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RESEARCH ARTICLE

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Visceral and ectopic fat are more predictively associated with primary liver cancer than overall obesity from genetic sights: A Mendelian randomization study

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Abstract

Several observational studies have reported an association between obesity and primary liver cancer (PLC), while the causality behind this association and the comparison of the risk effects of different obesity indicators on PLC remain unclear. In this study, we performed two-sample Mendelian randomization (MR) analyses to assess the associations of genetically determined liver fat, visceral adipose tissue (VAT), and body mass index (BMI) with the risk of PLC. The summary statistics of exposures were obtained from two genome-wide association studies (GWASs) based on the UK Biobank (UKB) imaging cohort and the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. GWAS summary statistics for PLC were obtained from FinnGen consortium R7 release data, including 304 PLC cases and 218 488 controls. Inverse-variance weighted (IVW) was used as the primary analysis, and a series of sensitivity analyses were performed to further verify the robustness of these findings. IVW analysis highlighted a significant association of genetically determined liver fat (OR per SD increase: 7.14; 95% CI: 5.10-9.99; $P = 2.35E-30$) and VAT (OR per SD increase: 5.70; 95% CI: 1.32-24.72; $P = .020$) with PLC but not of BMI with PLC. The findings were further confirmed by a series of MR methods. No evidence of horizontal pleiotropy between these associations existed. Our study suggested that genetically determined liver fat and VAT rather than BMI were associated with an increased risk of PLC, which suggested that visceral fat distribution is more predictive of the clinical risk of PLC than common in vitro measures.

Abbreviations: BMI, body mass index; CI, confidence interval; CT, computed tomography; GERA, Genetic Epidemiology Research on Adult Health and Aging; GIANT, Genetic Investigation of Anthropomorphic Traits; GWAS, genome-wide association study; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; IL, interleukin; IVW, inverse-variance weighted; LCPP, Liver Cancer Pooling Project; MR, Mendelian randomization; MRI, magnetic resonance imaging; MR-PRESSO, MR-pleiotropy residual sum and outlier; MR-RAPS, MR-robust adjusted profile score; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odd ratio; PLC, primary liver cancer; SNP, single-nucleotide polymorphism; TNF-α, tumor necrosis factor alpha; UKB, UK Biobank; VAT, visceral adipose tissue.

Fei-Qi Xu and Qing-Yun Xu have contributed equally to this study.

KEYWORDS
liver fat, mendelian randomization, obesity, primary liver cancer, visceral adipose tissue

What's new?

Obesity is associated with increased risk of primary liver cancer (PLC). However, the causality of obesity in PLC is difficult to determine based on existing observational studies, and little is known about whether specific fat distribution impacts PLC risk. Here, the authors employed Mendelian randomization to investigate associations between PLC risk and genetically determined liver fat deposition and visceral fat distribution. Genetically predicted liver fat and visceral adipose tissue (VAT) distribution were more strongly linked to increased PLC risk than body mass index. VAT and especially fat deposition in the liver are promising clinical measures for predicting PLC risk.

1 | INTRODUCTION

Primary liver cancer (PLC) is the sixth most commonly diagnosed cancer and the third leading cause of malignant tumor-related mortality.[1,2] Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the two principal classifications of PLC. HCC accounts for approximately 80% of the overall PLC cases, followed by ICC, which represents 14.9% of cases.[3] The most common cause of PLC is chronic viral hepatitis (including hepatitis B or hepatitis C virus); however, nonalcoholic fatty liver disease (NAFLD) is projected to emerge as the leading cause of PLC in many countries in the near future.[4] As the underlying condition of NAFLD, obesity has been reported to be independently associated with an increased risk of PLC in a majority of previous observational studies.[5-7]

Due to the convenience of measurement, body mass index (BMI) is most commonly used as an indicator of obesity. However, as an indirect indicator, BMI only reflects overall obesity and fails to account for the distribution of fat (ie, central, peripheral or in a specific organ).[8] Visceral adipose tissue (VAT) and liver fat, indicators of abdominal obesity and ectopic fat deposition in the liver, respectively, have become preferable indicators reflecting the distribution of fat and discriminating obesity-related disease risk, which can be accurately measured by magnetic resonance imaging (MRI) or computed tomography (CT).[9,10] Several observational studies also previously demonstrated that VAT and liver fat were independent risk factors for PLC.[11,12] Although associations between obesity and PLC were reported by these observational studies, it remains difficult to determine the causality behind these associations due to the limitations of reverse causality and confounding bias in observational studies. In addition, the comparison of the detrimental effects of overall obesity and specific fat distribution on PLC was rarely considered in previous studies.

Mendelian randomization (MR) has become a powerful method to identify the potential causal relationship between risk factors and diseases by utilizing single-nucleotide polymorphisms (SNPs) as instrumental variants to effectively avoid the confounding and reverse-causality biases of causal estimation and strengthen causal inference.[13-15] In this study, we performed two-sample MR analyses to assess the association of genetically determined obesity with the risk of PLC and to compare the strength of the predictive effect of different indicators that reflect overall obesity and specific fat distributions on PLC risk.

2 | DESIGN AND METHODS

2.1 | Study overview

We employed genetic variation as an instrumental variants to assess the associations of genetically determined overall obesity (BMI) and fat distribution (ectopic fat deposition [liver fat], abdominal obesity [VAT]) with PLC utilizing MR methods. As depicted in Figure 1, three important assumptions underpin the MR analysis. First, genetic variants proposed as instrumental variables must be related to the exposures. Second, genetic variants must be independent of all potential confounders. Third, genetic variants must affect the outcomes only through the exposures, not via alternative pathways. The summary data of the genetic variants used in this study were obtained from three publicly available genome-wide association studies (GWASs) of patients of European ancestry.

2.2 | Data sources for instrument-outcome associations

The summary statistics for liver fat and VAT were obtained from the GWAS based on the UK Biobank (UKB) imaging cohort of patients of European ancestry, which produced the largest sample size (including measurements of liver fat in 32 858 patients and VAT in 32 860 patients) for data of abdominal imaging-derived phenotypes, where liver fat and VAT were calculated with percentage and volume as continuous variables, respectively (GWAS ID of liver fat: ebi-a-GCST90016673; GWAS ID of VAT: ebi-a-GCST90016671).[16] We acquired genetic variants of BMI from a GWAS based on the large, ethnically diverse Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort with 427 509 calendar year-averaged BMI measurements from 100 418 adults, including 315 347 European-ancestry BMI measurements in the MRC-IEU Project (GWAS ID: ebi-a-GCST006368).[17] GWAS summary statistics for the outcome of PLC were obtained from FinnGen consortium R7 release data, and the phenotype "malignant neoplasm of liver and intrahepatic

bile ducts" was adopted in the present study, which included 304 PLC patients and 218 488 controls (GWAS ID: finn-b-C3_LIVER_INTRAHEPATIC_BILE_DUCTS).[18] FinnGen is a public-private partnership research project that combines imputed genotype data generated from newly collected and legacy samples from Finnish biobanks and digital health record data from Finnish health registries (https://www.finngen.fi/en) with high coverage of Finnish descent.[18] All the aforementioned GWASs were available from the IEU GWAS database (https://gwas.mrcieu.ac.uk/).

2.3 | Genetic instrument selection

In this study, all genetic variants significantly associated with the exposures ($P < 5 \times 10^{-8}$) were identified, and only those that were not in linkage disequilibrium with other SNPs within a 5000 kb window with a threshold of $r^2 < 0.3$ were considered instrumental variants of the exposures. To ensure that the genetic instruments could link the exposure to outcome, SNPs that were not available in the outcome dataset were excluded. The intensity of instrumental variants was assessed by calculating the F-statistic via the formula $F = \left(\frac{N-K-1}{K}\right)\left(\frac{R^2}{1-R^2}\right)$, where R^2 represents the proportion of the variation in exposures explained by the SNPs, N represents the sample size and K represents the number of SNPs in genetically proxied exposures.[19] An F-statistic of at least 10 was required to rule out bias from weak instrumental variables.[20] Ultimately, 37 SNPs for liver fat, 8 SNPs for VAT and 353 SNPs for BMI were selected as genetic instruments in this MR study. The characteristics of all SNPs used as instrumental variants are presented in Tables S1-S3.

2.4 | Mendelian randomization estimates

A series of two-sample MR studies were conducted to explore the associations of genetically determined liver fat, VAT and BMI with PLC. In the primary analysis, inverse-variance weighted (IVW) was used to examine the effect of genetically determined liver fat, VAT and BMI on the risk of PLC.[13] For each genetic variation that satisfied the instrumental variable hypothesis, IVW used a meta-analysis approach combined with the Wald estimates for each SNP result to obtain an unbiased overall estimate.[21] In the sensitivity analyses, penalized IVW, maximum likelihood, MR-robust adjusted profile score (MR-RAPS) and MR-pleiotropy residual sum and outlier (MR-PRESSO) were applied to further validate the robustness of the primary analysis by their respective strengths. Penalized IVW can improve the robustness and accuracy of estimates by attenuating partial candidate instruments.[22] When standard errors are corrected for the presence of many weak instruments, maximum likelihood can provide unbiased robust estimates.[23] In addition, MR-RAPS corrects for horizontal multiplicity by using robust adjusted contour scores, thereby reducing the bias caused by horizontal multiplicity.[24] Finally, MR-PRESSO was utilized to automatically detect outliers in IVW linear regression and provide corrected MR estimates with outlier correction.[25]

Cochran's Q statistic was calculated to quantify the heterogeneity among the genetic instruments and provide evidence for selecting the appropriate analytical methods.[26] In addition, we employed the intercept term of MR-Egger regression methods to reflect directional horizontal pleiotropy across all variants.[27] The iterative "leave-one-out" analysis was performed by omitting each instrument SNP in turn to determine whether the results were caused by any individual SNP.[25] Additionally, the statistical power of this MR study was evaluated using a noncentrality parameter-based approach on a publicly available mRnd web tool (https://shiny.cnsgenomics.com/mRnd/).[28]

The results in this study are presented as odds ratios (ORs) per SD increase with 95% confidence intervals (95% CIs). All statistical tests were 2-sided, and a P value <.05 was considered to indicate statistical significance. All statistical analyses were carried out using the "MendelianRandomization", "TwoSampleMR", "MR-PRESSO", "gtx" and "mr.raps" packages in R software, Version 4.2.3.

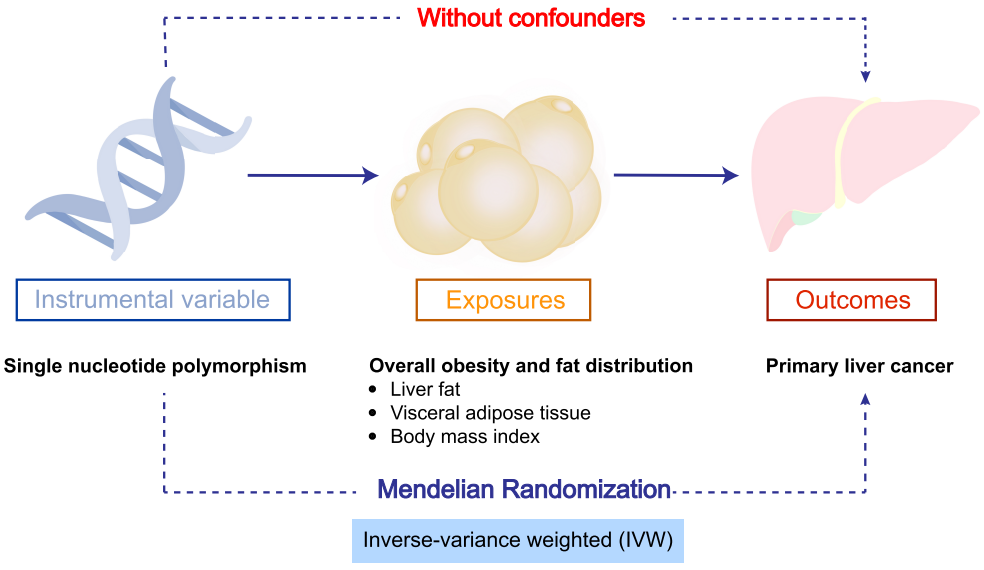

FIGURE 1 Conceptual framework for this two-sample Mendelian randomization study on the association of overall obesity and fat distribution with primary liver cancer.

3 | RESULTS

3.1 | Instrumental variants

Table 1 presents a characteristic overview of the instrument variants employed in this MR study, with further details available in Tables S1-S3. As displayed in Table 1, the phenotypic variances of liver fat, VAT and BMI interpreted by the corresponding instrumental variants were 10.43%, 0.86% and 5.90%, respectively. The *F*-statistics for the genetic instruments of liver fat, VAT and BMI were 103.24, 35.48 and 55.89, respectively, indicating that the bias of weak instruments in this MR study was almost nonexistent.

3.2 | Effect of genetically determined fat distribution on PLC

Since a *P* value >.05 for the Cochran's Q statistic test indicated that there was no heterogeneity among the instrumental variants, fixed-effect IVW models were employed in the primary analysis (Table S4). As shown in Figure 2, the results of the primary IVW analysis highlighted a significant association of genetically determined liver fat (OR per SD increase: 7.14; 95% CI: 5.10-9.99; $P = 2.35E-30$) and VAT (OR per SD increase: 5.70; 95% CI: 1.32-24.72; $P = .020$) with PLC but not of BMI with PLC (OR per SD increase: 1.53; 95% CI: 0.99-2.38; $P = .058$). Consistent with the stronger OR of liver fat, it could be inferred that genetically determined liver fat may have a more significant effect on PLC than genetically determined VAT, while BMI does not exhibit these associations.

3.3 | Sensitive analyses

In the sensitive analyses, a significant association of increased genetically determined liver fat percentage with the risk of PLC was further confirmed by a series of MR methods, including penalized IVW (OR: 6.17; 95% CI: 4.30-8.78; $P = 1.79E-23$), maximum likelihood (OR: 7.47; 95% CI: 5.31-10.51; $P = 7.00E-31$), MR-RAPS (OR: 7.29;

TABLE 1 Characteristics for the genetic variants used in present Mendelian randomization study.

Exposure	SNPs	Used SNPs	Sample size	Population	Variance, %[a]	F-statistic[b]	Power, %[c]
Liver fat	41	37	32 858	European	10.43	103.24	100
Visceral adipose tissue	8	8	32 860	European	0.86	35.48	100
Body mass index	356	353	315 347	European	5.90	55.89	100

[a]Phenotypic variance explained by the corresponding genetic instruments in this Mendelian randomization study (Associations of liver fat/visceral adipose tissue/body mass index with primary liver cancer).
[b]F-statistics that quantify the strength of the selected instrumental variables were done with the formula of $F = \left(\frac{N-K-1}{K}\right)\left(\frac{R^2}{1-R^2}\right)$, where R^2 is the proportion of variation in exposures explained by the SNPs, *N* is the sample size and *K* is the number of SNPs in genetically proxied exposures.
[c]Power was calculated using the previously described online method (https://shiny.cnsgenomics.com/mRnd/).

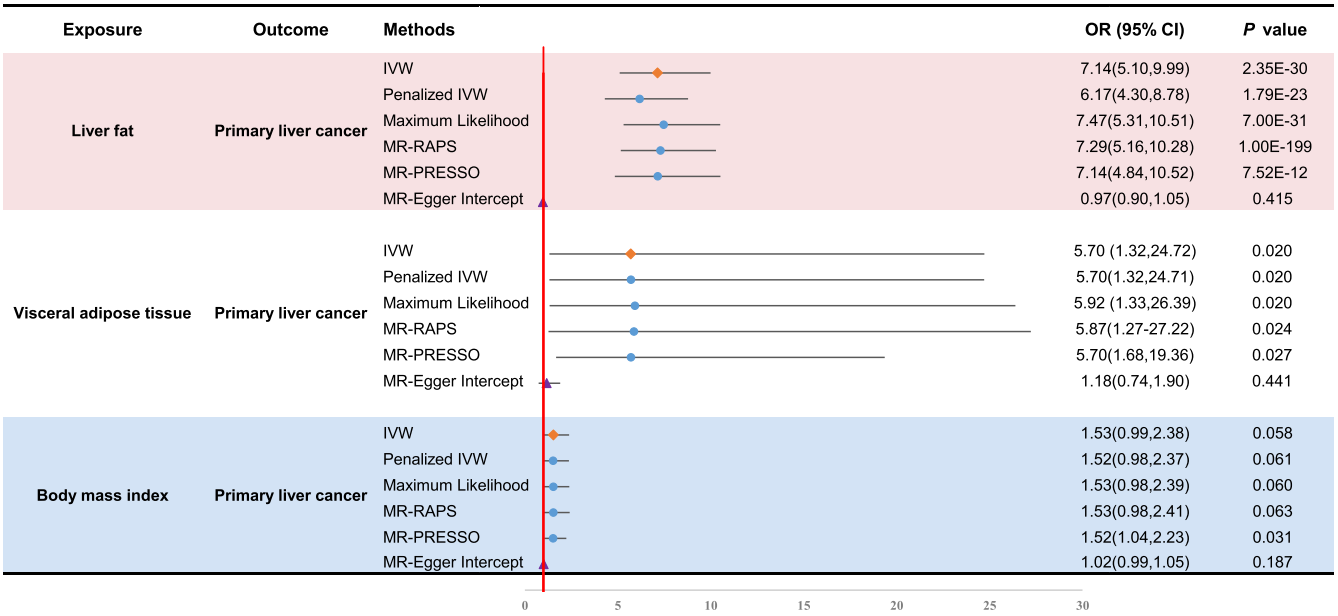

FIGURE 2 Summary Mendelian randomization estimates of the associations of liver fat/visceral adipose tissue/body mass index with primary liver cancer.

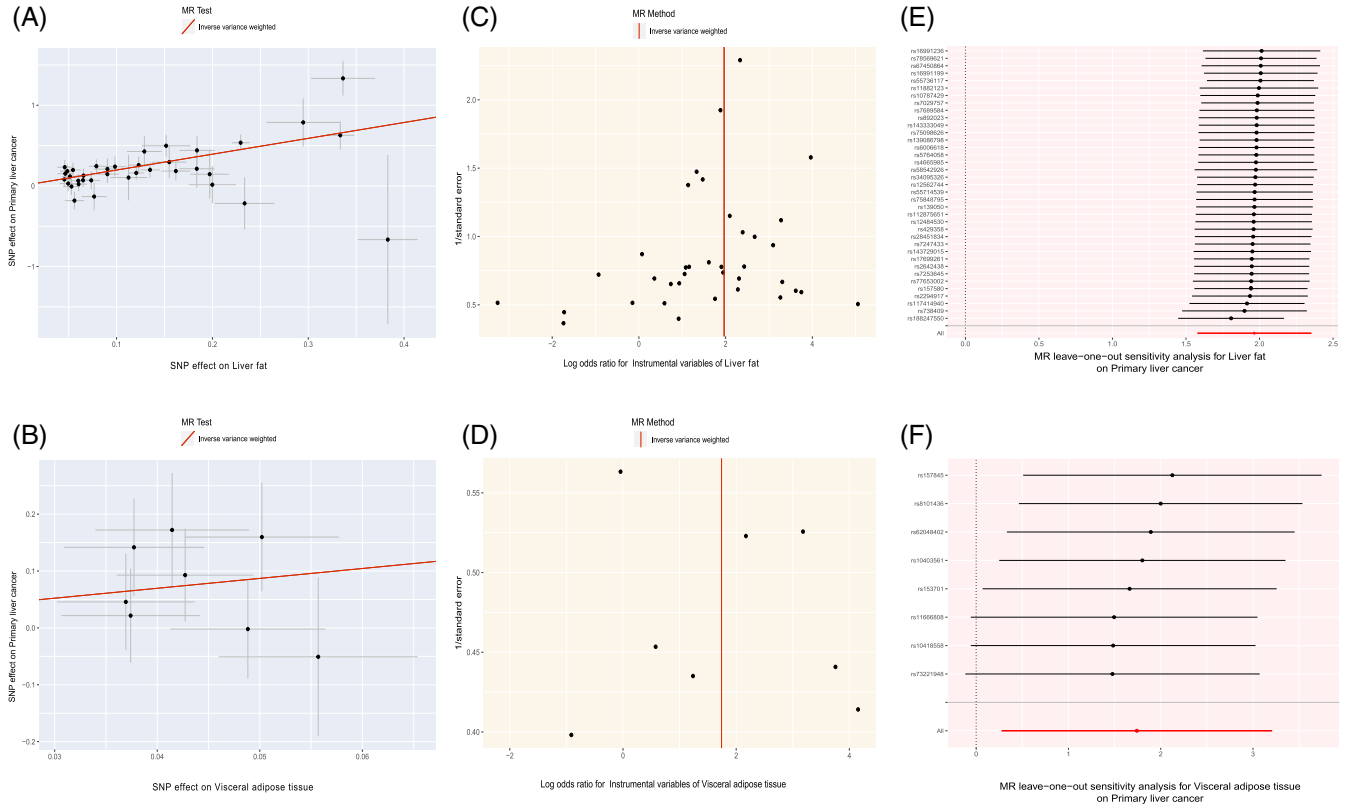

FIGURE 3 Associations of SNPs for liver fat/ visceral adipose tissue/ body mass index with primary liver cancer. (A) Scatter plot for SNPs of liver fat associated with primary liver cancer; (B) Scatter plot for SNPs of visceral adipose tissue associated with primary liver cancer; (C) Funnel plot for instrumental variables of liver fat in relation to primary liver cancer; (D) Funnel plot for instrumental variables of visceral adipose tissue in relation to primary liver cancer; (E) Forest diagram for leave-one-out of the association between liver fat variants and primary liver cancer and (F) Forest diagram for leave-one-out of the association between visceral adipose tissue variants and primary liver cancer.

95% CI: 5.16-10.28; $P = 1.00E-199$) and MR-PRESSO (OR: 7.14; 95% CI: 4.84-10.52; $P = 7.52E-12$). In addition, the association of genetically determined VAT with the risk of PLC were robust according to the results of penalized IVW (OR: 5.70; 95% CI: 1.32-24.72; $P = .020$), maximum likelihood (OR: 5.92; 95% CI: 1.33-26.39; $P = .020$), MR-RAPS (OR: 5.87; 95% CI: 1.27-27.22; $P = .024$) and MR-PRESSO (OR: 5.70; 95% CI: 1.68-19.36; $P = .027$). Furthermore, although the association of BMI with PLC did not reach statistical significance in the primary analysis and other sensitivity analyses ($P > .05$), MR-PRESSO (OR: 1.52; 95% CI: 1.04-2.23; $P = .031$) still implicated a potentially detrimental role of BMI in the risk of PLC (Figure 2).

In addition, MR-Egger regression indicated no evidence of directional pleiotropy for the associations of genetically determined liver fat ($P_{Intercept} = .415$), VAT ($P_{Intercept} = .441$) and BMI ($P_{Intercept} = .187$) with the risk of PLC. Associations between each instrumental variant for liver fat and VAT and the risk of PLC are shown in Figure 3.

4 | DISCUSSION

In the present study, we performed two-sample MR methods to investigate the potential causal associations between obesity and the risk of PLC in the European population. Our study demonstrated that of three indicators of obesity, genetically determined liver fat and VAT (reflecting specific fat distribution), but not BMI (reflecting overall obesity), were significantly associated with PLC. Furthermore, the comparison of ORs indicates a stronger effect of genetically determined liver fat on PLC than VAT. These results suggest that specific fat distribution, especially ectopic fat deposition in the liver, is a major determinant for PLC.

With recent advances in the treatment of HBV and HCV infection, the burden of PLC due to viral hepatitis is declining, while the prevalence of NAFLD-related PLC is rising rapidly.[4] As the underlying condition of NAFLD, obesity has previously been reported to be independently associated with an increased risk of PLC in substantial observational studies. A meta-analysis including 28 prospective cohort studies with 8 135 906 subjects indicated that obesity (high BMI) is an independent risk factor for the occurrence of PLC (hazard ratio = 1.69).[7] Another study utilized the Liver Cancer Pooling Project (LCPP), based on a consortium of 13 US prospective cohort studies with data from 1 541 143 people, and found that obesity was associated with a 62% increased risk of ICC.[6] Moreover, a comprehensive systematic literature review and meta-analysis of observational studies showed that higher body fatness at a young age increased the risks

of developing HCC later in life.[5] However, given that observational studies inevitably have confounding and reverse causality bias due to the methodological limitations, the MR method can be used to compensate for these defects.[29] In addition, previous studies mostly used indicators that reflect overall obesity as exposures while ignoring some indicators that can reflect specific fat distribution. Therefore, we used MR methods to test the effects of genetic predisposition to exposures on outcomes, eliminating confounders and reverse causality to assess and compare the causal effects of different indicators reflecting overall obesity (BMI) and specific fat distributions (VAT and liver fat) on the risk of PLC.

As the predominant indicator for assessing obesity, BMI has some inevitable drawbacks. It can only reflect overall obesity, neglecting fat deposition in specific areas,[8] rendering it inadequate for a comprehensive explanation of the pathophysiological mechanisms associated with the development of PLC. With the development of imaging technology and superiorities in medical artificial intelligence, we can use MRI to calculate fat levels in specific parts of the body, which is generally regarded as the gold standard for the measurement of body composition.[16] VAT and liver fat are two indicators reflecting abdominal obesity and ectopic fat deposition in the liver, respectively. Studies have reported that a large amount of VAT contributes to a high prevalence of NAFLD, supporting the utilization of these two indicators for a more accurate interpretation of the mechanisms underlying NAFLD-related PLC.[30] With the help of MRI and image processing technology such as triple-echo chemical shift MR technology, we can calculate the volume of VAT and percentage of liver fat precisely and assess their levels.[31]

Our study revealed that genetically determined liver fat and VAT, as opposed to BMI, were significantly associated with PLC, which provided several referential clinical inspirations. Certain individuals may have a normal BMI with nonvisible abdominal obesity or ectopic fat deposition in the liver,[10] resulting in missed screening and surveillance for PLC in this population. Thus, employing in vitro measures such as BMI as an indicator of obesity to screen the population at high risk of PLC may be limiting. Therefore, it may be practical to conduct a further comprehensive assessment in conjunction with imaging examinations to assess VAT and liver fat levels instead of focusing solely on BMI, thereby screening high-risk groups and monitoring them more frequently for PLC. In addition, effective preventive measures such as a healthy low-fat diet and even the application of relevant lipid-lowering drugs in patients with high VAT and liver fat are of great significance for the secondary prevention of PLC. More experimental studies are needed to explore the effect of fat distribution on PLC clinical risk by intervening in VAT and liver fat.

Liver fat deposition leads to NAFLD, nonalcoholic steatohepatitis (NASH) and cirrhosis, eventually leading to PLC, which is the main mechanism by which obesity leads to PLC,[32] and previous studies have reported some of the molecular mechanisms involved. The low-grade chronic inflammatory environment of obesity facilitates macrophage aggregation and the large release of proinflammatory cytokines (eg, tumor necrosis factor alpha [TNF-α] and interleukin [IL]-6), affecting key signaling pathways and leading to progression from hepatic steatosis to more advanced NAFLD and NASH.[33,34] Fat-induced TNF-α leads to insulin resistance by inducing activation of the JNK signaling pathway and is involved in cell apoptosis, proliferation and angiogenesis of gene transcription, while IL-6 activates STAT3 and promotes cell growth and differentiation.[35,36] In addition, IL-1 and TNF-α are key to both liver fat accumulation (NAFLD) and fat-induced liver inflammation (NASH) via TNFR6 signaling.[33] In addition, oxidative stress caused by liver fat activates immune cells in the liver, produces large amounts of reactive oxygen species and exacerbates liver damage and fibrosis, playing an important role in the progression of NAFLD to PLC.[37] Moreover, it was documented that liver fat is associated with the generation of lipotoxic lipid species (eg, triacylglycerols, diacylglycerols and sphingolipids), which further contributes to NAFLD.[38] Furthermore, metabolic disorder, driven by excessive obesity in the context of high leptin and low adiponectin, leads to the progression of NAFLD and hepatocellular carcinomas.[39,40]

To our knowledge, this is the first study using BMI, VAT and liver fat as indicators of obesity to explore the associations between genetically determined obesity and PLC by the MR method, with almost negligible bias of weak instrumental variants and horizontal pleiotropy. Moreover, our conclusions were corroborated by multiple sensitivity analyses, suggesting higher robustness of the findings. However, there are several undeniable limitations of this study. First, the number of PLC cases accounted for a relatively low proportion of the total sample size in the original GWAS, which may affect the statistical power, and no other suitable large-sample GWAS of PLC is available for replication.[14] However, we ensured that the study had high statistical power (100%) through authoritative online calculations. Second, plausible heterogeneity may exist among the participants of the exposure cohorts (GERA and UKB) and the outcome cohort (FinnGen), which might have potentially influenced the findings of our two-sample Mendelian randomization study.[41] Third, given that GWASs are a meta-analysis of multiple population studies without individual-level data, it is difficult to completely rule out potential population stratification bias. However, the population in our study was mostly from European backgrounds; thus, the possibility of population stratification bias was minimal. Fourth, we cannot rule out the possibility that the Finnish population is a genetic isolate, which may cause biased estimation of the relationships between risk loci for liver fat, VAT and BMI with PLC. Future studies based on large-sample GWASs of PLC covering the entire European population are needed to validate our findings. Fifth, the accurate calculation of VAT and liver fat is particularly dependent on image processing software and AI algorithms. In the future, more advanced processing software and algorithms are needed to accurately calculate VAT and liver fat to better predict PLC.

In summary, our study suggested that genetically determined liver fat and VAT but not BMI were significantly associated with an increased risk of PLC, which suggested that visceral fat distribution is more predictive of the clinical risk of PLC than common in vitro measures. Therefore, it is of great practical significance for the clinical prevention of PLC to screen high-risk groups by evaluating VAT and liver fat levels with internal imaging examination. In the future, more high-quality GWASs of total PLC as well as the HCC and ICC subtypes

based on the same large-sample population are needed to conduct subgroup analyses to verify and supplement our findings.

AUTHOR CONTRIBUTIONS

Conceptualization: Feiqi Xu, Qingyun Xu and Weifeng Yao; Data curation and formal analysis: Feiqi Xu, Qingyun Xu, Zhangji Zhu, Lei Jin and Weifeng Yao. Funding acquisition: Liming Jin and Weifeng Yao; Drafting the article and figures: Feiqi Xu and Qingyun Xu; Validation: Feiqi Xu, Qingyun Xu, Zhangji Zhu, Lei Jin, Taiwei Ye, Chengfei Du, Zhenyu Gao, Xiaokun Huang, Zhe Zhang and Liming Jin; Writing original draft: Feiqi Xu and Qingyun Xu; Reviewing and editing: Weifeng Yao. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in this study, and data sources and handling of these data are described in the Materials and Methods. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

All original studies included in the GWAS cited here were approved by the ethics committee, and written informed consent was obtained from each participant before data collection as described in the included GWAS.

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REFERENCES

1. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol*. 2022;77(6):1598-1606.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
3. Rumgay H, Ferlay J, de Martel C, et al. Global, regional and national burden of primary liver cancer by subtype. *Eur J Cancer*. 2022;161:108-118.
4. Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. *J Hepatol*. 2021;75(6):1476-1484.
5. Hidayat K, Du X, Shi BM. Body fatness at a young age and risks of eight types of cancer: systematic review and meta-analysis of observational studies. *Obes Rev*. 2018;19(10):1385-1394.
6. Petrick JL, Thistle JE, Zeleniuch-Jacquotte A, et al. Body mass index, diabetes and intrahepatic Cholangiocarcinoma risk: the liver cancer pooling project and meta-analysis. *Am J Gastroenterol*. 2018;113(10):1494-1505.
7. Sohn W, Lee HW, Lee S, et al. Obesity and the risk of primary liver cancer: a systematic review and meta-analysis. *Clin Mol Hepatol*. 2021;27(1):157-174.
8. Barberio AM, Alareeki A, Viner B, et al. Central body fatness is a stronger predictor of cancer risk than overall body size. *Nat Commun*. 2019;10(1):383.
9. Beller E, Lorbeer R, Keeser D, et al. Hepatic fat is superior to BMI, visceral and pancreatic fat as a potential risk biomarker for neurodegenerative disease. *Eur Radiol*. 2019;29(12):6662-6670.
10. Zeng Q, Wang L, Dong S, et al. CT-derived abdominal adiposity: distributions and better predictive ability than BMI in a nationwide study of 59,429 adults in China. *Metabolism*. 2021;115:154456.
11. George J, Kawaguchi T. Liver fat and a perturbed metabolic milieu: a consilience of factors driving liver cancer development. *Hepatol Int*. 2022;16(4):733-736.
12. Montano-Loza AJ, Mazurak VC, Ebadi M, et al. Visceral adiposity increases risk for hepatocellular carcinoma in male patients with cirrhosis and recurrence after liver transplant. *Hepatology*. 2018;67(3):914-923.
13. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658-665.
14. Davies NM, Holmes MV, Davey SG. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601.
15. Smith GD, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22.
16. Liu Y, Basty N, Whitcher B, et al. Genetic architecture of 11 organ traits derived from abdominal MRI using deep learning. *Elife*. 2021;10:e65554.
17. Hoffmann TJ, Choquet H, Yin J, et al. A large multiethnic genome-wide association study of adult body mass index identifies novel loci. *Genetics*. 2018;210(2):499-515.
18. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508-518.
19. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40(3):755-764.
20. Zheng J, Baird D, Borges MC, et al. Recent developments in Mendelian randomization studies. *Curr Epidemiol Rep*. 2017;4(4):330-345.
21. Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization:

comparison of allele score and summarized data methods. *Stat Med*. 2016;35(11):1880-1906.
22. Rees JMB, Wood AM, Dudbridge F, Burgess S. Robust methods in Mendelian randomization via penalization of heterogeneous causal estimates. *PLoS One*. 2019;14(9):e0222362.
23. Davies NM, von Hinke Kessler Scholder S, Farbmacher H, Burgess S, Windmeijer F, Smith GD. The many weak instruments problem and Mendelian randomization. *Stat Med*. 2015;34(3):454-468.
24. Zhao Q, Wang J, Hemani G, Bowden J, Small DS. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. *Ann Stat*. 2020;48(3):1742-1769. 1728.
25. Ong JS, MacGregor S. Implementing MR-PRESSO and GCTA-GSMR for pleiotropy assessment in Mendelian randomization studies from a practitioner's perspective. *Genet Epidemiol*. 2019;43(6):609-616.
26. Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: a review. *Res Synth Methods*. 2019;10(4):486-496.
27. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32(5):377-389.
28. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol*. 2013;42(5):1497-1501.
29. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614-1621.
30. Milić S, Lulić D, Štimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. *World J Gastroenterol*. 2014;20(28):9330-9337.
31. Nougaret S, Monsonis B, Molinari N, et al. Quantification of liver fat content in liver and primary liver lesions using triple-echo-gradient-echo MRI. *Eur Radiol*. 2020;30(9):4752-4761.
32. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397(10290):2212-2224.
33. Park EJ, Lee JH, Yu GY, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell*. 2010;140(2):197-208.
34. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology*. 2007;132(6):2169-2180.
35. Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. *Nature*. 2002;420(6913):333-336.
36. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. *Eur J Cancer*. 2005;41(16):2502-2512.
37. Brahma MK, Gilglioni EH, Zhou L, Trépo E, Chen P, Gurzov EN. Oxidative stress in obesity-associated hepatocellular carcinoma: sources, signaling and therapeutic challenges. *Oncogene*. 2021;40(33):5155-5167.
38. Ooi GJ, Meikle PJ, Huynh K, et al. Hepatic lipidomic remodeling in severe obesity manifests with steatosis and does not evolve with non-alcoholic steatohepatitis. *J Hepatol*. 2021;75(3):524-535.
39. Jiang N, Sun R, Sun Q. Leptin signaling molecular actions and drug target in hepatocellular carcinoma. *Drug des Devel Ther*. 2014;8:2295-2302.
40. Parida S, Siddharth S, Sharma D. Adiponectin, obesity, and cancer: clash of the bigwigs in health and disease. *Int J Mol Sci*. 2019;20(10):2519.
41. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. *Wellcome Open Res*. 2019;4:186.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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