Liver Fat Content, Non-Alcoholic Fatty Liver Disease and Risk of Ischaemic Heart Disease

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We congratulate the authors for attempting to address the question of whether high hepatic fat content is a causal risk factor for ischaemic heart disease (IHD) (1). Despite confirming the known observational association of hepatic fat content (and NAFLD) with risk of prevalent IHD, the authors have suggested that fatty liver due to PNPLA3 variant is not causally associated with IHD (1). We believe that it is crucial to point out certain caveats that need to be considered when interpreting these results.

1) Based on the ICD-8 codes (and computed tomography scanning), the prevalence of NAFLD (i.e. 0.7% of the whole cohort; 633 out of 94708) was extraordinarily low and it is also likely there was contamination bias (with up to 25-30% of subjects in the reference group possibly having undiagnosed NAFLD).

2) Using a Mendelian randomization approach, the authors failed to show any increase in the risk of prevalent IHD with the presence of the PNPLA3 148 M allele in a subgroup of 1439 individuals in whom liver fat content was detected by computed tomography scanning. However, many subjects in this analysis did not have NAFLD (because liver fat percentage was <5.6%), and it is also noteworthy that the mean liver fat percentage was extremely low and similar in all three PNPLA3 genotypes (II=5.1%, IM=6.0% and MM=6.5%, respectively). Moreover, as shown in eTable 1, this subgroup of individuals was not well representative of the whole cohort of the study.

3) The authors also tested whether the PNPLA3 genotype was associated with risk of prevalent IHD in the whole cohort, of whom nearly 99% did not have known NAFLD. Since PNPLA3 148 MM was associated with a tiny increase in liver fat percentage in people with imaging-diagnosed NAFLD, it is perhaps not surprising that in the general population without NAFLD, PNPLA3 148 MM was not associated with IHD. Although a subsequent meta-analysis also confirmed the lack of a significant association between this genetic variant and IHD, again no information was available about NAFLD status in the CARDIOGRAMplusC4D consortium.

To date, a consensus is emerging that there are at least two distinct forms of NAFLD, i.e. the obese/metabolic NAFLD and the PNPLA3-associated NAFLD, which may have different consequences for risk of IHD (2-4). Less than 5-6% of European individuals with NAFLD carry the PNPLA3 148MM genotype and this genotype is neither sufficient nor necessary to cause non-alcoholic steatohepatitis, cirrhosis, or primary liver cancer (5). The contribution of genetic polymorphisms to inter-individual variation in NAFLD phenotype is relatively small and the role of the PNPLA3 148M allele in the general population without NAFLD is far from clear (4).

In summary, we consider that further research is urgently needed to test the effect of PNPLA3 148 MM genotype on risk of incident cardiovascular outcomes in cohorts with proven NAFLD where it has also been shown that the reference population does not have NAFLD.

References

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