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Reply to “The association between primary hypobetalipoproteinemia and hepatic diseases: evidence from genetic studies”

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Abbreviations:

ApoB: Apolipoprotein B

CONSTANCES: « *CONSULTANTS des Centres d’Examens de Santé* » (French)

GWAS: genetic wide association studies

(F)HBL: (familial) hypobetalipoproteinemia

LDL-C: low-density lipoprotein cholesterol

MR: Mendelian randomization

SNP: single nucleotide polymorphism

TC: total cholesterol

In a recent letter published in the *Journal of Hepatology*, Zhang *et al.* offered a critical analysis of our work on the association between primary hypobetalipoproteinemia (HBL) and the risk of liver complications, including liver cirrhosis and liver cancer [1,2]. They specifically highlighted the lack of “detailed analysis of the genetic correlation” between primary HBL and hepatic diseases in our study. To address this concern, they conducted a two-sample Mendelian randomization (MR) analysis to investigate the causal relationship between low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and apolipoprotein B (ApoB) with liver complications. Their findings revealed significant inverse associations between LDL-C and TC with cirrhosis and between LDL-C and ApoB with liver cancer [2].

We appreciate the thoughtful feedback and efforts of the authors; however, the additional data they present require careful interpretation and raise several concerns.

First, we want to emphasize that our initial study focused on individuals with primary HBL that is defined by plasma levels of LDL-C and ApoB below the 5th percentile of the population distribution [3]. While Zhang *et al.* reference the same article, they describe primary HBL as individuals with “LDL-C and apoB below the population distribution”, which reflects not only a matter of semantics but also fundamentally alters the research question they address. Although our study was based on a general population, we applied strict selection criteria to identify patients with primary HBL by excluding known secondary causes of HBL and severe liver disease at the time of inclusion. These individuals were compared to those with average LDL-C levels, between the 40th and the 60th percentiles. Approximately 30% of primary HBL cases have a monogenic origin, with a large majority involving variants that cause premature truncation of APOB [4]. It is crucial to highlight that the genetic basis of monogenic HBL significantly impacts the risk of liver complication[4,5]. For instance, the development of hepatic steatosis, which can progress to cirrhosis and liver cancer, is observed in *APOB* mutations that impair hepatic lipoprotein secretion, particularly VLDL₂ in monogenic HBL with secretion defects [5]. Notably, the severity of liver damage is proportional to the extent of ApoB truncation[6]. In contrast, a reduction in LDL-C resulting from increased hepatic catabolism of lipoproteins, as seen in carriers of loss-of-function variants in *PCSK9* or *ANGPTL3*, does not pose a risk of liver damage [7].

Commenté [MOU1]: Ref 5 (et le reste des refs est décalé)

Thus, Zhang et al. did not investigate the association between primary HBL and liver diseases but instead examines the relationship between TC, LDL-C, and ApoB levels with liver complications, which represent a fundamentally different focus.

Second, Zhang et al.'s study lacks detailed information on the MR methods used. Specifically, the study does not specify the cohorts from which the instrumental variables (SNPs) for the exposures (LDL-C, TC, ApoB) were selected or the independent cohort on which the outcomes were tested. Additionally, the criteria for selecting instrumental variables, such as the clumping threshold or the number of SNPs per phenotype, are not provided. Furthermore, most contemporary MR studies require replication using multiple algorithms (e.g., Egger, IVW), which is not discussed in their study.

Finally, from a pathophysiological perspective, it is concerning that the study reports a strong association between LDL-C and cirrhosis (OR (95% CI) 0.47, 0.32-0.70, adjusted p-value=0.001), while no association was found with ApoB (OR (95% CI) 1.06, 0.90-1.24, adjusted p-value=0.635), despite ApoB being the major apolipoprotein in LDL particles. Moreover, it is surprising that the reverse MR analysis did not support a causal link between cirrhosis and hypocholesterolemia, despite this relationship being consistently observed in previous observational studies [9,10].

One of the limitations of our genetic study is the small number of liver cancer cases among individuals with monogenic primary HBL (carriers of *APOB* truncating variants). This may be attributed to the limited statistical power and the relatively young age of our study populations (45 years for Constances and 56 years for UK Biobank). These factors likely contribute to the lack of statistical significance in the observed increased liver cancer risk among individuals carrying *APOB* truncating variants (HR: 3.36; 95% CI: 0.84-13.5; p=0.12). However, this does not negate the hepatic risk associated with monogenic HBL. This is demonstrated by the significantly elevated risk of cirrhosis (HR: 6.20; 95% CI: 2.31-16.6; p=0.0045), a condition that typically arises earlier in the disease course.

In line with this, our recent findings using FibroScan® to measure liver stiffness revealed that the risk of liver fibrosis significantly increases with age in HBL patients, affecting over half of individuals over

50 years of age [11]. This progression is likely due to the slow transition from steatosis to fibrosis over several years.

In conclusion, we firmly believe that primary HBL should be recognized as an independent risk factor for liver complications and warrants early diagnosis and vigilant monitoring by hepatologists.

References

- [1] Wargny M, Goronflot T, Rimbert A, Boursier J, Kab S, Henny J, et al. Primary hypocholesterolemia is associated with an increased risk of hepatic complications in the general population. *J Hepatol* 2024;S0168-8278(24)00108-9. <https://doi.org/10.1016/j.jhep.2024.01.030>.
- [2] Zhang Y, Chen J, Su S. The association between primary hypobetalipoproteinemia and hepatic Diseases: evidence from genetic studies. *J Hepatol* 2024;S0168-8278(24)02328-6. <https://doi.org/10.1016/j.jhep.2024.06.022>.
- [3] Tarugi P, Averna M. Hypobetalipoproteinemia: genetics, biochemistry, and clinical spectrum. *Adv Clin Chem* 2011;54:81–107.
- [4] Rimbert A, Vanhoye X, Coulibaly D, Marrec M, Pichelin M, Charrière S, et al. Phenotypic Differences Between Polygenic and Monogenic Hypobetalipoproteinemia. *Arterioscler Thromb Vasc Biol* 2020;ATVBAHA120315491. <https://doi.org/10.1161/ATVBAHA.120.315491>.
- [5] Bredefeld C, Peretti N, Hussain MM, Medical Advisory Panel. New Classification and Management of Abetalipoproteinemia and Related Disorders. *Gastroenterology* 2021;160:1912–6. <https://doi.org/10.1053/j.gastro.2020.11.040>.
- [6] Bredefeld C, Peretti N, Hussain MM, Medical Advisory Panel. New Classification and Management of Abetalipoproteinemia and Related Disorders. *Gastroenterology* 2021;160:1912–6. <https://doi.org/10.1053/j.gastro.2020.11.040>.
- [7] Rimbert A, Smati S, Dijk W, Le May C, Cariou B. Genetic Inhibition of PCSK9 and Liver Function. *JAMA Cardiol* 2021;6:353–4. <https://doi.org/10.1001/jamacardio.2020.5341>.
- [8] Bredefeld C, Hussain MM, Averna M, Black DD, Brin MF, Burnett JR, et al. Guidance for the diagnosis and treatment of hypolipidemia disorders. *J Clin Lipidol* 2022;16:797–812. <https://doi.org/10.1016/j.jacl.2022.08.009>.
- [9] McIntyre N. Plasma lipids and lipoproteins in liver disease. *Gut* 1978;19:526–30. <https://doi.org/10.1136/gut.19.6.526>.
- [10] Loria P, Marchesini G, Nascimbeni F, Ballestri S, Maurantonio M, Carubbi F, et al. Cardiovascular risk, lipidemic phenotype and steatosis. A comparative analysis of cirrhotic and non-cirrhotic liver disease due to varying etiology. *Atherosclerosis* 2014;232:99–109. <https://doi.org/10.1016/j.atherosclerosis.2013.10.030>.
- [11] Smati S, Wargny M, Boursier J, Moulin P, Di Filippo M, Cariou B. Prevalence of Liver Steatosis and Fibrosis in Adults With Primary Hypobetalipoproteinemia: Results From the HYPOCHOL Study. *Clin Gastroenterol Hepatol* 2024;S1542-3565(24)00606-2. <https://doi.org/10.1016/j.cgh.2024.06.031>.