**Protocol: Global Prevalence of NAFLD and NASH in an Overweight and Obese Population. A Meta-Analysis**

**Background:**

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease and represents an alarming global health crisis affecting 25-33% of the global population1-4. NAFLD comprises a spectrum of clinicopathologic entities ranging from the more benign5 nonalcoholic fatty liver (NAFL) to the more advanced non-alcoholic steatohepatitis (NASH) with the later identified by lobular inflammation and hepatocyte ballooning with or without fibrosis6. While overweight and obesity status are thought to be an effective dichotomy for NAFLD screening, the exact prevalence remains unknown. Current analysis has been limited to only the general population and the spectrum of lean and non-obese NAFLD7, 8. Furthermore, while the stage of fibrosis in NAFLD has been closely associated with end organ damages with a significant increase risk of mortality with each stage9, the prevalence of fibrosis in the overweight and obese NAFLD population remains in contention.

Hence, we sought to report the prevalence of NAFLD, NAFL and NASH in an overweight and obese population.

**Aims:**

1. To determine the global prevalence of NAFLD, NAFL and NASH in an overweight and obese population
2. To examine for sources of heterogeneity by performing subgroup analyses of the prevalence of NAFLD, NAFL and NASH (diagnostic modality, study setting, study period and the country of origin)
3. To determine the prevalence of liver fibrosis staging in overweight and obese NAFLD

**Inclusion and Exclusion criteria:**

A date filter will be applied to include only articles after 2000, and only studies written or translated to English language will be included. Cross-sectional and longitudinal observational studies, will be considered for inclusion. Studies will be included if they report crude data needed to calculate the prevalence of NAFLD, NAFL or NASH in an overweight and obese population (total sample size and event sample size). Articles will be included if NAFLD was diagnosed based on imaging or histological features, while NAFL and NASH was diagnosed by definitive liver biopsy5.

Reviews, commentaries and editorials will be excluded. Also, paediatric studies (aged <18 years) or a combined cohort of paediatric and adult populations, in which it is not possible to extract data estimates for adults, will also be excluded.

**Analysis:**

All analyses will be conducted in R studio (version 4.2.0). A random effect model will be used in all analyses. A meta-analysis of proportions will be conducted using a generalized linear mixed model with Clopper- Pearson intervals to determine the prevalence of NAFLD, NAFL and NASH in an overweight and obese population. To assess between-study heterogeneity, further subgroup analyses will be conducted based on diagnostic modality and study period. Regional variances between studies will also be assessed with a subgroup analysis between eastern and western countries, geographical regions as specified by the World Health Organisation (WHO) regional offices10 and individual countries. Publication bias will also be assessed with funnel plots of study size against logit transformed prevalence11, while quality assessment of included articles will be done with the Joanna Briggs Institute (JBI) Critical Appraisal Tool12.

**References**

1. Paik JM, Kabbara K, Eberly KE, Younossi Y, Henry L, Younossi ZM. Global burden of NAFLD and chronic liver disease among adolescents and young adults. Hepatology. 2022;75(5):1204-17.

2. Sanyal AJ. Past, present and future perspectives in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2019;16(6):377-86.

3. Lim GEH, Tang A, Ng CH, Chin YH, Lim WH, Tan DJH, et al. An Observational Data Meta-analysis on the Differences in Prevalence and Risk Factors Between MAFLD vs NAFLD. Clin Gastroenterol Hepatol. 2021.

4. Le MH, Yeo YH, Li X, Li J, Zou B, Wu Y, et al. 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. Clinical Gastroenterology & Hepatology. 2021;07:07.

5. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57.

6. Peng C, Stewart AG, Woodman OL, Ritchie RH, Qin CX. Non-Alcoholic Steatohepatitis: A Review of Its Mechanism, Models and Medical Treatments. Front Pharmacol. 2020;11:603926.

7. Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(8):739-52.

8. Lu FB, Zheng KI, Rios RS, Targher G, Byrne CD, Zheng MH. Global epidemiology of lean non-alcoholic fatty liver disease: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2020;35(12):2041-50.

9. Ng CH, Lim WH, Hui Lim GE, Hao Tan DJ, Syn N, Muthiah MD, et al. Mortality Outcomes by Fibrosis Stage in Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2022.

10. WHO Regions [Available from: <https://www.who.int/countries>.

11. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol. 2014;67(8):897-903.

12. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. International journal of health policy and management. 2014;3(3):123.