Therefore, the current PRS may not be generalizable to other populations, such as African Americans, Asians, and Hispanics. To address this important issue, quantitative genetic features of ethnicity should be included as covariates in the association tests, which could help adjust the ethnicity-specific effects in the primary PRS to a certain degree. Moreover, to improve the utility and generalizability of these results for all ethnicities, future PRS research should include analyses of genetic data from different ethnic backgrounds rather than only a Eurocentric pool.

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The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
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Author names in bold designate shared co-first authorship

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Reply to: "Polygenic risk score: A promising predictor for hepatocellular carcinoma in the population with non-alcoholic fatty liver disease"

To the Editor:
We thank Long *et al.* for their positive comments on the novelty and the potential clinical impact of our recent study on the use of polygenic risk scores (PRSs) to infer causality between hepatic fat and carcinogenesis, and to predict hepatocellular carcinoma (HCC) development in individuals with dysmetabolism and non-alcoholic fatty liver disease (NAFLD).[1,2]

As highlighted by Long *et al.*,[2] the PRS prediction for HCC in a large European NAFLD cohort was largely superior to that of the single genetic risk variants. However, the AUC was relatively low (<0.7) and, in fact, we refrained from proposing the clinical use of PRS as a standalone diagnostic test. Additionally, in our study, PRS and classical risk factors were independently associated with HCC and together conferred a significant improvement in diagnostic accuracy compared to each of them alone.[1]

We observed a non-linear relationship between PRS and HCC risk, and in line with previous data, a synergistic effect between PRS and severity of insulin resistance in determining liver disease.[1,3,4] Therefore, we identified the optimal thresholds to discriminate HCC risk and validated these thresholds in participants with obesity and type 2 diabetes from the UK Biobank cohort. In this population-based study, PRS alone had and AUROC of 0.70 for detecting HCC. A positive PRS test was observed in approximately 1 in 10 individuals and it was able to predict HCC with 90% specificity. We reasoned that, as part of the ability of a PRS to predict HCC is mediated by the life-long burden of genetic variants on liver damage,[1] the PRS may be

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Table 1. PAF of PRSs of hepatic fat accumulation for HCC and cirrhosis in the UK Biobank cohort (n = 358,342 unrelated European individuals). The PAF of the single genetic variants included in the score and the PAF of classical risk factors are shown as comparison.

	Cirrhosis				HCC			
Predictor	**p-adj***	**OR**	**95% CI**	**% PAF**	**p-adj***	**OR**	**95% CI**	**% PAF**
PRS-5	1.54E-46	3.97	3.29-4.79	17.28	1.40E-32	16	10.1-25.2	57.49
PRS-HFC	3.96E-42	3.73	3.09-4.52	17.28	7.90E-29	15	9.31-24.1	57.49
PRS-5 ≥0.495	2.67E-32	1.94	1.73-2.16	8.03	3.81E-27	3.88	3.04-4.97	21.87
PRS-HFC ≥0.532	1.61E-34	1.96	1.76-2.19	8.43	4.59E-26	3.77	2.95-4.83	21.64
rs738409	4.79E-23	1.51	1.39-1.64	15.72	3.44E-09	1.97	1.57-2.47	26.92
rs58542926	1.02E-05	1.27	1.14-1.42	3.77	1.98E-06	1.88	1.45-2.44	11.76
rs641738	0.0619	1.09	0.996-1.19	6.16	0.026	1.34	1.04-1.73	19.25
rs1260326	0.252	1.05	0.965-1.14	1.36	0.0723	1.24	0.98-1.58	10.49
rs72613567	1.81E-03	0.877	0.808-0.953	7.28	7.03E-03	0.731	0.582-0.918	16.21
Combined PAF (genetic risk)				**30.39**				**60.95**
Age, >45 years	4.83E-14	2.00	1.67-2.39	54.85	1.17E-04	4.38	2.07-9.28	81.33
Sex, Male	1.42E-53	1.97	1.81-2.15	37.1	2.54E-17	3.19	2.44-4.17	58.57
Obesity, yes	2.21E-30	1.66	1.52-1.81	23.85	2.69E-07	1.85	1.47-2.35	33.35
Type 2 diabetes, yes	4.70E-167	3.97	3.6-4.38	24.89	2.79E-46	5.97	4.67-7.63	41.78

*Logistic regression models adjusted for age, sex, BMI, type 2 diabetes, first 10 genomic principal components and genotyping array batch. HCC, hepatocellular carcinoma; PAF, population attributable fraction; PRS-HFC, polygenic risk score hepatic fat content; PRS-5, polygenic risk score of fatty liver disease.

optimal to identify young at-risk individuals for whom preventive measures and surveillance programs can be implemented long before cirrhosis development.[1]

As Long *et al.* suggested, we now report the fraction of HCC variability explained by genetic predisposition to NAFLD in order to assess the relative burden compared to classical risk factors. The population attributable fraction (PAF) of cirrhosis and HCC accounted for by PRS compared to the single genetic variants in the UK Biobank population-based cohort is shown in Table 1.[5] Remarkably, genetic predisposition to NAFLD jointly accounted for 30.39% and 60.95% of cirrhosis and HCC variability, respectively (17.28 and 57.49% for the PRS). Considering HCC, this compares to 58.57% accounted for by male sex, and 33.35% and 41.78% by obesity and type 2 diabetes, respectively. It is important to bear in mind that sex, a major determinant of HCC risk, is also genetically determined, and that adiposity and type 2 diabetes also share a large inherited fraction predisposing to liver disease.[3] In our paper, the PRS was based on *PNPLA3-TM6SF2-GCKR-MBOAT7-HSD17B13* variants and in agreement with Long *et al.*[2] we believe the PRS will be improved by the inclusion of novel genetic determinants,[6] including those recently identified in novel exome-wide association studies.[6,7] Nevertheless, the estimated combined PAF should be interpreted cautiously, mainly because protective variants (such as *HSD17B13*) can result in counter-intuitive large PAF estimates. Furthermore, part of the impact of genetic predisposition to NAFLD is mediated through the interaction with environmental risk factors or mediated by dysmetabolic features.

Lastly, Long *et al.* point out that, although the fatty liver PRS was developed in a US general population where it predicted liver damage in African/Hispanic/European Americans,[8] it was validated for HCC risk assessment in large multicenter cohorts consisting exclusively of Europeans. This remark is in line with our thought that additional studies will be necessary in multi-ethnic populations prior to clinical implementation of this or similar diagnostic scores. An advantage of our approach is that we chose only the more robust common causal variants of NAFLD already validated in all major ethnicities.[4,9] Furthermore, the *PNPLA3* variant alone accounts for 50% of inter-ethnic variability in the susceptibility to fatty liver.[10] At the price of reducing the number of considered genetic markers, this choice would theoretically render the instrument more robust in different ethnic groups. However, it is important to note that, as remarked in the manuscript,[1] in specific populations some rarer variants may be more prevalent or the presence of specific environmental risk factors may modulate the impact of genetic variants.

In conclusion, we have shown that genetic predisposition to hepatic fat accumulation accounts for a large fraction of HCC susceptibility. After all, our study represents a proof of concept that will hopefully encourage new research efforts, leading to improvements in the current PRS instruments, validation in multi-ethnic cohorts and optimization of their possible use to improve the prevention and clinical management of liver disease.[1]

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Conflict of interest

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Authors' contributions

All authors were involved in the writing of this commentary and reviewed it prior to submission.

Supplementary data

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