Peer Review File

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Reviewer #1

Comment 1: Njei B et al. demonstrated the clinical feature of genetic and epigenetic characteristics of NAFLD in Lean participants. Despite of lack of data of meta-analysis and several limitations including selection bias and so on, the manuscript had an important feature of genetic imformation in patients with lean-NAFLD.

Reply 1: We would like to express our gratitude to Reviewer #1 for their thoughtful review and valuable feedback on our manuscript. We acknowledge and appreciate the reviewer's comments regarding the clinical features, genetic, and epigenetic characteristics of NAFLD in lean participants.

Changes in text: N/A

Reviewer #2

Comment 1: ABSTRACT -Line 39 – Need to include the abbreviation for NOS that is shown on Line 43.

Reply 1: Thank you for your feedback. We have now included the abbreviation for NOS (Not Otherwise Specified) in the abstract, as indicated in Line 43. Your suggestion has been incorporated into the revised manuscript.

Changes in text: Line 39: "The Newcastle Ottawa Scale (NOS) was used for…"

Comment 2: It would be beneficial to provide a definition for lean NAFLD (BMI, waist circumference) as well as perhaps mention the genotype for PNPLA3 – especially given its ubiquitous nature in the genetic epidemiology literature on NAFLD –

Reply 2: Thank you for your valuable feedback. We appreciate your suggestion to provide a definition for lean NAFLD and mention the genotype for PNPLA3 in the manuscript.

Defining lean NAFLD poses a challenge due to the variability in definitions across studies. We recognize the importance of this aspect and have taken a comprehensive approach by including relevant data in Table 1, which outlines the various definitions utilized, ranging from BMI thresholds to percentile cut-offs. To address this variability, we have also incorporated a discussion in the limitations section, acknowledging the diversity of definitions and its potential impact on the interpretation of our findings.

Furthermore, we have heeded your advice and enriched the introduction section with additional information on the genotype of PNPLA3. This addition aims to provide a clearer context for the genetic epidemiology literature on NAFLD. Additionally, we want to assure you that the genotype

of PNPLA3 is presented in the results section, enhancing the reader's understanding of its implications within the context of our systematic review. We truly appreciate your input, as it has contributed to the refinement of our manuscript. Your suggestions have been instrumental in ensuring the completeness and clarity of our work.

Changes in text: Lines 89 – 91: "The PNPLA3 gene (rs738409) emerges as a key player in the genetic landscape of NAFLD. This polymorphism exhibits three distinct genotypes—CC, CG, and GG—each associated with varying degrees of susceptibility to NAFLD development and progression"

Comment 3: Introduction – As this is a review, it may be worth mentioning how NAFLD is defined/measured (i.e, MRI, ultrasound) and how this may impact the results that you describe in the paper.

Reply 3: Thank you for your feedback. We appreciate your suggestion to provide information on how NAFLD is defined and measured in the introduction. We have incorporated a sentence to address this point, highlighting that the clinical definition of lean NAFLD usually relies on BMI cut-offs or percentiles, which can introduce variability across studies and potentially impact research comparability and generalizability. We also want to assure you that we have accounted for this variability by including it in Table 1 and discussing it in the limitations section. Your valuable insights have contributed to enhancing the clarity and scope of our manuscript.

Changes in text: Lines 78 – 79: "Notably, the clinical definition of lean NAFLD often relies on BMI cut-offs or percentiles, leading to variability across studies and potentially limiting the comparability and generalizability of research efforts."

Comment 4: Discussion: I'm assuming that all these studies are on adult but there is an emerging literature on liver fat measures in children and adolescents and wonder if age along with ethnicity could be an issue with lean NAFLD and might be worth mentioning in your discussion.

Reply 4: We greatly appreciate your valuable insight. While our study incorporated results from various ethnicities and age groups, we acknowledge that no specific themes emerged regarding age and ethnicity in the context of lean NAFLD, despite attempting to highlight any differences. In light of your valuable suggestion, we have revised our discussion section. In our future research section, we have mentioned the importance of conducting further research on this specific aspect of lean NAFLD, to further elucidate any themes that may have not emerged from the very preliminary research to date in the literature. Thank you for your suggestion.

Changes in text: Lines 478 – 482: By expanding research efforts to include individuals from different ethnicities, geographic locations, and socioeconomic backgrounds, we can better understand potential variations in genetic and epigenetic determinants of NAFLD across populations. Additionally, such efforts can elucidate the role of age and ethnicity in relation to lean NAFLD, which can in turn direct further research and clinical guidelines.