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Comment on "Circulating fatty acids and risk of severe non-alcoholic fatty liver disease in the UK biobank: a prospective cohort of 116 223 individuals" by P. Zhuang, Y. Ao, X. Liu, H. Ye, H. Li, X. Wan, Y. Zhang and J. Jiao, *Food & Function*, 2024, 15, 10527†

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We read with great interest the recent article by Zhuang *et al.*,[1] titled "Circulating fatty acids and risk of severe non-alcoholic fatty liver disease in the UK biobank: a prospective cohort of 116 223 individuals". The authors conducted an impressive prospective study involving over 116 000 participants to explore the relationship between circulating fatty acid (FA) profiles and the risk of severe non-alcoholic fatty liver disease (NAFLD). Although they adjusted for key confounders such as age, sex, ethnicity, and education, the observational nature of the study limits the ability to draw causal conclusions from the findings, as the authors themselves noted.

Mendelian randomization (MR) analysis, using genetic variants as instrumental variables (IVs) for specific risk factors, is widely employed to clarify causal links between exposures and outcomes, including various human diseases.[2] For our MR study on FAs and NAFLD, we sourced datasets from OpenGWAS (https://gwas.mrcieu.ac.uk/). The exposure dataset on FAs included 115 006 samples and 11 590 339 single nucleotide polymorphisms (SNPs), while the outcome dataset for NAFLD (ebi-a-GCST90091033) comprised 778 614 samples and 6 784 388 SNPs. The data sources used in the present MR study are summarized in Table S1.† Using the summary data from the aforementioned genome-wide association study (GWAS), we followed a rigorous protocol to identify eligible SNPs as IVs. First, SNPs had to show a strong association with the exposure, meeting the genome-wide significance threshold of $p < 5 \times 10^{-8}$. Second, linkage disequilibrium (LD) analysis was performed to select independent SNPs, defined by LD $R^2 <$ 0.001 and an LD distance of 10 000 kb. Third, the strength of the IVs was evaluated using the F statistic, with a threshold of $F > 10$ deemed sufficient to minimize weak instrument bias. The strength of each IV was calculated using the following formulas:

$$R^2 = \frac{(2\beta^2 \times \mathrm{EAF} \times (1 - \mathrm{EAF}))}{(2\beta^2 \times \mathrm{EAF} \times (1 - \mathrm{EAF}) + 2N \times \mathrm{EAF} \times (1 - \mathrm{EAF}) \times \mathrm{SE}^2)}$$

and

$$F = \frac{(R^2 \times (N - 2))}{(1 - R^2)}$$

Here, EAF represents the effect allele frequency, β and SE denote the effect size and standard error of the SNP–antibody association, respectively, and N indicates the sample size. A total of 778 SNPs were selected as IVs for 15 distinct FA types and their composition ratios, following the established IV selection criteria (Table S2†). The inverse variance weighted (IVW) method, commonly used with summary statistics data, was the primary approach for assessing the potential causal effect of FAs on NAFLD risk, allowing for the calculation of causal effect sizes without the need for individual-level data.

In our recent MR study, we examined the causal relationship between FAs and NAFLD, with a focus on different fatty acid subtypes. Our results indicated that monounsaturated fatty acids (MUFAs) significantly increase the risk of developing NAFLD (OR = 1.232, 95% CI: 1.040 to 1.461, $P = 0.016$). In contrast, omega-6/total FA (OR = 0.776, 95% CI: 0.640 to 0.941, $P = 0.009$), polyunsaturated fatty acids (PUFAs)/total FA (OR = 0.722, 95% CI: 0.620 to 0.839, $P < 0.001$), and PUFA/MUFA ratios (OR = 0.795, 95% CI: 0.708 to 0.894, $P < 0.001$) demonstrated a protective effect against NAFLD (Fig. 1). Meanwhile, pleiotropy analysis indicated that our findings are not influenced by pleiotropy, further strengthening the reliability of the results (Table S3†). These findings align with and complement

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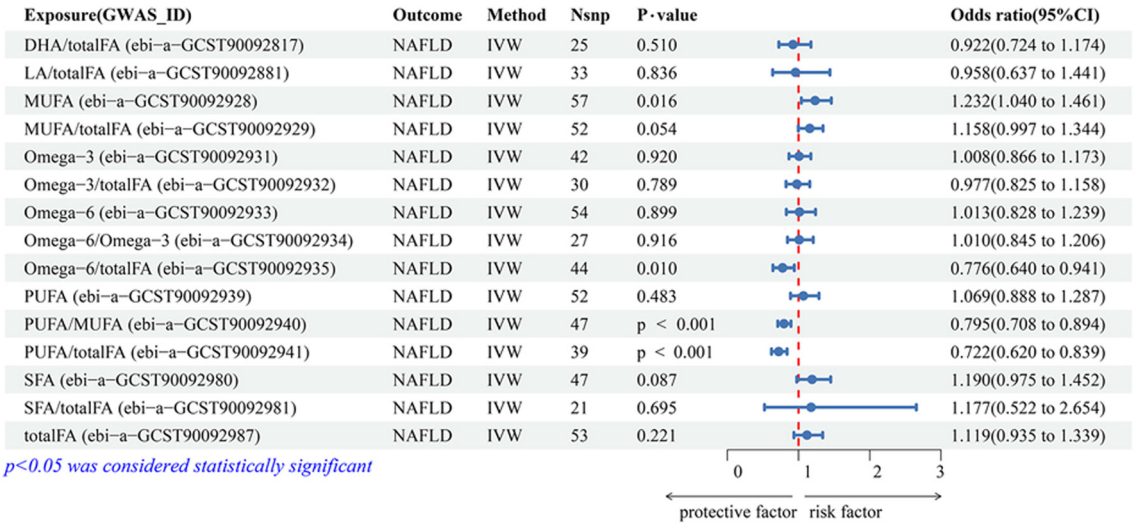

Fig. 1 Investigating the causal relationships between fatty acids (FAs) and the risk of developing non-alcoholic fatty liver disease (NAFLD). DHA, docosahexaenoic acid; FAs, fatty acids; LA, linoleic acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; and SFA, saturated fatty acid.

Zhuang *et al.*'s work, adding to the growing evidence of the complex role fatty acid subtypes play in liver disease development.

The difference between the present MR study, which found no significant link between circulating saturated fatty acids (SFAs) and NAFLD, and Zhuang *et al.*'s findings, which identified SFAs as a risk factor, can be explained by several factors: (1) Zhuang *et al.*'s observational cohort study is susceptible to confounding, reverse causation, and residual confounding, even with adjustments for various factors. In contrast, MR analysis uses genetic variants as IVs, reducing these biases and providing more reliable insights into causal relationships. (2) Zhuang *et al.* focused on severe NAFLD cases, identified through hospitalization or death records, while our study may have included a broader range of NAFLD cases, including milder forms. The association between SFAs and NAFLD could be stronger in more advanced cases, possibly explaining the differing results.[3] (3) Zhuang *et al.* measured baseline plasma SFAs, which reflect short-term dietary intake or metabolic status at a single time point and can fluctuate due to changes in diet, lifestyle, or metabolism. In contrast, our MR study used genetic variants related to lifelong FA metabolism, offering a more consistent long-term exposure measure, which may account for the absence of a significant association with NAFLD in our results.

In conclusion, we applaud Zhuang *et al.* for their valuable contribution to understanding the role of circulating fatty acids in NAFLD. We believe that integrating prospective cohort data with genetic approaches like Mendelian randomization can provide deeper insights into the prevention and management of NAFLD. Therefore, we encourage future studies to incorporate genetic data, particularly focusing on fatty acid metabolism genes such as FADS1/2, to further explore these associations.

Author contributions

All authors made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data; took part in drafting the article and revising it critically for important intellectual content; agreed to submit the manuscript to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Abbreviations

MR	Mendelian randomization
FAs	Fatty acids
NAFLD	Non-alcoholic fatty liver disease
IVs	Instrumental variables (IVs)
IVW	Inverse variance weighted
MUFAs	Monounsaturated fatty acids
PUFAs	Polyunsaturated fatty acids
SFAs	Saturated fatty acids

Data availability

The datasets used and analyzed in the present study are available from the corresponding authors upon reasonable request. The datasets generated and/or analyzed during the current study are available in the GWAS (**https://gwas.mrcieu.ac.uk/**) database.

Conflicts of interest

The authors declare no competing interests.

References

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