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Obesity and risk for liver disease: a two-sample Mendelian randomisation study

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Abstract

The associations between obesity and liver diseases are complex and diverse. To explore the causal relationships between obesity and liver diseases, we applied two-sample Mendelian randomisation (MR) and multivariable MR analysis. The data of exposures (BMI and WHRadjBMI) and outcomes (liver diseases and liver function biomarker) were obtained from the open genome-wide association study database. A two-sample MR study revealed that the genetically predicted BMI and WHRadjBMI were associated with non-alcoholic fatty liver disease, liver fibrosis and autoimmune hepatitis. Obesity was not associated with primary biliary cholangitis, liver failure, liver cell carcinoma, viral hepatitis and secondary malignant neoplasm of liver. A higher WHRadjBMI was associated with higher levels of biomarkers of lipid accumulation and metabolic disorders. These findings indicated independent causal roles of obesity in non-alcoholic fatty liver disease, liver fibrosis and impaired liver metabolic function rather than in viral or autoimmune liver disease.

Keywords: **BMI: Liver disease: NAFLD: Mendelian randomisation: Liver fibrosis**

Obesity has become a severe health challenge worldwide and contributes to a decline in both quality of life and life expectancy[1]. With the changes in modern lifestyles, factors such as unhealthy eating habits and lack of exercise have led to a rapid increase in obesity[2]. Previous studies have shown that the obesity epidemic is closely associated with the prevalence and severity of non-alcoholic fatty liver disease[3,4] The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing at a rate of 1 % per year, afflicting 30 % of the worldwide population[5].

Several studies have shown that obesity is positively associated with NAFLD[6–8]. Although NAFLD is typically identified in individuals with obesity, up to 7–20 % are characterised as having lean non-alcoholic steatohepatitis[9]. The relationship between obesity and NAFLD is also influenced by a combination of factors, such as genetics, metabolic abnormalities, lifestyle and other potential comorbidities[8].

The relationships between obesity and other liver diseases are still complex and diverse. A positive correlation between obesity and the aggravation of viral hepatitis has been reported[10,11]. In contrast, several studies have suggested an inverse correlation between obesity and virus activity and the success rate of antiviral treatment[12–14]. Additionally, the relationship between obesity and autoimmune liver disease is ambiguous[15–17]. The results from prior studies are inconsistent,

Abbreviations: GWAS, genome-wide association study; MR, Mendelian randomisation; NAFLD, non-alcoholic fatty liver disease; IVW, inverse-variance weighted; WHRadjBMI, waist-to-hip ratio adjusted for BMI.

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and these differences may be attributed to limited sample sizes, residual confounding and reverse causation bias. These studies have explored correlation rather than causal relationship and lacked evidence from randomised controlled trials. It remains controversial whether causal effects exist between obesity and the development of liver disease.

As genetic variants are fixed at conception and not influenced by disease status, Mendelian randomisation (MR) has the potential to use genetic variants as instrumental variables to evaluate the causal relationship between exposure and lifelong differences in disease outcomes[18]. Public large-scale genome-wide association study (GWAS) data can be used to explore the effects of life-long perturbations in risk factors and rare diseases, which require large sample sizes and long-term follow-up for sufficient occurrence of endpoints in a randomised controlled trial[19].

BMI, as a commonly used index to measure the degree of obesity[6], mainly considers the relationship between height and weight and cannot fully capture individual differences in visceral fat, which is closely related to liver disease and function[20,21]. The waist-to-hip ratio adjusted for BMI (WHRadjBMI) is a surrogate for abdominal fat and is less influenced by muscle and bone mass than BMI[22]. The waist–hip ratio may be superior to BMI in predicting liver-related outcomes[23,24].

This study used both BMI and WHRadjBMI, as instrumental variables to explore the causal relationships between obesity and liver disease and function. Through comprehensive analysis and integration of existing research findings, we hope to deepen the understanding of obesity, and in the occurrence and development of liver diseases, and provide more targeted strategies for the prevention, diagnosis and treatment of related liver diseases, thereby improving public health.

Method

Study design and selection of SNP

The two-sample MR method was used to explore the causal relationships between exposures (BMI and WHRadjBMI) and outcomes (liver diseases and liver function) (Fig. 1). Suitable SNP should meet three criteria. First, SNP associated with BMI at a significance threshold of $P < 5 \times 10^{-8}$ were selected. Second, the independence among the selected SNP was assessed by pairwise-linkage disequilibrium. SNP were clumped at $r^2 < 0{\cdot}01$ via a 10 000 kb window. Third, we calculated the F-statistic to assess the strength of individual SNP. SNP with F-statistics >10 are considered sufficient to eliminate potential bias[25].

Data sources

GWAS summary statistics for BMI (n 461 460) were obtained from the UK Biobank study, which assessed the relationships between BMI and SNP. WHRadjBMI data (SNP = 4 238 887) were obtained from an open GWAS dataset. Eight liver disease-related datasets and nine liver biomarker-related datasets were obtained from the open GWAS database[26]. Liver disease outcomes were NAFLD, fibrosis and cirrhosis of liver, autoimmune hepatitis, viral hepatitis, hepatic failure, liver cell carcinoma, secondary malignant neoplasm of liver and primary biliary cholangitis. Liver function outcomes were alanine aminotransferase, aspartate aminotransferase, bilirubin, blood plate count, HDL, LDL, very LDL, apolipoprotein B and fasting blood insulin.

Detailed information on GWAS of liver diseases and related biomarkers, including the number of participants and adjusted covariates, is presented in online Supplementary Table 1 and online Supplementary Table 2, respectively.

Multivariable Mendelian randomisation

Multivariable MR can be applied for multiple genetic variants and independent exposures in an instrumental-variable analysis to determine the direct causal effect of each risk factor included in the model[27]. Multivariate MR was used to reveal the relationships between multiple exposure variables (BMI and WHRadjBMI) and liver diseases.

Mendelian randomisation analysis

The inverse-variance weighted (IVW) method under a random-effects model was used for the primary analysis. Sensitivity analyses, including the MR pleiotropy residual sum and outlier test (MR-PRESSO)[28] and the MR-Egger method[29], were conducted to check if the associations were consistent and to adjust for any horizontal pleiotropy.

If significant heterogeneity was detected, weighted median analysis was used to estimate the MR effect size. If significant pleiotropy was detected, MR-Egger was used to estimate the MR effect size. The Cochrane's Q-value can indicate heterogeneity among selected instrumental variables, and the P-value should be greater than 0·05[30]. Additionally, leave-one-out sensitivity analysis was used to check whether the overall estimates were affected by an individual SNP. The funnel plot was used to focus on whether the points on the left and right sides of the IVW line were roughly symmetric. These SNP that affected overall estimates were removed, and effect estimates were recalculated. To account for multiple comparisons of in BMI with liver disease outcomes, Bonferroni-corrected thresholds of $P < 0{\cdot}05$ were used for liver disease outcomes. All tests were two-sided and performed via the TwoSampleMR (0·5·5), MR-PRESSO (1·0), multivariable Mendelian randomisation (0·3) packages in the R software (version 4.0.3).

Results

SNP validation

In summary, 458 SNP in the BMI database exhibited significant genome-wide differences, and all F-statistics were greater than 10. Alcohol is a major cause of liver disease[31]. SNP of alcohol were the confounders of the studies. In contrast, thirty-one of the 458 traits associated with alcohol consumption were excluded for traits with alcohol consumption. Finally, 427 SNP were included. 218 SNP in the WHRadjBMI database fulfilled the inclusion criteria and did not meet the exclusion criteria (Fig. 1).

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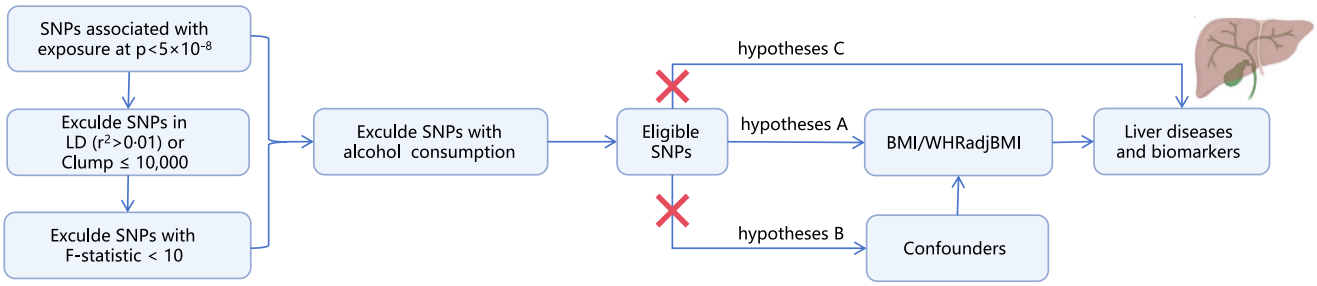


Fig. 1. Study design overview. The MR study should have three core three hypotheses: (1) genetic variants (SNP) are strongly related to the exposure; (2) SNP are independent of known confounders and (3) SNP cannot directly affect the outcome but only through the exposure of interest. LD, linkage disequilibrium; SNP, single-nucleotide polymorphisms; WHRadjBMI: waist-to-hip ratio adjusted for BMI.

Univariable Mendelian randomisation analysis of the associations between BMI or WHRadjBMI and the risk of liver disease

The IVW analysis revealed that the genetically predicted BMI was associated with four of the eight liver diseases, including non-alcoholic fatty liver disease (OR = 2·12; 95 % CI, 1·49, 3·02; $P = 2{\cdot}9 \times 10^{-5}$), liver cell carcinoma (OR = 1·00; 95 % CI, 1·000, 1·001; $P = 0{\cdot}006$), fibrosis and cirrhosis of the liver (OR = 1·78; 95 % CI, 1·18, 2·68; $P = 0{\cdot}006$) and autoimmune hepatitis (OR = 1·47; 95 % CI, 1·055, 2·041; $P = 0{\cdot}023$). BMI was positively associated with liver cell carcinoma ($P = 5{\cdot}6 \times 10^{-3}$). However, the OR is 1·000 (1·000–1·001), which means that morbidity in obese people and non-obese people is almost equal. Therefore, the positive correlation is meaningless. In contrast, no associations were observed for hepatic failure, viral hepatitis, secondary malignant neoplasm of the liver or primary biliary cholangitis. No evidence of directional heterogeneity or pleiotropy was detected (Table 1).

WHRadjBMI was associated with three of the eight liver diseases, including non-alcoholic fatty liver disease (OR = 1·89; 95 % CI, 1·31, 2·7; $P = 7{\cdot}5 \times 10^{-4}$), fibrosis and cirrhosis of liver (OR = 2·33; 95 % CI, 1·54, 3·52; $P = 5{\cdot}7 \times 10^{-5}$) and autoimmune hepatitis (OR = 1·84; 95 % CI, 1·26, 2·68; $P = 5{\cdot}7 \times 10^{-5}$) (Table 1).

The leave-one-out sensitivity analysis and the funnel plot of the association between BMI, WHRadjBMI and liver diseases are shown in online Supplementary Fig. S1–S2 and Fig. S5–S6, respectively.

Univariable Mendelian randomisation analysis of the associations between BMI or WHRadjBMI and the risk of liver-function biomarkers

The IVW analysis revealed that a genetically predicted BMI increase was positively associated with ApoB (OR = 1·19; 95 % CI, 1·11, 1·28; $P = 1{\cdot}4 \times 10^{-6}$). Because significant heterogeneity was detected in some exposures, weighted median analysis was used to estimate the MR effect size. The weighted median analysis suggested that BMI had positive causal relationships with higher serum levels of very LDL (OR = 1·06; 95 % CI, 1·01, 1·11; $P = 0{\cdot}01$), platelet count (OR = 0·953; 95 % CI, 0·929, 0·976; $P = 1{\cdot}2 \times 10^{-4}$) and fasting blood insulin (OR = 1·15; 95 % CI, 1·09, 1·23; $P < 0{\cdot}001$). Genetically predicted BMI increase was a negative association with HDL level (OR = 0·81; 95 % CI, 0·75, 0·87; $P = 4{\cdot}1 \times 10^{-8}$). The IVW and MR-Egger analyses revealed similar estimates but of low precision. No evidence of directional pleiotropy was detected in the majority of biomarkers except for very LDL (Table 2).

The IVW analysis revealed that genetically predicted higher WHRadjBMI was associated with alanine aminotransferase (OR = 1·38; 95 % CI, 1·07, 1·78; $P = 0{\cdot}01$). Weighted median analysis was used to estimate the MR effect size when heterogeneity was detected in exposures. The weighted median analysis implied that a genetically predicted higher WHRadjBMI was associated with higher serum level of few biomarkers, including LDL (OR = 1·10; 95 % CI, 1·02, 1·20; $P = 0{\cdot}01$), very LDL (OR = 1·21; 95 % CI, 1·44, 1·29; $P = 0{\cdot}01$), ApoB (OR = 1·22; 95 % CI, 1·06, 1·39; $P = 0{\cdot}01$) and fasting blood insulin (OR = 1·19; 95 % CI, 1·12, 1·27; $P = 0{\cdot}001$). A higher WHRadjBMI was also associated with lower serum levels of some biomarkers, including HDL (OR = 0·80; 95 % CI, 0·74, 0·86; $P = 4{\cdot}0 \times 10^{-9}$) and no evidence of directional pleiotropy was detected (Table 2).

The leave-one-out sensitivity analysis and the funnel plot of the association between BMI, WHRadjBMI and liver-function biomarkers are shown in online Supplementary Fig. S3–S4 and Figs. S7–S8 respectively.

Multivariable Mendelian randomisation: direct causal effects of obesity on liver disease and function

As shown in Figs. 2 and 3, genetically high BMI and WHRadjBMI were both associated with increased risk of NAFLD, liver fibrosis and several liver-function biomarkers (alanine aminotransferase, HDL, fasting blood insulin). Moreover, a genetically high WHR was associated with increased LDL, very LDL and ApoB when BMI was accounted for. A genetically high BMI was associated with a decreased platelet count when WHRadjBMI was accounted for. However, they were no longer related to liver cell carcinoma or autoimmune hepatitis.

Discussion

Using a genetic approach, our study suggested a causal relationship between obesity and some liver diseases, as well as aberrant liver function and lipid metabolism markers. According to univariable and multivariable MR analyses, higher BMI and WHRadjBMI were positively associated with the increased risk of NAFLD and liver fibrosis. A genetically higher

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Table 1. Associations between genetically predicted obesity and liver diseases in sensitivity analyses using the weighted-median and MR-Egger methods (OR and 95 % CI)

Outcome		Inverse variance weighted			Weighted Median			MR-Egger			Pleiotropy	Heterogeneity		
	Variable	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*	Intercept	*P*	Q	*P*
NAFLD	BMI	2·12	1·49, 3·02	< 0·001	1·57	0·94, 2·60	0·084	1·33	0·43, 4·06	0·62	$8{\cdot}558 \times 10^{-3}$	0·37	461	0·05
	WHRadjBMI	1·9	1·31, 2·76	< 0·001	2·07	1·15, 3·71	0·01	5·70	2·21, 14·66	< 0·001	$-1{\cdot}98 \times 10^{-2}$	0·48	243	0·35
HCC	BMI	1·00	1·00, 1·001	0·01	1·00	1·00, 1·001	0·20	1·00	0·99, 1·001	0·28	$2{\cdot}026 \times 10^{-5}$	0·05	360	0·34
	WHRadjBMI	1·00	0·99, 1·00	0·38	1·00	0·99, 1·001	0·84	1·00	0·99, 1·001	0·87	$1{\cdot}549 \times 10^{-6}$	0·90	187	0·45
Fibrosis and cirrhosis of liver	BMI	1·78	1·18, 2·68	0·01	1·65	0·89, 3·06	0·11	0·79	0·17, 3·69	0·76	0·01	0·28	312	0·22
	WHRadjBMI	2·33	1·54, 3·54	< 0·001	2·29	1·22, 4·32	0·02	5·97	2·10, 16·95	< 0·001	0·020	0·11	241	0·10
Autoimmune hepatitis	BMI	1·47	1·06, 2·04	0·02	1·40	0·88, 2·31	0·19	1·29	0·45, 3·63	0·64	0·002	0·79	427	0·17
	WHRadjBMI	1·84	1·26, 2·69	< 0·001	1·73	0·91, 3·27	0·09	1·83	0·70, 4·80	0·22	$1{\cdot}008 \times 10^{-4}$	0·99	216	0·34
Viral hepatitis	BMI	1·34	1·00, 1·78	0·05	1·09	0·79, 1·69	0·72	1·57	0·65, 3·79	0·31	0·007	0·70	415	0·16
	WHRadjBMI	1·16	0·84, 1·59	0·38	1·07	0·64, 1·77	0·81	1·10	0·49, 2·49	0·81	$9{\cdot}985 \times 10^{-4}$	0·91	214	0·48
Hepatic failure	BMI	1·33	0·85, 2·07	0·20	1·09	0·53, 2·20	0·81	0·57	0·14, 2·33	0·43	0·02	0·22	371	0·68
	WHRadjBMI	1·35	0·81, 2·26	0·25	1·26	0·53, 2·99	0·60	1·36	0·37, 5·26	0·64	$-2{\cdot}083 \times 10^{-4}$	0·99	214	0·59
Secondary malignant neoplasm of liver	BMI	1·00	0·99, 1·00	0·49	0·99	0·99, 1·00	0·79	1·00	0·99, 1·00	0·53	$-1{\cdot}652 \times 10^{-5}$	0·63	197	0·58
	WHRadjBMI	1·00	0·99, 1·00	0·77	1·00	0·99, 1·00	0·96	1·00	0·99, 1·00	0·45	$3{\cdot}55 \times 10^{-5}$	0·49	101	0·09
PBC	BMI	1·09	0·67, 1·77	0·72	1·09	0·55, 2·15	0·80	1·00	0·11, 8·81	1·00	$1{\cdot}455 \times 10^{-3}$	0·94	68	0·89
	WHRadjBMI	0·87	0·53, 1·44	0·61	0·85	0·46, 1·58	0·23	0·23	0·05, 0·99	1·00	0·02	0·94	99	< 0·001

HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease; PBC: Primary biliary cholangitis; IVW: inverse-variance weighted; WHRadjBMI: waist-to-hip ratio adjusted for BMI.

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Table 2. Associations between genetically predicted obesity and liver biomarkers in sensitivity analyses using the weighted-median and MR-Egger methods (OR and 95 % CI)

Biomarker	Variable	Inverse variance weighted			Weighted Median			MR-Egger			Pleiotropy		Heterogeneity	
		OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*	Intercept	*P*	Q	*P*
ALT	BMI	1·22	0·99, 1·52	0·06	1·26	0·91, 1·73	0·16	1·40	0·67, 2·94	0·37	$-2{\cdot}43 \times 10^{-3}$	0·71	385	0·35
	WHRadjBMI	1·38	1·07, 1·78	0·01	1·22	0·82, 1·81	0·20	1·45	0·66, 3·19	0·36	$7{\cdot}81 \times 10^{-3}$	0·90	190	0·86
AST	BMI	1·11	0·95, 1·31	0·19	1·20	0·94, 1·53	0·15	1·68	1·02, 2·79	0·04	$-7{\cdot}52 \times 10^{-3}$	0·09	387	0·72
	WHRadjBMI	0·98	0·81, 1·19	0·87	1·26	0·93, 1·70	0·14	1·09	0·69, 1·75	0·70	$-2{\cdot}43 \times 10^{-3}$	0·62	215	0·34
Bilirubin	BMI	1·01	0·95, 1·07	0·76	1·03	0·95, 1·13	0·45	1·09	0·90, 1·33	0·38	$1{\cdot}83 \times 10^{-4}$	0·92	161	0·90
	WHRadjBMI	1·01	0·96, 1·07	0·65	0·99	0·91, 1·08	0·89	0·96	0·81, 1·14	0·69	$9{\cdot}85 \times 10^{-4}$	0·56	139	0·97
HDL	BMI	0·80	0·76, 0·85	< 0·001	0·81	0·75, 0·87	< 0·001	0·79	0·67, 0·94	0·01	$2{\cdot}15 \times 10^{-4}$	0·89	244	< 0·001
	WHRadjBMI	0·74	0·65, 0·83	< 0·001	0·80	0·74, 0·86	< 0·001	0·82	0·61, 1·10	0·20	$-2{\cdot}33 \times 10^{-3}$	0·46	132	< 0·001
LDL	BMI	1·04	0·97, 1·11	0·247	1·04	0·96, 1·13	0·31	0·94	0·77, 1·14	0·53	$1{\cdot}85 \times 10^{-3}$	0·29	159	0·25
	WHRadjBMI	1·13	1·06, 1·21	< 0·001	1·11	1·02, 1·19	0·01	1·15	0·99, 1·35	0·08	$-4{\cdot}18 \times 10^{-4}$	0·80	132	< 0·001
VLDL	BMI	1·09	1·06, 1·14	< 0·001	1·06	1·01, 1·11	0·01	0·95	0·85, 1·07	0·42	$2{\cdot}52 \times 10^{-3}$	0·11	407	< 0·001
	WHRadjBMI	1·19	1·11, 1·28	< 0·001	1·21	1·14, 1·28	< 0·001	1·18	0·99, 1·41	0·07	$2{\cdot}27 \times 10^{-4}$	0·90	216	< 0·001
PLT	BMI	0·96	0·93, 0·99	0·03	0·95	0·93, 0·98	< 0·001	0·93	0·83, 1·04	0·17	$7{\cdot}05 \times 10^{-4}$	0·48	403	0·03
	WHRadjBMI	1·07	0·99, 1·16	0·07	1·03	0·99, 1·06	0·17	0·95	0·79, 1·14	0·59	$2{\cdot}70 \times 10^{-4}$	0·16	216	< 0·001
ApoB	BMI	1·193	1·110, 1·281	< 0·001	1·213	1·090, 1·350	< 0·001	1·13	0·90, 1·42	0·29	$9{\cdot}65 \times 10^{-4}$	0·63	441	0·06
	WHRadjBMI	1·15	1·02, 1·29	0·02	1·22	1·06, 1·39	0·004	1·13	0·82, 1·54	0·46	$4{\cdot}10 \times 10^{-4}$	0·90	215	< 0·001
Fasting blood insulin	BMI	1·15	1·10, 1·19	< 0·001	1·16	1·09, 1·23	< 0·001	1·20	1·04, 1·38	0·01	$-8{\cdot}38 \times 10^{-4}$	0·48	191	0·20
	WHRadjBMI	1·15	1·10, 1·20	< 0·001	1·19	1·12, 1·27	0·001	1·25	1·09, 1·43	$2{\cdot}2 \times 10^{-3}$	$-1{\cdot}65 \times 10^{-4}$	0·22	132	0·01

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Apo B: apolipoprotein B; MVMR: multivariable Mendelian randomisation; IVW: inverse-variance weighted; VLDL: very LDL; WHRadjBMI: waist-to-hip ratio adjusted for BMI; PLT: platelet count.

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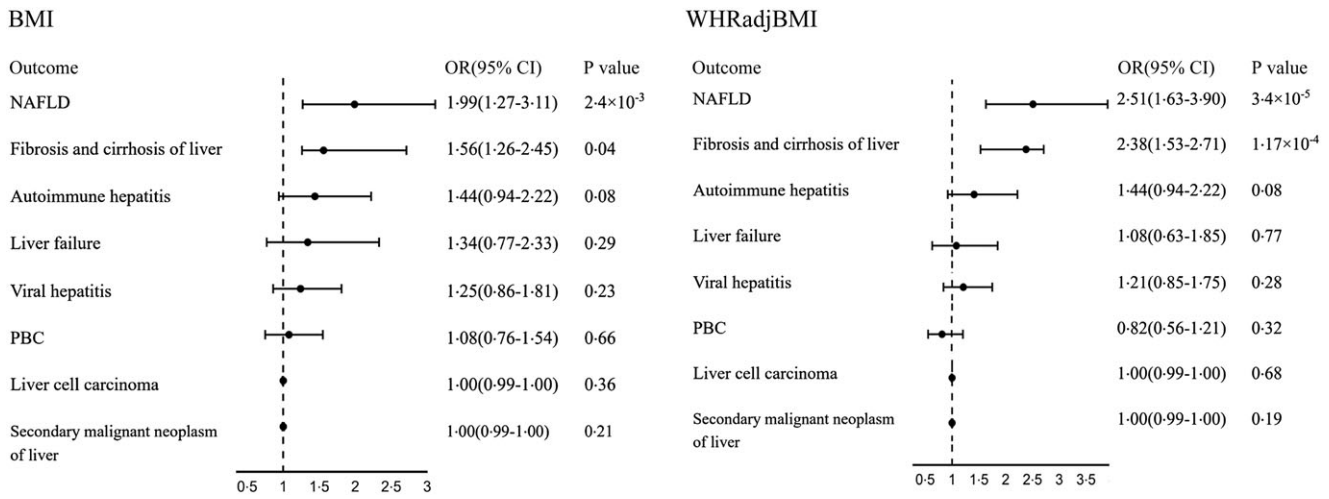


Fig. 2. Multivariable MR estimated the direct causal effects of BMI and WHRadjBMI on liver disease while accounting for each other. WHRadjBMI: waist-to-hip ratio adjusted for BMI; NAFLD: non-alcoholic fatty liver disease; PBC: primary biliary cholangitis.

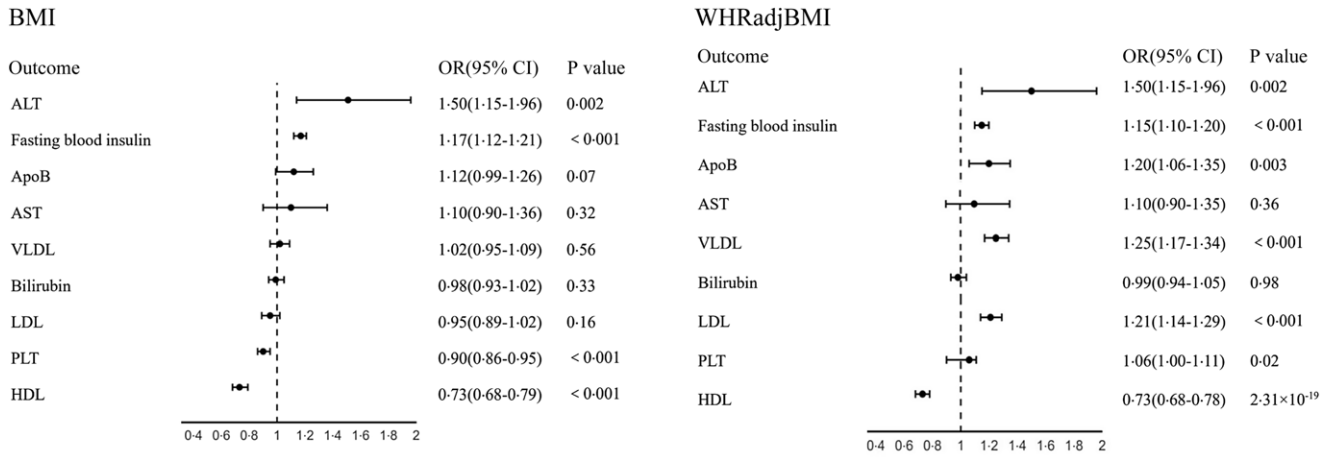


Fig. 3. Multivariable MR estimated the direct causal effects of BMI and WHRadjBMI on liver function, while accounting for each other. ALT: alanine aminotransferase; AST: aspartate aminotransferase; Apo B: apolipoprotein B; VLDL: very LD:; WHRadjBMI: waist-to-hip ratio adjusted for BMI; PLT: platelet count.

BMI and WHRadjBMI were associated with impaired liver and lipid metabolism function.

Our study suggested that total and abdominal fat are both risk factors for NAFLD and liver cirrhosis, which is consistent with several studies[7,32,33]. Unlike observational studies, MR analysis can reduce bias from confounding factors and reveal a causal relationship between obesity and liver disease. The waist-to-hip ratio adjusted for the BMI can measure abdominal obesity[34]. A high WHRadjBMI implies a high burden of abdominal fat and is associated with fibrosis severity in obese and non-obese NAFLD patients[35,36]. Our results suggested that the WHR is a marker for diagnosing NAFLD and fibrosis patients. Without active intervention, NAFLD may even progress to non-alcoholic steatohepatitis, which has been the fastest-growing and second-leading indication for liver transplantation in the past 20 years[37,38]. For these patients, active treatment is especially necessary. Our research confirmed that obesity was also a real cause of liver cirrhosis in the European population. Two large studies from the UK have also demonstrated that obesity increases the incidence of liver cirrhosis and liver-related mortality[39,40].

A positive correlation between obesity and the aggravation of viral hepatitis has been reported[10,11]. In contrast, several studies have suggested that an inverse correlation between obesity and virus activity and the success rate of antiviral treatment[12–14]. Unlike those studies, multivariable MR analysis did not find a causal relationship between obesity and viral hepatitis, autoimmune liver disease or hepatocellular carcinoma. Metabolic risk factors rather than obesity seem to independently facilitate hepatocarcinogenesis[13]. Compared with virus infection or immune system disorders, abnormal lipid metabolism may not be the core trigger of these liver diseases[41–44]. The endemicity of hepatitis virus infection varies according to regional hygienic standards and lifestyles[45]. This may also be attributed to the influence of confounding factors and ethnic differences, which may require further exploration in larger cohorts.

BMI is a commonly used index to assess the degree of obesity and reflects total body fat mass[6]. The WHRadjBMI is a surrogate

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for abdominal fat and is less influenced by muscle and bone mass than BMI[22]. The waist–hip ratio may be superior to BMI in predicting liver-related outcomes[23,24,46]. Our results revealed that a high WHRadjBMI rather than BMI was associated with higher levels of biomarkers of lipid metabolism, indicating that a high WHRadjBMI can better and more sensitively reflect the presence of lipid accumulation and metabolic disorders. Our research also explored a positive association between obesity and elevated serum insulin levels. These findings suggested that elevated BMI and WHR may be risk factors for insulin resistance. Obesity can interfere with the normal regulation of lipid metabolism through various pathways, such as influencing hormone secretion, altering the function and activity of adipose tissue and causing insulin resistance. Insulin resistance is the most likely link between obesity and obesity-related metabolic disorders, where obesity leads to insulin resistance, and insulin stimulates the degradation of apolipoprotein B-100 while inhibiting the secretion of very LDLs from the liver[47,48].

In the diagnosis of liver fibrosis, the clinical application of liver biopsy is limited, owing to its inherent limitations, including its invasive nature, difficult sampling operation, high time consumption, false negatives, subjectivity and low degree of patient acceptance[49]. Our study found that high BMI leads to abnormally elevated alanine aminotransferase and abnormally reduced platelet count, which is consistent with several previous non-invasive diagnostic models. In 2007, Paul *et al.* published the NAFLD Fibrosis Score (NFS), which for the first time included BMI to assess the risk of non-alcoholic steatohepatitis progressing to liver fibrosis[50]. In the future, we need to break through the traditional definition, establish a new model to predict the reversal of liver fibrosis with BMI and verify it in prospective studies to provide a reference index for the clinical monitoring of the reversal tendency of liver fibrosis after antiviral treatment. MR studies can effectively mitigate the influence of individual differences and confounding factors, thereby enabling a more accurate and reliable evaluation of the effects of intervention measures[18].

The strengths of this study were as follows: first, we used BMI and WHR to evaluate total body fat and abdominal fat. We used large GWAS summary datasets to explore the causal associations between two indices and liver diseases. Second, we tested the direct effects of the two indices on liver disease and function via multivariable MR. However, there were several limitations: most of the GWAS data we used were from individuals of European ancestry, and the results may not be extrapolated to those of different races. Sarcopenia is a disorder characterised by loss of muscle mass, strength and function[51]. Sarcopenia is an independent predictor of mortality in NAFLD and cirrhosis[52]. An index that can accurately measure skeletal muscle mass and sarcopenia is not available in GWAS. Therefore, we only evaluated the causal association of fat mass.

BMI and WHR, which are widely used and simple indicators, are extensively applied in clinical practice. Our study suggested a causal relationship between obesity and liver fibrosis, NAFLD, as well as aberrant lipid metabolism markers. Neither BMI nor WHRadjBMI had a causal relationship with viral hepatitis, primary biliary cholangitis and secondary tumour of liver. A higher WHRadjBMI rather than BMI was associated with higher levels of biomarkers of lipid accumulation and metabolic disorders. These findings indicated that the waist–hip ratio may be superior to BMI in predicting liver metabolic disorders.

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The authors have no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452400237X

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