations and data processing methodology were as described in the original publication of these data [2, 6]. Information on deaths within the study period was collected *via* the study reporting forms while information on deaths out with the study period were obtained from the NHS Information Centre Data Linkage service. Tests for allelic association were performed using logistic regression analysis with introduction of a multiplicative interaction term for rs738409 genotype and sex. Cox regression analysis was used to examine for associations between survival, rs738409:G, sex and a return to drinking with incorporation of a multiplicative interaction term for rs738409:G and sex.

Eight-two (20.7%) of the 397 patients included in the analysis died during the follow-up period Information on the cause of death was only available in 60 (73%); the deaths in 47 (78%) were classified as definitely liver-related; two were definitely not liver-related whilst the remaining 11 deaths were not classifiable as such. There was a highly significant multiplicative interaction between rs738409 genotype and sex in relation to medium-term mortality (hazard ratio [HR] 0.30, 95% CI 0.14 – 0.62, P=0.001) which was independent of the return to drinking (HR 2.91, 95% CI 1.88 – 4.50, P<0.001). Of particular note was the sex-specific difference in the survival in homozygous carriers of rs738409:G; thus all eight female homozygotes survived to day 450 compared with only ten (48%) of their 21 male counterparts (Figure 1).

The comparative survival advantage in women with alcohol-related cirrhosis is well-documented [7-10]. Nevertheless, its occurrence is unexplained, although differences in

body composition which result in relative preservation of lean muscle mass in women may play a significant role. [11,12] However, the findings reported by Meffert *et al*, [1] and confirmed in the reanalysis of our study data suggest that the sex-related differences in the risk of liver-related deaths may relate to sex-variant interaction with rs738409:G in *PNPLA3.* Sex-variant interactions have previously been described in the field of cardiovascular medicine [13] and are worthy of further exploration in the field of liver medicine.

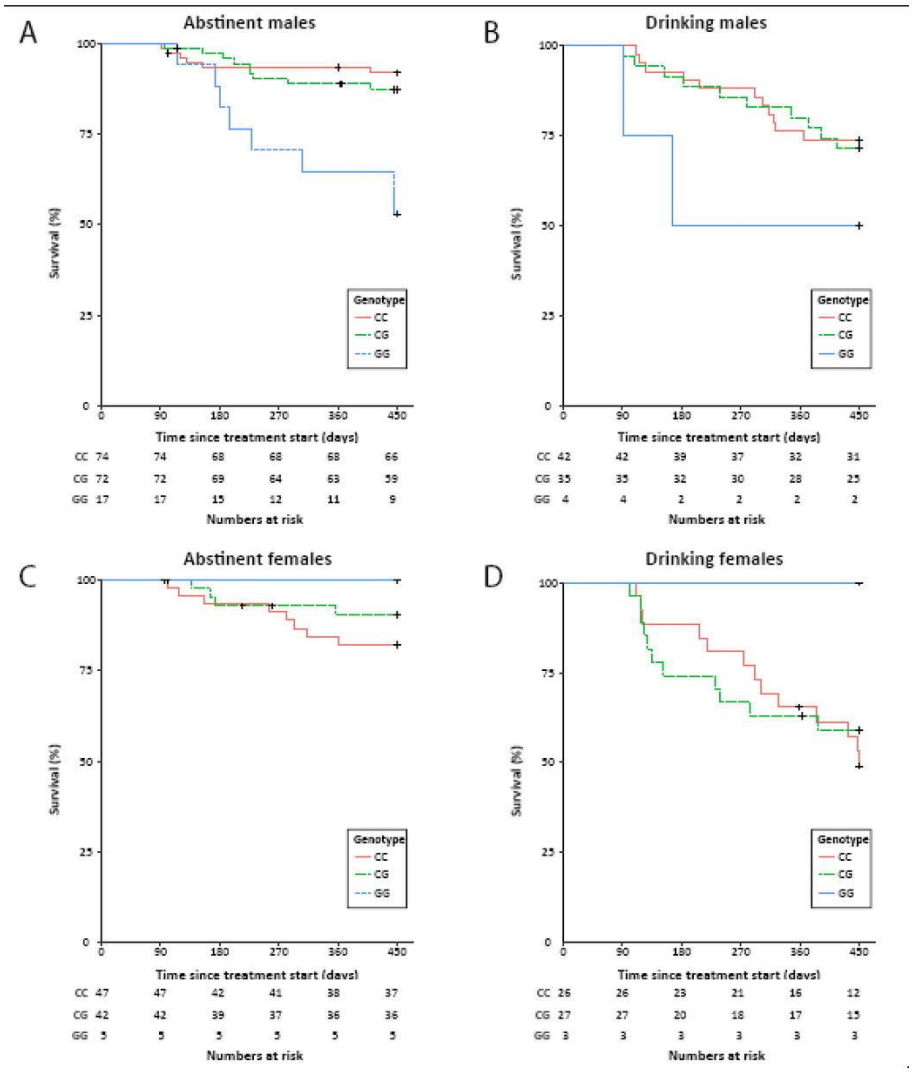

Figure 1

Medium-term survival in cases with severe alcoholic hepatitis surviving at least 90 days, by gender and drinking status. (A) In male patients who maintain abstinence rs738409:G is associated with an apparent reduction in survival over the 90-450 day period. (B) The same pattern is seen in male patients who return to drinking. In female patients the pattern appears to be reversed (C and D).

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Conflict of interest

The authors have no conflicts of interest to declare

Authors' contribution

SRA performed genotyping, statistical analyses and drafted and revised the manuscript. MJW performed genotyping. AQ, MYM and MRT recruited participants and critically appraised and revised the manuscript.

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