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The causal effect of mTORC1-dependent circulating protein levels on nonalcoholic fatty liver disease: A Mendelian randomization study

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ABSTRACT

Background: The mechanistic target of rapamycin (mTOR) signal pathway plays a crucial role in the development of nonalcoholic fatty liver disease (NAFLD). However, the causal effect of mTOR downstream proteins on NAFLD remains unknown.

Aims: We conducted a two-sample Mendelian randomization (MR) study to investigate whether the mTOR-dependent circulating proteins, including Eukaryotic Initiation Factor 4E Binding Proteins (eIF4EBPs), Ribosomal Protein S6K kinase 1 (RP-S6K), Eukaryotic Initiation Factor 4E (eIF4E), Eukaryotic Initiation Factor 4A (eIF4A) and Eukaryotic Initiation Factor 4 G (eIF4G), have causal effects on the risk of NAFLD.

Methods: The causal estimate was evaluated with the inverse-variance weighted (IVW) method in discovery stage and validation stage. The single-nucleotide polymorphisms (SNPs) were selected to genetically predict exposures from Genome-Wide Association Studies (GWAS). Exposures with statistically significant effects in the discovery dataset would be further validated in the validation dataset.

Results: MR study revealed that eIF4E had a causal effect on NAFLD in both discovery stage (OR = 1.339, P = 0.037) and validation stage (OR = 1.0007, P = 0.022). Sensitivity analyses confirmed robustness of the results.

Conclusion: The genetically predicted higher level of mTOR-dependent eIF4E in plasma might have a causal effect on the occurrence of NAFLD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide [1]. Incidence of NAFLD rises with increased living standards, changed eating habits and lifestyles, threatening nearly a quarter of the global population. If not treated, NAFLD tends to develop severe liver damage, 25 % of which would progress to liver fibrosis and 1.5 %–8 % of which would progress to liver cirrhosis, even hepatocellular carcinoma (HCC) [2,3]. However, the pathogenesis of NAFLD remains unclear. Currently, there is still no clinical intervention approved by the Food and Drug Administration (FDA) for NAFLD. Thus, further exploration of NAFLD pathogenesis and finding novel therapeutic targets remain topics of intense research.

The mechanistic target of rapamycin (mTOR) signaling pathway controls cell growth, proliferation, and metabolism depending on hormones, growth factors, and nutrient availability, which nucleates two biochemically and functionally distinct complexes, known as mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [4,5]. mTORC1 consists of mTOR and the regulatory-associated protein of mTOR (Raptor), an adaptor protein, activating anabolic pathways such as lipid synthesis, as well as attenuating catabolic pathways such as oxidation [4,6]. Therefore, this renders mTORC1 an attractive target to regulate the lipid homeostasis of livers. However, existing studies reached conflicting conclusions [7–9]. This indicates a complex role of mTORC1 in NAFLD, which remains poorly understood.

The function of mTORC1 is dominantly regulated by the phosphorylation of downstream proteins, mainly including Eukaryotic Initiation Factor 4E Binding Proteins (eIF4EBPs) and Ribosomal Protein S6K kinase 1 (RP-S6K). eIF4EBP is a binding protein of Eukaryotic Initiation Factor 4E (eIF4E). As a result of phosphorylation, eIF4EBP is disassociated from eIF4E, leading to the activation of 5′cap-dependent protein translation [10,11]. eIF4E, together with Eukaryotic Initiation Factor 4A (eIF4A) and Eukaryotic Initiation Factor 4 G (eIF4G), forms Eukaryotic Initiation Factor 4F (eIF4F) complex [5]. Besides, phosphorylated RP-S6K also activates Eukary-

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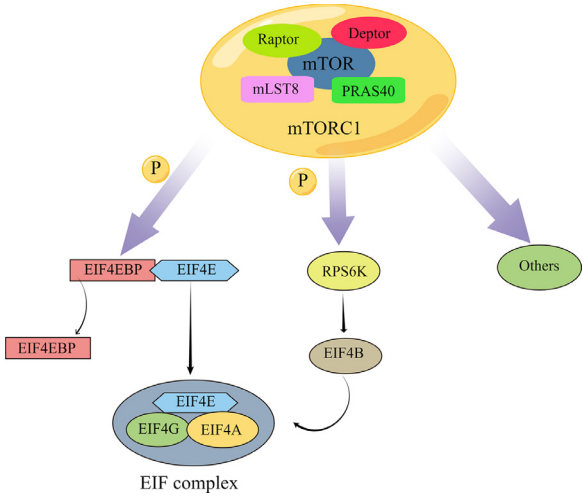

Fig. 1. Composition and main downstream proteins of mTORC1 signal pathway. mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; eIF4EBP, Eukaryotic Initiation Factor 4E Binding Proteins; RP-S6K, Ribosomal Protein S6K kinase 1; eIF4E, Eukaryotic Initiation Factor 4E; eIF4A, Eukaryotic Initiation Factor 4A; eIF4G, Eukaryotic Initiation Factor 4 G; Raptor, regulatory-associated protein of mTOR; mLST8, Target of rapamycin complex subunit LST8; PRAS40, Proline-Rich AKT Substrate; Deptor, DEP domain containing mTOR-interacting protein.

otic Initiation Factor 4B (eIF4B), which in turn, positively modulates eIF4F [12]. Main proteins of mTORC1 are present in Fig. 1.

Randomized Controlled Trials (RCTs) are regarded as the optimal type of design for evaluating causal effects. However, restricted by medical ethics, subject compliance, study period, and other factors, appropriate RCTs are difficult to implement in many cases. Mendelian Randomization (MR) is a statistical model using genetic variation as Instrumental Variables (IVs), which is widely applied in causal inference in recent years [13]. IVs are usually obtained from Genome-Wide Association Studies (GWAS). During gametogenesis, genetic variants underwent random segregation and combinations. MR capitalizes on this feature of genetic variants to simulate the random allocation of the population. When an individual was born, randomly allocated genetic variants affecting specific phenotypes had been already determined. This process is commonly unrelated to acquired environmental confounders. Thus, differences in the specific outcome of the population with or without such genetic variants can be attributed to exposures, thereby ruling out interferences of confounders [14].

In this study, we performed an MR study to investigate the causal effect between the risk of NAFLD and mTORC1-dependent circulating protein levels, including eIF4EBPs, eIF4A, eIF4E, eIF4G, and RP-S6K. Considering the role of mTORC1 in regulating lipid homeostasis and oxidation of the liver, we hypothesized that mTORC1-dependent circulating protein levels had a causal effect on NAFLD.

2. Method

2.1. Summarized statistics of mTORC1-dependent proteins

Defined as exposures, we applied 5 different mTORC1-dependent circulating proteins, including eIF4EBPs, eIF4A, eIF4E, eIF4G, and RP-S6K. SNPs related to the mTORC1-dependent proteins were obtained from a recent proteomics GWAS of European participants, the INTERVAL study (https://www.phpc.cam.ac.uk/ceu/proteins)[15,16]. In this genomic bioresource, 50,000 blood donors from 25 centers across England were recruited from 2012 to 2014. A GWAS of 3301 participants from the INTERVAL study was performed where a SomaLogic (https://somalogic.com) aptamer-based plasma protein assay had been applied to identify 3622 plasma proteins, in which protein levels were estimated by relative fluorescent units [15,17]. Ethical approval can be found in the original literature, and we used publicly available statistics.

For IVs, we selected significant genetic variants associated with mTORC1-dependent circulating proteins from the GWAS (significant $P < 5 \times 10^{-6}$). Linkage disequilibrium (LD) describes correlations of genetic variants, which were due to the distance of physical locations. To ensure the selected SNPs were independent for each exposure, LD was satisfied in the given region ($R^2 < 0.05$, kb > 10,000). SNPs of palindromic structures were eliminated. Cragg-Donald F-statistic was used to evaluate the power of SNPs. SNPs of $F < 10$ would be considered weak instruments [18].

2.2. Summarized statistics of NAFLD

We extracted two summarized GWAS statistics of NAFLD, defined as the discovery dataset and validation dataset respectively. For the discovery dataset, the GWAS statistics were obtained from FinnGen (https://r8.finngen.fi), which included 1908 cases and 340,591 controls, adjusting for sex, age, genotyping batch, genetic relatedness, and first 10 principal components. For the validation dataset, statistics were obtained from UK Biobank (UKB, https://biobank.ctsu.ox.ac.uk) with 361,194 samples, adjusting for sex, age, and the first 20 principal components. For the remaining IVs, we used PhenoScanner (https://phenoscanner.medschl.cam.ac.uk) to find possible correlations with NAFLD. We imputed the remaining IVs associated with each exposure to determine associations with NAFLD and confounders. Ethical approvals can be found in each GWAS. In FinnGen Biobank, the FinnGen team conducted the GWAS, and FinnGen Steering Committee approved the study. In UKB, Neale Lab performed the GWAS and the Ethics Advisory Committee of the UKB approved the study. We used the publicly available summarized statistics, and all the data can be downloaded without restriction.

2.3. MR design

Being as effective IVs, genetic variants need to be met with the following three core assumptions. (i) Genetic variants are associated with mTORC1-dependent circulating proteins. (ii) Genetic variants are independent of confounders that have an impact on NAFLD and may affect the “exposure-outcome” association. (iii) Genetic variants affect NAFLD only by each exposure. The effect of an SNP on an outcome and exposure must be harmonized to be relative to the same allele. After harmonizing, a two-sample MR will be performed. When assessing causal effects between mTORC1-dependent circulating proteins and NAFLD, the summarized statistics of NAFLD from the discovery dataset FinnGen were initially used. Exposures with statistically significant effects in the discovery dataset would be further validated in the validation dataset UKB. If statistically significant effects were found in both the discovery dataset and validations dataset, the exposure could be considered to have causal effects with NAFLD. The MR flowchart is shown in Fig. 2.

2.4. Statistical analysis and sensitivity analysis

Due to the highest estimating efficacy, the Inverse Variance Weighted method was initially used for the MR analysis, and a random-effect model was applied. In IVW, based on the association of IVs on exposures and the outcome, Wald estimates were calculated, the variance of which was then used as weights to integrate each Wald estimates [19]. In addition, we performed the following MR methods as supplementary analysis of IVW. (i) Egger’s regression for MR, where the horizontal pleiotropy was assumed to exist.

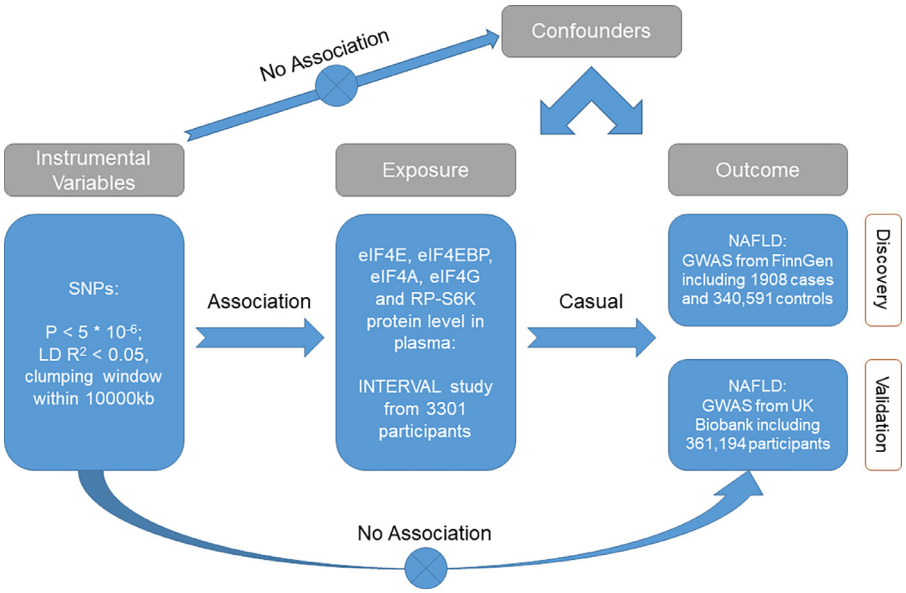

Fig. 2. Flowchart of Mendelian randomization study design. SNPs, single-nucleotide polymorphisms; NAFLD, nonalcoholic fatty liver disease; GWAS, Genome-Wide Association Studies; LD, linkage disequilibrium.

(ii) The Weighted Median (WM) method, the result of which was robust to outlier IVs. Results were presented as Odds Ratios (ORs) with P-values and 95 % confidence intervals (CIs) or Beta-values with P-values and standard errors (SEs).

Multiple methods were applied for sensitivity analysis. We explored the heterogeneity of IVW and MR-Egger through Cochrane Q Test [20]. Horizontal pleiotropy was tested using the following methods. (i) The MR-Egger method was used for both MR analysis and pleiotropy test, in which intercept was returned [21]. (ii) The MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) test allows for the evaluation of pleiotropy in MR. MR-PRESSO tests the existence of pleiotropy by removing outlier SNPs and estimating corrected results, thus testing the difference before and after the removal of outlier SNPs [22]. To acquire results of authenticity, the number of bootstrap replications was set at 10,000. In addition, we performed multivariable MR analysis in the validation stage to further verify the robustness of the results. Considering potential heterogeneity, pleiotropy, and the problem of collinearity of each exposure, a following Absolute Shrinkage and Selection Operator (LASSO) feature selection method was utilized to select features and only retain relevant features and instruments, thus performing multivariable MR on remaining data [23].

Statistical analysis and sensitivity analysis were performed using the R software (https://r-project.org), version 4.2.2, with "TwoSampleMR" and "MRPRESSO" packages. The figures were drawn by Figdraw (https://www.figdraw.com/static/index.html#/) and the R software.

3. Result

3.1. MR analysis of eIF4E and RP-S6K in discovery stage

Of 135 SNPs associating eIF4E, 117 variants were removed due to LD with other variants or absence from LD reference panel. After merging clumped SNPs and GWAS of FinnGen, 16 SNPs remained, and 2 variants rs531476076 and rs7862784 were removed for being palindromic with intermediate allele frequencies. IVW method indicated that eIF4E protein level in plasma was statistically associated with a higher risk of NAFLD with OR of 1.339, P-value of 0.037. MR-Egger (OR = 1.417, P-value = 0.269) and WM (OR = 1.411, P-value = 0.068) methods did not show opposite results.

Of 181 SNPs associating RP-S6K, 160 variants were removed due to LD with other variants or absence from LD reference panel. After merging, 18 SNPs remained and 3 variants rs17412698, rs74353857, and rs79549584 were removed for being palindromic with intermediate allele frequencies. No statistical association was found between RP-S6K protein level in plasma and NAFLD using IVW (OR = 1.162, P-value = 0.219) and MR-Egger (OR = 1.042, P-value = 0.863) methods. However, WM method (OR = 1.389, P-value = 0.041) showed a higher risk of NAFLD with RP-S6K protein level in plasma.

To further validate the results mentioned above, eIF4E and RP-S6K protein levels in plasma will be included in the validation dataset to further test the causal effect on NAFLD. Results of MR analysis were shown in Table 1, and scatterplots were shown in Fig. 3. IVs were shown in supplementary materials.

3.2. MR analysis of eIF4EBPs, eIF4A, and eIF4G in discovery stage

After removing SNPs due to LD with other variants and being palindromic with intermediate allele frequencies, there were 9 SNPs predicting eIF4EBPs, 9 SNPs predicting eIF4A, and 7 SNPs predicting eIF4G. All of IVW, MR-Egger, and WM methods did not show statistically significant association between eIF4EBPs, eIF4A, and eIF4G protein levels in plasma and the risk of NAFLD. Given the above results, eIF4EBPs, eIF4A, and eIF4G will not further test in the validation dataset. Results of MR analysis were presented in Table 1.

3.3. MR analysis of eIF4E and RP-S6K in validation stage

Due to the different source of the validation dataset, remaining SNPs got different sections from those in discovery stage. After merging clumped SNPs and GWAS of UKB, 8 SNPs remained associating eIF4E and 16 SNPs remained associating RP-S6K. Similar results were successfully obtained. Results in validation stage aligned with the discovery stage. IVW method showed that eIF4E protein level in plasma (Beta = 3.028×10^{-4}, P-value = 0.022) was associated with a higher risk of NAFLD, while RP-S6K protein level (Beta = 1.598×10^{-4}, P-value = 0.12) in plasma was not. WM method further validated this association of eIF4E and NAFLD (P-value = 0.015). For RP-S6K, although significant statistical associations were found by MR-Egger (P-value = 0.096) and WM (P-

Table 1
The Mendelian randomization estimates, test of heterogeneity and pleiotropy of eIF4E, eIF4EBP, eIF4A, eIF4G and RP-S6K on NAFLD in discovery datasets.

Exposure	NSNP	MR Method	Effect Estimates NAFLD		Heterogeneity		Pleiotropy		P
			OR	95 % CI	P	Cochrane Q	P	Egger Intercept	
eIF4E	14	IVW	1.339	(1.018,1.763)	0.037	11.711	0.551	−0.0074	0.835
		MR-Egger	1.417	(0.786,2.56)	0.269	11.665	0.473		
		WM	1.411	(0.975,2.04)	0.068				
eIF4EBP	9	IVW	0.819	(0.466,1.439)	0.488	16.139	0.04	−0.05	0.549
		MR-Egger	1.229	(0.309,4.958)	0.78	15.273	0.033		
		WM	0.745	(0.405,1.37)	0.345				
eIF4A	9	IVW	1.092	(0.796,1.497)	0.586	9.647	0.291	−0.024	0.404
		MR-Egger	1.352	(0.766,2.388)	0.335	8.672	0.277		
		WM	1.354	(0.944,1.943)	0.102				
eIF4G	7	IVW	0.743	(0.356,1.55)	0.43	13.675	0.033	−0.135	0.049
		MR-Egger	3.148	(0.94,10.55)	0.123	5.826	0.323		
		WM	0.69	(0.332,1.434)	0.32				
RP-S6K	15	IVW	1.162	(0.923,1.462)	0.219	16.368	0.291	0.015	0.597
		MR-Egger	1.042	(0.664,1.637)	0.863	16.006	0.249		
		WM	1.389	(1.014,1.905)	0.041				

NSNP stands for the number of SNPs selected; OR stands for Odds Ratio, which is per 1-SD increase; 95 % Confidence Interval (CI) shows upper and lower limits of 95 % CI; IVW, inverse-variance weighted; WM, weighted median.

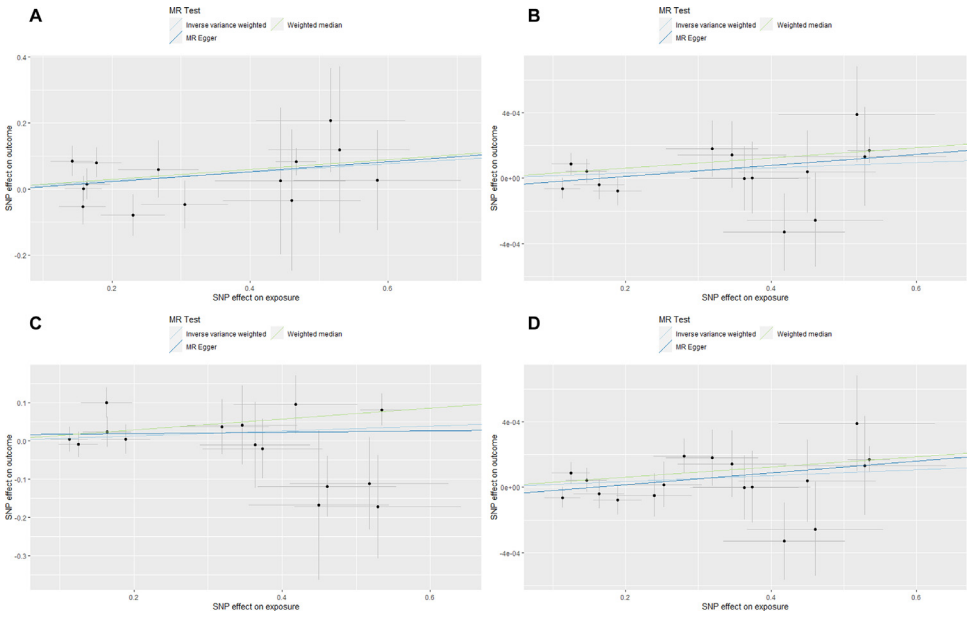

Fig. 3. Scatter plots of eIF4E and RP-S6K in discovery stage and validation stage. (A) MR results of eIF4E on NAFLD in discovery stage from FinnGen; (B) MR results of eIF4E on NAFLD in validation stage from UK Biobank; (C) MR results of RP-S6K on NAFLD in discovery stage from FinnGen; (D) MR results of RP-S6K on NAFLD in validation stage from UK Biobank.

value = 0.024) methods, the causal effect still cannot be determined with certainty, since IVW method gives the most promising results. The causal effect of RP-S6K and NAFLD remains ambiguous. Results in validation stage were shown in supplementary Table S1, and scatterplots were present in Fig. 3.

3.4. Sensitivity analysis

Heterogeneity and pleiotropy tests of the discovery stage and validation stage were shown in Table 1 and supplementary Table S1. Apart from eIF4EBPs (P-value = 0.04) and eIF4G (P-value = 0.033), no heterogeneity was found across exposures in both stages using Cochrane Q Test. The source of heterogeneity was considered the low sample size, leading to a small number of selected SNPs.

MR-PRESSO and MR-Egger methods were applied for the pleiotropy test. Through MR-PRESSO method, the robustness of results was pruned by correcting outlier SNPs of each exposure. No outlier SNPs were found across all exposures in both discovery and validation stages. This abolished the effects of heterogeneity mentioned above. However, pleiotropy was found in eIF4EBP with an MR-PRESSO P-value of 0.047. Besides, through MR-Egger methods, an intercept of each exposure was returned reflecting the size of pleiotropy (Fig. 3). There was no statistically significant pleiotropy existing across all exposures except eIF4G, with an MR-Egger intercept of −0.135 and a P-value of 0.049.

Forrest plots of multivariable MR analysis were shown in Fig. 4. Before LASSO feature selection, no statistical significance was found across all exposures, although there was a strong trend toward significance in eIF4E (P-value = 0.069). After LASSO feature selection, eIF4E showed the statistically significant causal effect on NAFLD once again, with a P-value of 0.0188. Multiple methods demonstrated that this causal effect of eIF4E on NAFLD was of well robustness and stability.

4. Discussion

To the best of our knowledge, this study is the first to examine the potential causal effect of mTORC1-dependent circulating proteins and NAFLD risk through the MR approach. According to our

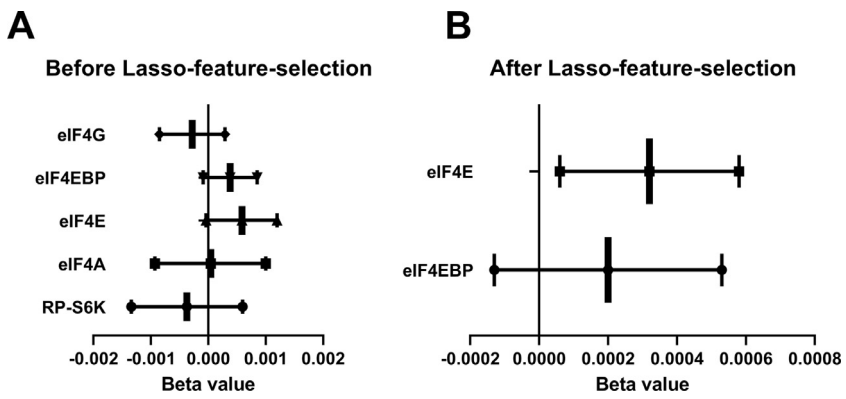

Fig. 4. Forrest plots of supplementary multivariable MR analysis in validation stage before and after Lasso-feature-selection method. (A) Forrest plots of supplementary multivariable MR analysis before Lasso-feature-selection; (B) Forrest plots of supplementary multivariable MR analysis after Lasso-feature-selection.

results, higher eIF4E protein level in plasma may play a causal role in the occurrence of NAFLD in the European population. Levels of eIF4EBP, eIF4A, eIF4G, and RP-S6K in plasma were not found to be causally associated with the risk of NAFLD. In addition, pleiotropy and heterogeneity were not identified in our main findings through sensitivity analyses, and similar results were replicated using multivariable MR analysis. This further suggested the robustness of our results.

Indeed, there has been evidence for effects of mTOR on NAFLD progression. Existing data indicate that mTOR regulates NAFLD through lipid metabolism [24,25], insulin resistance [26], oxidative stress [27], intestinal flora [28], autophagy [29], hepatic inflammation [30], and liver genetic polymorphisms and epigenetics [31]. However, it has not been sufficiently proven that the downstream proteins in mTORC1 pathway are involved. Wang et al. [32,33] observed activated mTORC1 and increased downstream proteins including eIF4E due to inflammation stress-induced hepatic steatosis *in vivo* and in vitro, and mTOR inhibition could reverse this process and lead to alleviation of hepatic steatosis. Given inflammation stress could result in hepatic lipid accumulation, this result was consistent with our findings. Study by Liu et al. [34] demonstrated similar results that increased mTORC1 activity along with phosphorylated downstream proteins exacerbated the progression of NAFLD by disrupting cholesterol homeostasis, in which hepatic inflammation was induced by using 10 % casein injected apolipoprotein E knockout mice *in vivo* and interleukin-1 stimulated hepG2 hepatoblastoma cell line *in vitro*. In another study by Liu et al. [24], they observed that the impaired activity of mTORC1 decreased lipid droplets in hepatocytes. In parallel, restored mTORC1 activity inhibited lipophagy and lipid droplet degradation. Again, increased mTORC1 activity was observed in liver tissues of NAFLD patients by restricting hepatic lipophagy. In addition, a clinical trial conducted by Kubrusly et al. [35] demonstrated that the expression of downstream effector of mTORC1 including eIF4E increased in nonalcoholic steatosis hepatitis-related cirrhosis. These also provided supporting evidence for our hypothesis.

Currently approved treatment for NAFLD is recommended to promote healthy lifestyle behaviors and favorable lifestyle modification (hypocaloric diets, regular physical activity, weight loss, etc.). Patients suffering from NAFLD have shown improvement through such approaches. However, the pharmacotherapy for NAFLD is poor. Finding eligible targets for pharmacological treatment of NAFLD remains a topic of intense research. So far, research conducted on mTOR suggested a vast potential for studying mTOR as a therapeutic target for NAFLD. Study by Shen et al. [36] found that geniposide could alleviate NAFLD by suppressing the phosphorylation of mTORC1 and its related proteins in mice. Similarly, Quan et al. [37] demonstrated that mTOR and RP-S6K were reduced when hepatocytes were treated with betulinic acid, thereby ameliorating hepatic lipid accumulation. Nevertheless, several other cellular pathways are also regulated by mTORC1. It is possible to create unexpected effects by blunting the modulation of mTORC1. Thus, a recent study by Gosis et al. [38] used folliculin-deleted mice to selectively inhibit mTORC1-mediated phosphorylation of the transcription factor E3/B, while other mTORC1 targets were hardly affected. Their results showed that this selected inhibition of mTORC1 could be a promising approach for the treatment of NAFLD. Our study found a definite causal association of eIF4E with NAFLD. Therefore, we hypothesized that selected modulation of mTORC1 targets such as eIF4E could alleviate NAFLD, and there need to be more attempts at such approach to developing specific treatments for NAFLD in the future.

In this study, we performed a two-sample MR analysis. A major strength of using genetic variation as IVs is that genetic variation is independent of social contexts, life habits, and other traits. This feature ensures balanced confounders in different subgroups, theoretically avoiding effects of confounders. On the other hand, the formation of genetic variation precedes exposures, confounders, and the progression of diseases. Therefore, exposures represented by SNPs also precede the outcomes, thus excluding reverse causality [39]. To fulfill the assumptions of MR design, firstly, we strictly selected IVs strongly associated with mTORC1-dependent circulating protein levels, as well as removing confounding SNPs. IVW method was primarily adapted for its highest power of test. MR-Egger and WM were used as supplementary methods. Then, MR-Egger intercept and MR-PRESSO methods confirmed little pleiotropy existing. Multiple methods of sensitivity analyses evaluated the robustness and reliability based on discovery stage and validation stage, and multivariable MR analysis in validation stage with LASSO-feature-selection method further confirmed our results.

Several limitations exist in this MR study. Firstly, only 3301 participants were included in the GWAS from the INTERVAL study due to the complicated technology of measuring plasma proteins. As a result, we had to increase the threshold of IVs selection with $P < 5 \times 10^{-6}$ instead of $P < 5 \times 10^{-8}$, which might introduce a bias of weak IVs. Though there is a relatively small number of included individuals in this GWAS, it is large enough to select IVs and then perform MR study, and the threshold and sensitivity analyses guaranteed the authenticity of our results and conclusions. Secondly, GWAS data of NAFLD patients and mTOR-dependent circulating proteins was derived from European populations. Whether this causal effect of eIF4E on NAFLD is generalized to other populations remains unclear. Larger GWAS from different populations and regions are needed in the future. Besides, a key question for NAFLD community is finding NAFLD severity-related SNPs and exploring

association of risk factors with the severity or stages of NAFLD. However, since there is no GWAS of NAFLD severity, we cannot perform an MR study on such associations. At last, although we did not find effects of heterogeneity and pleiotropy in our main finding through multiple methods of sensitivity analyses, the difference in the included populations does exist. Thus, potential heterogeneity and partial pleiotropy might exist.

5. Conclusion

In conclusion, this two-sample MR study supports that genetically predicted eIF4E protein level in plasma is causally associated with the risk of NAFLD. A novel finding of this research suggests that European ancestry populations with a higher level of mTOR-dependent eIF4E protein in plasma have a higher risk of NAFLD. Nevertheless, our conclusion is based on GWAS data, and high-quality research is required in the future to explore the detailed functional relevance and clinical utility.

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Conflict of interest

Nothing to report.

Author contribution

Xiangyu Yan: Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Data curation, Formal analysis. **Songhan Huang:** Data curation. **Hongxin Li:** Formal analysis. **Zichen Feng:** Formal analysis. **Junjie Kong:** Writing – review & editing. **Jun Liu:** Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.09.017.

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